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Surgical Pathology of the Head and Neck, Third Edition is a complete stand-alone reference covering all aspects of head and neck pathology. Providing an interdisciplinary approach to the diagnosis, treatment, and management of head and neck diseases, this source promotes clear communication between pathologists and surgeons. This is the reference of choice for a variety of clinicians, including oral and general pathologists; oral and maxillofacial, plastic, reconstructive, head and neck, orthopedic, and general surgeons; otolaryngologists; radiologists; and dentists.

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SURGICAL PATHOLOGY OF THE HEAD AND NECK
VOLUME 3

SURGICAL PATHOLOGY OF THE HEAD AND NECK

Third Edition

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52 Vanderbilt Avenue
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No claim to original U.S. Government works
Printed in India by Replika Press Pvt. Ltd.
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-9163-8 (V1; Hardcover)
International Standard Book Number-10: 1-4200-9164-6 (V2; Hardcover)
International Standard Book Number-13: 978-1-4200-9164-9 (V2; Hardcover)
International Standard Book Number-10: 1-4200-9165-4 (V3; Hardcover)
International Standard Book Number-13: 978-1-4200-9165-6 (V3; Hardcover)
International Standard Book Number-10: 0-8493-9023-0 (Set; Hardcover)
International Standard Book Number-13: 978-0-8493-9023-4 (Set; Hardcover)

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.Library of Congress Cataloging-in-Publication Data
Surgical pathology of the head and neck / edited by Leon Barnes. – 3rd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-10: 0-8493-9023-0 (hb : alk. paper)
WE 705 5961345 2008]
RC936.587 2008
617.5’10754–dc22
2008026087

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to:
Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

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Preface to Third Edition

Seven years have elapsed since the second edition of *Surgical Pathology of the Head and Neck* was published. During this interval there has been an enormous amount of new information that impacts on the daily practice of surgical pathology. Nowhere is this more evident than in the area of molecular biology and genetics. Data derived from this new discipline, once considered to be of research interest only, have revolutionized the evaluation of hematolymphoid neoplasms and are now being applied, to a lesser extent, to the assessment of mesenchymal and epithelial tumors. While immunohistochemistry has been available for almost 30 years, it has not remained static. New antibodies are constantly being developed that expand our diagnostic and prognostic capabilities.

Although these new technologies are exciting, they only supplement and do not replace the “H&E slide,” which is, and will continue to be, the foundation of surgical pathology and this book particularly. This edition has been revised to incorporate some of these new technologies that further our understanding of the pathobiology of disease and improve our diagnostic acumen, while at the same time retaining clinical and pathological features that are not new but remain useful and important.

Due to constraints of time and the expanse of new knowledge, it is almost impossible for a single individual to produce a book that adequately covers the pathology of the head and neck. I have been fortunate, however, to secure the aid of several new outstanding collaborators to assist in this endeavor and wish to extend to them my sincere thanks and appreciation for lending their time and expertise. In addition to new contributors, the illustrations have also been changed from black and white to color to enhance clarity and emphasize important features.

This edition has also witnessed changes in the publishing industry. The two previous editions were published by Marcel Dekker, Inc., which was subsequently acquired by Informa Healthcare, the current publisher. At Informa Healthcare, I have had the pleasure of working with many talented individuals, including Geoffrey Greenwood, Sandra Beberman, Alyssa Fried, Vanessa Sanchez, Mary Araneo, Daniel Falatko, and Joseph Stubenrauch. I am especially indebted to them for their guidance and patience.

I also wish to acknowledge the contributions of my secretary, Mrs. Donna Bowen, and my summer student, Ms. Shayna Cornell, for secretarial support and Ms. Linda Shab and Mr. Thomas Bauer for my illustrations. Lastly, this book would not have been possible without the continued unwavering support of my family, Carol, Christy, and Lori, who have endured yet another edition!

Leon Barnes
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Odontogenic Tumors

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INTRODUCTION

The term “odontogenic tumors” comprises a group of neoplasms and hamartomatous lesions derived from cells of tissues involved in the formation of teeth or remnants of tissues that has been involved in the odontogenesis. Few of them are odontogenic in the sense that the formation of dental hard tissues takes place in them; it is primarily the case in the ameloblastic fibro-odontoma (AFOD), the odontomas, and the cementoblastoma (CEMBA).

The tumors occur exclusively in three locations (i) intraosseous (centrally) in the jaws, (ii) extraosseous (peripherally) in the gingiva or alveolar mucosa overlying tooth bearing areas, and (iii) in the cranial base, as one of the variants of the craniopharyngioma, a tumor arising from cell rest derived from the hypophyseal stalk or Rathke’s pouch. The craniopharyngioma occurs as subtypes, which resembles ameloblastoma, calcifying odontogenic cyst (COC) or AFOD with intracranial formation of tooth-like elements (1–4). The craniopharyngiomas are not further described in this chapter.

Odontogenic tumors are rare, with some of them being exceedingly rare. Our knowledge of these tumors is primarily based on published reports of cases, reviews of such cases, and reviews of cases from files from institutions. In the later years, the use of electron microscopy, immunohistochemistry, and molecular biological techniques has increased our knowledge of the biology of the tumors considerably (5). Development of experimental models of odontogenic tumors in animals have been tried, but with limited success; although it has been possible to breed animals that develop tumors resembling, e.g., ameloblastomas and odontomes (6,7), they are not true equivalents to odontogenic tumors in humans—their histology is similar, but their biological behavior is different (8). Tissue culture has been more successful and has primarily been used in studies of the molecular biology of the tumors.

The accumulated knowledge has led to numerous attempts at classification of odontogenic tumors, reviews of older classifications have been written by Gorlin et al. (9) and Baden (10), and valuable information about older references is found in these articles. A short, but more recent review, including the classifications issued by World Health Organization (WHO) in 1971, 1992, and 2005 has been published by Philipsen et al. (11). The description of the tumors in the present chapter is based on the WHO 2005 classification (12) (Table 1), apart from a diverging conception of the odontogenic ghost cell lesions and the inclusion of some very rare tumors, which were left out of the 2005 WHO classification as they were considered insufficiently defined.

The etiology of the odontogenic tumors is essentially unknown, apart from indications that genetic factors play a role as cofactor in some cases. The pathogenesis is incompletely understood, the subject has been discussed in several articles (13–17).

Since odontogenic tumors appear to develop from remnants of odontogenic tissues and many of the histomorphological and other biological features of the normal odontogenesis are retrieved in odontogenic tumors, particularly in the group consisting of odontogenic epithelium and odontogenic ectomesenchyme, with or without hard tissue formation, a certain knowledge of the normal odontogenesis is required to identify and understand the tissue changes observed. Apart from chapters in textbooks like Oral Cells and Tissues by Garant (18), shorter reviews have been published by Theslaff et al. (19), Peters et al. (20), Coubourne et al. (21), and Philipsen et al. (16).

The histomorphological variants of odontogenic tumors are numerous and cannot be fully illustrated in a single treatise. Additional photos in colors are accessible in the three publications by WHO (12,22,23), in Sciubba et al. (24) and Reichart et al. (25).

I. BENIGN ODONTOGENIC TUMORS

1. Tumors of Odontogenic Epithelium with Mature, Fibrous Stroma Without Odontogenic Ectomesenchyme

This group of tumors covers the following recognized entities: ameloblastoma, squamous odontogenic tumor (SOT), calcifying epithelial odontogenic tumor (CEOT), and adenomatoid odontogenic tumor (AOT).
1.1 Ameloblastoma

1.1.1 Solid/Multicystic Ameloblastoma-Central.

Introduction. The central solid/multicystic ameloblastoma (s/mAM) is a slowly growing, locally invasive epithelial odontogenic neoplasm of the jaws with a high rate of recurrence but with a very low tendency to metastasize (26).

ICD—O 9310/0

Synonyms: Conventional ameloblastoma; classical intraosseous ameloblastoma.

Clinical Features. The prevalence and incidence of the s/mAM is unknown apart from two studies, both of which comprised all variants of ameloblastoma, not only the s/m. Shear et al. (27) calculated age-standardized incidence rates of the tumor in the population of the Witwatersrand region of South Africa from 1965 to 1974. The annual incidence rates, standardized against the standard world population, for all variants of ameloblastomas per million populations were 1.96, 1.20, 0.18, and 0.44 for black males, black females, white males, and white females, respectively. The figures show that ameloblastoma is very much more common in blacks than in whites in the population at risk. Gardner (28) recalculated the figures without separating the two genders and found the incidence rates to be 2.29 new cases each year per one million people for blacks and 0.31 for whites. It is unknown whether this marked difference is caused by genetic or environmental factors.

Another valuable study of the incidence of ameloblastomas was published by Larsson et al. (29). All cases of ameloblastoma reported to the Swedish Cancer Register in the period 1958–1971 (except the years 1966 and 1969) were reexamined histologically with criteria indicated in the 1971 WHO classification (22); 31 cases of ameloblastoma (peripheral and unicystic included) were accepted. The number of annual cases varied between 1 and 5, corresponding to 0.13 to 0.63
annual cases per one million people, and an average of 0.3 annual case per one million inhabitants. On the basis of the study of the files of two major hospitals, the authors estimated an under registration of about 50%. The true incidence was thus close to 0.6 cases each year per one million people, a figure which can be accepted as a reasonable estimate of the incidence of ameloblastoma in a Caucasian population.

The relative frequency of the tumor is known from several studies, it is the second most common odontogenic tumor after the odontomas. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 11.0% to 73.3% in studies comprising more than 300 samples of odontogenic tumors. Except for one study [Buchner et al. (30)] subdivision in ameloblastoma variants (s/m, peripheral, desmoplastic, and unicystic) have not been made in these studies. The results are indicated as follows: number of odontogenic tumors/number of ameloblastomas/percentage. Regezzi et al., Michigan, U.S.A. (31): 706/78/11.0%, Günhan et al., Turkey (32): 409/149/36.4%, Daley et al., Canada (33): 392/53/13.5%, Mosqueda-Taylor et al., Mexico (34): 349/83/23.7%, Ochsensius et al., Chile (35): 362/74/20.4%, Adebayo et al., Nigeria (36): 318/233/73.3%, Fernandes et al., Brazil (37): 340/154/45.3%, Ladeinde et al., Nigeria (38): 319/201/63.0%, Buchner et al., California (30): 1088/127/11.7% [unicystic ameloblastoma (UNAM) 5.3%, solid/multicystic (s/m) 6.3%], Jones et al., England (2006, pooled figures from two studies)(39,40): 523/111/21.2%, Olga et al., Turkey (41): 527/133/25.2%, and Jing et al., China (42): 1642/661/40.3%. The data are skewed, however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetic or environmental factors.

The most comprehensive review of ameloblastomas has been published by Reichart et al. (43) who evaluated 3677 cases published in various languages between 1960 and 1993, including 693 case reports and 2984 cases from reviews.

In this review, figures were reported for occurrence in the three major racial groups (Caucasoid, Mongoloid, Negroid), no conclusions can be drawn from this information. As pointed out by Gardner (28) the numbers do not reflect the occurrence of ameloblastomas in the three major racial groups but rather the number of published cases in those groups, and the number of published cases does not reflect the actual prevalence in a population.

Details for age (including peripheral and unicystic variants) were retrieved from 2280 cases (1630 from reviews, 650 from case reports) the age range at time of diagnosis was 4 to 92 years, and the median age was 35 years. The mean age from case reports was 37.4 years and from reviews 35.4 years. The figures for the individual variants were “hidden” in the review, but recalculated by Gardner (28) who estimated a mean age of 39 years for s/mAM, 51 years for peripheral, and 22 years for UNAMs. In comparison Ledesma-Montes (44) found (N = 163) that the mean age was 41.4 years for s/mAM and 26.3 years for UNAM (p < 0.001).

The majority of ameloblastomas in Caucasian children, but not in African are unicystic. Ord et al. (45) reported 11 own cases of ameloblastoma in children (2 s/m AM and 9 unicystic) and reviewed the literature on ameloblastoma in children in Western reports (85 children) and reports from Africa (77 children). The mean age was 15.5, 14.3, and 14.7 years, respectively. UNAMs accounted for 76.5% of the Western and only for 19.5% of the African children. The pattern in African children seems to resemble the pattern of adults. These findings were confirmed by Arotiba et al. (46).

Reichart et al. (43) found the mean age of patients with tumors of the maxilla to be 47.0 years compared with tumors of the mandible with a mean age of 35.2 years. The difference may at least partly be explained by the fact that UNAMs are rare in the maxilla and about 30% of solid/multicystic ameloblastomas-peripheral (PERAMs) occur in the maxilla.

The gender distribution has varied in different reviews but is often close to 50:50; in the review by Reichart et al.(43) 53.5% were males and 46.7% were females (N = 3677).

The location of the tumor was recorded in the same review, but only for all variants combined. The ratio between maxillary (N = 185) and mandibular (N = 404) ameloblastomas was 1.22 when case reports were evaluated. If, however case reports and reviews were considered together (N = 1932) the ratio between maxillary and mandibular tumors was 1.58. The difference is presumably because ameloblastomas, as they are more unusual, are reported more often in case reports. The incisor region and ramus of the mandible were affected more often in females than in males. The premolar region and the maxillary sinus were affected more often in males than in females, whereas the molar region was affected equally in both genders. The predilection site is the posterior part of the mandible in which 44.4% of the tumors (all variants) were located. In the study by Ledesma-Montes et al. (44) 79.3% of the s/mAM were located in the maxilla.

The tumor is slowly growing and with few symptoms apart from the swelling. Some published cases of mandibular ameloblastomas have been extremely large (25 cm or more), a huge tumor reported by Carlson et al. (47) had been present for 16 years. The duration of symptoms varied from half a year to 40 years (for all variants, N = 198) in the review by Reichart et al (43); the median duration was six-and-a-half months, and the mean duration time was 27 months. Ledesma-Montes et al. (44) reported a range of duration time from 1 to 39 years for s/mAM (N = 163), with a mean of 4.5 years. In this review, the most common clinical findings were swelling (97%), pain (34.4%), ulceration (12.5%), and tooth displacement (12.5%). Delayed tooth eruption and mobility of teeth has also been reported (43). In large tumors with expansion and resorption of the jawbone a crepitation
may be elicited, perforation of the cortical bone is a late feature, however. Paresthesia of the lower lip is a rare symptom (48).

**Imaging.** A radiolucent, often well-demarcated, sometimes corticated, multilocular radiolucency is a characteristic radiological appearance of the s/mAM, but it is not diagnostic (Fig. 1). The radiographic image may vary considerably. Among 55 cases reviewed by Ledesma-Montes et al. (44) 88.1% were radiolucent, 66.7% were unilocular, and 66.7% were well defined. The radiographic descriptions of 1234 cases (377 case reports and 857 cases from reviews) were evaluated by Reichart et al. (43), but were only reported for all four variants combined, 102 were of the unicystic type. The appearance was unilocular in 51.1%, and multilocular (“soap-bubble-like”) in 48.9%. Embedded teeth were detected in 8.7%, root resorption of neighboring teeth in 3.8%, and undefined borderline in 3.6%. Embedded teeth were not surprisingly seen more often in younger patients. The size of the tumor was stated in 129 cases, the maximum size was 24 cm. The mean size was 4.3 cm, and the median size 3.0 cm. Ledesma-Montes et al. (44) reported (N = 55) a mean size of 6.7 cm for mandibular s/mAM and a mean size of 4.6 cm for the maxillary tumors.

Some s/mAM particularly those with a plexiform growth pattern show a highly vascular stroma, this feature may have an impact on the radiographic image making the lesion resemble a poorly-defined fibro-osseous lesion (49). In such cases, and in the diagnosis of ameloblastomas in general the use of computed tomography (CT) and magnetic resonance imaging (MRI) is highly recommended (47). Asaumi (50) demonstrated the quality of MRI and dynamic contrast-enhanced MRI in the study of 10 ameloblastomas. Solid and cystic portions of the tumor could be identified, mural nodules and thick walls could be detected, and solid and fluid areas could be distinguished. No differences in the signal intensities between primary and recurrent cases were found.

**Pathology.** The etiology of the s/mAM is unknown. The pathogenesis is insufficiently understood. The tumor is believed to arise in remnants of odontogenic epithelium, primarily rests of the dental lamina, which however have been found primarily in the overlying gingiva or oral mucosa (14). The remnants of the epithelial root sheet (islands of Malassez) are usually not considered a likely source of ameloblastomas although some cases of early ameloblastoma in the periodontal area might suggest this as a possibility (51,52). Dentigerous cysts as a source of ameloblastoma cannot be excluded but it seems unlikely as discussed in the section on UNAM. It has some times been suggested that an ameloblastoma could develop from the basal cells of the overlying surface epithelium; it is well known that intraosseous ameloblastomas, which progress through the cortical bone and reaches contact with the surface epithelium may cause induction of the surface epithelium to produce ameloblastomatous proliferations. Since benign PERAMs do not invade the underlying bone, it is difficult to envision that intraosseous ameloblastomas should develop from the surface epithelium. Studies of cytokeratins (CK) (53) have also supported the hypothesis that ameloblastomas are of odontogenic origin and not direct derivates of basal cells of oral epithelium.

The macroscopical appearance of the operation specimen depends on the size of the tumor and the treatment modality. Resected tumors are surrounded by normal bone and may contain teeth. The tumor area is grayish and does not contain hard tissue apart from the border areas, it usually presents as a mixture of solid and multicystic areas, but some lesions are completely solid, and others are dominated by formation of cysts. The cysts are of varying size, usually most of them are small some are microscopic, but in large tumors several may be quite conspicuous. They are filled with a brownish fluid, which often is of low viscosity, but may be more gelatinous.

Microscopically the tumor consists of odontogenic epithelium growing in a relatively cell-poor collagenous stroma. Two growth patterns and four main cell types are recognized within the histopathological range of the entity (Table 2). The two growth patterns are named **follicular** and **plexiform**.

In the follicular pattern the tumor epithelium (Figs. 2, 3) primarily presents as islands of various size and shape (23,54). They usually consist of a

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**Table 2** Ameloblastoma Growth Patterns and Cell Types

<table>
<thead>
<tr>
<th>Growth patterns</th>
<th>Cell types</th>
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<tbody>
<tr>
<td>Follicular growth pattern</td>
<td>Stellate reticulum-like cell type</td>
</tr>
<tr>
<td>Plexiform growth pattern</td>
<td>Acanthomatous (squamous cell) cell type</td>
</tr>
<tr>
<td></td>
<td>Granular cell type</td>
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<td>Basal cell type</td>
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central mass of polyhedral or angular cells with prominent intercellular contact and conspicuous intercellular spaces. The morphology has some resemblance to the stellate reticulum of the normal enamel organ, but many details are different. The peripheral cells are palisaded, columnar, or cuboidal with dark nuclei. The columnar cells contain elongated nuclei, which may show reverse polarity and have a histomorphological likeness to preameloblasts (Fig. 4). Mitoses are absent or very infrequent. The term follicular alludes to a certain resemblance of the structure of the epithelial islands to enamel organs. The stellate reticulum-like cells may be replaced by squamous cells, granular cells, or basal cells (vide infra). If cysts develop, they arise in the center of the islands.

In the plexiform growth pattern (Fig. 5) the tumor epithelium is arranged as a network (plexus), which is bounded by a layer of cuboidal to columnar cells and includes stellate reticulum-like cells (23). The width of the epithelial cords in the network may vary considerably. Sometimes double row of columnar or cuboidal cells are lined up back to back. The peripheral cells are similar to those seen in the follicular pattern, although they are more often cuboidal and may even be squamous. In the plexiform type as well, but more rarely, the stellate reticulum-like cells may be replaced by squamous cells, granular cells, or basal

Figure 2 Solid/multicystic ameloblastoma with follicular growth pattern and stellate reticulum-like cells in the islands. Squamous metaplasia is seen in a few islands. Minor cysts are seen in the islands, as well as in the stroma. H&E stain.

Figure 3 Solid/multicystic ameloblastoma with follicular growth pattern in a stroma consisting of narrow strands of collagenous connective tissue. H&E stain.

Figure 4 Ameloblastoma. Peripheral cells of a tumor island. The basal cells are palisaded and columnar with reverse polarity of the nucleus and show some morphological similarity to preameloblasts. The suprabasal cells are stellate reticulum-like. van Gieson stain.

Figure 5 Solid/multicystic ameloblastoma with a plexiform growth pattern. van Gieson stain.
cells. The stroma is generally looser than in the follicular pattern, and if cyst formation occurs, it is usually due to stromal degeneration rather than to a cystic change within the epithelium.

Each of the two growth patterns may be dominating in a s/mAM, but often both patterns are present in the same tumor. It is generally believed that the growth pattern is unrelated to the clinical behavior of the tumor, but some reports have suggested a higher tendency for recurrence in follicular than in plexiform ameloblastomas (55) and many molecular biological findings are different (5).

Squamous cell metaplasia of the central areas of the tumor epithelium is not unusual (Fig. 6), and is particularly seen in tumors with a follicular growth pattern. When extensive squamous metaplasia is seen, sometimes with keratin formation the term acanthomatous ameloblastoma is applied. This variant accounted for 12.1% of 397 cases reviewed by Reichart et al. (43). When cysts are formed in the epithelium, they are lined by squamous cells. The squamous cells are sometimes plump or fusiform and may exhibit few junctions.

Rarely an s/mAM shows formation of orthokeratinized or more often parakeratinized horn pearls in central areas of the tumor epithelium. It may even be seen in areas, which are not dominated by squamous cell metaplasia (Fig. 7). Very rarely calcifications are seen in these horn pearls (56).

The central stellate cells may be replaced by large eosinophilic rounded or polyhedral granular cells. The granules may be diastase resistant period acid-Schiff (PAS)-positive and they represent lysosomes. Most nuclei in these cells are placed at the periphery of the cells (Fig. 8). The granular cells may take up a complete epithelial island and then even the basal cells are granular. When a conspicuous part of the tumor or the entire tumor is composed of granular cells, the tumor is usually called a granular cell ameloblastoma.

Such tumors are infrequent, particularly those with a plexiform growth pattern (Fig. 9) (57,58).

Hartman (59) studied 20 cases of granular cell ameloblastom, which accounted for 5% of all ameloblastomas in their file and stated that they occurred predominantly in the posterior regions of the mandible (which is a predilection site for all s/mAMs). He observed that they had a marked tendency to recur after conservative treatment, but this behavior seems related to the treatment modality and not to the histology of the tumor.

Rarely, an ameloblastoma may show a predominantly basaloid pattern (Fig. 10), and this tumor is referred to as a basal cell ameloblastoma, or basaloid ameloblastoma (23). It is the least common of the cytological variants and accounted for 2% of the case reports reviewed by Reichart et al. (43). The epithelial
elements are composed almost exclusively of islands of plump cells with a high nucleus to cytoplasm ratio, and reticulum-like cells are few or absent. The periphery is dominated by cuboidal rather than columnar cells. Cystic changes in the epithelial component are infrequent.

Mucous cell metaplasia may be seen in the tumor epithelium, but is very rare. Clear cells may be found in an s/mAM; if they occur in more than a few areas, a clear cell odontogenic carcinoma (CCOC) should be considered. The significance of clear cells is discussed in the section on that tumor.

Tumor cells containing melanin granules may be observed. Various amounts of ghost cells may be seen, but they are not frequent. A dentinogenic ghost cell tumor (DGCT) should be considered, but the diagnosis requires that the tumor has formed dentinoid in the stroma adjacent to the epithelial tumor component.

The connective tissue stroma varies in amount, vascularity, and collagen content. No dental hard tissue is formed. The basement membrane may be thick and hyalinized, and this juxtaepithelial hyalinization may be conspicuous. If clear cells, if any are seen in the hyalinized zone. Scattered lymphocytes may be observed, but there is no inflammation, except caused by secondary factors.

In ameloblastomas with a plexiform growth pattern, a highly vascular stroma may be seen, and it may be in terms of several highly dilated vessels. The pattern should be considered within the spectrum of appearances of an ameloblastoma. Previously such cases were called hemangioameloblastoma.

Cystic degeneration of the stroma is not unusual in s/mAMs with a plexiform growth pattern. Residual capillaries may be found in these stromal cysts and cellular debris is a common finding in the cysts.

In a study of 31 cases of s/mAM Müller et al. (64) observed that infiltration of the surrounding spongy bone is frequent, but there was little tendency to invade cortical bone. They also found that periosteum largely prevented extension of the tumor. Gortzak et al. (65) studied five voluminous mandibular ameloblastomas after resection and confirmed the invasive growth pattern. Small tumor nests were found in the cancellous bone at a maximum distance of 5 mm from the bulk of the tumor (Fig. 12). Expansive and invasive growth in the Haversian canals was observed, but there was no invasion of the inferior alveolar nerve. The mucoperiosteal layer was invaded but not perforated, and no invasion was observed in the surrounding soft tissues of the periosteum and in the skin tissues. The authors stated that when the tumor is radiologically closer than 1 cm to the inferior border of the mandible, a continuity resection is mandatory.
Immunohistochemistry. Because ameloblastoma is one of the more common odontogenic tumors and because of the florid development of the immunohistochemical technique, the literature concerning immunohistochemical investigations of ameloblastomas is very extensive. Several investigators have used immunohistochemistry together with molecular biological methods to study a special subject, many of these reports published before the middle of 2005 were reviewed by Kumamoto in 2006 (5). These studies will primarily be reviewed in the section on molecular-genetic data.

The following summaries comprise primarily reports regarding cytofilaments, extracellular matrix proteins, basement associated molecules, protein kinases, and cell proliferation markers.

Heikinheimo et al. (53) studied the presence of CKs and vimentin in nine s/mAMs and three fetal human tooth germs at bell stage. They used eight antibodies against CKs, which individually or in combination could detect CK-4, CK-5, CK-6, CK-8, CK-10, CK-11, CK-13, CK-16, CK-17, CK-18, and CK-19. Most, but not all ameloblastomas lacked CKs typical of keratinization. CK-8 and CK-19 were expressed in all, and CK-18 in the epithelial component of most of the ameloblastomas, including the granular cell type, which expressed CK-8, CK-18, and CK-19 very distinctly. Vimentin was detected in the epithelial cells of all ameloblastomas except the granular cell type. The ameloblastomas and the human tooth germ epithelia shared a complex pattern of CK polypeptides together with the expression of vimentin. The authors concluded that the findings strongly supported that ameloblastomas are of odontogenic origin and not derived from basal cells of the gingiva or oral mucosa.

Crivelini et al. (66) performed a similar study on 10 ameloblastomas and four other types of odontogenic tumors. They used monoclonal antibodies against single CK types CK-7, CK-8, CK-10, CK-13, CK-14, CK-18, CK-19 and against vimentin. The results differed somewhat from those of Heikinheimo et al.; all ameloblastomas were CK-8, CK-18, and vimentin negative. They were all, including the granular cell type immunoreactive to CK-14. They also reacted to CK-13 and CK-19, but only in metaplastic squamous cells, central stellate cells and in the lining of cystic structures.

Extracellular matrix proteins and basement membrane associated molecules have been studied.

Ito et al. (67) detected versican, a large aggregating chondroitin sulfate proteoglycans in 17 ameloblastomas. All samples showed a positive reaction for versican in the connective tissues, whereas positive staining of epithelial nests was observed in only some samples.

Tenascin, an extracellular matrix glycoprotein was detected by Heikinheimo et al. (68) in the stromal component of all 11 ameloblastomas. The epithelial component was negative. Nagai et al. (69) got very variable results in the study of 10 ameloblastomas. Hyalinized stroma was both positive and negative. Cystic stroma was negative. The basement membranes showed an irregular linear positive reaction with focal accumulation of tenascin. Mori et al. (70) on the other hand detected a strong reaction to tenascin in the interface around the epithelial component, although with frequent breaks. A positive reaction was found in stellate reticular-like cells and granular epithelial cells as well.

Nadimi et al. (71) studied laminin in 29 ameloblastomas. An intense linear deposit was found in the basement areas of all of them. Heikinheimo et al. (68) confirmed these results.

Nadimi et al. (71) were unable to detect fibronectin except in areas with inflammation. Nagai et al. (69) got very variable results but detected an irregular linear immunoreaction in basement areas. Heikinheimo et al. (68) detected an extra domain sequence-A-containing form of fibronectin in the extracellular matrix of all ameloblastomas (N = 11), and an oncofetal domain containing form of fibronectin in most ameloblastomas. They studied collagen type VII as well; the immunoreaction was very similar to that of laminin: most ameloblastomas exhibited a continuous staining of the basement membranes.

Farikka et al. (72) detected collagen XVII, a hemidesmosomes transmembrane adhesion molecule, in the cytoplasm of basal and suprabasal cells in 11 s/mAMs and 2 UNAM using immunohistochemistry and in situ hybridization (ISH).

Poomsawat et al. (73) used antibodies against laminins 1 and 5, collagen type IV, and fibronectin on 14 ameloblastomas. An intense staining of laminin 1 and a weak to moderate intensity of laminin 5 were seen as continuous linear deposits at the basement membrane zone surrounding tumor islands. Collagen type IV showed irregular patterns; focal loss of staining was observed. A weak to moderate staining for fibronectin was occasionally present; fibronectin was also present in the fibrous stroma. The tumor cells also showed reaction to laminin 1 and 5, collagen type IV, and fibronectin. In general, laminin 1 showed moderate to strong intensity in the cytoplasm of both central
and peripheral cells; collagen type IV was rarely observed. Laminin 5 was expressed in peripheral cells, but less often.

Collagen type IV was also studied by Nakano et al. (74) and Nagatsuka et al. (75). Nakano et al. found that ameloblastoma (N = 2) basement membranes expressed five of six genetically distinct forms of collagen IV: α1(IV), α2(IV), α5(IV), and α6(IV)—chains occurred as intense linear stainings without disruption around neoplastic epithelium. A similar study of 5 ameloblastomas by Nagatsuka et al. (75) gave the same results.

Integrin, a plasma membrane protein, which plays a role in the attachment of cell to cell and cell to the extracellular matrix, and as a signal transducer has been studied by Souza Andrada et al. (76). Integrin α2β1, α3β1, and α5β1 were detected in 20 s/mAMs, 10 UNAMs, and 12 AOT. The labeling intensity was considerably stronger in the ameloblastomas than in the AOTs, but no significant differences were found between the two variants of ameloblastoma. In s/mAMs the immunoreaction was detected in intercellular contacts and at the connective tissue interface.

Using immunohistochemistry, in situ hybridization, immunoprecipitation, and reverse transcriptase polymerase chain reaction (RT-PCR), Ida-Yonemochi et al. (77) detected basement-type heparan sulfate proteoglycan (HSPG), also known as Perlecain in the intercellular spaces of the epithelial component and in the stroma of 20 ameloblastomas and cultured ameloblastoma cells. The studies indicate that ameloblastoma cells synthesize HSPG.

The roles of mitogen-activated protein kinases (MAPKs) in oncogenesis and cytodifferentiation of odontogenic tumors were investigated by Kumamoto et al. (78), using antibodies against phosphorylated c-Jun NH2-terminal kinase (p-JNK), phosphorylated p38 mitogen-activated protein kinases (p-p38 MAPK), and phosphorylated extracellular signal-regulated kinase 5 (p-ERK5) on 47 ameloblastomas (including 4 desmoplastic), 2 metastasizing ameloblastomas (METAMs), 3 ameloblastic carcinomas (AMCA), and 10 human molar tooth germs. Almost all s/mAMs were p-JNK negative. From 84% to 91% of the various histological types of ameloblastomas were moderately p-p38 MAPK positive. The basal cell ameloblastomas (N = 3), however, and the desmoplastic ameloblastomas (DESAMs) (N = 4) were 100% positive, three of six granular cell ameloblastomas were positive. Between 64% and 66% of the histological types of ameloblastoma were p-ERK5 positive, except basal cell and DESAM, which were 100% positive. The authors suggested that these MAPK signaling pathways contribute to cell proliferation, differentiation, or apoptosis in both normal and neoplastic odontogenic tissues.

Cell proliferation markers have been studied by several investigators. The results have been somewhat contradictory. Kim et al. (79) used antibodies against proliferating cell nuclear antigen (PCNA) on 25 s/mAMs and 13 unicystic types and a case of AMCA. There was no significant difference between the proliferating activities of the different histological types of s/mAM, but a recurrent ameloblastoma and the AMCA showed remarkably higher PCNA activity. Funaoaka et al. (80) measured the PCNA index in 23 s/mAMs, they found a higher, but not significantly higher index in follicular than in plexiform ameloblastomas. Interestingly, they found a remarkable difference in the index of biopsies of the same tumor taken at different times. Ong’uti et al. (81) measured the Ki-67 index in 54 s/mAMs, 24 follicular, and 30 plexiform. They found a significantly higher labeling index (L.I.) in ameloblastomas with a follicular growth pattern than in those with a plexiform pattern. They did not find any significant correlation between the Ki-67 L.I. and clinical features like age, gender, and tumor size.

Piantelli et al. (82) evaluated the proliferative activity of 22 ameloblastoma among which 13 were s/mAM by measuring the immunoreactivity of PCNA. Recurrent ameloblastoma (N = 4) presented higher PCNA positive cell counts than other types of ameloblastoma.

Sandra et al. (83) used antibodies against PCNA and Ki-67 on 25 s/mAMs, 5 unicystic, and 3 DESAMs, and measured the indices. There was a strong correlation between the PCNA and the Ki-67 labeling indices. Positively stained cells were primarily found in the peripheral layers. The basal cell types of ameloblastomas showed the highest L.I., but it was not significantly higher than that of follicular, plexiform, and acanthomatous types. It was significantly higher, however, than the labeling indices measured in unicystic and DESAMs. On the contrary, Meer et al. (84) found a statistically significantly higher PCNA and Ki-67 L.I. in unicystic (N = 10) than in the s/m variant (N = 10).

Thosaporn et al. (85) used antibodies against a novel cell proliferation marker, IPO-38 (N-L 116) on 10 ameloblastomas, 10 keratocystic odontogenic tumors (KOTs), 7 orthokeratinized odontogenic cysts, and 8 dentigerous cysts. Positive nuclei were found in the peripheral cell layers of the ameloblastomas. The L.I. was similar to that of the KOTs, but twice as high as that of the orthokeratinized odontogenic cysts and 14 times higher than that of the dentigerous cysts.

Payeras et al. (86) evaluated the proliferation activity in 11 cases of s/mAM by means of quantification of the argyrophilic nuclear organizer regions (AgNORs) and the pattern of immunohistochemical expression of the epidermal growth factor receptor (EGF-R). There was no significant statistical difference as per quantification of the AgNORs, the expression of the EGF-R on the epithelial islands of ameloblastoma was not uniform, and the location of the expression was also variable. The authors concluded that the tumor presents an irregular growth, and that smaller epithelial islands could be responsible for tumor infiltration since they are associated with a higher proliferation activity.

Granular cell ameloblastoma has been studied in particular by Kumamoto et al. (87). Granular cells were positive for CK, CD68, lysozyme, and alpha-1-antichymotrypsin, but negative for vimentin, desmin, S-100 protein, neuron-specific enolase (NSE) and CD 15, indicating epithelial origin and lysosomal
aggregation. The authors suggested that the cytoplasmic granularity in granular cell ameloblastomas might be caused by increased apoptotic cell death of neoplastic cells and associated phagocytosis by neighboring neoplastic cells.

**Electron Microscopy.** Several studies have reported the ultrastructure of the ameloblastoma. Moe et al. (88), Sujaku et al. (89), Csiba et al. (90), Navarrette et al. (91) Lee et al. (92), Mincet et al. (93), Cutler et al. (94), Tandler et al. (95), Kim et al. (96), Matthiessen et al. (97), Rothouse et al. (98), Chomette et al. (99), Nasu et al. (100), Takeda et al. (101), Smith et al. (102), and Farman et al. (103). Some of the earlier studies concentrated on ultrastructural similarities between the columnar peripheral epithelial cells of the s/mAM and the plexiform lobules of the normal enamel organ (88,89,92,93). Kim et al. (96) and Matthiessen et al. (97) confirmed this similarity and further observed that the stellate cells of the tumor epithelium were in many respects similar to the stellate reticulum of the normal enamel organ. They were joined by desmosomes and the nucleus occupied a central position within the cell. The perinuclear cytoplasm contained mitochondria, tonofilaments, endoplasmic reticulum, and dense granules. Some epithelial cells contained numerous lipid granules and mitochondria formed a network of cords. Matthiessen et al. (97) found that the low peripheral cells in s/mAM were very similar to the external enamel epithelium cells. The central cells of the islands had a certain resemblance to the stellate reticulum and stratum intermediate cells. The high peripheral cells of the s/mAM had no counterpart in the enamel organ. Unlike the enamel organ, the ameloblastoma showed extremely few and small gap junctions.

The ultrastructural features of squamous epithelial cells were similar to those described for basal cells and lower prickle cells of the oral mucosa. The granular cells in particular were studied by Navarrette et al. (91) and Tandler et al. (95) and Nasu et al. (104). The granular cells commonly occur in the islands of ameloblastomas with a follicular growth pattern, in one of these cases reported by Nasu et al. (104), they were in a plexiform pattern. The cytoplasmic granules were identified as lysosomes, supported by the fact that they were intensively stained for acid phosphatase; no cytoplasmic components were found in the numerous lysosomes; they do not seem to be engaged in autophagy, their function is unknown. The occurrence of intracytoplasmic desmosomes was described by described by Cutler et al. (94) in an ameloblastoma from the maxilla. Hyaline bodies, a structure that is relatively common in odontogenic cysts, were observed by Takeda et al. (101), ultrastructurally they did not differ from those found in the epithelium of the wall of odontogenic cysts. Farman et al. (103) studied the interface between the tumor component and the stroma in seven ameloblastomas. All showed differing degrees of thickening of lamina densa by a granulofilamentous material having a range of width of approximately 80 to 800 nm. Fragmentation of the granulofilamentous material was seen in several instances. The resulting defects were less linear and had more of a soap bubble appearance. The hyaline cell free zone, which may be seen adjacent to the epithelium, comprised relatively cell-free, normally banded, mature collagen. The stroma contains fibroblasts and collagen fibers. Multinucleated giant cells near the epithelial component were described by Kim et al. (96). Rothouse et al. (98) detected myofibroblasts in the stroma, a finding that was confirmed by Smith et al. (102) in a case of recurrent s/mAM.

**Molecular-Genetic Data.** It is not possible within the frame of this chapter to review all studies of the molecular pathology of the ameloblastoma. A comprehensive review of the molecular pathology of odontogenic tumors covering the literature till the middle of 2005 was published by Kumamoto (5), the majority of the studies deals with ameloblastomas. For the following summaries the same subheadings as used by Kumamoto have been used; the majority of articles have been selected because they were not mentioned in Kumamoto’s review or were published subsequently.

1. Molecules Involved in Tumorigenesis and/or Cell Differentiation of Ameloblastomas.

   a. Oncogenes. In ameloblastomas, p21Ras is expressed in the epithelial cells and overexpression has been detected (105). c-Myc oncoprotein is expressed predominantly in the tumor cells neighboring the basement membrane (106). On cDNA microarray and subsequent real-time reverse transcriptase RT-PCR overexpression of Fos has been detected (107).

   b. Gene Modifications. Jääskeläinen et al. (108) used immunocytochemical staining with MIB-1 antibodies and comparative genomic hybridization (CGH) to study cell proliferation and chromosomal imbalances in 20 cases of ameloblastoma. CGH involved hybridization of FITC-dUTP-labeled tumor DNA with Texas-red-labeled normal DNA. The MIB-1 index was low for all tumors and was not correlated to the tendency to recur; it does not seem helpful in assessing future clinical behavior of the tumor. Chromosomal aberrations were only detected in 2 of 17 cases.

   Carinci et al. (109) compared the expression profiles of three ameloblastomas and three malignant odontogenic tumors by hybridization to microarrays containing 19,200 cDNAs to identify genes, which were significantly differentially regulated when compared with nonneoplastic tissues. The investigators detected 43 cDNAs, which differentiated the three malignant tumors from the three ameloblastomas. The cancer specific genes included a range of functional activities like transcription, signaling transduction, cell-cycle regulation, apoptosis, differentiation, and angiogenesis. The authors suggested that the identified genes might help to better classify borderline odontogenic tumors.

   A study for loss of heterozygosity of tumor suppressor genes in 12 ameloblastomas revealed that DNA damage in ameloblastomas seems to be sporadic and cumulative (110). The frequency of allelic loss and intratumoral heterogeneity did not correlate with age, gender, histological subtype, or prognosis.
In a study performed to identify possible genes involved in the development and progression of ameloblastomas the investigators used microarray analysis, semiquantitative RT-PCR and immunohistochemistry on selected genes (111). Tissue from dentigerous cysts was used as control. Overexpression of 73 genes was detected and 49 genes were underexpressed.

Mutations in microsatellite sequences have been studied in 24 ameloblastomas by DNA sequencing analysis (112) and supplied with an evaluation of the Ki67 L.I. of the tumors. The occurrence and the pattern of microsatellite alterations, in form of loss or length variation, was evaluated and correlated with the Ki67 L.I. and with other clinicopathological parameters. Alterations of at least one of the selected loci were observed in all (100%) the ameloblastomas with a mean of four altered microsatellites for each tumor. Microsatellite alterations were more frequent in tumors displaying a high Ki67 L.I., and in a univariate analysis, their occurrence was found to be a predictor of increased risk of recurrence, but no correlation was found to the patient’s age or gender, or to tumor size, location and histology.

c. Tumor Suppressor Genes. Increased immunohistochemical reactivity for p53 has been detected in ameloblastomas (113,114), although it has been shown in several studies that p53 mutations are infrequent in ameloblastomas (115-117). Regulators of p53, murine double minute 2 (MDM2), and p14 (ARF), are also expressed in ameloblastomas, and overexpression has been detected (118,119).

Two members of the TP53 gene family, named p73 and p63, have been identified and analyzed by immunohistochemistry and RT-PCR in ameloblastomas. They seem to function differently from p53 in odontogenic tissue (120). Immunohistochemical reactivity for p63 was detected by Lo Muzio et al. (121) in 26 s/mAMs and several other benign and malignant odontogenic tumors. Benign odontogenic, locally aggressive tumors with a high risk of recurrence exhibited statistically higher p63 expression than benign odontogenic, nonaggressive tumors with a low risk of recurrence.

The immunohistochemical reactivity for the APC gene that inhibits cell proliferation was found to be lower in benign and malignant ameloblastomas than in tooth germs (122). Retinoblastoma protein (RB) is a product of the retinoblastoma (RB) tumor suppressor gene, which acts as a signal transducer connecting the cell cycle with the transcription machinery. Kumamoto et al. (123) used antibodies against RB, E-2 promoter-binding-factor-1(E2F-1), and phosphorylated RB on 40 ameloblastomas (including 4 desmoplastic), 2 METAMs, 3 AMCs, and 10 human tooth germs to clarify their roles in cell-cycle regulation in oncogenesis and cytodifferentiation of odontogenic tumors. Ki-67 antibody was used as a marker of cell proliferation. The levels of immunoreactivity for RB, E2F-1, phosphorylated RB, and Ki-67 were slightly higher in benign and malignant ameloblastomas than in tooth germs. Plexiform ameloblastomas showed significantly higher expression of RB than follicular ameloblastomas. Expression of RB, E2F-1, and phosphorylated RB was considered to be involved in cell proliferation and differentiation of odontogenic epithelium via control of the cell cycle.

d. DNA-Repair Genes. Errors during DNA replication or repair are maintained by DNA-repair genes belonging to the human DNA mismatch repair (hMMR) system. It is composed of at least six genes. The protein expression of two of the genes, hMSH2 and hMLH1 was studied by means of antibodies in 25 cases of ameloblastoma, including three peripheral and three unicystic (124). All ameloblastomas showed a nuclear expression of the proteins in the peripheral layers of the epithelial component. These data suggest that the development and progression of these tumors do not depend on a defect in the hMMR system.

e. Oncoviruses. Although several investigators have reported detection of human papillomavirus (HPV) (125–128) and Epstein–Barr virus (EBV) (129) in ameloblastomas the etiological role of the viruses remains controversial.

f. Growth Factors. Using ISH Heikinheimo et al. (130) detected EGF-R and transforming growth factor alpha (TGF-α) mRNA in 4 ameloblastomas; EGF transcripts was not found. The findings have been confirmed (131,132). The growth factors seem to be involved in the tumogenesis. Transforming growth factor beta (TGF-β), a multifunctional growth factor has been demonstrated in ameloblastomas and has been attributed an important role in cell differentiation and matrix formation (133,134).

Hepatocyte growth factor (HGF), which has mitogenic, motogenic, and morphogenic functions, has been found in ameloblastomas (134).

Various types of fibroblast growth factors (FGF) and their receptors (FGFR) have been studied. FGF-1 and FGF-2 are mitogenic polypeptides that have been demonstrated to enhance cell growth in a dose dependent manner of cultured ameloblastoma epithelial cells (135). In tissue specimens, FGF-1 was localized in the epithelial component, whereas FGF-2 was primarily found in the basement membranes. In another study (136), ameloblastomas showed a weak and focal reaction for FGF-1 and FGFR3 in the tumor epithelium, while FGF-2 and FGFR2 exhibited significant cytoplasmic staining of all layers of the neoplastic epithelium.

Expression of platelet-derived endothelial cell growth factor/thymidine phosphorylase (PD-ECGF/TP) and of angiopoietins have been detected immunohistochemically in the stroma of ameloblastomas and in the ectomesenchymal cells of human tooth germs (137). The level of PD-ECGF/TP reactivity was significantly higher in ameloblastomas than in tooth germs. Granular cell ameloblastoma showed PD-ECGF/TP reactivity in granular neoplastic cells as well as in stromal cells. Immunoreactivity for angiopoietins-1 and -2 was detected predominantly in odontogenic epithelial cells near the basement membrane in tooth germs and in the ameloblastomas.
The authors suggested that these angiogenic factors participate in tooth development and odontogenic tumor progression by regulating angiogenesis.

The immunohistochemical expression of insulin-like growth factors (IGFs), platelet-derived growth factor (PDGF), and their receptors has been analyzed in 47 ameloblastomas and 10 human tooth germs (138) by use of antibodies against IGF-I, IGF-II, IGF-I receptor (IGF-IR), PDGF A-chain, PDGF B-chain, PDGF z-receptor, and PDGF b-receptor. The reactivity for IGFs, PDGF chains, and their receptors was detected predominantly in odontogenic epithelial cells near the basement membrane in tooth germs as well as in ameloblastomas. The expression levels of IGF-II and PDGF chains were significantly higher in the tumors than in the tooth germs, and the expression level of PDGF chains were significantly higher in follicular ameloblastomas than in plexiform ameloblastomas. DESAMs showed higher expression of IGFs and IGFIR when compared with other ameloblastoma subtypes. These growth factor signals thus contribute to cell proliferation or survival in both normal and neoplastic odontogenic tissues.

g. Telomerase. Ameloblastomas have been consistently positive for telomerase activity suggesting that telomerase activation is associated with the tumorigenesis of the neoplastic epithelium (139,140). Telomerase is a specialized reverse transcriptase that synthesizes telomeric DNA at the ends of chromosomes and compensates for its loss with each cell division, and is thus a participant in cell immortalization. The immunoreactivity for telomerase in ameloblastomas shows a similar distribution pattern to that of the c-Myc oncoprotein. This oncogenic protein is known to activate telomerase transcription directly, so it possibly induces telomerase activity in ameloblastomas.

h. Cell Cycle Regulators. The immunoreaction of cell cycle-related factors were examined by Kumamoto et al. (141) in 8 human tooth germs and 31 ameloblastomas by means of antibodies against cyclin D1, p16INK4a, p21WAF1/Cip1, p27Kip1, and DNA topoiso merase II and by ISH of histoneH3 mRNA. Cyclin D1, p16 protein, p21, and p27 were all expressed in the epithelium of tooth germs and ameloblastomas, although p21 was not expressed in granular epithelial cells and keratinizing cells. It is suggested that the odontogenic epithelium is strictly controlled by these cell cycle regulators.

i. Apoptosis-Related Factors. Physiological cell death, apoptosis is mediated by two alternative apoptotic pathways, death by receptors or death by mitochondria. A commonly used method to detect apoptosis is called TUNEL (Terminal deoxynucleotidyl transferase biotin-dUTP-nick-end labeling). Other ways of detection of apoptotic cells and specific parts of the apoptotic pathway are detection of caspase, fas-ligand, and annexin V activity. TUNEL and single-stranded DNA (ssDNA), fas-ligand, and caspase-3 antibodies have been used to detect apoptotic cells in ameloblastomas and ghost cell odontogenic carcinoma (GCOC) (87,114,142-145). Death receptors such as fas, tumor necrosis factor (TNF) receptor I, and TNF-related apoptosis-related ligand (TRAIL) 1 and 2 have been demonstrated in ameloblastomas, but expression of caspase-8, an apoptosis initiator has been extremely limited, suggesting that apoptotic cell death in ameloblastomas is minimally affected by signaling of death factors (144,146).

Bcl-2 and inhibitor of apoptosis (IAP) family proteins are modulators of the mitochondrial apoptotic pathway. In ameloblastomas, apoptosis inhibitory factors, such as Bcl-2, Bcl-x, surviving, and X chromosome-linked IAP (XIAP) are predominantly expressed, which may indicate that these apoptosis modulators are associated with survival and neoplastic transformation of the odontogenic epithelial cells (147-149).

Factors involved in the apoptosis signaling pathways mediated by mitochondria have been investigated in ameloblastomas and normal human tooth germs (150). Tissue specimens were examined by RT-PCR and antibodies against cytochrome c, apoptotic protease-activating factor-1 (APAF-1), caspase-9, and apoptosis-inducing factor (AIF). The mRNA expression of APAF-1, caspase-9, and AIF was detected in all samples and immunoreactivity for cytochrome c, APAF-1, caspase-9, and AIF was positive in all samples. The results suggest that the mitochondria-mediated apoptotic pathway has a role in apoptotic cell death of normal and neoplastic odontogenic epithelium.

Expressions of tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL/Apo2L), a potent ligand in inducing apoptosis, has been studied in 32 ameloblastomas and in AM-1 cells (an HPV-16 infected ameloblastoma cell line) together with death receptor 4 (DR4) and 5 (DR5). It was observed that TRAIL cleaved caspase-8, -9, and -3, lowered mitochondrial membrane potential and markedly induced apoptosis in AM-1 cells. The results suggested that TRAIL is a potent apoptosis-inducing ligand in ameloblastoma (151). Osteoprotegerin (OPG) is a receptor that is capable in inhibiting receptor activator of nuclear factor-kB ligand (RANKL) in inducing osteoclastogenesis. As mentioned above TRAIL is a potent apoptosis-inducing ligand in ameloblastomas. The expression of OPG in ameloblastomas has been investigated by immunohistochemistry, immunofluorescence, and Western blot (152), and was observed in tissue samples from 20 ameloblastomas as well as in cultured ameloblastoma cells (AM-1). An apoptosis assay was performed to investigate the potential of TNF-z, TRAIL, and RANKL in inducing apoptosis. It was found that TRAIL had the highest potential in inducing apoptosis compared with TNF-z and RANKL. A binding assay revealed that OPG preferably binds with RANKL, rather than with TRAIL. The results suggest that the binding of OPG to TRAIL might cause TRAIL to induce apoptosis in ameloblastomas.

TNF-z is involved in inducing cell survival, proliferation, differentiation, and apoptosis. Its expression has been studied in 24 ameloblastomas and in AM-1 cells, and TNF-z as well as its receptors (TNFRI and TNFRE2) were clearly observed in all ameloblastoma samples and in AM-1 cells.
TNF-\(\alpha\)-induced Akt (protein kinase) and MAPK signals were studied as well (153). The results suggested that TNF-\(\alpha\) can induce Akt and p44/42 MAPK activation through PI3K (phosphatidylinositol-3-OH kinase), which might later induce cell survival and proliferation in ameloblastoma. In a subsequent study (154), it was observed that prolonged treatment of AM-1 cells with TNF-\(\alpha\) induced the cells into apoptosis.

j. Regulators of Tooth Development. Underexpression of Sonic Hedgehog (SHH) gene and of Patched (PTCH), a cell-surface transmembrane protein has been shown in ameloblastomas on cDNA microarray (107). SHH is involved in the morphogenesis and cytodifferentiation of teeth. SHH signals control cell-to-cell interactions and cell proliferation in tissue patterning of various organs, including teeth. By means of RT-PCR and immunohistochemistry, Kumamoto et al. (155) detected expressions of SHH, PTCH, Smo (SMO), a membrane bounded protein, and GLI1 (a zinc finger DNA-binding protein) in ameloblastomas. Expression of SHH, PTCH, and GLI1 was more evident in epithelial than in mesenchymal cells, whereas SMO reactivity was marked in both components. Keratinizing and granular cells showed no or little reactivity.

The Wnt signaling pathway is a complex network of proteins involved in embryogenesis (including odontogenesis) and oncogenesis. Wnt signaling is regulated by the levels of the protein \(\beta\)-catenin. Mutations of \(\beta\)-catenin are detected frequently in COCs but are rare in ameloblastomas (156,157). The \(\beta\)-catenin protein is expressed in the nuclei of the ameloblastomas (122).

The transmembrane heparan sulfate proteoglycan, Syndecan-1 (SDC-1), also known as CD 138 and Wingless type 1 glycoprotein (Wnt1), which belongs to a large family of 19 secreted signal transducers and promotes cell proliferation has been detected in 29 s/ mAMs, but not consistently (158). Immunostaining of SDC-1 was observed in the epithelial component as well as in the stroma cells. Wnt1 was almost exclusively seen in the epithelial tumor cells. The authors suggested that SDC-1 is a critical factor for Wnt-induced carcinogenesis in the odontogenic epithelium.

k. Hard Tissue-Related Proteins. Immunohistochemical expression of enamel proteins, such as enamelin, enamelysin, and sheathlin could not be detected in ameloblastomas (159–161). Amelogenin, however has been demonstrated immunohistochemically (162,163) and by mRNA phenotyping in combination with Northern blot analysis and ISH analysis of mRNA (164). Ameloblastin (AMBN) gene mutations were detected in two s/mAMs, an exon 11 mutation in a follicular ameloblastoma and a compound exon 4 mutation in a follicular ameloblastoma (165). The expression pattern of X and Y amelogenin genes (AMGX and AMGY) was studied in 19 ameloblastomas (9 male and 10 female) by RT-PCR, ISH, immunohistochemistry, and restriction enzyme digestion (166). All tumor samples expressed amelogenin mRNA. An increased level of AMGX expression, higher than that of AMGX was detected in all male samples, in contrast to normal male tooth development, where expression of AMGY is very much lower than that of AMGX.

Bone sialoprotein (BSP) has been detected in the neoplastic epithelial component of ameloblastoma, but not in the stroma using cRNA ISH and immunohistochemistry (167). BSP is synthesized and secreted by bone-dentine- and cementum-forming cells and is implicated in de novo formation of bone formation and mineralization, but seems also involved in oncogenesis.

Gao et al. (168) were unable to detect bone morphogenetic protein (BMP) in 20 ameloblastomas by means of antibodies. On the contrary, Kumamoto et al. (169) demonstrated BMP, bone morphogenetic protein receptor (BMPR), core-binding factor \(\alpha\) and \(\beta\) (CBFA1) (also known as run-related protein 2 (RUNX2)), and osterix, a zinc finger-containing transcription factor in the epithelial component as well as in the stroma cells of 31 ameloblastomas; 6 granular cell ameloblastomas, however showed no reaction in the granular cells. Acanthomatous ameloblastomas exhibited increased reactivity of BMP-7 in keratinizing cells. The investigators used RT-PCR and immunohistochemistry.

2. Molecules Involved in Progression of Ameloblastomas.

1. Cell Adhesion Molecules. Ameloblastomas express vascular endothelium cell adhesion molecules such as the cellular adhesion receptors ICAM-1, E-selectin, and VCAM-1 suggesting that stromal blood vessels are activated in these tumors (170).

E-cadherin and its undercoat protein \(\alpha\)-catenin were detected in 24 ameloblastomas by means of monoclonal antibodies (171). There was a loss of expression in keratinizing areas and reduction in granular cell clusters. Several integrin subunits, \(\alpha_2\), \(\alpha_3\), and \(\beta_1\) and CD 44 exhibited immunoreaction in 22 ameloblastomas that were studied to clarify the role of these cell adhesion molecules in epithelial odontogenic tumors (172). CD 44 showed decreased expression in keratinizing areas in acanthomatous ameloblastomas. Integrins and CD 44 are both families of cell surface glycoproteins that mediate cell-cell and cell-extracellular matrix adhesion. In an immunohistochemical study of 14 ameloblastomas with antibodies against integrin subunits, \(\alpha_2\), \(\alpha_3\), \(\alpha_5\), \(\alpha_v\), \(\beta_1\), \(\beta_3\), and \(\beta_4\) all integrins were detected. The immunoreaction showed variations in distribution and staining intensity (173).

m. Matrix-Degrading Proteinases. The role of proteolytic enzymes in extracellular matrix degradation has been studied by several investigators (174–178). Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) were found in 22 ameloblastomas by means of antibodies against MMP-1, MMP-2 and MMP-9, and TIMP-1, and TIMP-2 (174). Intense reactivity for these antibodies was found in the cytoplasm of stromal fibroblasts, a weak reaction for MMP-2, MMP-9, and TIMP-1 was found in the tumor cells of some s/mAMs. A strong expression of TIMP-2 was found on the basement membrane and in the stromal cells. These results were essentially confirmed by Pinheiro et al. (175) using immunohistochemistry, zymography, and...
Western blotting. They observed expression of latent and active forms of MMP-1, -2 and -9, and compared the results with AgNOR analysis, which was used simultaneously. They found a strong reaction for the MMPs in granular cells of ameloblastomas. The MMPs might digest bone matrix and release mitogenic factors. The hypothesis was supported by the finding of an increased proliferation index in tumor cells in the vicinity of the bone. In a study of matrix-degrading proteases regulators the immunohistochemical expression of MMP, membrane type 1-matrix metalloproteinase (MT1-MMP), MMP inhibitor RECK (reversion-inducing cysteine-rich protein with Kazal motifs), and EMMPRIN (extracellular matrix metalloproteinase inducer) were detected in the majority of 40 ameloblastomas (176). The reactivity was seen predominantly in tumor cells near the basement membrane. Follicular ameloblastomas showed significantly lower expression of RECK than plexiform ameloblastomas.

Heparanase, an endo-glucuronidase enzyme that specifically cleaves heparan sulfate has been detected by immunohistochemistry and mRNA ISH in 23 ameloblastomas (177). The enzyme was strongly expressed in the tumor epithelium of all samples. A weak reaction was seen instromal cells adjacent to tumor cells, a stronger reaction was seen in inflammatory cells and endothelial cells of small blood capillaries. Heparanase is believed to contribute to the local invasiveness of the tumor.

The roles of EMC-degrading serine proteases in progression of ameloblastomas has been evaluated by studying the immunohistochemical expression of urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), plasminogen activator inhibitor 1 (PAI-1), and maspin (a serine protease inhibitor) in 45 ameloblastomas (178). The uPA was recognized predominantly in mesenchymal cells, uPAR was evident in epithelial cells, PAI-1 was found in both epithelial and mesenchymal cells, and maspin was expressed only in epithelial cells. The findings suggest that interactions among these molecules contribute to EMC degradation and cell migration during tumor progression.

Angiogenic Factors. The association between vascular endothelial growth factor (VEGF) immunohistochemical expression and tumor angiogenesis has been studied in 35 ameloblastomas (179). Increased expression of VEGF, which enhances angiogenesis and vascular permeability, was found in peripheral tumor cells and in stromal cells adjacent to these cells, which suggests that VEGF is an important mediator of tumor angiogenesis in ameloblastomas. Granular cell clusters in granular cell ameloblastomas showed low reactivity.

Osteolytic Cytokines. The balance between bone formation and bone resorption is regulated by a wide variety of hormones, growth factors, and cytokines. Synthesizing of inflammatory cytokines with osteolytic activity such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α in ameloblastomas has been demonstrated by several investigators (146,170,180,181).

Osteoclast differentiation and activation is stimulated by binding of receptor activator of RANKL to its receptor RANK, which is expressed on osteoclast precursors. Osteoprotegerin (OPG) functions as a decoy receptor for RANKL and inhibits osteoclastogenesis and osteoclast activation. RANKL and OPG have been detected in ameloblastomas predominantly in the stromal cells rather than in the neoplastic cells (182,183). The secretion of RANKL and TNF-α in ameloblastomas and its role in osteoclastogenesis has been confirmed (184).

Differential Diagnosis. Ameloblastomas with a plexiform growth pattern may be difficult to distinguish from hyperplastic odontogenic epithelium so commonly seen in the walls of odontogenic cysts. At low-power microscopy, a network of epithelial strands embracing islands of loose connective tissue is seen in both cases. If the basal cells are cuboidal or squamous in stead of columnar this criteria is not very helpful, and if the suprabasal epithelial cells are squamous rather than reticulum cell-like it may lead to diagnostic confusion (54). Inflammation is usually seen in the cystic environment and is rare in ameloblastomas and may be a useful feature, and the clinical and radiographic features should be included in the diagnostic decision.

The ananchomatous ameloblastoma should be distinguished from the SOT. In the latter, the stroma is more abundant; in the tumor component all cells are squamous cells, no stellate reticulum-like cells are seen, cyst formation is absent, and the peripheral cells are flattened.

The granular cell type of the s/mAM may be confused with the granular cell odontogenic tumor (GCOT). The main difference is that the s/mAM is an epithelial tumor and that the granular cells are epithelial, while the tumor component of the granular cell tumor is ectomesenchymal and the granular cells of the same origin. Cords and islands of odontogenic epithelium are seen, but they are quite different from the proliferating epithelium of an ameloblastoma.

A dental papilla–like connective tissue is never seen in an ameloblastoma, if it is observed in the tumor together with odontogenic epithelium with the morphology of an ameloblastoma, the extremely rare odonto-ameloblastoma (O-A) should be considered. If dental hard tissue has been produced in the dental papilla–like areas, the diagnosis is more straightforward.

The intraosseous basal cell ameloblastoma should be differentiated from the AMCA. Although hypercellularity and hyperchromatic nuclei may be seen in a basal cell ameloblastoma, numerous mitoses, nuclear and cellular pleomorphism, vascular and neural invasion are signs of malignancy and not a feature of this tumor.

Treatment and Prognosis. There has been some difference of opinion about the preferable methods of treatment of the s/mAM, and there is still no consensus. Nakamura et al. (185) reported on a long-term follow-up of treatment of 27 unicystic, 21 multicystic, and 30 solid ameloblastomas. In spite of a recurrence rate of 33.3% after conservative surgery compared with 7.1% after radical surgery, the authors advocated for conservative treatment except when the
tumor invades and destroys the inferior border of the mandible, or when the tumor infiltration is close to the skull base. Huang et al. (186) advocated for a conservative treatment of ameloblastomas of children on the basis of a study of 8 unicystic and 7 s/mAMs. They stated that recurrence is probably not the most important consideration in the treatment of ameloblastomas in children. Other investigators have strongly advocated for radical surgical procedures in the treatment of s/mAM (187). Hong et al. (55) reported on a long-term follow-up of the treatment of 305 ameloblastomas and concluded that recurrence of an ameloblastoma in large part reflects the inadequacy or failure of the surgical procedure. In a review of the literature, Carlson et al. (47) stated that conservative treatment has an unpredictable course and that the presumption that small foci of persistent disease can always be treated adequately is inaccurate. They studied 82 cases of resected s/mAMs and showed that the tumor extends with a range of 2 to 8 mm (mean 4.5 mm) beyond its radiographic demarcation on specimen radiographs. They recommended resection with 1 to 1.5 cm linear bone margin. Ghandhi et al. (188) compared 22 cases from West Scotland with 28 cases from San Francisco with very similar clinical features. Primary care by conservative treatment led to recurrence in approximately 80% of cases, including cases of UNAM. The recurrence rate following local enucleation and curettage was unacceptably high, and this included cases of UNAM as well. Görtzak et al. (65) advocated for radical surgery and recommended continuity resection of the mandible if the tumor is radiologically closer than 1 cm to the inferior border of the mandible. They did not consider removal of an excess of perimandibular soft tissue indicated, but the overlying attached mucosal surface should be excised together with the underlying bone.

Radiotherapy and chemotherapy is discouraged. Recurrence may occur several years after surgical treatment. Demeulemeester et al. (189) reported five cases with multiple and extremely late recurrences, some were diagnosed 24 and 27 years after primary surgery. Hayward (190) reported a case, which recurred first 3 years and then 30 years after conservative treatment.

Chapelle et al. (191) recommended partial maxillectomy or marginal or segmental resection as the treatment of intraosseous ameloblastoma, independent of imaging (unicocular or multicocular) with subsequent yearly follow-up the first five years, and every two years thereafter, for at least 25 years.

1.1.1.2 Solid/Multicystic Ameloblastoma—Peripheral.

Introduction. The PERAM is a rare, benign, slowly growing, exophytic lesion occurring on the gingiva or the attached alveolar ridge mucosa in edentulous areas. Histologically it consists of an unencapsulated focal mass of neoplastic odontogenic epithelium, which may show any of the features characteristic of the intraosseous ameloblastoma.

ICD-O code 9310/0

Synonyms: Soft tissue ameloblastoma, ameloblastoma of mucosal origin, ameloblastoma of the gingiva.

Clinical Features. The prevalence and incidence of the PERAM is unknown; it is a rare tumor. In reviews of material received for histological diagnosis in services of diagnostic pathology, a subdivision of the ameloblastoma has not been made, so the relative frequency in such studies is unknown.

Philipsen et al. (192) reviewed published cases and cases from earlier reviews, mounting to 160 cases. Other cases have been published since then (110,193–205). The estimated number of published cases is 176.

On the basis of 135 cases reviewed by Philipsen et al. (192), the age range is 9–92 years, but the majority of patients are in the fourth to eighth decades, very few patients have been younger than 30 years and older than 80. The mean age was 52.1 years [compared with 37.4 years for intraosseous ameloblastoma (43)]. The mean age for men was slightly higher (52.9 years) than that of females (50.6 years).

The gender distribution (N = 160) was 104 males (65.0%) and 56 females (35.0%). The gender distribution for intraosseous ameloblastoma [Reichart et al. 1995 (43)] was 54.5% in males and 45.5% in females.

The majority of cases, 112 (70.9%) were located in the gingiva or alveolar mucosa of the mandible (N = 158), 46 (29.1%) were located in the maxilla. The most common site was the mandibular premolar region (32.6%) and the anterior mandibular region (20.7%), quite different from the posterior mandible predilection of the intraosseous ameloblastoma. The majority of PERAMs in the mandible were located on the lingual aspect of the gingiva. In the maxilla, the most common location was the soft, palatal tissue of the tuberosity area, accounting for 11.1% of all cases. Multicentric occurrence of PERAM has been reported by Balfour et al. (206) and Hernandez et al. (207).

Six cases have been reported of PERAM occurring in nontooth-bearing areas of the mouth, buccal mucosa, and floor of the mouth, and have been reviewed by Yamanishi et al. (208). Since they are encapsulated in contrast to PERAMs, and occur in areas without any remnants of odontogenic epithelium they are more likely to be a rare type of benign salivary gland tumor, which mimic the histopathology of an ameloblastoma, as already suggested by Wesley et al. (209) and Moskow et al. (210).

Cases of basal cell carcinomas of the gingiva have been published, they are believed to be PERAMs (26,211), and have been included in most reviews (192). Basal cell carcinoma is derived from hair-bearing epithelium and arises on hair-bearing skin exclusively.

The size of the PERAM varies; in a review by Buchner et al. (212), the majority of lesions were between 0.3 and 2.0 cm, but two lesions were 4 and 4.5 cm. The mean size was 1.3 cm. A review about a tumor that measured 5 cm in greatest extent was published by Scheffer et al. (213). Like other peripheral odontogenic tumors, the growth rate is slower than that of the intraosseous counterpart.

Buchner et al. (212) reported the duration of symptoms before diagnosis to be between one month and two years, in most cases with a mean
duration of one year. In some cases the duration has been up to five years (214). The lesions are generally painless; the exophytic growth is the main symptom. Some cases have given light symptoms (200,214). The clinical appearance varies considerably, most are sessile (Fig. 13), fewer are pedunculated, and the surface may be smooth, granular, nodular, papillary, or warty. The color varies from that of the surrounding normal mucosa to pink or dark red. Some become traumatized, which may lead to ulceration.

Since the PERAM is less common than many other types of hyperplastic growths on gingiva or alveolar mucosa and they may present with many different variations of color, morphology, and consistency, they are rarely diagnosed as ameloblastomas before they are examined histologically. The most common preoperative diagnoses are fibrous hyperplasia, teleangiectatic granuloma, peripheral giant cell granuloma, and papilloma. A few have been mistaken for squamous cell carcinoma (SCC) (212).

**Imaging.** Generally the PERAM shows no radiological changes of the underlying bone (212). In a review of the literature Reichart et al. (43) found 73 cases of PERAM. Radiographic findings were reported in 36 cases, in 28 of these there were no radiographic findings, in 5 cases there was slight erosion (“saucerization”) of the surface of the bone below the tumor. Cases have been published, however, where quite conspicuous erosion was detected (200,215) and even deeper invasion into the jaw bone (195,196); in such cases an AMCA should be suspected.

**Pathology.** The etiology of the PERAM is unknown. Some lesions are clearly separated from the surface epithelium, they are supposed to arise in remnants of the dental lamina (14). In other cases there is continuity between the tumor epithelium and the surface epithelium (213,216,217), in such cases there is a possibility that the tumor may have arisen from the basal cells of the surface epithelium. It is difficult to prove, however, it is well known from intraosseous ameloblastomas, which progress through the cortical bone and reaches contact with the surface epithelium that induction of the surface epithelium to ameloblastomatous proliferations may occur.

In a review of 27 cases by Buchner et al. (212), a band of connective tissue was found between the tumor and surface epithelium in 8 cases (30%) and a continuity was seen in 19 cases (70%); in 7 cases (26% of all cases) there was multiple areas of continuity. Macroscopically the lesion presents as a firm to slightly spongy mass with an outline that partly depends on its clinical aspect (26). The cut surface may show minute cystic spaces.

Microscopically, the tumor is composed of a neoplastic odontogenic epithelium that shows the same growth patterns and cell types as the intraosseous solid/cystic ameloblastoma, although granular cells seems to be very rare or nonexisting. It is not encapsulated (Fig. 14). Many PERAMs display a follicular growth pattern with islands composed of a central area of stellate reticulum-like cells and a peripheral layer dominated by cuboidal and columnar cells (199–201). Some tumors exhibit more than one typical pattern. Many tumors are partly or totally acanthomatous with squamous cell metaplasia of the central areas. A minority of lesions are dominated by basal cells and may be histomorphologically indistinguishable from basal cell carcinoma (26). Clear cells (218) and ghost cells as well as calcifications, and formation of keratin pearls have been described (211). The stroma is composed of narrow strands of collagenous connective tissue with low cellularity.

Cases with cytological signs of malignancy have been described and should be considered AMCAs (195,219,220).

**Immunohistochemistry.** In contrast to the s/m intraosseous ameloblastoma relatively few immunohistochemical studies have been performed on tissue from PERAM. The investigators have mainly concentrated on CKs in the neoplastic epithelium. Takeda
et al. (221) used polyclonal antibodies against CK and found comparable reactions in the tumor and the gingival epithelium; the central cells of the tumor islands and the covering epithelium were positive, whereas the peripheral cells of the tumor islands and the elongated rete pegs were negative.

Yamamoto et al. (215) used four types of lectins, polyclonal antibodies (“total keratin,” or TK) against 56 and 64 kDa CKs and monoclonal antibodies against 45 kDa and 56.6 kDa CK on a case of PERAM, 4 cases of intraosseous ameloblastoma and 3 cases of cutaneous basal cell carcinomas. No clear difference could be found in either lectins or keratins among the peripheral and central ameloblastomas and the basal cell carcinomas. Most tumors showed reaction to TK, but only one intraosseous ameloblastoma reacted to monoclonal keratin antibodies.

Lentini et al. (197) used antibodies against CK-19 and Ber-EP4 on a PERAM with basaloïd features. Ber-EP4 is an antibody against a cell membrane glycoprotein, which has been detected in cutaneous basal cell carcinoma, trichoepithelioma, eccrine, and apocrine ducts and other epithelial tissues. The investigators found a diffuse immunoreaction for CK-19 in the neoplastic cells, in some areas more marked in the palisading peripheral cells. Some scattered positive areas were seen in the gingiva as well. Ber-EP4 was negative except some rare areas of faint reaction in basaloïd cells. Since it has been reported in the literature that cutaneous basal cell carcinomas are negative for CK-19, and react positive to Ber-EP4, the authors suggest that the method might be useful in distinguishing basal cell carcinoma from PERAMs.

Lo Muzio et al. (121) studied the immunohistochemical expression of p63, a member of the Tp53 gene family, in the epithelial layers of four cases of PERAM, and in several other types of epithelial odontogenic tumors. Immunohistochemical reaction was detected in the epithelial cells of all odontogenic tumors and the positivity was only nuclear. P63 expression was found in both peripheral and central epithelial cells. Benign odontogenic locally aggressive tumors with a high risk of recurrence exhibited statistically significant higher p63 expression than benign odontogenic, nonaggressive tumors with low risk of recurrence.

Electron Microscopy. The ultrastructure of the PERAM has been studied by Greer et al. (222), Gould et al. (216), and Takeda et al. (221). In a case with continuity between the tumor epithelium and the surface epithelium, the latter showing extensions of rete pegs into the tumor area, the ultrastructural examination showed that the rete pegs gradually became transformed into double-stranded epithelial cords as they elongated deeply (221). The end of these cords gradually became transformed into tumor islands. The ultrastructure of the tumor islands was similar to that of intraosseous follicular ameloblastoma, but was different from that of cutaneous basal cell carcinoma.

Molecular-Genetic Data. Nodit et al. (110) studied 12 ameloblastomas (2 peripheral, 8 s/m, 2 mandibular UNAMs, and 3 AMCAs) for loss of heterozygosity of tumor suppressor genes on chromosomes 1p, 3p, 9p, 10q, and 17p (L-myc, hOGG1, p16, pten, and p53). L-myc (71% frequency of allelic loss) and pten (62% frequency of allelic loss) had the most frequent allelic loss. The overall frequency of allelic loss and intramural heterogeneity were higher in mandibular and in unicystic tumors, and lower in tumors that recurred/metastasized. There was no significant differences in rates of allelic loss between the benign and malignant tumors (46 vs. 52%, p = 0.71). The DNA damage in ameloblastomas and AMCAs seemed sporadic and cumulative and unrelated to aggressive growth.

Differentiation Diagnosis. As mentioned above the PERAM may exhibit a histomorphology which is similar to that of a basal cell carcinoma. When such a tumor appears on the gingiva or alveolar mucosa it is considered a PERAM. Some PERAMs are in intimate contact with the gingival surface epithelium. In such cases it is important to distinguish the tumor from an initial SCC from the gingival epithelium and from a peripheral AMCA. Cellular and nuclear pleomorphism and mitoses are not present in PERAM and suggest a malignant tumor (223). The cytology of an AMCA may vary, but peripheral palisading of tall columnar cells must be present in some areas, and inverted nuclear polarity may also be present (224). The differential diagnosis should also include adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma, although these will be extensions of tumors in adjacent areas, since salivary glands are absent in the gingiva.

The odontogenic gingival peripheral hamartoma, or hamartoma of the dental lamina, rest is a rare epithelial lesion located to the gingiva and presenting as small nodules often at the lingual aspect of the oral mucosa (225). They were originally described by Baden et al. (226). They are foci of apparently inactive odontogenic epithelium and they are not hamartomas, since they do not develop during odontogenesis, which ceases about the age of 22 years. The term “hamartoma” indicates a tumor-like developmental anomaly and cannot be legitimately used for tumor-like lesions of odontogenic epithelium with self-limiting growth potential, which primarily occur in patients past the age of odontogenesis. It has been suggested that such lesions should be considered a variant of PERAM if they contain many epithelial islands with some although moderate proliferative activity (225,227). If they consist of a few islands of inactive odontogenic epithelium they are not PERAMs but rather related to the inactive proliferations of odontogenic epithelium, which may be found in the wall of dentigerous cysts (228).

Treatment and Prognosis. Apart from cases with invasive growth in the underlying bone with or without cytological signs of malignancy (195,196,223), lesions that should be considered AMCAs and treated radically, the PERAM does not exhibit invasive growth with destruction of bone. The lesion is adequately treated by conservative, supraperiosteal surgical excision with disease-free margins. Long-term follow-up is necessary, 10 years or more. Recurrence
rates are much lower than for the intraosseous ameloblastoma, which is a much more aggressive tumor. Buchner et al. reviewed 26 published cases of PERAM with follow-up information ranging from six months to eight years after treatment. There was no recurrence in 21 cases. In five cases (19%) recurrence developed, although the lesion was believed to be adequately removed. The recurrences were diagnosed after two months, one and a half years, five years (2 cases), and seven years, respectively.

1.1.2 Desmoplastic Ameloblastoma.

Introduction. The DESAM is a rare, benign, but locally infiltrative, epithelial odontogenic tumor, which is considered a variant of ameloblastoma in spite of aberrant clinical, imaging, and histological features (26).

ICD-O code 9310/0.

Synonym: Ameloblastoma with pronounced desmoplasia.

The special features of this tumor were first reported from Japan in 1981 and 1983 (229), but it was the article by Eversole et al. (230), which created more general awareness of this uncommon neoplasm, which is characterized by an epithelial neoplastic component surrounded by extensive, dense collagenous stroma.

Clinical Features. The prevalence and incidence of the DESAM is unknown. DESAM is a rare tumor; Philipsen et al. (231) reviewed 100 cases from the literature; since then about 21 cases have been published, accounting to 121. In reviews of material received for histological diagnosis in services of diagnostic pathology a subdivision of the ameloblastoma has not been made. In five published series of DESAM, the tumor has accounted for between 5.3% and 12.1% of all ameloblastomas, Waldron et al. (232): 12.1% (N = 116), Keszler et al. (233): 8.8% (N = 159), Lam et al. (234): 8.6% (N = 81), Takata et al. (235): 7.9% (N = 89), and Kishino et al. (236): 5.3% (N = 189).

The age, gender, and site distribution has varied somewhat in the reports of larger series of cases. Waldron et al. (232) reported 14 cases from United States, 7 males and 7 females with an age range of 21 to 68 years, mean age 45.5 years; 7 tumors were located in the maxilla (6 in the anterior region), and 7 in the mandible. Ng et al. (237) reported 17 cases from Malaysia, 5 males and 12 females with an age range of 21 to 60 years, mean age 36.6 years, median age 38 years; 7 lesions were in the maxilla, and 10 in the mandible. Ng et al. (237) reported 17 cases from Malaysia, 5 males and 12 females with an age range of 21 to 60 years, mean age 36.6 years, median age 38 years; 7 lesions were in the maxilla, and 10 in the mandible. Ng et al. (237) reported 17 cases from Malaysia, 5 males and 12 females with an age range of 21 to 60 years, mean age 36.6 years, median age 38 years; 7 lesions were in the maxilla, and 10 in the mandible. Ng et al. (237) reported 17 cases from Malaysia, 5 males and 12 females with an age range of 21 to 60 years, mean age 36.6 years, median age 38 years; 7 lesions were in the maxilla, and 10 in the mandible.

The age range was 19 to 62 years, the mean age 37.8 years; 2 were located in the maxilla and 10 in the mandible (N = 12). Kishino et al. (233) reported 10 cases from Japan, 9 males and 1 female. The age range was 17 to 58 years, mean age 44.7 years, median age 50 years. The site distribution was 4 in the maxilla and 6 in the mandible. Philipsen et al. (231) published a review of 100 cases from the literature. The gender distribution was equal M:F = 50:50, the age range (N = 63) was 17 to 72 years (21–68 for females), the mean age was 35.9 years (39.2 for males and 35.2 for females). The distribution in decades showed two female peaks in the fourth and fifth decades, but a male peak in the sixth decade. Few patients were younger than 30 years or older than 59 years. In contrast to solid/multicystic ameloblastoma (s/mAM) the site distribution (N = 76) was almost equal; 39 tumors were located in the maxilla and 37 in the mandible. Seven cases occupied an entire maxillary quadrant, 15 cases crossed the mid-line (3 maxillary and 12 mandibular), 34 cases were located in the anterior regions, and only 4 cases (5.4%) were found in the mandibular molar region versus 39% of conventional ameloblastoma (43).

Generally the DESMA has a predilection for the anterior part of jaws, the distribution between the maxilla and mandible is much more even than for the s/mAM, and there is no predilection for the posterior region of the mandible. Estimated from the reviews of the literature the mean age at the time of diagnosis seems to be about five years higher than for the s/mAM.

A single case of peripheral DESMA has been published by Smullin et al. (238). The tumor was an asymptomatic, nonulcerated slowly growing mass in the premolar area of the left hard palate of a 44-year-old female; it had begun to enlarge recently. It did not invade the underlying bone. The histology showed some similarity to the SOT.

A painless hard swelling that has been known for a long time—often for years—is the most common symptom reported. Occasional pain has been reported in very few cases (237,239).

Imaging. In most cases the radiological picture of the DESAM differs from the picture usually seen in conventional ameloblastomas (26). Kaffe et al. (240) described the radiological features of 14 cases of DESAM reported in the literature and a case of their own. Among 13 of the cases one showed multilocular small unilocular lesions, 5 were unilocular, and 7 were not loculated. The borders of the lesion (N = 15) were well defined in 3 cases, poorly defined in 5 cases, and diffused in 7 cases. Three tumors developed in edentulous areas, among the remaining 12, tooth displacement was seen in 11 cases (92%), and root resorption of neighboring teeth in 4 cases (33%). Most lesions were larger than 3 cm. In the literature review by Philipsen et al. (231) the size varied from 1.0 to 8.5 cm at the longest diameter, and an association with an unerupted or impacted tooth was seen in only three cases (3.4%) compared with 8.7% among conventional ameloblastomas. An unusual finding is a single large cyst associated with the tumor. It was reported in the maxilla by Iida et al. (241) and in the mandible by Kawai et al. (242).

A mixed radiolucent-radiopaque pattern usually with ill-defined margins making the lesion more suggestive of a fibrous-osseous lesion than of ameloblastoma was found in 53% of cases reviewed by Philipsen et al. (231) and in 60% of 17 cases reported by Ng et al. (237) and in 6 of 10 cases reported by Kishino et al. (236).

The ill-defined borders and the mixed pattern of the lesion are caused by bone resorption and bone formation at the margins of the lesion. Thompson
et al. (243) demonstrated the value of CT and MRI in the diagnosis of DESMA. The information about the margins of the lesion is markedly improved and it was detected that the mixed fine and course trabecular pattern predominated at the periphery of the lesion.

Pathology. The etiology of the DESAM is unknown and the pathogenesis is poorly understood; it only occurs in the jaws and is believed to develop from remnants of odontogenic epithelium.

Macroscopically it presents as a white solid mass with gritty consistency on cross sectioning.

The histopathology was described in details by Eversole et al. (230) and Waldron et al. (232). The tumor resembles the conventional ameloblastoma in some aspects, and the SOT in other. It is composed of small islands and strands of tumor epithelium with high cellular density (Fig. 15). The epithelial cells are small, spindle-shaped or polygonal and sometimes arranged in a whorled pattern. The epithelium is lacking stellate reticulum cells and columnar basal cells, most of the latter are flattened or cuboidal (Fig. 16). Sometimes central squamous cell metaplasia and a few foci of keratinization is seen. There is a scant tendency in about 50% of the tumors (232) to form cystic or duct-like structures, which may fill out the whole island. Many islands, particularly the larger ones are very irregularly shaped with pointed extensions and long very narrow whipcord-like offshoots. The latter is composed of a single row of small cells with hyperchromatic nuclei. An occasional island may show columnar peripheral cells and a few islands with stellate reticulum-like cells in the center may be seen; Waldron et al. (232) detected such islands in 3 of 14 tumors. The stroma is conspicuously abundant with pronounced collagen formation and moderate cellularity. Oxytalan fibers, which are characteristic for periodontal membrane connective tissue, have been detected by Kawai et al. (242) and Kishino et al. (236). Acellular, amorphous, eosinophilic material may be seen adjacent to the epithelium, and quite often zones with myxomatous changes are seen around the epithelial islands. Spicules or trabeculae of mature laminar bone, resorption of bone trabeculae and new bone production around the resorbed trabeculae may be found about the periphery of the tumor, where invasion of tumor tissue into surrounding bone is seen some cases (232,236).

There are several clinical and pathological differences between DESAM and conventional ameloblastoma (Table 3), which raises the question if DESAM should be considered an entity of its own. The weightiest argument for considering the DESAM as a variant of the ameloblastoma and not as a separate entity is the existence of tumors that show the histopathological features of DESMA and of conventional intraosseous ameloblastoma simultaneously. About 10 such cases have been published, and have been called “hybrid” tumors (232,239,244–246).

Hirota et al. (247) reported a case of DESAM in the anterior maxilla of a 17-year-old woman who had symptoms for eight years. The tumor showed focal dedifferentiation with nuclear pleomorphism and mitoses. It is the only case of DESAM hitherto published with signs of malignancy. It was treated by maxillectomy and there was no recurrence after seven years.

Immunohistochemistry. Siar et al. (248) used antibodies against S-100 protein, keratin, desmin, and vimentin on sections of DESMA; the results were weak and variable apart from vimentin, a fibroblast marker, which was totally negative in the epithelium.
TGF-β immunoreactivity was studied by Takata et al. (249) in seven cases of DESAMs, including a hybrid lesion and compared with 10 cases of conventional follicular and plexiform ameloblastomas. TGF-β is one of the most potent local factors for modulating extracellular matrix formation. A marked immunoreactivity was observed in both peripheral and central cells in tumor nests in all DESAMs except one. In the hybrid lesions TGF-β was detected in the DESAM areas, but not in areas of follicular ameloblastoma. The TGF-β produced by tumor cells is believed to play a part in the desmoplastic matrix formation.

Tenascin (an extracellular matrix protein), fibronectin (an extracellular matrix molecule), and collagen type I was studied by dos Santos et al. (246) in conventional ameloblastomas and hybrid DESAMs. There was a positive immunoreaction in fibrils of the conventional ameloblastoma, but the DESAMs were negative. There was a strong fibronectin positive immunoreaction from fibrils in the stroma of DESAMs with a linear marking along the interface between epithelium and connective tissue. There was a positive reaction in fibers of the stroma along the interface and an intense immunoreaction in the extracellular matrix.

Nagatsuka et al. (75) studied the presence of type IV collagen in three DESAMs, five solid/cystic ameloblastomas, and a number of other odontogenic tumors. Type IV collagen is the major component of basement membrane. The expression of α1(IV)/α2(IV) and α5(IV)/α6(IV) chains was stronger in desmoplastic than in conventional ameloblastomas. A marked immunoreactivity in the basement membrane presented as thin continued lines demarcating the tumor epithelium from the surrounding connective tissue stroma. A random intracellular staining of the tumor islands without differences in various cell types was seen. Collagen α4(IV) chains were not detected. Takata et al. (249) detected type IV collagen in the basement membrane of blood vessels in DESAMs, follicular, and plexiform ameloblastomas. No remarkable differences in the immunoreactivity between the types of ameloblastomas were found.

Philipsen et al. (239) detected an intense staining for collagen type VI in the stroma adjacent to tumor islands. Conventional ameloblastomas were negative. Kumamoto et al. (178) investigated the immunoreaction of extracellular matrix-degrading serine proteinase in odontogenic tumors, and detected expression of uPA, uPAR, PAI-1, and maspin in four cases of DESAM.

To evaluate roles of the Akt-signaling pathway in oncogenesis and cytodifferentiation of odontogenic tumors Kumamoto et al. (250) investigated the expression of phosphorylated Akt, P13K, and PTEN in four cases of DESAM, which all reacted positive.

The roles of MAPKs in oncogenesis and cytodifferentiation of odontogenic tumors were investigated by Kumamoto et al. (78), who detected expression of p-p38 MAPK, and p-ERK5, but not p-JNK in four cases of DESAM.

Leocata et al. (158) studied the immunoreactivity of aberrant Wingless type 1 glycoprotein (Wnt1) and
SDC-1 in seven human tooth buds and 29 ameloblastomas, including four desmoplastic. A shift of SDC-1 expression from epithelial to stromal cells has been described in invasive nonodontogenic neoplasms. Wnt1-positive epithelial cells were mainly seen in follicular and acanthomatous intraosseous ameloblastomas, but was also found in some plexiform and desmoplastic ones. SDC-1 was not expressed in tumor epithelial cells of follicular and desmoplastic intraosseous ameloblastomas, but SDC-1 reactivity was variously observed in tumor stroma cells and the extracellular matrix of follicular, plexiform, acanthomatous, and desmoplastic intraosseous ameloblastomas.

Electron Microscopy. No data are available.

Molecular-Genetic Data. No data are available.

Differential Diagnosis. SOT is a very difficult differential diagnosis, both tumors show an abundant fibrous stroma, and some published cases of SOT are likely to be DESMA (251–253). The clinical picture of the two tumors may differ; lesions larger than 2 cm at longest diameter are unlikely to be SOT; the mixed radiolucent–radiopaque pattern often seen in DESMA is not seen in SOT; resorption of tooth roots is a common finding in DESMA and has not been reported in SOT. Histologically the DESMA may contain islands with ameloblastoma features, which are not found in SOT, like peripheral columnar cells with reverse nuclear polarization and central areas with stellate reticulum-like cells. If they are absent, attention must be drawn to other histomorphological differences. Although the epithelial islands of SOT may be irregular and show indentations, most of them are rounded or oval, while the islands of DESMA generally have a very irregular outline with pointed extensions, and show interconnecting cords between the islands, and long, ramifying whiplash-like offshoots of single layered epithelium, which are not a hallmark of the SOT. Both tumors are composed of squamous cells; in SOT they are larger, polygonal, and with a more abundant cytoplasm, in DESMA they are smaller, there is a higher cellular density, and the cells are spindle-shaped or polygonal and often arranged in a streaming pattern, which is not seen in the SOT. In DESMA the peripheral cells are more often cuboidal than flattened; the opposite is the case in SOT. Central cysts may be seen in the islands of the DESMA, sometimes filling the whole island, which is not a feature of SOT, where microcysts may be seen, which are about the size of a few epithelial cells. The stroma is abundant in both tumors, often myxoid changes are present in the juxtaepithelial stroma in DESMA, and they are not seen in SOT.

If nuclear pleomorphism and mitoses are observed an intraosseous SCC should be considered, these features should not be present in a DESMA.

Treatment and Prognosis. The treatment strategy for DESMA is the same as that for the solid/cystic ameloblastoma. Resection with a 1 cm margin of spongy bone is recommended. Cortical bone may be resected more sparingly (254). Partial hemimaxillectomy may be necessary for larger maxillary tumors and partial mandibullectomy or semimandibullectomy may be required in the mandible. Curettage increases the risk of recurrence; Pillai et al. (255) reported a case of DESAM in the maxilla of a 24-year-old woman with involvement of antrum; two months after curettage a partial maxillectomy was required.

Recurrence rates are difficult to estimate because of limited information. One of the 17 cases reported by Ng et al. (237) recurred four years after “excision.” One of seven cases reported by Takata et al. (235) recurred. Kishino et al. (236) reported 10 cases with a follow-up time between 5 and 23 years for nine of them. None of them recurred. Two smaller ones, one measuring 12 × 12 mm, the other one 30 × 26 mm had been enucleated, the remaining seven had been resected.

1.1.3 Unicystic Ameloblastoma.

Introduction. The UNAM is an odontogenic cystic neoplasm with a single often large lumen and development of an initial intralining or intraluminal or intramural ameloblastoma, or combinations of these. The accurate diagnosis and the character and the extent of the tumor cannot be made on the basis of an incisional biopsy; it requires microscopic examination of the entire specimen.

ICD-O code 9310/0

Synonym: Cystogenic ameloblastoma

The UNAM has been published under several other different diagnoses: plexiform UNAM, intracystic ameloblastoma, cystic ameloblastoma, unilocular ameloblastoma, extensive dentigerous cyst, and intracystic ameloblastic papilloma. The UNAM was proposed as an entity by Robinson and Martinez (256).

Clinical Features. The prevalence and incidence of the UNAM is unknown. In most reviews of material received for histological diagnosis in services of diagnostic pathology a subdivision of the ameloblastomas has not been made. Buchner et al. (30), however, subdivided the UNAM from other variants of ameloblastomas in a review of 1.088 odontogenic tumors from Northern California. Among these 127 were ameloblastomas, 69 were of the s/m variant and 58 were UNAMs that account for 5.3% of all the tumors, and 45.7% of the ameloblastomas. The relative frequency has varied in other reviews. The UNAM accounted for 15% (N = 380) of all cases of ameloblastoma reviewed by Ackermann et al. (257), for 18.9% (N = 175) in the review by Li et al. (258). In a comprehensive review of the literature Philipsen et al. (259) observed relative frequencies of UNAM varying between 5% and 22%.

Although the age range in some studies have included teenagers and young adults only (232,260,261), the age range in the study by Robinson et al. (256) was 10 to 79 years (N = 20), and in the Ackermann et al. study (257) 6 to 77 years (N = 57). The latter study consisted of 90% blacks, the mean age was 23.8 years (SD 14.9); 86% of the patients were in the second, third, and fourth decades. In 33 Chinese patients with UNAM (262) the age range was 8 to 60 years, with a mean age of 25.3 years, and a peak (70%) in the second and third decades. Waldron et al. (232) noted that the average age of 12 UNAMs among 116 ameloblastomas was 22 years compared with 45.5 years for all patients.
Prætorius

with ameloblastomas. This finding was confirmed by Philipsen et al. (259) in their review of the literature.

A large percentage of the UNAMs are associated with an unerupted tooth, often a lower third molar (257,259,260,262). The association may simulate a dentigerous cyst; although it has not been possible to exclude the origin of an UNAM from a dentigerous cyst, it is considered highly unlikely by several investigators (257,262,263). In a review of 193 cases of UNAM from the literature, Philipsen et al. (259) observed that the mean age for patients with UNAM associated with a cyst (16.5 years) was considerably lower than the mean age for patients with UNAM not associated with a tooth (35.2 years). They also found a slightly different gender ratio in the two groups; the M:F ratio for the first group was 1.5:1 (N = 90) and for the latter 1:1.8 (N = 101). The age difference may at least in part be explained by the fact that more unerupted teeth are present in the jaws of patients below 22 years than past that age. If the UNAM develops in the posterior mandible before the eruption of the third molar there is an increased risk that it impedes the eruption of the tooth.

In most of the larger series published there have been a predominance of males, Gardner (264) 12 M:7 F, Eversole et al. (260) 20 M:13 F, Leider et al. (265) 20 M:13 F, and Ackermann et al. (257) 30 M:23 F. Some have found a female predominance, Rosenstein et al. (263) 10 M:11 F, and Lee et al. (266) 12 M:17 F.

All investigators have found a marked predominance for the mandible as to the UNAM and it is mostly seen in the posterior part of the mandible. Ackermann et al. (257) reported 3 tumors (6%) in the maxilla and 53 (92%) in the mandible. Li et al. (262) found 3 (9%) in the maxilla and 30 (91%) in the mandible. Among 31 cases reported by Leider et al. (265) all located in the mandible, 24 lesions (77.4%) were found in the ramus/molar area, 3 (9.7%) in the cuspid/premolar area, and 4 (12.9%) in the mandibular symphysis.

Larger lesions can produce jaw swellings and displace teeth. Swelling is the most common symptom. Many cases are found on radiograms taken for other purposes. Occasional pain, signs of lower lip numbness, and discharge or drainage in cases of secondary infection have been reported (259). In 21 cases reported by Olaitan et al. (267) all occurring in the mandible, swelling was present in all cases, and expansion of both cortical plates in 18 cases. The median age of onset of symptoms was 18 years, and the average time from onset of symptoms to presentation for clinical evaluation was four years.

**Imaging.** Although all lesions are unicystic histomorphologically, they do not necessarily present as a uniculicular lesion on a radiogram, but most do present as well-corticated unilocular radiolucencies (Fig. 17). According to Eversole et al. (260), the predominant radiographic patterns of the UNAM include unilocular and scalloped or macromultilocular periconal, interradicular, or periapical expansile radiolucencies. Multilocularity is more often seen in older patients (263). Among the 33 cases reported by Li et al. (262) 22 were unilocular and 7 were multilocular. Seven

![Figure 17 Unicystic ameloblastoma between the lower left incisors of a 9-year-old girl. Divergence but no resorption of the roots of the teeth is seen.](image-url)
dentigerous relationship with a tooth, usually a lower third molar. The internal aspect may show a smooth surface or an exophytic extension into the lumen from the wall. In some cases it may almost fill the cyst lumen. If there are areas of mural thickening or if there are friable masses of intraluminal tissue present, these must be sampled extensively (269).

Three histological variants of the UNAM have been described by Ackermann et al. In the first, usually called luminal or intralining or intraepithelial type, the epithelial lining is inconspicuous except in focal areas where cuboidal or columnar basal cells with hyperchromatic nuclei are seen with nuclear palisading with reverse polarization, cytoplasmic vacuolization with intercellular spacing, and subepithelial hyalinization (23). Vickers et al. (270) described these histological changes as early histopathological features of ameloblastoma. The second variant is termed the “intraluminal type (Fig. 18); it is sometimes referred to as the “plexiform unicystic ameloblastoma” (271). The lining is similar to that of the interlining type, but a localized nodule arises containing ameloblastomatous epithelium usually with a plexiform growth pattern. It may be an abundant intraluminal growth of hyperplastic, often inflamed, epithelium, which may not show the characteristic ameloblastoma criteria. The fibrous wall is devoid of neoplastic epithelium unless the lesion is a combination of more than one type. In the third type, which is referred to as the “intramural type (mural)” type (Fig. 19), some part of the connective tissue wall is infiltrated to a variable extent—from initial to extensive—with ameloblastoma growing in a plexiform or follicular pattern or both. Deeper extensions are sign of infiltrating ameloblastoma.

Combinations of these patterns are seen; the intraluminal and the intramural type often show simultaneous features of ameloblastoma in the epithelial lining, and some lesions may show the characteristics of all three types. In the review of 193 cases from the literature by Philipsen et al. (259) about two-thirds of the cases were the intramural type, either alone or in combination with one or both the other types. The intraluminal type is seen more often in UNAM associated with an unerupted tooth.

The development of ameloblastoma is usually only present in focal areas, with remaining areas showing features that may be seen in a dentigerous or a radicular cyst.

The grouping into three types is related to treatment and prognosis. Variations of minor importance have been described; granular cells like those seen in solid/cystic ameloblastoma have been described by Buchner (272) and Siar et al. (273), and ghost cells have been observed (274).

**Immunohistochemistry.** Calretinin, a 29-kDa calcium-binding protein, which is expressed widely in normal human tissue and is considered a marker for ameloblastic epithelium, has been studied by several investigators (275–277). Altini et al. (275) detected calretinin in 22 of 27 (81.5%) UNAMs and in 29 of 31 s/mAMs. The immunoreactivity presented as a diffuse, intense nuclear and cytoplasmic staining of several cell layers of the more superficial cells both in the characteristic and nondescript areas of the cyst linings in UNAMs. In a later study, Coleman et al. (276) investigated calretinin in 22 odontogenic keratocysts, 26 residual cysts and 20 dentigerous cysts; they were all negative. The authors suggested that calretinin could be considered an immunohistochemical marker for neoplastic ameloblastic epithelium. The results were partly confirmed by Piattelli et al. (277), who found a negative reaction to calretinin in 24 radicular cysts, 24 dentigerous cysts, and 10 orthokeratinized keratocysts. However, 8 of 12 parakeratinized keratocysts showed immunoreactivity for calretinin in the intermediate and parabasal layers. The findings still support the possibility of using calretinin as a marker for neoplastic ameloblastic epithelium, though.
The immunoreactivity of AgNOR, Ki-67, and PCNA in UNAM has been studied to measure the proliferative potential of the tumor cells.

Coleman et al. (278) counted the AgNOR activity in odontogenic keratocysts, residual cysts, dentigerous cysts, UNAMs, and solid/cystic ameloblastomas, 15 of each. The AgNOR count was significantly lower in the UNAM than in the dentigerous cysts. The authors concluded that AgNOR counts were of no diagnostic significance in distinguishing UNAMs from odontogenic cysts. The opposite conclusion was reached by Eslami et al. (279), but on basis of similar results. They found statistically significant differences in the AgNOR counts in four different lesions but not within each group, the coefficient of variation was 34 in dentigerous cysts, 28 in odontogenic keratocysts, 15 in UNAMs, and 13 in s/mAMs.

Antibodies against PCNA and/or Ki-67 have been used in four investigations to estimate the LI in UNAMs, s/mAMs, and dentigerous cysts (84,263,280,281). The results have been discrepant.

Lo Muzio et al. (121) studied the immunohistochemical expression of p63, a member of the Tp53 gene family, in the epithelial layers of 13 cases of UNAM, 3 intralining, 4 intraluminal, and 6 intramural. They were all positive. The immunoexpression was found in cells in the basal cell layer and in two-thirds of the cases also in the superficial layer, signifying abnormal control of the cell cycle. The intensity was comparable to that of other odontogenic tumors with high risk of recurrence.

Electron Microscopy. No data are available.

Molecular-Genetic Data. Nodit et al. (110) studied 12 ameloblastomas (2 peripheral, 8 s/mAM and 2 mandibular UNAMs) and 3 AMCAs for loss of heterozygosity of tumor suppressor genes on chromosomes 1p, 3p, 9p, 10q, and 17p (L-myc, bOOG1, p16, pten, and p53). L-myc (71% frequency of allelic loss) and pten (62% frequency of allelic loss) had the most frequent allelic loss. The frequency of allelic loss (%) and intratumoral heterogeneity (%) was relatively high in the 2 UNAMs compared to most of the s/mAMs and the AMCAs. The overall frequency of allelic loss and intratumoral heterogeneity were higher in mandibular and in unicystic tumors, and lower in tumors that recurred/metastasized. The DNA damage in ameloblastomas and AMCAs seemed sporadic and cumulative and unrelated to aggressive growth.

Differential Diagnosis. Although the diagnosis of an UNAM is made on basis of a combination of clinical, radiographic, and histological features, the diagnosis is made primarily histologically after examination of the entire lesion. The diagnosis cannot be predicted preoperatively on clinical or radiographic grounds, and many cases are diagnosed as UNAM only after removal by enucleation, the preoperative diagnosis having been a nonneoplastic odontogenic cyst (23,54). The differential diagnosis toward other ameloblastic odontogenic tumors is not particularly difficult, the essential problem is not to overlook the characteristics of the UNAM; they may be moderate and only seen in a few areas. It is important not only to look for intraluminal and intramural proliferations, but to inspect the lining of the cyst to exclude areas with changes compatible with initial development of ameloblastoma as described above. Since the changes may be present in a few areas only, adequate sampling is mandatory. A dentigerous cyst shows a flat basal cell layer, but may present inactive-looking islands of odontogenic epithelium in the connective tissue wall. A KCOT (odontogenic keratocyst) of the parakeratinizing type will show prominent palisaded columnar basal cells with dark staining nuclei, but no vacuolization or stellate reticulum-like cells, but rather small polygonal eosinophilic cells with large nuclei and a parakeratinized surface.

Treatment and Prognosis. Unless the lesion has been suspected to be an ameloblastoma preoperatively, it is usually removed by enucleation and curettage as a nonneoplastic odontogenic cyst. Since the final diagnosis can only be made after histological
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1.1.4 Keratoameloblastoma. Keratoameloblastoma is a very rare, slowly growing, benign, but nonencapsulated and locally invasive, epithelial odontogenic neoplasm with a unique histological pattern characterized by solid sheets, islands, and strands of epithelium with central para- or orthokeratin plugs and peripheral cuboidal to low columnar palisaded basal cell layer mixed with multiple variable sized cysts, with an epithelial lining suggestive of odontogenic keratocyst (KCOT).

ICD-O code: None
Synonyms: None

The neoplasm was mentioned in the second edition of the WHO Histological Typing of Odontogenic Tumors (23) as an ameloblastoma variant, but was left out in the WHO Head and Neck Tumor classification published in 2005 (12) because the lesion was considered insufficiently defined.

Six examples of this rare lesion have been published by Siar et al. (284), Norval et al. (285), and Said-al-Naief et al. (286). A similar case was published by Ide et al. (287); the primary tumor showed a histomorphology, which was undistinguishable from a keratoameloblastoma. Tissue from three following recurrences treated by curettage had essentially similar histological pattern. After a forth recurrence an en bloc resection was made and the lesions presented now exclusively as multiple keratinizing cysts, for which reason the authors changed the diagnosis to a ‘solid-cystic variant of odontogenic keratocyst.’

The six patients mentioned above were of various ethnic extractions, Caucasian, Afro-American, Malay, and Chinese. They were 3 men, 26-, 30-, and 35-years-old, respectively and 3 women, 26-, 35-, and 39-years-old, respectively. The age range was thus 26 to 39 years; mean age was 31.8 years, and median age 35 years.

Two of the lesions were located in the maxilla, and four in the mandible, in the anterior as well as in the posterior region.

The most common symptoms were a painless, slowly growing, hard swelling, which had been present for months or years. One was tender to palpation.

Radiography shows an often large radiolucent multilocular destruction of bone, some with distinct, others with indistinct borders. Encroachment of the maxillary sinus has been reported (286), and erosion of the buccal mandibular cortical plate was reported in one case (285). Resorption of roots of teeth has not been described.

The pathogenesis of the neoplasms is unknown. There can be little doubt that they are of odontogenic origin, they have only occurred in tooth-bearing regions and show histological similarities to the ameloblastoma and to the KCOT (odontogenic keratocyst).

The tumor must be distinguished from an ameloblastoma with keratinization in terms of horn pearls like the case published by Pindborg and Weinmann (56), it has a totally different histomorphology. The tumor presents as sheets, islands, and strands of an epithelium, which consists of stellate reticulum-like cells in the peripheral areas, and shows acanthomatous changes in the center with conspicuous para- or orthokeratinization (Fig. 20). Dystrophic calcification may be present in the keratin. Intermingled with these islands multiple smaller or larger keratinized cysts are seen resembling keratocysts, but without the uniform thickness of the wall and the tendency for separation of the epithelial lining from the underlying connective tissue, which is typically seen in a keratocyst. The stroma consists of mature connective tissue that may
show some degree of chronic nonspecific inflammation. The tumor is nonencapsulated and invades marrow spaces and erodes adjacent bone.

Siar et al. (284) studied their tumors immunohistochemically. TK polyclonal antibodies reacting with 41 to 64 kDa CKs yielded a strong expression in all epithelial cells. S-100 protein staining was focal and weak in the tumor cells, and was probably negative. Antibodies against desmin gave a similar result. Within the tumor elements there was no immunoreactivity with vimentin. A tumor in the anterior maxilla of a 45-year-old white man, published by Whitt et al. (288), showed many histomorphological similarities with other cases of keratoameloblastoma, but on top of these showed numerous Pacinian corpuscle-like stacks of lamellar parakeratin in the connective tissue without foreign body response. The epithelial tumor cells and the keratinized areas in this tumor reacted positively to pancytokeratin (AE1/AE3) antibodies. The authors used Ki-67 immunoreactivity to measure the proliferative index and found a high number of Ki-67 positive cells above this zone. The Ki-67 proliferative index was 22.8%.

The ultrastructure of the tumor has not been studied, and molecular-genetic data are not available.

The differential diagnosis may be difficult. The papilliferous keratoameloblastoma shows keratinizing cysts similar to those seen in the keratoameloblastoma, but consists mainly of cystic follicles lined with a papilliferous epithelium and lack the peripheral palisaded, columnar, or cuboidal cell layer. Lurie et al. (289) published a case named keratoameloblastoma, where the tumor consisted of relatively large islands of squamous epithelium with slightly parakeratinized central clefts and a basal cell layer consisting of flat cells in some areas and well-oriented cuboidal cells with polarized nuclei in other areas. No similar neoplasm seems to have been published, and despite the title of the paper, the histomorphology is markedly different from other cases of keratoameloblastoma. Another important differential diagnosis, not for the surgeon, but for the pathologist is the so-called solid variant of odontogenic keratocyst published by Omura et al. (290) and by Vered et al. (291). The macroscopic appearance of these tumors is solid with multiple small cystic spaces. Microscopically they consist of multiple keratocysts of varying size, some with basal proliferation and budding, but with no evidence of follicles and islands resembling ameloblastoma. In the case published by Ide et al. (287), however, a case of keratoameloblastoma apparently converted into a solid variant of odontogenic keratocyst after several recurrences, so the relationship between the two lesions may be closer than believed.

The required treatment of the tumor is en-bloc resection with margins free of tumor. Curettage has lead to recurrences (286,287), except in the case published by Whitt et al. (288), but the follow-up time was only 10 months.

1.1.5 Papilliferous Keratoameloblastoma. Papilliferous keratoameloblastoma is an exceedingly rare, slowly growing, benign, but nonencapsulated and locally invasive, epithelial odontogenic neoplasm with a unique histological pattern characterized by multiple epithelial cysts of varying size. Some of the cysts resemble keratocysts and are filled with desquamated keratin, but the vast majority of the cysts are lined by a nonkeratinized papilliferous epithelium and filled with necrotic desquamated epithelial cells.

ICD-O code: None

Synonym: None

The neoplasm was mentioned and illustrated in the second edition of the WHO Histological Typing of Odontogenic Tumors (23) as an ameloblastoma variant, but was left out in the WHO Head and Neck Tumor classification published in 2005 (12) because the lesion was considered insufficiently defined.

Only two examples are known of this rare tumor. The first case was illustrated by Findborg in a textbook (292). The tumor occurred in the left side of the mandible of a 57-years-old edentulous, Caucasian woman. She had experienced an increasing swelling of the area for the last two years. The radiogram showed a multilocular destruction from the second premolar area and included the entire ramus. It was treated by sectional mandibulectomy posterior to the canine. The case was distributed as IRC 6 by the International Reference Center to Collaborating Centers for preparation of the first WHO classification of odontogenic tumors, (22), and was later included as case No. 10 in the Slide Seminar on Odontogenic Tumours at the First scientific meeting of the International Association of Oral Pathologists in Gothenburg, Sweden, 1–4 June 1981. A second case was published by Altini et al. (293). It occurred in the right side of the mandible of a 76-years-old black edentulous woman.

Figure 20 Keratoameloblastoma. The tumor occurred in the anterior maxilla of a 28-year-old man and consists of numerous cysts of varying size lined with a parakeratinizing squamous epithelium. The morphology is unique and distinctly different from the solid variant of the odontogenic keratocyst (solid keratocystic odontogenic tumor). H&E stain. Source: From Ref. 289 and by courtesy of Professor M. Shear, Cape Town.
who complained of a slowly enlarging swelling of one-year duration. The radiographic examination showed a large multilocular radiolucent lesion with scalloped margins extending from the right bicuspid area to the sigmoid notch. The coronoid process was completely destroyed. CT scans showed marked expansion of the mandible with perforation of the cortical plates, both buccally and lingually in several places. This is a rare finding in ameloblastomas. A hemimandibulectomy was done, and there was no recurrence after one year.

The histological findings were similar in the two cases. The tumor is nonencapsulated and consists of multiple cysts of varying size separated by rather narrow bands of fibrous connective tissue. Some of the cysts are lined with a parakeratinized stratified squamous epithelium and contain desquamated keratin (Fig. 21). The vast majority of the cysts are lined by a pseudopapilliferous epithelium 2 to 5 cells in thickness (Fig. 22), consisting of large rounded cells with centrally placed nuclei (Fig. 23) with prominent nucleoli (293). There is a loss of intercellular adherence in the surface layers, resulting in desquamation and necrosis of the cells. In some cysts true papillary projections into the lumen with connective tissue cores were seen covered with a similar epithelium. Both cases have lacked the peripheral palisaded columnar basal cell layer with polarization of the nuclei, subnuclear vacuolation, and stellate reticulum-like epithelium characteristic of ameloblastoma. For this reason the authors (293) question if the tumor is in fact a histological variant of the ameloblastoma or a separate, as yet unclassified odontogenic tumor.

No data on immunohistochemistry, ultrastructure, molecular biology, or genetics are available.

Because of the very characteristic histomorphology the differential diagnosis is uncomplicated. Only one case of odontogenic cystic tumor with papillary proliferating keratinizing epithelium has been published (294). The tumor occurred in a 76-year-old Japanese man as a multilocular radiolucent lesion in the left side of the mandible extending from the left canine to the second molar area. Despite the papillary lining of the multiple cysts the histology was markedly different from that of the papillary keratoameloblastoma. The papillary projections were conspicuous and contained a core of connective tissue; they were keratinized on the surface, in some places with lamellar accumulation of keratin. The epithelial lining was broad, resembled stellate reticulum, and the basal cells were columnar and palisaded. Formation of hard tissue without relation to the odontogenic epithelium was seen in the stroma. A similar tumor has not been published.
Considering the destructive nature of the papilliferous keratoameloblastoma resection with tumor-free margins seems to be required treatment.

1.2 Squamous Odontogenic Tumor.

Introduction. SOT is a rare, benign but locally infiltrative, odontogenic, epithelial neoplasm consisting of islands of well-differentiated squamous epithelium in a fibrous stroma (23,295).

ICD-O code 9312/0

The tumor was described as a new entity by Pullon et al. in 1975; they created the term (296).

Clinical Features. The prevalence and incidence of the tumor is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 0.0% to 2.1% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of SOTs/%

- Günhan et al., Turkey (32): 409/5/1.2%, Daley et al., Canada (33): 392/0/0.0%, Ochsenius et al., Chile (35): 362/2/0.6%, Adebayo et al., Nigeria (36): 318/1/0.3%, Fernandes et al., Brazil (37): 340/5/1.5%, Ladeinde et al., Nigeria (38): 319/6/1.9%, Buchner et al., California (30): 1088/3/0.3%, Jones et al., England (2006, pooled figures from two studies) (39,40): 523/1/0.2%, Olgac et al., Turkey (41): 527/11/2.1%, and Jing et al., China (42): 1642/3/0.2%.

Our knowledge of SOT is based on the publication of a little more than 40 cases of which 36 have been reviewed by Philipsen et al. (297). If dubious cases are excluded, i.e., cases that are more likely SOT-like proliferations, DESAMs or other lesions, the literature reviewed by Philipsen et al. (297). If dubious cases are excluded, i.e., cases that are more likely SOT-like proliferations, DESAMs or other lesions, the literature (1975–2005) contains 35 acceptable cases of SOT (296,298–318). Among these 35 cases 20 occurred in men and 15 in women; Caucasians, blacks, and Asians. The ratio men:women is thus 1.0.75. Most cases have been diagnosed in young adults or middle aged persons; 21 patients were between 22- and 46-years-old. The age range is 11 to 74 years. The mean age is 38 years (37.5 for men and 39 for women). The median age is 31 years (32 for men and 31 for women).

Multifocal and familial occurrences in three siblings have been reported (311), and another multicentric case has been described (306).

SOT usually develops intraosseously and often in proximity to a periodontal ligament. Some have been diagnosed in edentulous areas, and at least one case has developed in the follicle around the crown of an embedded lower third molar (318). A few cases with extra osseous location have been published, some with a histology, which points more at PERAM or DESAM (319), but one case (314) appears convincing.

The tumor has been diagnosed in all regions of the jaws. Location was given in 34 of the accepted cases. Among the 34 cases 14 were located in the maxilla, 7 in the anterior, 5 in the posterior part, 1 of which was bilateral; 2 cases involved both the anterior and posterior part. Fourteen lesions were located in the mandible, five in the anterior and nine in the posterior area. Six cases were multicentric and included both the maxilla and mandible, one was found in 2 quadrants, three in 3 quadrants, and two in 4.

Only a few cases have been associated with an impacted tooth (308,318).

Clinical signs are generally few. Some SOTs have caused bony enlargement and/or moderate pain. Mobility of the associated tooth/teeth has been described as well as sensitivity to percussion. In about 25% of the cases the patient had no symptoms.

Imaging. On radiograms the typical lesion shows a triangular-shaped (pointing toward the marginal gingiva) or oval radiolucent defect between the diverging apices of the adjacent roots of teeth (Fig. 24). The lesions seldom exceed 1.5 cm at longest diameter. No periodontal ligament is visible between the lesion and the root of the tooth. In some instances vertical periodontal loss of bone has been seen, and erosion of the cortical plate of the mandible may be seen (320). The radiolucent area usually has a well-defined sclerotic margin, but may be somewhat ill defined. Resorption of adjacent roots of teeth has not been described.

The minute calcifications found in some SOT are not visible on the radiograms. The diagnosis cannot be made on the basis of the radiogram alone.

Pathology. The etiology and pathogenesis of the SOT is unknown. Because of the close proximity of most SOTs to dental roots and periodontal tissue it is generally believed that they arise from remnants of the epithelial root sheet (‘‘islands of Malassez’’). At least one case (318) arose in the tissue covering the crown of an embedded mandibular molar.

Macroscopically the tissue is pink, firm, and rubbery, sometimes gristly in consistency with an irregular, smooth surface (296).

Histologically the SOT is composed of numerous islands of well-differentiated squamous epithelium, dispersed rather uniformly in an abundant fibrous connective tissue stroma with a moderate number of...
plumb, ovoid to spindle-shaped fibroblasts and sometimes with a light sprinkling of inflammatory cells (Fig. 25). The tumor is not encapsulated. Most of the epithelial islands are rounded or oval, but some may show indentations (Fig. 26). The islands may vary in size and shape, and some are narrow and elongated. A few of the larger islands may have pointed extensions (296,299,304,311,314).

The polygonal epithelial cells of the SOT have a uniform size and stainability with an abundant eosinophilic cytoplasm. Intercellular bridges (desmosomes) are numerous. There is virtually no mitotic activity. The islands are delineated by a flattened layer of basal cells. No differentiation of central stellate reticulum and peripheral cylindrical basal cells is seen. Ghost cells have not, and clear cells have rarely been described. In some of the tumor islands, particularly the larger ones, small areas of microcystic vacuolization may be seen (300). Individual cell keratinization is a common feature and in some cases laminated, calcified bodies develop in the epithelial islands (304).

Hyperplastic islands of epithelium with morphology similar to those seen in SOT are sometimes seen in the wall of odontogenic cysts (321) and are not neoplastic. Several cases have been published in which conspicuous proliferation of SOT-like islands have been found in the mural connective tissue of odontogenic cysts (321–325). The term “squamous odontogenic hamartoid lesions” (SOHLs) have been suggested for such lesions (324). Apart from the extent of the proliferations no histological criteria exist to differentiate between SOHL and a genuine SOT. The question whether extensive SOT-like proliferations in a wall of an odontogenic cyst is in fact an initial neoplasm has not been solved.

**Immunohistochemistry.** No studies have detected any specific histochemical marker for the SOT, so the diagnosis is still based on histomorphology. The presence of CKs, involucrin, tumor suppressor gene products (p53), cell cycle regulators, amelogenin, and tenascin have been studied. In Tatemoto and coworkers’ studies (251) of SOT (in tissue though with morphological resemblance to a DESAM), the tumor cells were negative for monoclonal PKK-1 detectable CK (40, 45 and 52, 5 kDa). Positive staining with monoclonal KL-1 (55–57 kDa CK) and polyclonal TK (41–65 kDa CK) was strong and confined to centrally located cells in tumor islands. Reichart and Philipsen (313) used monoclonal CK antibody ICN 8.12, which stains CK-13 (51 kDa) and CK-16 (48 kDa); tumor cells were strongly positive for both.

Yamada et al. (326) studied the presence of involucrin in SOT, and found a strong reaction in the center of the tumor islands. In the same study 31 of 40 ameloblastomas were negative and 9 faintly positive.

Tumor suppressor gene product p53 and cell cycle regulators PCNA and Ki-67 were studied by Ide et al. (315) on tissue from a recurrence of a SOT with initial SCC development. An overexpression of p53 was found in SCC cells, but SOT cells were negative. PCNA and Ki-67 was predominantly found in SCC cells. A weak reaction in some SOT islands was interpreted as related to beginning dysplastic changes. The presence of amelogenin and tenascin was studied by Mori and coworkers (70,162). Moderate reaction for amelogenin was found in the epithelium of tumor islands; in centrally located, keratinized cells it was weak though. Tenascin (a multifunctional matrix glycoprotein, which can either promote or inhibit cell adhesion, depending on the cell type) was found in the interface (basement membrane) between tumor epithelium and the connective tissue, exclusively. Some areas were negative.
Electron Microscopy. No ultrastructural markers for SOT have been found. Studies (296,302,308) have shown tumor islands surrounded by a distinct basal lamina. The islands are composed of polyhedral epithelial cells of varying size and with irregular shape. Intercellular spaces are irregular, and in some areas edema is seen. The nuclei are large with many indentations. The chromatol is evenly distributed, nucleoli are few. In the cells of the center of some islands the nuclei are disintegrating. The cytoplasm contains few organelles: altered mitochondriae, some flattened cistermnae of granular endoplasmic reticulum, a small Golgi apparatus, and glycogen granules, which are abundant in some cells and absent in others. Laminar structures (myelin bodies) have been described, but are few (296). Many cells have numerous tonofilaments in thick bundles. The connective tissue is striking (308); many fibroblasts exhibit an unusual shape with indented and convoluted nuclei and prominent endoplasmic reticulum. Often they are arranged concentrically around the epithelial islands. The fibrous component is very dense and often without clear typical periodic striation of collagen.

Molecular-Genetic Data. Leider et al. (311) reported one family with three affected siblings, each with multiple lesions. Mutations of the AMBN gene, which in humans maps to chromosome 4q21 have been detected in SOT, as well as in ameloblastoma and AOT (165), and were considered tumor-specific mutations. The SOT had a splicing mutation in exon 11 (IVS11-2A>G; A605G).

Differential Diagnosis. The most important differential diagnoses are: ameloblastoma (s/m, desmoplastic, and peripheral); SOHL in odontogenic cysts (324), pseudocarcinomatous hyperplasia in the gingival submucosa, and SCC.

Differentiation toward s/mAM and PERAM should not be difficult, even when they are acanthomatous. It is usually possible in some areas to find stellate reticulum-like epithelium and palisading, cylindrical basal cells with nuclei polarized away from the basement membrane, and sometimes a plexiform growth pattern can be seen as well; none of these features are seen in SOT. DESAM is a very difficult differential diagnosis; both tumors show an abundant fibrous stroma, and some published cases of SOT are likely to be DESAM (251–253). The clinical picture of the two tumors may differ; resorption of tooth roots is a common finding in DESAM. Histologically the DESAM may contain areas with ameloblastoma features (see above), if they are absent the most important differences found in DESAM are the many large and very irregular tumor islands with pointed extensions, interconnecting cords between the islands, presence of long, ramifying cords of single layered epithelium, and epithelial islands with increased cellular density with small sometimes spindle-shaped epithelial cells and cuboidal rather than flattened basal cells, as well as myxoid changes in the juxtaepithelial stroma. The SOT-like proliferations, which may be found (rarely) in an odontogenic cyst, have a morphology similar to that of the SOT. If they are extensive, a SOT should be considered and the follow-up of the patient adjusted accordingly. The most important differential diagnosis is intraosseous SCC. One convincing case of development of a SCC in a SOT in the lower left molar area of the mandible of a 53-year-old man has been published by Ide et al. (315). Norris et al. (306) published a case with bilateral maxillary SOT and a simultaneous mandibular SCC possibly arising in a SOT in a 26-year-old man. In the former case cytological signs of epithelial dysplasia were evident in parts of the tumor. Benign SOT does not show cellular atypia.

Treatment and Prognosis. Conservative surgical procedures in terms of enucleation, curettage, or local excision are considered adequate (295). If one lesion is diagnosed it is important to remember that multifocal occurrence has been described. Recurrence has been described in two cases (296,316) and requires more extensive surgical excision. At least one case of SOT (315) has transformed into a carcinoma.

1.3 Calcifying Epithelial Odontogenic Tumor

Introduction. The CEOT is a slowly growing, benign, but nonencapsulated and locally invasive, epithelial, odontogenic neoplasm with a singular histomorphological pattern characterized by irregular sheets and islands of eosinophilic, polyhedral, and often pleomorphic cells, which eventually disintegrate into an eosinophilic, amorphous substance, which stains with amyloid markers and tend to calcify (327,328).

ICD-O code 9340/0

Synonyms: Pindborg tumor.

The tumor was defined as an entity by Pindborg in 1955 (329,330).

Clinical Features. The tumor is rare; no data about prevalence and incidence are available. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 0.5% to 2.5% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of CEOTs/%. Regezzi et al., Michigan, U.S.A. (31): 706/6/0.8%, Günhan et al., Turkey (32): 409/6/1.5%, Daley et al., Canada (33): 392/5/1.3%, Mosqueda-Taylor et al., Mexico (34): 349/3/0.8%, Ochsensius et al., Chile (35): 362/2/0.6%, Adebayo et al., Nigeria (36): 318/3/1.0%, Fernandes et al., Brazil (37): 340/4/1.2%, Ladeinde et al., Nigeria (38): 319/5/1.6%, Buchner et al., California (30): 1088/5/0.5%, Jones et al., England (2006, pooled figures from two studies)(39,40): 523/13/2.5%, Olgc et al., Turkey (41): 527/5/0.9%, and Jing et al., China (42): 1642/10/0.6%.

The data are skewed; however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetical or environmental factors.
The number of published cases is close to 190. Major reviews of the literature have been published by Franklin et al. (331): 113 cases, Philipson et al. (332): 181 cases, and Kaplan et al. (333): 67 cases.

Like most odontogenic tumors the CEOT occurs as an intraosseous and as a rarer and less aggressive extraosseous variant. The male:female ratio for the intraosseous variant is between 1:1 (332) and 1:1.5 (333), and for the extraosseous variant 1:0.8 (based on 11 cases only) (332).

The age range is between 8 and 92 years at the time of diagnosis, with a mean of 36.9 years for both topographic variants. The mean for the intraosseous variant is 38.9 years and for the extraosseous variant 34.4 years, which may be explained by the fact that the extraosseous variant presents as a gingival enlargement, which is likely to be diagnosed at an early stage. The age peak for men is in the third decade and for women in the fourth decade (332,334). The majority of intraosseous cases are diagnosed in patients between 20 and 60 years of age.

There is a predilection for peripheral (extraosseous) cases to occur in the anterior segment of the jaws (335). They present as a gingival swelling covered by mucosa of normal color (Fig. 27). The intraosseous tumors on the other hand occur primarily in the mandible and particularly in the premolar and molar regions. The mandible: maxilla ratio is 2:1 (332,333). Simultaneous occurrence of CEOT in more than one location has been described, but is exceedingly rare (336–338).

The growth rate is slow. The tumor is usually symptomless, apart from a slowly progressive swelling of the jaw. There are a few reports associated with pain, nasal obstruction, epistaxis, and proptosis (331). An unusual case of maxillary CEOT, which caused displacement of the eye in a 30-year-old woman, was published by Bridle et al. (339).

Figure 27  Peripheral calcifying epithelial odontogenic tumor in the upper left lateral incisor area of a 29-year-old woman. The lesion, which had existed for 5 years, was firm and symptom less apart from the swelling. There were no radiographic changes. Source: Ref. 348.

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About 60% of the intraosseous tumors are associated with an unerupted permanent tooth, most often a mandibular molar (333).

Imaging. Radiograms of CEOTs may show a considerable variation; its appearance may range from a diffuse, poorly demarcated, or well-circumscribed unilocular radiolucency to a combined pattern of radiolucency and radiopacity with small intralesional septa producing a multilocular pattern. The pattern showing flecks of calcification scattered in an area of radiolucency has been called “driven snow.” Early cases are radiolucent and resemble a dentigerous cyst or an ameloblastoma. With increasing calcification radio-opacities become visible and differential diagnoses are ossifying fibroma and odontogenic fibroma.

Kaplan et al. (333) have reviewed the radiographic features of 67 patients with CEOT (68 lesions), primarily from the literature. There were 27 males and 39 females in the group (N = 66) with an age range from 13 to 77 years (mean 43.5 years). The most frequent was a mixed radiolucent–radiopaque pattern, which was present in 44 (65%) of the lesions. Radiolucent lesions were present in 22 (32%) and radiopaque in two (3%). The mixed radiolucent–radiopaque type was nearly twice as prevalent as the radiolucent type in both jaws. Among 55 lesions 32 (58%) were unilocular; 15 (27%) were multilocular, and 8 (15%) were not loculated (diffuse).

The definition of the border of the tumor was described in 61 lesions, of which 12 (19.7%) had well defined or corticated borders, 36 (59%) had defined but not corticated borders, and 13 (21.3%) had diffuse borders.

In 41 cases (60%), one or more impacted teeth were involved. The specific tooth was indicated for 45 teeth: Three (7%) were incisors, five (11%) canines, seven (16%) premolars, 28 (62%) molars, and two (4%) were supernumerary or unidentified teeth. Among the molars 18 (40%) were first or second molars, and 10 (22%) were third molars. Cases with increased radiopacity close to the occlusal surface of an impacted molar (“coronal clustering”) was described by Pindborg (330) and by others (Fig. 28). Coronal clustering was found in eight (12%) of the cases studied by Kaplan et al. (333). The driven snow pattern was clearly recognizable in only one case. Displacement of teeth was evident in 28 cases (41%), and root resorption in six (4%) cases.

The size of the lesions at time of surgery varied between 0.5 and 10 cm (mean 3.5 cm). Most of the small lesions (<3 cm) were radiolucent (89%) and none were mixed; most of the large lesions were mixed (74%) and only 21% were radiolucent.

Peripheral CEOTs usually contain little or no calcifications that is not detected on radiograms; some have shown superficial erosion of the underlying bone.

A clear-cell variant of the CEOT has been described and a more aggressive behavior has been attributed to them. Anavi et al. (340) reviewed 19 cases of this variant and found 12 central and 7 peripheral.
The proportion of peripheral cases with clear cells is higher than in the conventional CEOT; they seem to have a greater tendency to develop on the gingiva. The radiographic picture of the central clear-cell variant differed in several ways. Of particular interest were a higher proportion of tumors with cortical perforation, 67% compared with 6.7% in conventional CEOT, which may indicate a more aggressive behavior.

Pathology. The etiology and source of origin of the tumor is unknown. It was believed for a long time (17,330,341) that the tumor arises in the reduced enamel epithelium of an embedded tooth (Fig. 29). Since not all CEOTs develop in association with an embedded tooth, there must be other sources, and remnants of the dental lamina is an obvious candidate (16,342). Proliferating odontogenic epithelium at the top of the dental follicle of an unerupted tooth (343) at the lower orifice of the gubernaculum dentis is another possibility.

Although the tumor is in some cases relatively easily enucleated, it is nonencapsulated apart from focal areas in some tumors, and it resorbs and infiltrates the surrounding bone. Macroscopically it presents as a firm mass of varying color and at bisecting the specimen usually reveals calcified particles. There may be minute cystic spaces in the tissue, but only one case of unicystic lesion with the tumor developing apparently in the wall of a dentigerous cyst has been published (344).

The classic histological picture of an intraosseous CEOT as described by Pindborg (330) shows irregular sheets and islands often with many pointed extensions, which consist of polyhedral epithelial cells with abundant eosinophilic cytoplasm (Fig. 30), sharply defined cell borders, and well developed intercellular bridges (328). The nuclei are round and sometimes slightly lobulated, most of them are strongly basophilic, and they are frequently pleomorphic, but the number of pleomorphic nuclei differs from tumor to
tumor. Mitotic figures are rarely encountered, and the nuclear pleomorphism is not a sign of malignancy. In a rare case of malignant transformation the number of mitoses is conspicuously increased, tumor cells are found within the vessels, and the Ki-67 index is considerably elevated (345–347). Double-nucleated cells may be seen, and the nucleoli may be prominent.

Within the sheets of tumor cells are various amounts of rounded, eosinophilic homogeneous masses (Fig. 30). The substance can be observed intracellularly in swollen epithelial cells with disintegrated nuclei displaced to the cellular border, which has lost its integrity (341,348–350) and presumably represents perished tumor cells, although it has also been interpreted as a secretion product (350), and even as enamel matrix (351,352). Most of the substance is found extracellularly and when it is distributed in foci within a tumor island the pattern is cribriform. Extensive amounts of the eosinophilic, homogeneous substance may be seen in the connective tissue at some distance from intact tumor islands. They may still represent areas of perished tumor cells, although they have been interpreted differently. Often small clusters of compressed cells remain in the areas.

Vickers et al. (353) demonstrated the substance to react positively to amyloid staining like Congo red and fluorescence with thioflavine T (Fig. 31). This finding has been confirmed by numerous later investigators (352,354–356). The eosinophilic, homogeneous, positive amyloid reacting substance eventually becomes calcified. Calcified foci are initially seen as tiny spots in small areas of the substance (Fig. 32). With increasing calcification they form spherules showing appositional basophilic concentric rings (Liesegang rings). Eventually the calcified areas coalesce, forming large calcified aggregates. Before calcification the homogeneous substance is faintly PAS-positive, but with progressive calcification the areas become more PAS-positive (355). Calcified spherules may also be seen scattered in the connective tissue without association to the homogeneous substance. In some tumors formation of rounded islands of hard tissue is seen; it is a cellular product that contains collagen and has morphology-like cementum.

There is a considerable histomorphological variation from tumor to tumor and within the individual tumors. Some are dominated by large irregular epithelial sheets, other show numerous small islands and strands of tumor epithelium in the connective tissue stroma, which always consist of mature collagenous connective tissue. Calcification may be sparse or conspicuous; extensive calcification is primarily seen in large tumors of long duration.

The extraosseous variant of CEOT shows principally the same histomorphology, but the tumors cells form rather strands and small islands than large sheets, and the amount of calcified material may be minimal or lacking. The extraosseous variants are undoubtedly diagnosed at an earlier stage than the intraosseous tumors.

In a few cases Langerhans cells have been described in the tumor (357,358); the cells were S-100 protein-positive and identified ultrastructurally on the finding of rod- and tennisracket-shaped Birckbeck’s granules. Their function in the tumor is unknown.

The presence of numerous clear cells in CEOT is uncommon; Krolls and Pindborg (359) reported the first two examples of this rare tumor in 1974; Philipsen and Reichart reviewed 15 cases in 2000 (332), and further cases have been published (340,360,361). In some of the cases the clear cells component has been so dominating that the tumors are probably better classified as CCOC (340,362) with patterns of CEOT. Such CEOT patterns are also seen in AOTs. There is evidence that CEOTs with numerous clear cells are more aggressive than CEOTs without clear cells (340).

A hybrid tumor with areas showing the histomorphology of a CEOT and others with that of a typical s/mAM was published by Seim et al. (363).
Immunohistochemistry. Several investigators have detected various types of CKs in the tumor cells. Broad spectrum keratin antibodies and CK “cocktail” antibodies like KL-1, AE1/AE3, and TK have given consistently positive reaction particularly in strongly eosinophilic cells (352,360,362,364–366). Monoclonal antibodies against single CKs have given more controversial results (66,163,360,362,365). High molecular weight (mw) CKs, CK-1, CK-5, and CK-14 were detected by Kumamoto et al. (362); the finding of CK-14 were confirmed by others (66,360). The low mw CK-19 was detected in several studies, but not in all tumors (362) (66,320,365). A CK antibody reaction was found in the amyloid-like material in two studies (352,367).

Epithelial membrane antigens (EMAs) have been detected in tumor cells (346,365) as well as filagrin (362). Vimentin (filaments) have been detected in a few studies (364,365).

Tenascin, an extracellular matrix protein has been found in the stroma and in moderate amount in tumor cells, particularly cells bordering amyloid-like substance (70,360).

Basement membrane–associated molecules have been studied by Sauk et al. (367) who detected laminin and type IV collagen in the amyloid-like deposits. Aviel-Ronen et al. (352) could not confirm these findings. Poomsawat et al. (366) detected laminin 1, laminin 5, and fibronectin in tumor cells, but they were collagen type IV negative.

Hard tissue–related proteins have been studied. BMP could not be detected (168), but BSP was clearly demonstrated by means of antibodies and ISH in calcified material and in tumor cells adjacent to calcified particles (167).

Enamel proteins are demonstrable in CEOTs. The results of the studies of amelogenin have been controversial. Mori et al. (162) found amelogenin in the amyloid-like substance in the periphery of well-calcified material, but not in the tumor cells. Saku et al. (159) detected amelogenin in small mineralized foci and in the tumor cells surrounding them. Kumamoto et al. (163) found amelogenin in tumor cells and in intercellular amyloid-like material, but not in the calcified tissue. Enamelin has been demonstrated in small mineralized foci and in the tumor cells surrounding them (159).

Enamelysin (MMP-20) was detected by Takata et al. (160) at weak to moderate levels in amyloid-like material and in the adjacent tumor cells as well as in epithelial cells in the tumor islands. Some mineralized foci were positively stained.

The enzyme alkaline phosphatase, which is related to mineralization has been demonstrated in the tumor cells, particularly at the cell membrane by several investigators (368–370).

The amyloid-like material has been tested by means of antibodies against amyloid A, and was found negative in both studies (352,360).

Langerhans cells have been encountered in CEOT also within the tumor islands; they have been shown to be S-100 protein-positive (356,357,365,366).

Studies with the proliferation marker Ki-67 have shown that the index is low in benign CEOTs, but increased five times in tumors with signs of malignancy (346). In a case of malignant CEOT with metastases to the lung, Kawano et al. (371) assessed the proliferative activity with Ki-67 L.I. The Ki-67 index was significantly higher in the recurrent and the metastatic lesion than in the original lesion. An increase in Ki-67 L.I. was associated with the appearance of histological features suggestive of malignancy.

Electron Microscopy. Ultrastructural studies of tumor cells have shown polyhedral epithelial cells with abundant cytoplasm with a large number of electron-dense bundles of tonofilaments (CKs) (355,358,368,370–373). The most peripheral part of the cytoplasm shows finer and less electron-dense filaments except at the desmosome junctions to which tonofilaments are attached. Some cells contain large numbers of mitochondria, a Golgi apparatus and pinocytotic vesicles, but no secretory vacuoles. The rough endoplasmic reticulum (RER) is generally poorly developed and free ribosomes are numerous in some cells, but sparse in others. Lysosomes of autophagic type are seen in some cells, and occasionally small clusters of glycoprotein are present. Most nuclei are large and rounded with foci of condensed heterochromatin. Nucleoli are prominent with a pronounced nucleolmma. Some nuclei have irregular outlines, and in between nuclei with very deep indentations are encountered. Tumor cells with more than one nucleus can be seen. A very conspicuous finding, which has been confirmed by all investigators is a large number of closely clustered delicate microvilli on the surface of the cells, only punctuated by the prominent desmosome connections between the cells. Lamina densa and hemidesmosomes are seen in the basal cells, and sometimes, replicated basal lamina is found around the peripheral cells.

Page et al. (372) reported that many cells within the tumor appeared to be in various stages of cellular necrosis and dissolution judged primarily from the irregular and pyknotic nuclear forms. Cells in an early stage showed light nuclear changes, loss of microvilli, and discontinuities in the outer cellular membrane. In later stages of dissolution pronounced karyorrhexis and dense nuclear pyknosis was observed, and the cytoplasm became divided in an inner almost empty area with few recognizable elements and an outer area with poorly formed electron-dense material arranged in laminar pattern. Neighboring tumor cells within the same field were well preserved.

Many investigators have studied the homogenous amyloid-staining positive material (350,352,355, 358,370,374). Intracytoplasmic location of the substance has been observed by Mainwaring et al. (350), Chaudhry et al. (355), and Chomette et al. (370), but most studies have concentrated on the more abundant occurrence of the material extracellularly. It has been described as a granulofilamentous material with sheets of fine filaments measuring 10 to 12 nm (352,374). Numerous hypotheses have been forwarded regarding the formation and the nature of the
substance; some have considered it a product from degeneration of the epithelial cells, some suggested it is a secretion product of the cells, and others have regarded it as a type of amyloid formed in the connective tissue. Studies of the molecular biology of the material has revealed it as a unique protein (375), but its pathogenesis is still poorly understood.

Some investigators have paid attention to other types of cells in the tumor. El-Labban et al. (373) observed myoepithelial cells peripheral and juxtaposed to the epithelial cells. Kumamoto et al. (362) described clear cells in CEOT and found abundant glycogen granules and a paucity of organelles in the cytoplasm.

Besides the calcifications in a CEOT some of them show varying amounts of islands of a hard tissue with cementum-like morphology (376,377). The outer layer of these consists of typical banded calcified collagen and has banded collagen fibers like Sharpey fibers arranged perpendicularly to the surface to the calcified lamellar bodies. Cells similar to cementoblasts or osteoblasts are seen in close association with the surface.

**Molecular-Genetic Data.** The amyloid-reacting substance in CEOT has been studied by Solomon et al. (375). They used microanalytic techniques to characterize the protein nature of the CEOT-associated substance isolated from specimens obtained from 3 patients. As evidenced by the results of amino acid sequencing and mass spectrometry, the fibrils were found to be composed of a polypeptide of approximately 46 mer. This component was identical in sequence to the N-terminal portion of a hypothetical 153-residue protein encoded by the FLJ20513 gene cloned from the human KATO III cell line. That the amyloid protein was derived from this larger molecule was demonstrated by RT-PCR amplification of tumor cell RNA where a full-length FLJ20513 transcript was found. Furthermore, immunohistochemical analyses revealed that the amyloid within the CEOTs immunostained with antibodies prepared against a synthetic FLJ20513-related dodecapeptide. The authors claim that the studies provide unequivocal evidence that CEOT-associated amyloid consists of a unique and previously undescribed protein, which they designated APin in recognition of Dr. Jens J. Pindborg’s initial reports of the tumor (330,348,354). Subsequently the name was changed to ODAM because the protein was detected in other odontogenic and non-odontogenic epithelial neoplasms (378).

**Differential Diagnosis.** Microscopically the classic CEOT is quite distinctive and not too difficult to diagnose. In absence of calcification and presence of cellular pleomorphism a primary intraosseous squamous cell carcinoma (PIOSCC) or metastatic tumor should be ruled out. In contrast to these the CEOT is characterized by none or few mitotic figures and a low Ki-67 index.

In cases with a considerable amount of clear cells the differential diagnoses are CCOC, central mucoepidermoid carcinoma, central acinic cell carcinoma, and metastatic renal carcinoma.

Tumors consisting of short strands and small islands of epithelium in abundant fibrous connective tissue stroma and with little or no eosinophilic, homogeneous, amyloid-staining positive substance or calcification may be difficult to distinguish from an epitheliun-rich odontogenic fibroma. Both may show foci of calcified material and cementum-like hard tissue. As the connective tissue is the tumor component, it is conspicuously more cellular than the stroma of a CEOT. Amyloid staining (Congo red and fluorescent thioflavine T) in most cases will disclose minute areas of amyloid-positive homogeneous substance in a CEOT; it is not supposed to be present in an odontogenic fibroma. Dunlap (379) reported, however, two cases of what they considered epithelium-rich odontogenic fibromas, which both contained solitary or clustered eosinophilic hyaline droplets, which were weakly positive for amyloid staining. A similar case was published by Smith et al. (380) as a CEOT. In such atypical cases, particularly if the connective tissue component is moderately cellular, the differential diagnosis may be extremely difficult, but would have no consequence for the treatment.

**Treatment and Prognosis.** Methods of treatment have varied from simple enucleation or curettage to hemimandibulectomy or hemimaxillectomy. Treatment is dictated to some extent by the location and the size of the tumor. Complete removal is necessary, so resection of the entire mass, with tumor-free surgical margins and long-term follow-up is indicated (24). Reports with long time follow-up are not numerous. Franklin et al. (331) reviewed 17 cases with a follow-up of 10 years or more, and reported a recurrence rate of 14%, which was believed mostly to be due to inadequate treatment. There is a need for long-term follow-up; the longest period over which any CEOT has been reported to recur is 31 years (349). None of the peripheral cases have been reported to recur (332). Although the clear cell variant of CEOT can be considered more aggressive, it does not seem to recur more often with adequate treatment (340). Four cases of malignant transformation have been reported (345–347,371).

### 1.4 Adenomatoid Odontogenic Tumor

**Introduction.** The AOT is a slowly growing, encapsulated, epithelial odontogenic tumor with a singular histomorphological pattern with whorled nodules of spindle cells, plexiform double cell strands and formation of microcystic or duct-like spaces. It has a limited growth potential, and generally it is not believed to be a neoplasm (23,334,381,382).

ICD-O code 9300/0

Synonyms: Adenoameloblastoma (obsolete).

**Clinical Features.** The prevalence and incidence of the AOT is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 1.7% to 7.5% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of AOTs%. Regezzi et al., Michigan, U.S.A.
Although AOT is an uncommon lesion, more than 750 cases have been published (334), and it is the third or fourth most common odontogenic tumor in several of the studies after odontomas, ameloblastoma, and myxoma. In a review (383) comprising cases published to the end of 2005, cases collected from files in institutions in 12 different counties, and cases published in Chinese and Japanese languages 1082 cases were found.

Females are affected nearly twice as common as males. On the basis of a survey of more than 500 cases from the literature, the male-female ratio was 1:1.9 (334,384). The ratio was confirmed in the review of 1082 cases (383). An analysis of 67 cases from a Thai population (385) showed a ratio of 1:1.8. In the surveys from the oral pathology biopsy services mentioned above the ratio has varied from 1:0.8 to 1:2.7. It is uncertain if racial differences exist.

The age range has varied between 3 and 82 years, at the time of diagnosis (384). However, almost 70% of the tumors have been diagnosed in patients in their second decade of life and more than 50% in patients between 13- and 19-years-old (384). Few patients have been older than 30 years (383).

A peripheral (extra osseous) counterpart exists (386,387); Buchner et al. (212) reported six cases; a total about 20 cases have been published (384) and almost all have occurred in the anterior part of the maxilla. They are very rare in the mandible. Peripheral AOT presents as a pink gingival swelling. The mean age of 19 cases (range 3–21 years) was found to be 13.3 years (383).

More than 95% of all cases occur within the bone, however, and predominantly in the anterior regions. The maxilla is affected about twice as often as the mandible, ratio maxilla:mandible = 1:0.6 (383-385). The lower and particularly the upper canine area is a predilection site for development of the AOT (388), it occurs only rarely in the posterior regions. A total of 19 cases located to the third molar area have been reported (383).

The AOT is often asymptomatic; many of them are discovered during the course of a radiographic examination with the purpose of revealing the cause of a disturbance in tooth eruption. Larger lesions may cause painless expansion of the bone. The growth rate is slow.

**Imaging.** Since the majority of AOTs develop at an early age and often in the canine area, they easily become an obstacle in the way of eruption of the permanent canines. The consequence is that the eruption of the canines leads them in contact with the AOT, which wrap around the crown of the tooth or sometimes the entire tooth. This so-called “follicular” AOT simulates a dentigerous cyst (Fig. 33) and may be impossible to distinguish from a dentigerous cyst on a radiogram unless the radiolucency extends apically along the root past the cementoenamel junction. The tumor is well defined and unilocular; scattered fine radiopacities may be seen within the radiolucent area particularly on an intraoral film; they have been observed in between 50% and 75% of published cases (389,390). This follicular type is by far the most common and makes up about 70% of all AOTs (383,384,390). More rarely the AOT involves the second permanent incisor or the first permanent premolar. Involvement of other permanent teeth is rare and AOTs that surround deciduous teeth are exceedingly rare (385,391).

The intraosseous AOTs that are unrelated to an unerupted tooth (“extrafollicular” type) present as a well-delineated radiolucent lesion. Dependent on its location in relation to the teeth in the area the extrafollicular type can simulate a residual, a periapical radicular, a lateral radicular, or a lateral periodontal cyst. It may, however, also be located deep in the jaw without relation to any tooth (384,388). When situated adjacent to teeth, the tumor often causes displacement

![Figure 33](image-url) Adenomatoid odontogenic tumor in the maxillary canine area of a 12-year-old girl. On the radiogram the lesion simulates a dentigerous cyst around the crown of the canine and was diagnosed as such before removal.
of these. In isolated cases, root resorption (392–395), perforation of the bone corticals, and invasion of the maxillary sinus have been observed (388,390,396).

The size of the lesion has been between 1.5 and 3 cm in the vast majority of published cases (388). In a multicentric study including 39 cases, Leon et al. (390) found a range of size between 1 and 7 cm, with an average of 2.9 cm.

The peripheral type may occasionally show erosion (“saucerization”) of the alveolar bone crest (397).

Pathology. The pathology and pathogenesis of the AOT is unknown. The most likely source of tumor development is residues of the dental lamina and proliferations of odontogenic epithelium adjacent to the reduced enamel epithelium of unerupted teeth.

Macroscopically the tumor is well circumscribed and usually encapsulated. Some present as a solid mass, those situated around the crown of a tooth are cystic or partly cystic (Fig. 34).

The histopathology of the AOT is unrelated to its location in the jaws; all types show the same pattern. Solid lesions consist of a proliferating epithelium surrounded by a well-defined fibrous capsule (Fig. 35). Various patterns are seen in the epithelium. In some areas, which are often dominating, spindle cells and polyhedral cells in a swirled pattern form ball of yarn-like nodules. Several nodules of various sizes are placed close together with narrow strands of more orderly arranged epithelial cells in between. The stromal tissue is minimal in these areas. Some epithelial cells are forming small nests (“rosettes”) often enclosing droplets of an eosinophilic, PAS-positive diastase resistant substance, which is extracellular. Cystic spaces of different sizes may be seen between the nodules. They are usually referred to as “duct-like spaces” (334), but are globular, not tubular structures, irrespective of the direction in which they are cut. They are not present in all tumors and may be few in some of them. The lumen is lined by a layer of orderly arranged epithelial cells disposed radially. Around smaller cystic spaces the cells are columnar, around larger they are shorter or even cuboidal. The cytoplasm is lightly stained, and oval nuclei are polarized away from the lumen (381,398). Larger cystic spaces are lined by a cuboidal epithelium without polarization of the nuclei. In the lumen a wispy PAS-positive, diastase-resistant, eosinophilic material is often seen. Some of the cystic structures show invagination of part of the wall resulting in an almost horse-shoe formed structure with two layers of columnar cells separated by a narrow zone of PAS-positive, eosinophilic material and with the nuclei polarized away from that zone (Fig. 36).

There may be scattered foci of polyhedral squamous cells in the tumor. Another and conspicuous cellular pattern is characterized by long, narrow epithelial strands consisting of two layers or a single layer of cubic cells (Fig. 35). They form large loops, which are connected to each other in a plexiform pattern. The stroma inside the loop is often very loose and sometimes missing. This pattern is found in particular toward the periphery of the lesion. By some authors it is referred to as “cribriform” but most of the loops are large; they are not small apertures as in a sieve. A similar pattern is seen in O-As. In the stroma a perivascular hyalinization with concentric disposition of hyalinous layers in the surrounding connective tissue and degeneration of the endothelial layer is common finding (390,399).
Calciﬁed material in various amounts and sometimes dominating is seen in most of the tumors and often with a laminated pattern of concentric rings. The calcification takes place in the degenerated epithelium and in the extracellular, eosinophilic, PAS-positive material, which nature has been interpreted in many ways (400–402); the matter is not yet solved (334).

Eosinophilic, hyalinized, dentinoid material often with entrapped epithelium is seen in many cases (403), and part of it may be mineralized. During normal odontogenesis and in odontomes and ameloblastic ﬁbro-odontomes the development of tubular dentin takes place only if a cellular, embryonic pulp-like odontogenic ectomesenchyme is present. Nevertheless a few cases of AOT with tubular dentin without such mesenchyme have been published (404,405).

A common feature in AOT is minor areas of tumor tissue showing a histomorphology similar to that of the CEOT (397,406–409). Careful study of such cases (410) including follow-up of the postoperative course has shown that the occurrence of such areas with structure of a CEOT does not change the behavior of the AOT, the capsule remains intact and recurrence is unlikely.

Very uncommon is the occurrence of AOT-like structures in lesions (“Adenomatoid dentinoma”), which must be interpreted as a kind of odontomes (411–414).

Mitotic ﬁgures may be found occasionally in AOT, but dysplasia has never been described. Melanin occurs sometimes in AOTs (415,416), as in many epithelial odontogenic tumors.

Like the solid AOT, the cystic, follicular variant has a thick ﬁbrous capsule with a smooth surface. On section a large cystic cavity is seen, which is partially ﬁlled with solid tissue, and mineralized foci may be detected already macroscopically. In histological sections the tumor tissue is found on the inside and shows the same histomorphology as seen in the solid variant. Part of the luminal surface of the cystic lesion may be covered with a thin layer of squamous epithelium as seen in dental sacs and dentigerous cysts. If the tumor and the tooth were removed in toto it may be possible to see this layer in continuation with the reduced enamel epithelium of the dental sac.

Immunohistochemistry. A number of immunohistochemical studies with different types of antibodies have been published during the later years. AOT tumor cells are S-100 protein-negative (417,418). CK studies with AE1/AE3 (broad spectred CK antibodies) revealed a positive staining in epithelial tumor cells, primarily in nodular areas and in cells of the duct-like microcysts (390,419). The reaction to KL-1 was weaker (417). All epithelial cells in AOT react to pankeratin antibodies (159). Monoclonal antibodies against individual CKs were used by Leon et al. (390); the tumor cells reacted to the following type II CKs, CK-5, CK-7, and CK-8. CK-7 and CK-8 were mostly found in the loop forming narrow epithelial strands. Other investigators have been unable to detect CK-7 and CK-8 (66,420). Among the type I CKs, CK-10 and CK-13 are not expressed (66,390). Tumor cells have reacted strongly to CK-14 in several studies (66,390,420), Leon et al. (390) found, however, that columnar cell linings of the duct-like microcysts reacted negatively to CK-14, but positively to CK-19. Cells have been CK-18-negative in all studies (66,390,420). Crivelini et al. (420) could not detect CK-19 in AOTs.

Involucrin could not be detected (326). Nestin, an intermediate ﬁlament of the cytoskeleton, which is related to tooth development and repair of dentin was detected by Fujita et al. (422), who found an intense expression in small nodular foci and rosette patterns and in whorled spindle cells.

Integrin, a plasma membrane protein plays a role in the attachment of a cell to the extracellular matrix and to other cells, and as a signal transductor has been studied by Souza Andrada et al. (76). Integrin α2β1, α3β1, and α5β1 were detected in ameloblastomas and AOTs. The labeling intensity was considerably stronger in the ameloblastomas than in the AOTs.

Surprisingly, vimentin, an intermediate ﬁlament protein characteristic of ﬁbroblasts have been detected in the trabeculae and loop-forming strands areas and in the cuboidal cells peripheral to the nodules in 22 of 39 cases of AOT by Leon et al. (390). In other studies vimentin was not detected (417–421).

The presences of some growth factors have been studied. Kumamoto et al. (134) used antibodies against HGF, TGF-β, and their receptors C-Met and TβRs on sections from ﬁve AOTs. HGF expression was detected in tumor cells, and was especially prominent in pseudoglandular cells in duct-like structures. The reaction in the epithelium was moderate to strong.
for all four antibodies. The reaction in stroma cells to HGF and TGF-β was weak and to both receptors negative. Fibroblast growth factors FGF-1 and FGF-2 and receptors FGFR2 and FGFR3 were studied by So et al. in sections from three AOTs (136). FGF-2 and FGFR2 were detected in AOT epithelium, but reactions to FGF-1 and FGFR3 were negative.

Extracellular matrix proteins have been studied. Ito et al. (67) used antibodies against versican, a large chondroitin sulfate proteoglycan, and found a positive reaction in a few solid areas in the tumor cell nests and in calcified areas. Tenascin, a multifunctional glycoprotein involved in cell-to-cell and cell-extracellular matrix interactions during odontogenesis and several other functions was studied by Mori et al. (70). A positive staining was limited to the interface corresponding to the basement membrane of the pseudo-glandular epitheliums of microcysts and the loop forming single/double cell layer strands.

Basement membrane-associated macromolecules such as laminin, heparin sulfate proteoglycan, and fibronectin as well as collagen type IV and type V were studied by Murata et al. (402). Laminin, heparin sulfate proteoglycan, fibronectin, and type V collagen were localized in the luminal spaces of the duct-like microcysts and along the inner rim of the duct-like structures. They were also detected in the eosinophilic hyaline droplets and variously shaped inner stromal spaces of whorled or rosette-like foci. Crevelini et al studied laminin with similar results (420).

Hard tissue–related proteins have been studied by several groups. Gao et al. (168) did not find BMP in AOT. Kumamoto et al. (169) used RT-PCR analysis to identify expression of mRNA transcript for BMPs and their associated molecules and detected expression in three of six AOTs. A strong reaction to BMP-2, BMP-4, BMP-7, BMPRs, and CBFA1 was found in tumor spindle cells in whorled nodules and pseudoglandular cells in duct-like microcysts. A weak reaction was found in stromal cells.

Enamel protein has been detected by several investigators. Mori et al. (162) found amelogenin in epithelial cells surrounding pseudoductal microcysts. Saku et al. (159) detected amelogenin in hyaline droplets and a weaker concentration in the cells surrounding them. Amelogenin was also present in small mineralized foci and in the tumor cells surrounding them, as well as at the periphery of large mineralized, homogeneous material.

In a study of sections from 23 cases of AOT Takata et al. (160) observed a distinct enamelysin immunostaining in small mineralized areas and hyaline droplets. Surrounding tumor cells were stained as well, but at a weaker intensity. Columnar cells around microcysts and low columnar cells forming rosettes or whorled arrangements were negative. A strong positive reaction for enamelysin was found in large calcified areas. Dysplastic dentin-like, hyaline material was negative.

Sheathlin, an enamel sheath protein was studied by Takata et al. (161). Distinct immunostaining was seen in the homogeneous, eosinophilic substance in tumor cell nests. Mineralized foci within the eosinophilic material were negative. Tumor cells facing the substance usually expressed sheathlin in their cytoplasm. Columnar cells in duct-like microcysts and small polygonal cells between the duct-like cysts were negative. Dysplastic dentin-like material (dentinoid) in the stroma was negative.

Neither wild type nor mutant p53 protein, a product of the tumor suppressor gene Tp53, or MDM2, an oncogene product was detected in eight cases of AOT (119), in contrast to KCOT, ameloblastoma and CCOC, which were all positive.

Moderate expression of the Tp 63 gene, a member of the Tp 53 family was detected in epithelial cells in one case of AOT by Lo Muzio et al. (121) and by Vera Sempere et al. (419), who also detected Ki-67, a proliferation marker, but only in 2% to 3% of the cells and primarily in nodules of fusiform cells. Leon et al. (390) found the mean percentage of Ki-67-positive cells in AOT to be 1.66% ± 0.78 SD, ranging from 0.5% to 4.6% of the cells. PCNA was detected in tumor cells by Crivelini et al. (420).

**Electron Microscopy.** The epithelial nature of the tumor cells has been confirmed in several studies. Well-developed gap junctions, desmosomes, desmosome-like junctions, and tonofilaments have been described (423). The great variation in morphology of tumor cells seen in the light microscope is also cognizable at the ultrastructural level and has given rise to subclassification into two (424,425), three (423), or four cell types (426). Polygonal, cuboidal, and columnar cells show abundant ribosomes, a relatively sparse endoplasmatic reticulum and mitochondria with few cristae; lysosomes, some coated vesicles, and some tonofilaments are seen. Occasionally a Golgi complex can be detected, but it is often ill defined (401,423). The small spindled cells have a dense cytoplasm and contain many organelles. Tonofilaments are prominent and seen in thick bundles, many well-developed desmosomes are found, and lysosomes are present in great numbers. Endoplasmic reticulum, Golgi complexes, and occasional glycogen particles can be detected. The nuclei are small and have a condensed nucleoplasm (423). Squamous cells show the ultrastructural characteristics of spinous cells in a stratified squamous epithelium, with bundles of tonofilaments, well-developed desmosomes, and keratinosomes.
Many investigations have concentrated on the ultrastructure of the eosinophilic droplets and the eosinophilic material in the duct-like microcysts (374,401,423,427). The conclusions have been controversial, some put attention to a similarity to amyloid (428), others compared the structure to developing enamel (401,423) or degenerated collagen (429), the latter on the basis of the finding of three different types of fibrils, thin collagen fibrils, electron-dense fibrils, and amyloid filaments. Electron-dense polymorphous plaques have been observed in the tumor droplets, which show a variety of shapes and internal structures including tubular structures, which may be coated with a fine granular material (423). El-Labban and Lee (399) found degenerative changes in 70% to 90% of the blood vessels in the stroma affecting both the endothelial lining and the perivascular connective tissue.

**Molecular-Genetic Data.** Mutation of the AMBN, which in humans maps to chromosome 4q21 has been detected in one case of AOT (165) and was considered a tumor-specific mutation. The AOT had a 334G>T transversion, causing a R90W amino acid change.

**Differential Diagnosis.** Although a considerable amount of AOTs has been misdiagnosed before removal, the histopathological diagnosis is simple because of the tumor’s unique histomorphological pattern. If the lesion is small and found in the wall of a dentigerous cyst, it may be overlooked. The presence of a large amount of calcified material may confuse the pathologist.

**Treatment and Prognosis.** Enucleation of the tumor followed by curettage is the treatment of choice. The thick connective tissue capsule facilitates the enucleation from the bone. Although few cases have been published with a follow-up period of five years or more, the risk of recurrence is considered extremely low, only four cases have been reported, one recurred as late as 12 years after curettage (391,395,430). Malignant transformation has never been described.

Many authors consider the AOT a hamartoma. Although it is beyond doubt that the growth rate of the AOT is very slow, nobody has proved that the lesion stops growing at any time, and some lesions have reached a size of 6 to 7 cm (390,396,431), and in one case extension into the intracranial space of a recurrent tumor has been reported (334).

Removal of follicular or large AOTs may require removal of involved teeth. Impacted teeth do not necessarily need to be removed, though; in appropriate circumstances they can be preserved (432).

### 1.5 Keratocystic Odontogenic Tumor

At the editorial and consensus conference in Lyon, July 2003, in association with the preparation of the WHO volume *Pathology and Genetics of Head and Neck Tumours* (12), there was consensus that sufficient data about the neoplastic potential of the “odontogenic keratocyst” had been published to justify a change of its name into “keratocystic odontogenic tumour.” Since it clinically presents as a cyst, it is described in chapter 18. An extensive and up-to-date review of the lesion is published as Chapter 3 “Odontogenic Keratocyst” in the book *Cysts of the Oral and Maxillofacial Regions* by Shear and Speight (228).

### 2. Tumors of Odontogenic Epithelium with Odontogenic Ectomesenchyme with or without Hard-Tissue Formation

This group of tumors comprises three neoplasms and two hamartomas (15), which are truly odontogenic in the sense that they are composed of odontogenic epithelium and odontogenic ectomesenchyme, which under certain conditions are able to produce the dental hard tissues, dentin and enamel. This interaction takes place during the normal odontogenesis. Because they are composed of tissue derived from two germ layers, ectoderm and mesoderm, they are sometimes called “mixed” (433). The histomorphology of the entities in this group reflects various stages of the odontogenesis differing in potential for proliferation, histodifferentiation, and morphodifferentiation. To understand the nature of these tumors certain knowledge is required of the sequential and reciprocal mechanisms of the epithelial-ectomesenchymal interactions, which take place during odontogenesis. Many reviews have been written on the subject, among others those by Slavkin (434), Thesleff et al. (19), Peters et al. (20), Tucker et al. (435), Sharpe (436), and Cobourne et al. (21).

Briefly, the first evidence of tooth formation in humans is observed in fetuses at the age of one month as a thickening of the oral epithelium in the mandibular, maxillary, and medial nasal processes. The early-stage oral epithelium is capable of inducing tooth development in nonoral ectomesenchyme. At a slightly later stage the epithelial cord becomes lengthened and broadened as it migrates into the adjacent ectomesenchyme (434). At specific sites the epithelium proliferates to form enamel organs, which develop through a bud stage and a cap stage to a bell stage with a convex outer surface and a concave inner surface. The bell-shaped enamel organ embraces a very cell-rich part of the ectomesenchyme, the dental papilla, which is the primordium of the later dental pulp. The dental papilla controls the shape of the tooth. The cell-dense ectomesenchyme continues around the enamel organ and forms the dental sac. At this stage the dental papilla is capable of inducing an enamel organ with following tooth formation in a nonodontogenic epithelium, such as skin. At the interface between the enamel organ and the dental papilla, the dentin-producing cells, odontoblasts develop from the ectomesenchyme, and the enamel-producing cells, ameloblasts develop from the enamel organ. These highly specialized cells are mutual dependent and controlled by an alternative flux of biological information between ectomesenchymal and epithelial cells. The odontoblasts do not develop from the ectomesenchyme unless in contact...
with the inner enamel epithelium of the enamel organ, and ameloblasts capable of producing enamel do not develop till an initial mineralization of the adjacent dentine formed by the odontoblasts has taken place. Over time the dentin and the enamel of the dental crown is produced and after the crown of the tooth is formed, root formation is initiated (433).

These reciprocal inductive influences of one tissue on the other play a similar role in this group of tumors consisting of odontogenic epithelium and odontogenic ectomesenchyme. Formation of dentin only takes place where the odontogenic epithelium has developed preameloblasts, which are capable of inducing odontoblasts formation in the adjacent ectomesenchyme, and enamel is only formed where odontogenic epithelium is in contact with dentin, which shows an initial mineralization. These requirements were observed already by Pflüger et al. in 1931 (1).

In the tumors three histomorphological patterns may be seen: (i) A tumor consisting of strand and nests of odontogenic epithelium resembling the dental lamina and initial enamel organs, growing in a cellular odontogenic ectomesenchyme, and with no presence of dentine or enamel is called ameloblastic fibroma (AMF); (ii) A tumor showing various amount of dysplastic or more rarely tubular dentin besides the components found in the AMF is called ameloblastic fibrodentinoma (AFD); (iii) A tumor that furthermore contains various amount of regular or dysplastic enamel is termed “ameloblastic fibro-odontoma” (AFOD). All three tumors are considered neoplasms; they will grow continuously if not removed. An AMF does not differentiate into an AFD or an AFOD, and an AFD does not differentiate into an AFOD (13,433,437,438). At an initial stage of the development of an AFD or the AFOD, however, before the formation of the dental hard tissues the three variants will show a similar histomorphology. Two other lesions in the group are considered hamartomas. They consist of the same components as the AFOD but grow more slowly and eventually are made up primarily of the dental hard tissues with only a narrow peripheral rim with some soft tissue components. The growth abates. They are called odontomas. By and large they occur as two variants with a different level of morphodifferentiation. In the complex odontoma (ODTx) the dentin and enamel is organized in a non-tooth-shaped pattern. In the compound odontoma (ODTp) tooth-like structures are formed. A developing odontoma will resemble the AMF or AFD or AFOD during its stages of maturational development and this fact causes diagnostic problems, which will be discussed under the individual lesions. Some authors (31,381) prefer to pool the AMF, the AFD, and the AFOD into one group of neoplasms and the two variants of odontomas into one group of hamartomas. If treatment is the only concern this makes sense, apart from the fact that the AMF has been reported to recur more often than the AFD and the AFOD (439,440). For scientific purposes it is an advantage to keep the entities separated (440,441).

In the WHO classifications of odontogenic tumors the way of classifying the neoplasms has varied. In the 1971 edition (22) the AMF, AFD, and AFOD were kept separately; the AFD was called “dentinoma” at that time. In the 1992 edition (23) the AFD and the AFOD were pooled together and in the 2005 edition the AMF and the AFD were pooled together.

2.1 Ameloblastic Fibroma

Introduction. The AMF is a rare, benign odontogenic neoplasm consisting of an odontogenic epithelium, which resembles the dental lamina and primordial enamel organs. The epithelium is growing in an abundant and cell-rich ectomesenchymal tissue, which resembles the dental papilla. No formation of the dental hard tissue is seen.

ICD-O code 9330/0
Synonyms: None, but in the past the tumor has been published under various obsolete terms like “soft odontoma.”

Clinical Features. The differential diagnostic problems mentioned above have had an impact on the results of the surveys made of the tumor. Surveys and reviews may include cases of early odontomas, which have been diagnosed as AMFs. When diagnosing these tumors it is important to correlate the histological features with the clinical and radiographic findings.

The prevalence and incidence of the tumor is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amount of years ranges from 0.6% to 4.5% in studies comprising more than 300 samples of odontogenic tumors. In most of the surveys the percentage has been between 1.2% and 1.8%. The results are indicated as follows: number of odontogenic tumors/number of AMFs/%. Regezzi et al., Michigan, U.S.A. (31): 706/15/2.1%, Günhan et al., Turkey (32): 409/18/4.5%, Daley et al., Canada (33): 392/7/1.5%, Mosqueda-Taylor et al., Mexico (34): 340/5/1.4%, Ochsenius et al., Chile (35): 362/2/0.6%, Adibe et al., Nigeria (36): 318/4/1.2%, Fernandes et al., Brazil (37): 340/6/1.8%, Ladeinde et al., Nigeria (38): 319/6/1.8%, Buchner et al., California (30): 1088/17/1.6%, Jones et al., England (2006, pooled figures from two studies)(39,40): 523/8/1.5%, Olğac et al., Turkey (41): 527/8/1.5%, and Jing et al., China (42): 1642/19/4.5%. The data are skewed; however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetical or environmental factors.

The total number of published cases of AMF is between 150 and 200. Comprehensive reviews have been written by Slootweg (437) and Philipsen et al. (441). In a study of 55 cases Slootweg found an age range from 6 months to 47 years. The mean age at time of diagnosis was 14.6 years. The gender distribution was 29 males and 26 females, the ratio was thus
M:F = 1.1:1. The tumor was located in the maxilla in 9 cases (1 anterior, 8 posterior) and in the mandible in 45 cases (5 anterior, 40 posterior), making the ratio maxilla:mandible = 1.5. Philipsen et al. included the cases reviewed by Slookweg; they covered the period 1946 to 1978. They added another 40 cases from the literature and analyzed a total of 122 cases. The gender rate and particularly the location came out differently. The age range was 6 months to 62 years, but only two cases were older than 49 years. The mean age at time of diagnosis was 14.8 years. The gender rate of M:F was 1.4:1; 71 tumors were diagnosed in men, and 50 in women. The location was somewhat different from the findings by Slookweg, 33 tumors were located in the maxilla and 90 in the mandible, the ratio maxilla:mandible was thus 1.2:7. In both studies the majority of tumors were diagnosed in the posterior part of the mandible, 74.1% in Slookweg’s study and 68.9% in Philipsen et al.’s study, including eight cases, which covered more than one region. More recently Lu et al. (442) published 14 own cases, 6 in males and 8 in females. The mean age at time of diagnosis was 23.9 years. Four tumors were located in the maxilla (1 anterior, 3 posterior), 10 were located in the mandible (5 anterior, 5 posterior), the maxilla:mandible ratio was 1:2.5. Chen et al. (440) reported 13 cases of AMF from their own files. The patients were between 6 and 51 years (mean: 26 years). Seven patients were males and six, females. All tumors occurred in the mandible, with 10 in the posterior part, and 3 involving both the anterior and posterior part. Jing et al. (42) reported an additional five cases of AMF to those reported by Lu et al. (442). The 19 tumors were diagnosed in 9 males and 10 females. The mean age was 10 years lower: 19.6 years. The location distribution was about the same five AMF in the maxilla (2 anterior, 3 posterior), and 14 in the mandible (5 anterior, 9 posterior), ratio maxilla:mandible = 1:2.8.

In a study of 123 cases from the literature selected on the basis of well-documented follow-up data, Chen et al. (438) found the age at time of first presentation to range from 7 weeks to 54 years with a mean age of 15.9 years and a median age of 13 years. Only 30 patients were older than 22 years. The male:female ratio was 1.26:1 (68:54). The location of the tumors: 24 cases in the maxilla (1 anterior, 3 posterior), 99 cases in the mandible, ratio maxilla:mandible = 1:4.1:1. The majority, 75 of 102 AMFs (73, 5%) were found in the posterior region of the mandible.

A single case of peripheral AMF has been published by Kusama et al. (443). It was a pedunculated tumor on the gingiva in the lower right premolar region of a 40-year-old woman. The histopathology of the tumor had a certain similarity to the AMF, but it showed features of an epithelium-rich and cell-rich odontogenic fibroma, a much more common lesion (444,445) and it is probably better classified as such. Ide (446) commented on two cases published in Japanese. They both presented as gingival hyperplasia, but the histological documentation showed they were AMF-like proliferations in papillae. No other case of extrasosseous AMF has been published.

The AMF is usually painless; pain was recorded in 3 of the 24 cases reported by Trodahl (439) and in a single case reported by Chen et al. (440). The most common symptom is swelling, which is found in almost all cases (439–441). Chen et al. (438) registered the finding in 71.8% of 103 cases. Because of the insignificant symptoms about 20% of the tumors are discovered accidentally on radiograms (438). Unerupted teeth are associated with the tumors in three out of four cases (441).

Although the growth rate is slow, many of the tumors reach a considerable size. It varies between 0.5 and 16 cm; 9 out of 16 lesions reported by Trodahl (439) were larger than 4 cm, and 9 out 13 lesions reported by Chen et al. (440) were 4 cm or larger in greatest extent. In 39 cases from the literature the largest diameter of the tumor ranged from 0.7 to 16 cm, with a mean of 4.05 cm.

**Imaging.** Radiologically, the tumor appears as a well-defined, uni- or multilocular radiolucency, often with a radiopaque border. The multilocular appearance is particularly seen in larger lesions, which present with a swelling (438). In 8 of 10 lesions reported by Chen et al. (440), the radiolucency was multilocular; in 2 cases measuring 3 × 2 cm and 4.5 × 2 cm it was unilocular. Among 38 cases from the literature Chen et al (438) recorded 23 multilocular and 15 unilocular cases. The asymptomatic cases tended to show unilocular radiolucency.

In about 75% of the cases the tumors are related to an unerupted tooth. In the maxilla the AMF may encroach the maxillary sinus.

A CT scanning is recommended, particularly for large tumors; it improves the information about the outline of the tumor.

**Pathology.** The etiology of the tumor is unknown. It is interesting that four out of nine cases reported by Schmidt-Westhausen et al. (447) developed in areas of congenitally missing teeth. The tumor is supposed to arise from residues of odontogenic epithelium in the jaws. Since three out of four tumors are associated with an unerupted tooth and Philipsen et al. (448) have shown that in the opercula of 74 cases of unerupted first and second permanent molars 7 lesions were detected with a histopathology similar to the AMF, it is tempting to speculate that such proliferations of odontogenic tissue may be the source of origin in some cases.

Macroscopically, the tumor presents as a gray or whitish, rounded or oval soft mass with a lobular configuration and a smooth surface that seems covered with a thin capsule-like tissue. The cut surface is uniform; cystic changes are absent or inconspicuous, apart from the very unusual cases, where the tumor develops in the wall of a cyst, Pflüger (449) case 2, Nilsen et al. (450) case 2, and Edwards et al. (451).

Microscopically, the tumor is composed of strands and islands of odontogenic epithelium growing in a cell-rich mesenchymal tissue with a histomorphology similar to that of the dental papilla (Fig. 37). The periphery of the tumor is well demarcated, a thin capsule has been described in cases, which might
rather be early stages of an odontoma (452). The amount and density of epithelium varies from tumor to tumor and may vary considerably from area to area within the same tumor. The strands are usually composed of a double layer of cuboidal cells and resemble the dental lamina. In some areas the strands are broader and the central area occupied by stellate cells (Fig. 38). The strands are ramificating, a pattern that may be more or less conspicuous. Buds of varying sizes develop from the epithelial strands; they are composed of stellate cells bordered by a basal layer of cylindrical cells with a reverse nuclear polarity and morphology-like preameloblasts (Fig. 39). These bulbous thickenings resemble early stages of enamel organs. Cyst formation within the epithelium is very uncommon, and the cysts remain small. Artefactual splits along the plane between the layers of the bilaminar epithelial strands are not unusual. Acanthomatous changes are rare (54). Islands of tumor epithelium may be found in the adjacent connective tissue and might represent a growth pattern (453). The ectomesenchymal tumor component is highly cellular and shows a striking similarity to the dental papilla. The morphology of the cells varies, most are stellate with fine cytoplasmic processes and angular nuclei, others are plump, and fibroblast-like cells may also be seen. The matrix is myxoid and contains fine, fibrillar collagen. The cellularity and matrix composition may vary from tumor to tumor and within a given tumor (54), more mature collagenous fibers may be present in some areas. The vascularity is modest. Adjacent to the epithelial strands and particularly the bulbous extensions narrow, eosinophilic cell-free zones may be seen. More pronounced changes in terms of eosinophilic, hyalinized matrix is seen in some tumors. Such structural alterations are interpreted as the result of aberrant epithelial–ectomesenchymal inductive effects. Other types of reaction zones have been described. In some tumors enclaves of ramified strands of epithelium surrounded by broad zones of ectomesenchyme characterized by moderate cellularity are separated by plexiform strands of ectomesenchyme with high cellularity (449).

Figure 37 Ameloblastic fibroma. Section of a tumor from the molar and retromolar area of the left mandible of a 9-year-old boy. Ramified thin dental lamina-like strands of odontogenic epithelium are seen in a dental papilla-like ectomesenchyme, which exhibits variations in cellular density. The vascularity is low. H&E stain.

Figure 38 Ameloblastic fibroma. Higher magnification of the tumor in Figure 37. In this area the epithelial strands are broader with formation of some stellate reticulum-like cells and differentiation of preameloblasts-like cells along one side of the strands. The cellularity of the ectomesenchyme is reduced in the vicinity of these cells. H&E stain.

Figure 39 Ameloblastic fibroma. Higher magnification of the tumor in Figure 37. A bulbous thickening of the epithelium is seen which resembles an early stage of an enamel organ. The peripheral cells exhibit reverse polarity of the nuclei. Note the narrow cell free zone along the epithelial-ectomesenchymal interface. H&E stain.
Together with a high cellularity it may provoke suspicion of malignancy. If more than a few scattered mitoses are present and particularly in case of nuclear atypia this possibility must be taken in consideration (454).

Cases of “granular cell ameloblastic fibroma” have been published (455–457). The granular cells show a finely granular, eosinophilic cytoplasm and small, round, or oval nuclei, which are often eccentrically located. They are seen in the connective tissue and may be the dominating cell type. These tumors are clinically distinct from the AMF and are better classified as GCOs (458).

**Immunohistochemistry.** CKs were studied by Tatemoto et al. (459) in four cases of AMF. They used polyclonal TK antiserum-detecting 41 to 65 kDa keratins, and monoclonal antibodies KL-1-detecting 55 to 57 kDa keratins, as well as monoclonal PKK-1-detecting CK-8, CK-18, and CK-19. PKK-1 bound slightly or not at all. Dental lamina–like epithelium showed a relatively stronger staining with TK, KL-1, and PKK-1 compared with ameloblastic epithelial islands with peripherally located columnar cells. The ectomesenchymal cells, which were strongly positive for vimentin, showed some coexpression of keratin. Yamamoto et al. (417) also detected reactions to KL-1 CKs (broad spectated antibodies) in the dental lamina–like epithelial strands and the stellate reticulum of an AMF. Crivelini et al. (66) investigated CKs in five AMFs with monoclonal antibodies against CK-7, CK-8, CK-10, CK-13, CK-14, CK-18, and CK-19. Reaction to CK-7, CK-13, and CK-14 was detected. CK-14 was found in all types of epithelial tumor cells. CK-13 was seen in cords and stellate reticulum, but not in cyndindrical peripheral cells; reaction to CK-13 is not found in the stellate reticulum of normal tooth germs. CK-7 was found in one tumor only.

Nestin was detected by Fujita et al. (422) in focal areas of the ectomesenchyme particularly near the epithelial elements in two cases of AMF; the reaction was strong. Nestin was found to be upregulated in AMFs compared with normal tooth germs and was considered a marker of odontogenic ectomesenchyme in odontogenic tumors.

Vimentin has been studied by several investigators (459,460,417,461). All except Crivelini et al. (66) detected a positive reaction in the ectomesenchymal tumor cells.

No staining for desmin could be found in AMFs by Tatemoto et al. (459).

Neutral tissue markers were used by Yamamoto et al. (417) and Takeda et al. (462). NSE and glial fibrillary acidic protein could not be detected (462). In both studies S-100 protein were detected in a few scattered cells of the epithelial component. The ectomesenchyme was negative in one study (417), while the dendritic and spindle-shaped cells were positive in the other.

So et al. (136) studied the immunohistochemical localization of fibroblast growth factors FGF-1 and FGF-2, and receptors FGRFR2 and FGRFR3 in three AMFs and other odontogenic tumors and cysts. Immunoreaction to FGF-2 (some nuclear reaction) and to FGRFR2, but not to FGF-1 and FGRFR3 was found in the epithelium of the AMFs. The authors suggested that FGRFR-2 might be involved in directing nuclear activity at the histodifferentiation stage of odontogenesis.

Extracellular matrix proteins in AMFs have been studied. Ito et al. (67) detected versican, a large chondroitin sulfate proteoglycan in the ectomesenchymal tumor component in two cases of AMFs. Heikinheimo et al. (68) studied the immunohistochemical localization of two cellular fibronectins, tenasin, lammin, as well as type VII collagen in three AMFs. In two AMFs there was a notably weak immunoreactivity to an extradomain sequence-A-containing form of cellular fibronectin in the ectomesenchyme, the third tumor was bright-positive. A form of cellular fibronectin containing an oncofetal domain, which is found in carcinomas and ameloblastomas could not be detected. Tenasin was found in the ectomesenchymal component in all cases, the basement membrane bordering the tumor epithelium was clearly outlined. Laminin and type VII collagen had almost identical distributions; the basement membrane of the epithelial strands and islands of all AMFs exhibited an intense positive, linear staining with both antibodies. Mori et al. (70) and Yamamoto et al. (417) confirmed the findings of tenasin in AMFs.

The distribution of collagens type I, IV, and VI, procollagen type III, and undulin was studied in four cases of AMFs by Becker et al. (453). An excessive accumulation of collagen type VI was detected in the extracellular matrix of the ectomesenchymal tumor component showing a clear distinction to the connective tissue surrounding the tumor, while collagen type I, procollagen type III, and undulin showed a weak and amorphous distribution. Pronounced staining for collagen type I and IV was found in areas with high cellularity, though. The hyaline matrix seen around the epithelium in some areas showed a weak reaction for collagen type I, but was negative for type III, IV, and VI. This finding is in contrast to normal predentin and dentin, which is composed of collagens type I, III, and VI in a typical distribution. The author concluded that the ectomesenchyme of AMF represents an undifferentiated extracellular matrix.

Nagatsu et al. (75) examined the distribution of collagen IV α1 to α6 chains in three cases of AMF. In the tumor areas α1(IV)/α2(IV), α3(IV), and α5(IV)/α6 (IV) chains occurred as linear continuous patterns that clearly separated the epithelial islands and strands from the surrounding dental papilla–like ectomesenchyme.

Hard tissue–related proteins have been studied. Mori et al. (162) detected amelogenins in the tumor epithelium of four AMFs; the ectomesenchyme was negative.

PCNA was studied in a case of AMF by Yamamoto et al. (417) who detected scattered PCNA-positive cells in the dental lamina–like epithelium and in the ectomesenchymal tumor component.

Sano et al. (463) assessed the growth potential of AMF by means MIB-1 immunohistochemistry, which recognizes the epitope of the Ki-67 antigen. In an AMF
material similar to what may be seen in ameloblastomas. In some of the epithelial cells there was a loss of definition of the basal lamina associated with a “hair on end” arrangement of aperiodic fibrils running perpendicular to the basal lamina. The adjacent hyaline material seen in the light microscope proved to be dense regular mature collagen.

**Molecular-Genetic Data.** Heikinheimo et al. (460) used in situ and Northern hybridization to study CK-1, CK-4, CK-8, CK-18, and CK-19 and vimentin gene expression in 13- to 24-week-old human fetal tooth germs, including overlying oral epithelium and six odontogenic tumors (ameloblastomas and AMFs). The results were compared with immunohistochemistry using monoclonal antibodies. The normal and neoplastic epithelium revealed a relatively strong expression of simple epithelial CK-19 mRNA, and a low, but significant expression of CK-8 and CK-18 mRNAs. The ectomesenchymal cells of AMF expressed low amount of simple epithelial CK-8, CK-18, and CK-19 as well as vimentin. The results indicate that the differentiation and cytoskeletal gene expression programs of odontogenic epithelia upon neoplastic transformation are not fully retained.

EGF and TGF-α, which regulate cell proliferation and functional maturation through the EGF-R, was investigated in two AMFs by Heikinheimo et al. (130) by Northern analysis, Southern blotting, ISH, and immunohistochemistry. Human fetal teeth in cap stage to early hard tissue formation were included for comparison. EGF-R mRNA and immunoreactivity were confined to neoplastic epithelium. Transcripts for TGF-α but not for EGF were detected in the tumors. It was concluded that regulation of EGF-R expression is developmentally regulated in human odontogenesis and may also be involved in odontogenic tumorigenesis.

By means of ISH Papagerakis et al. (461) studied the expression of osteocalcin and collagen type III mRNA in normally developing postnatal teeth and five odontogenic tumors comprising AMF, AFOD, and ODTx. The study was combined with immunostaining with antibodies against human keratins (KL-1), vimentin, collagen type IV, fibronectin, osteonectin, osteocalcin, and bovine amelogenins. Abnormal expression of osteocalcin mRNA was observed in the high columnar epithelial cells of the odontogenic tumors. The mRNAs coding the α1 chain of collagen type III were found only in the ectomesenchymal cells of the tumors. Detection of keratin as well as vimentin in the epithelial cells of the tumors made the authors suggest that the level of differentiation corresponded to the cap and/or the bell stages of normal tooth development.

**Differential Diagnosis.** The main differential diagnoses are from ameloblastoma, AFD, AFOD, developing odontomes, AFs, and epithelium-rich odontogenic fibroma.

In contrast to ameloblastomas the epithelium in the AMF forms bilaminar strands with buds rather than broad strands and large islands with a tendency for acanthomatous changes and formation of cysts. The amount of stellate reticulum-like epithelium is

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In a 16-year-old woman the index was 2.9% in the epithelial component and 2.9% in the ectomesenchymal component. In a recurrent AMF in a 26-year-old man the index was 7.5% and 9.8%, respectively. In an ameloblastic fibrosarcoma (AFS) in a 38-year-old woman the index was 5.1% and 13.5%, respectively. The results suggest that the index can be used to assess the aggressiveness of the AMF.

The expression of the p21(ras) protein, a product of a RAS proto oncogene was measured in two cases of AMF and compared to findings in ameloblastomas and odontogenic myxomas (ODOMYXs). The AMFs showed an overexpression of p21(ras) and an almost identical staining pattern. Percentage of immunoreactive cells were 75% to 100% in the epithelial cells and 5% to 25% in the ectomesenchyme of one tumor and less than 5% in the other. The staining was somewhat more intense in the ectomesenchymal cells. The level was equal to that of some of the ameloblastomas and one of the myxomas.

**Electron Microscopy.** Csiba et al. (464) studied the ultrastructure of an AMF—the size of a hen’s egg—in the posterior part of the mandible of a 15-year-old boy. The cells of the small epithelial islands were oval or polygonal. The basement membrane was intact; the basal cells were connected to it with hemidesmosomes. They were connected to each other with desmosomes; the intercellular spaces were very narrow. The nuclei were large and oval with dispersed chromatin, but much of the chromatin was arranged along the inner nuclear membrane. Nucleoli were seen. The cytoplasm contained free ribosomes, a moderately developed endoplasmic reticulum, some vesicles, some mitochondria, and abundant tonofilaments. A Golgi apparatus could be seen but it was usually small. In the central area of the epithelial islands the intercellular spaces were large. The cells contained dense deposits of glycogen, which was arranged in a rim around the nucleus. Some of the centrally placed cells showed cytoplasmic extensions, which reached the basement membrane. The cells of the connective tissue resembled fibroblasts but had very voluminous and irregularly shaped nuclei with indentations and conspicuous cytoplasmic invaginations. Few organelles were seen, sporadically a less well-developed endoplasmic reticulum could be found, some vesicles and a few large mitochondria. The eosiophilic homogeneous zone, which may be seen adjacent to the epithelium in the light microscope was ultrastructurally heterogeneous. It contained residues of cells and a granular amorphous substance, which resembled the basement membrane together with collagenous fibrils without any specific orientation.

Farman et al. (103) investigated the ultrastructure of an AMF, which was removed from the posterior region of the maxilla in a five-year-old boy. The tumor had expanded the bone; it occurred two years after curettage. The basement membrane around the epithelial islands consisted of a regular bilamellar structure to which a varying number of hemidesmosomes were attached. Elsewhere there was a thickening of the lamina densa by a granulofilamentous
more pronounced in the ameloblastoma. The connective tissue component is very different. In the ameloblastoma it is a collagogenous connective tissue stroma with vascularization, and moderate cellularity. In the AMF there is no stroma; the connective tissue is an equal component of the neoplasm with a histomorphology like the dental papilla.

In contrast to the AFD and the AFOD the AMF does not contain the dental hard tissues, dentin and enamel. It may require extensive sampling to find the hard dental tissue. Some investigators do not consider the finding of dentinoid or dentin or even enamel to be very important. Sciubba (381) considered the AFOD to be a variant of AMF. Odell et al. (54) considered the presence of dentin as part of the spectrum of ameloblastic fibro-odontomes. In the 1992 WHO classification the AFD was categorized together with the AFOD. In the 2005 WHO classification the AMF and the AFD were categorized together. Regarding the AMF a certain tendency for recurrence and even malignant transformation has been documented (vide infra), which does not seem to be the case or at least to a lower degree for the two dental hard tissue–producing variants. The presence of dental hard tissue might not be without importance for the prognosis.

At an early stage a developing ODTx may be histologically indistinguishable from an AMF. There is no known histochemical or other kind of marker to separate them. A developing odontoma is probably more often diagnosed as an AMF than vice versa. The amount of epithelium in proportion to the connective tissue is greater in an early odontoma and there are more large bulbous extensions with stellate reticulum. A more orderly arrangement of the epithelium also points toward an odontoma. Clinical information is important; a tumor with AMF features developed in a patient who is 22 years or older and therefore past the period of normal odontogenesis is likely to be an AMF. A small globular tumor in a young child is likely to represent the early stage of a developing odontoma.

The most important differential diagnosis is toward the AFS. Malignant transformation is an uncommon, but well-documented possibility. The sarcomatous transformation takes place in the ectomesenchymal component, which shows hypercellularity, frequent and abnormal mitoses, as well as nuclear and cellular pleomorphism. Only a few scattered normal mitoses may be seen in a benign AMF. The amount of epithelium is reduced in the AFS and may eventually disappear altogether. Clinical features like sudden rapid growth and indistinct margins of the tumor on the radiogram are indicative, and malignant transformation is significantly more common in patients older than 22 years (438). In resection specimens the presence of infiltration of bone marrow spaces supports the impression of malignancy.

The differential diagnosis toward an epithelium-rich odontogenic fibroma may be difficult, particularly in case of the uncommon ameloblastomatoid central odontogenic fibroma (COF), which furthermore shows an increased cellularity of the connective tissue (465). The epithelium of the odontogenic fibroma has a different morphology; however, the strands are more irregular and their thickness varies from area to area, the center of the islands do not contain stellate reticulum-like cells. The peripheral cells may be cylindrical in some areas and even show reverse nuclear polarity, but in other areas they may be cuboidal or flattened. The cells in the connective tissue are generally more fibroblast-like and the content of collagenous fibers is higher in the odontogenic fibroma.

**Treatment and Prognosis.** AMF has been treated with conservative as well as radical surgery. For many years it has been known that the AMF is capable of recurrence (439), and sometimes even twice (466). In some cases it was a question of residual tumor after incomplete excision. In a few cases the recurrence has shown a higher differentiation with formation of dentin or even enamel indicating that perhaps the primary tumor was not a genuine AMF, but rather an early stage of AFOD. In more than 90% of the cases the recurrence show the same or a lower differentiation (438), and in some the recurrence show transformation into an AFS (467). Chen et al. (438) reviewed the available English language literature since 1891 and selected 123 cases of AMF with well-documented follow-up data to evaluate the clinical, pathological, and behavioral aspects of this tumor. The treatment was recorded as conservative (enucleation, curettage, simple excision) or radical (marginal resection, segmental resection, semiresection of the jaw). The treatment mode was detailed in 118 cases. Over 90% (108 cases) of the patients were primarily treated by conservative procedures; 10 patients were treated radically due to the extensive size of the tumor. Recurrence was reported in 41 cases (33.3%). The period of follow-up was stated in 94 cases. The 5-year and 10-year recurrence rate was 41.6% and 69.2%, respectively. Recurrence-free period ranged from 1 month to 96 months, with a mean of 33.2 months. A univariate analysis of all the data showed that only treatment mode of the patients was significantly related to recurrence. The recurrence-free period was significantly longer in patients treated with radical procedures. Malignant transformation was reported in 14 recurrent cases (11.4%). The 5-year and 10-year malignant transformation rate was 10.2% and 22.2%, respectively. The malignant transformation-free period ranged from 9 months to 264 months, with a mean of 79.0 months. In 11 cases, follow-up after the treatment of the malignant tumor was recorded; five patients were alive with no signs of recurrence, the other six cases recurred following surgery. Only one had extensive distal metastasis. Of the six recurrent cases, two died of disease. A statistical analysis of the recorded data showed that only the age of the patient at the first presentation was significantly related to the malignant transformation of AMF. Patients younger than 22 years were unlikely to develop malignant transformation in comparison with patients older than 22 years. It could be argued that the rates of recurrence and malignant transformation were overestimated because such cases are more likely to be documented. However, in two series with more than 10 cases reported, the recurrence rate was 36.4% (440).
and 45.5% (439), respectively, and the rate of malignant transformation in a series of 11 cases was even higher, 18.2%.

It was concluded that it is reasonable to treat patients younger than 22 years by conservative surgeries, and to apply a step-wise treatment principle to patients with multiple recurrences whose age was younger than 22 years. In patients older than 22 years, a radical surgery should be considered when the tumor is massive in size or when the tumor recurred more than once.

2.2 Ameloblastic Fibrodentinoma

Introduction. The AFD is a benign odontogenic tumor consisting of odontogenic ectomesenchyme resembling the dental papilla and epithelial strands and nests resembling dental lamina and enamel organ. Some formation of dentinoid and more rarely tubular dentine is seen in the tumor.

In the 2005 WHO classification of odontogenic tumors the AFD was categorized with the AMF (454); in the 1992 WHO classification it was categorized with the AFOD (23).

Already Gorlin (63) questioned the existence of the AFD as an independent entity, he suspected that many if not all were examples of odontomas prior to enamel formation. Cases have been published, however, with formation of mineralized and unmineralized dentin, which could not be expected to mature as odontomas (462,468–470), including a case of AMF in a six-year-old boy who recurred 21 after surgery as an AFD (440). Gardner (471) required evidence that the AFD had a different biological behavior than the AMF; otherwise their designation as a separate entity was not justified. Philipsen et al. and Reichart and Philipsen reviewed the cases published as AFD and stated that no case of recurrence has been published, a significant difference from the AMF.

The histopathological differences between the cases published as immature dentinoma and AFD has been discussed by Takeda (472).

ICD-O code 9271/0

Synonyms: Dentinoma, immature dentinoma (obsolete)

Clinical Features. The AFD is an exceedingly rare tumor. Reichart and Philipsen (25) reviewed 28 cases, and another 3 cases have been published by Chen (440). Some of the cases reviewed showed clinical and histological features, which differed somewhat from the definition of the lesions, the mesenchymal component being cell-rich, but not embryonic pulp-like (473). Among the 31 cases, 23 were diagnosed in males, and 8 in females, the ratio M:F is 1:0.3. The age ranged from 4 to 63 year, but 90% of the patients were younger than 30 years. Fourteen were found in the first decade (11M + 3F), nine in the second decade (7M + 2F), five in the third decade (4M + 1F), and one female in the fourth decade. Two patients were in the seventh decade, a 60-year-old man (474) and a 63-year-old woman (475). The histology was characteristic in the former case, but atypical in the second.

The majority (74%) of AFDs have been located in the posterior part of the mandible. Seven have been diagnosed in the maxilla (4 anterior, 3 posterior) and 24 in the mandible (1 anterior, 22 posterior, 1 anterior and posterior). Two cases of peripheral AFD have been described (476,477). The histology of the former case did not show typical embryonic pulp-like tissue, it is probably better classified as one of the much more common peripheral odontogenic fibroma with odontogenic epithelium and hard tissue formation. The second one exhibited dental papilla-like connective tissue and tubular dentin; it is likely to be an initial peripheral odontoma.

The AFD has been described as a slow-growing painless tumor, which may become quite large and cause swelling of the jaw (478). Some cases have been associated with unerupted teeth.

Imaging. The AFD has been described as a well-delineated sometimes multilocular radiolucency often with scalloped borders (468,473). Depending on the amount of dentin in the tumor varying degrees of irregular radiopacities may be seen. The size has varied from 1.5 to 6.5 cm in greatest extent. In cases where the tumor is associated with an embedded tooth it is usually located close to the crown of the tooth.

Pathology. The etiology is unknown. The pathogenesis is poorly understood, one case represented the recurrence of an AMF (440). The characteristic histopathological pattern shows an embryonic pulp-like ectomesenchyme with high cellularity in which strands of odontogenic epithelium with bulbous extensions are seen similar to what is seen in an AMF. Various amounts of dentinoid (dysplastic dentin) is seen adjacent to the odontogenic epithelium (Fig. 40). The dentinoid often contains entrapped cells.

Figure 40 Ameloblastic fibrodentinoma. Section of a tumor in the frontal maxillary area of a 9-year-old girl. Strands and islands of odontogenic epithelium in dental papilla-like ectomesenchyme are seen to the left. To the right and near the lower border formation of nontubular dentin is seen with inclusions of cells. No enamel was found in this tumor.
Differential Diagnosis. Many of the considerations discussed in the section on the differential diagnosis of the AMF also apply to the AFD. The main difference is the presence of dysplastic dentin (not just hyalinized areas) and sometimes even tubular dentin in the AFD. In some cases extensive sampling is necessary to find the areas with hard tissue; radiographs of the operation specimen may be helpful. If enamel stroma is found the tumor should be diagnosed as an AFOD. The correct differential diagnosis of the AFD toward the AMF and the AFOD has no therapeutic consequences, but the prognosis seems to differ. A relatively high recurrence rate has been found for AMFs (438), but not for AFD and AFOD, although cases of recurrent AFOD have been reported (480). Since the AFD, which is very rare, shares the ability to form dental hard tissue with the AFOD, and has the same low recurrence rate, it seems more meaningful to categorize the AFD together with the AFOD, as it was done in the WHO 1992 classification of odontogenic tumors (23), than to categorize it with the AMF (454). If the tumor is large and mainly consists of a hypercellular ectomesenchymal component with limited amount of odontogenic epithelium and a few scattered areas with dentinoid, it may be quite aggressive and should be treated like an AMF.

A cell-rich odontogenic fibroma with odontogenic epithelium and formation of hard tissue may be mistaken for an AFD. They occur in different age groups, the odontogenic fibroma contains much more collagen, the hard tissue is generally not in close contact with the epithelium, and the epithelium has a different morphology, it does not form ramifying bilaminar strands with bud formation.

Treatment and Prognosis. Surgical excision is the recommended treatment of AFD, and no recurrences have been reported. The literature is limited, however.

2.3 Ameloblastic Fibro-Odontoma

Introduction. The AFOD is a rare, benign, and noninvasively growing tumor, which almost exclusively occurs in children and young adults. It is composed of all the elements seen in odontogenesis: odontogenic epithelium, embryonic pulp-like ectomesenchyme, dentin, enamel, and now and then cementum. The AFOD is difficult, sometimes impossible to differentiate from an early stage of a large developing odontoma.

ICD-O code 9290/0
Synonyms: Ameloblastic odontoma (obsolete)

Clinical Features. Because a distinction between AFOD and early stages of odontomes has not been made in many previous publications, reviews and surveys often include both categories. The lesions share many biological features, but AFOD is a continuously growing neoplasm, while an odontoma is a hamartoma, which although it may in some cases become monstrous, it will gradually mature into dental hard tissues and stop growing.

The relative frequency of the tumor as diagnosed in material received for histological diagnosis in services of diagnostic pathology in various countries for
various amounts of years ranges from 0.0% to 3.1% in reviews comprising more than 300 samples of odontogenic tumors. In 8 of the 12 reviews the frequency was 1, 3% or lower. The results are indicated as follows: number of odontogenic tumors/number of AFOD/%. Regezzi et al. Michigan, U.S.A. (31): 706/11/1.6%, Günhan et al., Turkey (32): 409/3/0.7%, Daley et al., Canada (33): 392/12/3.1%, Mosqueda-Taylor et al., Mexico (34): 349/3/0.8%, Ochsenius et al., Chile (35): 362/6/1.7%, Adebayo et al., Nigeria (36): 318/1/0.3%, Fernandes et al., Brazil (37): 340/1/0.3%, Ladeinde et al., Nigeria (38): 319/0/0.0%, Buchner et al., California (39): 1088/19/1.7%, Jones et al., England (2006, pooled figures from two studies) (39,40): 523/6/1.1%, Olgac et al., Turkey (41): 527/7/1.3%, and Jing et al., China (42): 1642/4/0.2%. The data are skewed; however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetic or environmental factors.

Less than 100 cases have been published. Filipsson et al. (441) reviewed the literature and included cases reviewed by Slootweg (437), a total of 86 cases were found. If suspected immature odontomas are discarded then the following further cases have been published by Sekine (481), Favia et al. (482), Ozer et al. (483), Yagishita et al. (484), Olgac et al. (485), Fantasia et al. (486), Reichart et al. (487), and Ogli et al. (488).

In the review by Filipsson et al. the age range was found to be 1 to 22 years (N = 86), only one case was older than 20 years; the mean age was 9 years. Cases in patients older than 22 years have been reported, though (480,484). The AFOD was more common in males (54) than in females (37), the ratio M:F was 1.3:1. The majority (54%) of the AFODs were located in the posterior part of the mandible. Thirty cases were diagnosed in the maxilla (12 anterior, 18 posterior, 1 anterior and posterior), 55 tumors were located in the mandible (9 anterior, 46 posterior), the ratio maxilla:mandible was 1:1.8.

The AFOD is usually a painless, slowly growing, expanding tumor. Swelling of the jaw or an unerupted tooth in the area may lead to the diagnosis (440). The size has varied considerably; small ball-shaped tumors with little formation of dentin and enamel are usually impossible to differentiate from immature odontomas, but it has no consequences for the treatment. A considerable amount of the cases published have been quite large. AFOD is an expanding tumor; there is no bony infiltration.

Peripheral AFOD has not been described. Imaging. Radiographically the AFOD presents as a unilocular or multilocular radiolucency with well-defined hyperostotic borders (54,54,440,441). Radiopacities are seen in foci scattered in the lesion (Fig. 41), mainly in the central area (488). If they are small and few, they may not be visible on the radiogram. Tumors that present with a rounded, regular radiopaque center surrounded by a wide ball-shaped or oval radiolucency are likely to be immature odontomas (489). Small ball-shaped lesions located at the occlusal surface of an unerupted molar are almost certain to be immature odontomas. Displaced and impacted teeth may be seen, but root resorption is rarely found (484). In the mandible a tooth is sometimes missing in the area. Large tumors in the maxilla may encroach the maxillary sinus (482). CT scanning reveals details about the borders of larger lesion and facilitates the planning of treatment.

Pathology. The etiology of the tumor is unknown. There are indications, however, of causal relation to genetics. AFODs have been described as part of some rare syndromes. Savage et al. (490) described the simultaneous occurrence of a mandibular AFOD and a maxillary ODTp in a three-year-old boy with the neurocutaneous syndrome encephalophaci cutaneous lipomatosis. Herrmann (491,492) and Schmidseder et al. (493) described a father and his three children who all developed extensive AFODs bilaterally in the maxilla and mandible shortly after birth. The tumors were part of a possibly autosomal-dominant syndrome, which also included esophageal stenosis, pulmonary stenosis and hepatopathy, and other symptoms. It may be argued that the tumors were odontomes since they produced a high amount of dental hard tissues, even with high morphodifferentiation; they contained hundreds of small tooth-like elements (odontoids). Their potential for proliferation and the extension of their destruction of the jaws seems to indicate, however, that they were AFODs.

Macroscopically, the AFOD shows a solid mass with a smooth surface that is white to tan. On the cut surface the mineralized components are seen as granules or hard nodules dependent on the degree of formation of dental hard tissue.

Microscopically the AFOD is dominated by a cell-rich myxoid connective tissue of ectomesenchymal origin. Histomorphologically it is similar to the embryonic dental papilla. Branching strands of...
Oncogenic epithelium are seen in the ectomesenchymal tissue forming buds and more bulbous extensions (Fig. 42). The strands are primarily composed of bilaminar layers of cubic cells. The peripheral layer of the more voluminous extensions consists of palisading cylindrical cells with reversely polarized nuclei, the central cells are stellate; such structures mimic enamel organs at various initial stages (484). This part of the tumor’s morphology is undistinguishable from that of the AMF apart from a higher tendency for formation of enamel organ–like extensions. The surface of the tumor is smooth and sometimes bordered by a thin capsule (484), epithelial nests may be embedded inside the capsule. Scattered in the tumor dentin and enamel is seen, mostly in the central areas, and often as irregular structures (Fig. 43), and only rarely a higher morphodifferentiation in terms of odontoids is seen. The sponge-like structure of dental hard tissue typically seen in an ODTx is only found in minor areas, not as a single large element. In cases of limited dental hard-tissue formation extensive sampling may be necessary; a radiogram of the pathological specimen will facilitate the orientation. Cementum is usually only seen on the root surface of odontoids. The morphodifferentiation of the dentine may vary from dentinoid, a form of dysplastic dentine, which may contain entrapped mesenchymal cells to regular tubular dentine with or without mineralization. Enamel is only seen in contact with mineralized dysplastic or tubular dentine (Fig. 44).

Some AFODs have shown the presence of aggregations of melanophages (494). The AFOD may develop in association with a calcifying cystic odontogenic tumor (CCOT) (495).

Immunohistochemistry. Yamamoto et al. detected CK in the epithelial component of two AFODs by means of KL-1 antibodies, which react with CK-1, CK-2, CK-5-8, CK-11, CK-14, and CK-16-18. To investigate the presence of CK in an AFOD in the mandible of a three-year-old boy Miyauchi et al. (496) used KL-1, PKK-1 (which detects low mw CK-8, CK-18, and CK-19), and monoclonal antibodies against CK-4, CK-7, CK-8, CK-13, CK-13 + 16, CK-14, CK-18, and CK-19. There was no immunoreaction to CK-4, CK-7, and CK-13. The epithelial component showed a strong reaction to CK-16, CK-19, and KL-1 and PKK-1. There was a weak or partially positive reaction to...
CK-8, CK-14, and CK-18. There was no difference between the reaction of the epithelium in the soft tissue areas and in the areas with dental hard-tissue formation.

Nestin, an intermediate filament of the cytoskeleton was detected by Fujita et al. (422) in focal areas of the ectomesenchymal component, particularly near the epithelial elements with a strong activity. Some reaction was also found in the epithelial elements. The localization of nestin showed the same pattern in AMFs, AFDs, AFODs, and odontomas.

Vimentin showed a strong reaction in the ectomesenchymal component of two AFODs investigated by Yamamoto et al. (417). These findings were confirmed by Miyauchi et al. (496) who also detected some immunoreactivity in the basal portion of the peripheral epithelial cells in the areas with soft tissue, but not in areas with formation of dental hard tissue. S-100 protein could not be detected in the tumor cells by Yamamoto et al. (417).

Growth factors were studied by So et al. (136), who used antibodies against the acidic FGF-1, basic FGF-2, and fibroblast growth factor receptors (FGFR2 and FGFR3) on sections from three AFODs and other odontogenic tumors. The staining pattern was similar to that of the AMF. A significant immunoreaction to FGF-2 and FGFR2, but not FGF-1 and FGFR3 was found in the cytoplasm of the epithelial component, and nuclear staining was seen in some epithelial cells sharing interface with the mesenchymal component. The authors concluded that the staining patterns in general were related to odontogenic differentiation rather than pathogenesis.

Mori et al. (70) detected an intense linear bandlike immunostaining of the extracellular matrix protein, tenasin beneath the basement membrane of the odontogenic epithelium in two cases of AFOD. The odontogenic ectomesenchyme showed a weak diffuse staining. No reaction was found in calcified substance. Yamamoto et al. (417) found similar results in two cases of AFOD, but also observed that myxomatoid areas in the ectomesenchyme were negative for tenasin.

The presence of enamel proteins in AFODs has been investigated. Yagishita et al. (484) showed an intracellular immunoreaction to amelogenins exclusively in tumor epithelial cells, namely the cuboidal cells of tooth bud–like projections and the stellate reticulum–like cells inside the epithelial islands. In contrast, no positive staining was discernible in the cytoplasm of the columnar ameloblast-like cells, and there was no evidence for the massive secretion of amelogenins beyond the epithelial-mesenchymal junction into the ectomesenchymal tumor component, except for the restricted sites of enamel and dentinoid formation.

Takata et al. (160) observed an intense staining for enamelysin in immature enamel in four cases of AFOD. The dentine was negative. Neither the slender strands or islands of odontogenic epithelium nor the cellular mesenchymal dental papilla–like component showed immunexpression of enamelysin.

Sheathlin was detected in the areas where inductive hard tissue formation occurred, immature enamel and neighboring ameloblastic cells in four cases of AFOD by Takata et al. (161). Neither the epithelial nor the ectomesenchymal tumor component showed immunexpression of sheathlin.

Yamamoto et al. (417) estimated the number of PCNA-positive cells in two cases of AFOD and compared the findings with those in an AMF. While positive cells were frequent in the latter, very few PCNA-positive cells were found in the AFODs. Sekine et al. (481) used bromodeoxyuridine (BrdU) and PCNA immunohistochemistry to investigate the cell kinetics in case of AFOD. The L.I. for BrdU was 0.9% in the epithelial component and 2.1% in the ectomesenchymal component, for PCNA it was 2.2% and 7.7%, respectively. The authors suggested that the ectomesenchymal component was more proliferative than the epithelial component.

MIB-1 antibody, which recognizes the epitope of the Ki-67 antigen, was used by Sano et al. (463) on sections of two cases of AFOD, two AMFs, and one AFS to calculate the L.I. In the epithelial component of the two AFODs the L.I. was 3.3% and 4.6%, respectively compared with 2.9% in an AMF, 7.5% in a recurrent AMF, and 5.1% in the AFS. In the ectomesenchymal component the L.I. was 1.5% and 1.9% in the two AFODs compared with 2.9% in the AMF, 9.8% in the recurrent AMF, and 13.5% in the AFS. Thus the growth potential of the AFODs was relatively moderate, and the findings suggested that the method is valuable for estimating the aggressiveness in this group of odontogenic tumors.

Electron Microscopy. The ultrastructure of the AFOD was studied by Hanna et al. (497) who found that the ultrastructural features supported the light microscopic observations. The bilaminar epithelial strands consisted of cells with large indented nuclei. Intercellular spaces were found with microvilli that extended from the surface of the cells. Desmosomes were abundant between the cells and hemidesmosomes connected to the basal lamina. The cytoplasm contained few mitochondria and a poorly developed rough, endoplasmatic reticulum and Golgi apparatus. Tonofilaments were seen as dense bundles. In the ectomesenchymal component collagen fibers were randomly distributed, the density varied from area to area. The cells were stellate or elongated with an irregularly shaped nucleus. Mitochondria were obvious, and RER was usually well developed. Some cells displayed few organelles and a poorly developed endoplasmatic reticulum. The ectomesenchymal component seemed to be more active than the epithelial component.

Josephsen et al. (498) essentially confirmed these findings but concentrated on the ultrastructure of the epithelial–mesenchymal interface. The tumor tissue differed from that observed during normal odontogenesis by lacking matrix vesicles like those seen in the early formed predentin. The tumor cells were thus lacking the functional characteristics of developing odonto blasts. Enamel-like tissue was found in relation
to an organic matrix of either a tubular or a fine granular texture. Only the tubular type of matrix was seen in direct contact with the epithelial cells, it was believed that the tubular structures were secretory products of the epithelial cells. Unlike normal odontogenesis focal areas of enamel-like tissue were found without direct contact with dentin and apparently confined within small islands of epithelium.

Other ultrastructural studies have been performed by Slootweg (499), Reich et al. (500), and Reichart et al. (487). Slootweg (499) studied the ultrastructure of five cases of AFOD that lacked formation of tubular dentin. One of the conclusions of the study was that the failure of odontoblasts and preameloblasts to make contact was a consequence of arrest of differentiation of the cells. Reich et al. (500) confirmed the previous findings. Reichart et al. (487) observed a cementoid-like material that revealed a mineralized matrix with formation of tubules reminiscent of dentin tubules.

**Molecular-Genetic Data.** Papagerakis et al. (461) used ISH to study the presence of osteocalcin mRNA and collagen III mRNA in AFOD and other “mixed” odontogenic tumors. Osteocalcin transcripts were found in the peripheral columnar epithelial cells and collagen III transcripts in the ectomesenchymal cells. The findings were confirmed by immunohistochemical studies.

**Differential Diagnosis.** Differentiation toward an ameloblastoma should be easy. The AFOD is noninvasive, shows a cell-rich, embryonic dental papilla–like connective tissue component and presence of dental hard tissues in contrast to the ameloblastoma. More difficult is the differentiation toward the AFD and the AMF, since the AFOD undergoes progressive histo- and morphodifferentiation and therefore at an early stage is histomorphologically undistinguishable from an AMF and later from an AFD. The latter situation has no therapeutical consequences. The AMF, however, has been shown to have a higher tendency to recur (438). It is probable that more AFODs are misdiagnosed as AMFs rather than the converse. As pointed out by Odell et al. (54) extensive well-formed stellate reticulum suggests progression toward hard tissue formation and is sparse in AMF, and the amount of epithelium is higher in an AFOD than in AMF. It is important to include clinical information in the differential diagnosis, a tumor with the features of an AMF in a person older that 22 years is almost certain to be an AMF.

The differentiation toward an immature ODTx is discussed in the section on odontomas.

**Treatment and Prognosis.** Enucleation followed by careful and thorough curettage is the recommended treatment. The tumor usually shells out easily. If an unerupted tooth with eruptive potential is present, it may be spared. A large tumor, which fills out most of the posterior part of the mandible or has destroyed the cortex or has encroached the maxillary sinus may complicate surgery considerably, particularly in small children. Initial conservative treatment should be attempted with close follow-up. In case of recurrence and especially if it shows a lower histodifferentiation, marginal resection should be considered. Recurrence is unusual. Malignant transformation is rare, but has been reported in an 18-year-old woman, a 36-year-old man, and in a 14-year-old girl, respectively (480,501); in the latter case metastases to regional lymph nodes were found.

### 2.4 Odontomas, Complex and Compound

**Introduction.** Odontomas are tumor-like but nonneoplastic developmental anomalies (hamartomas) (15) composed of developed malformed teeth or tooth-like masses. They represent the most highly differentiated neoformations within the group of tumors composed of odontogenic epithelium and odontogenic ectomesenchyme. Two variants are recognized, complex and compound odontoma; the division is made according to the tumor’s degree of morphodifferentiation; the former shows a complex pattern of dentin and enamel, the latter consists of tooth-like structures (odontoides). The distinction is arbitrary; although most odontomas show a preponderance of one of the patterns, many but not all lesions show elements of both patterns.

ICD-O code 9280/0

**2.4.1 Complex Odontoma.** The ODTx is a hamartoma composed of a mass of intermixed enamel, dentin, and sometimes cementum with no morphological resemblance to teeth, either normal or miniaturized (433,502). Some lesions look poorly organized; larger tumors usually have a sponge-like structure.

ICD-O code 9282/0

**Synonym:** Complex composite odontoma

**Clinical Features.** The true prevalence and incidence of the ODTx is not known. The relative frequency has been reported by several authors, but it is obvious that the stimulus to submit an odontoma for histological examination varies considerably from place to place. The relative frequency of the ODTx in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 3.3% to 30.3% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of ODTx/.


The data are skewed; however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetic or environmental factors.

In a review, which included an earlier review by Slootweg (437), Philipson et al. (441) found the age range of 139 ODTx to be 2 to 74 years. The mean age
was 19.9 years. The mean age was somewhat higher in other reviews of larger material, Ochseni et al. (35): 20.8 years (N = 91), Fernandes et al. (37): 22.2 years (N = 52), and Hisatomi et al. (503): 23.0 years (N = 41).

The gender ratio has differed in the reviews published. In six reviews of more than fifty cases of ODTx there was a slight predominance of males in three (37,42,441) and of females in three others (35,41,504). In none of the cases were the differences statistically significant; there seems to be no gender predilection.

The location of the lesion has been studied in several reviews and some have found a predominant occurrence in the maxilla others in the mandible. In four reviews of more than 60 cases the distribution has been the following: Budnick et al. 1976 (505) maxilla:37, mandible: 25; O’Grady et al. (504) maxilla: 39, mandible: 37; Ochseni et al. (35) maxilla: 46, mandible: 40, and Olgu et al. maxilla: 17, mandible: 50. The ODTx may occur anywhere in the tooth-bearing areas of the jaws. In the majority of the reviews it has been revealed that within the maxilla the ODTx occurs primarily in the anterior region, and within the mandible it is most common in the posterior region (34,35,41,503-505).

Extraosseous odontomas are very rare and are more often of the compound type. Some diminutive lesions have been found in operculae as described by Philipson et al. (448). Location of odontomas in the maxillary sinus (506) has been described, and one has been diagnosed in nasopharynx (507). A retrotympanic odontoma has been published (508), as well as a case in the middle ear (509).

Multiple odontomas have been described and often termed odontomatosis (510,511). They present more often as ODTps than as ODTxs.

The growth rate of the ODTx is very slow. Symptoms are usually rare. Pain has been reported in some cases (512,513) but usually in relation to inflammation. Altered pattern of tooth eruption or impaction is a common symptom, which was found in 27 of 41 cases by Hisatomi et al. (503). If the lesion becomes sufficiently large, and some exceeds the size of a walnut, it causes expansion of bone; swelling was found in 19 of 33 cases by Chen et al. (440). In a few cases the odontoma has erupted into the oral cavity (513).

**Imaging.** Depending on the developmental stage and degree of mineralization the radiographic appearance of the ODTx ranges from a radiolucent well-demarcated area, via a radiolucent peripheral zone of variable width with a central core of densely opaque masses to a radiopaque mass of hard dental tissues surrounded by a thin radiolucent zone (514). Some show a pattern of irradiating radiopaque lines caused by the sponge-like architecture of the lesion. The majority of ODTx are diagnosed when they are in a late mature stage. They are often located above an unerupted tooth. Immature stages of large odontomas have been diagnosed as ameloblastic fibro-odontomes in some cases, Clausen (515) case 2, 3, and 4, Pantoja (516), Reich et al. (500), Hawkins (489), and Chen et al. (440) case 17 and 18. Unerupted teeth are a very common finding (517,518), and agenesis of the permanent tooth in the area may be encountered (512,513).

In contrast to odontoma-associated calcifying cystic odontogenic tumor (OaCCOT), resorption of neighboring teeth is a very rare finding.

The size of the tumor varies from a lesion that is only detectable in the microscope (519) to one that is 7 to 8 cm at the longest diameter (520–523). Amado-Cuesta et al. measured the size of 23 ODTx; the range of size at longest diameter was 10 to 60 mm (513).

**Pathology.** The etiology of the ODTx is unknown, but there are strong indications that genetic influence is an important etiological cofactor. Some laboratory animal strains develop odontoma-like lesions, and odontomas occur as part of Gardner’s syndrome (524) and other hereditary syndromes (525,528).

The tumor is primarily found in children and young adults and is believed to arise in remnant of odontogenic epithelium in the jaws from the dental lamina and from proliferations of odontogenic epithelium and ectomesenchyme close to the outer enamel epithelium in a dental sac (17) as it is seen in operculae (448,519).

Macroscopically the mature ODTx is covered with a smooth, white fibrous capsule, which veils the rounded and lobulated contour of the hard substance. If the soft tissue is removed the sponge-like architecture of the ODTx is clearly seen (Fig. 45). An immature odontoma is covered by a thick layer of soft tissue and a thin fibrous capsule at the periphery.

Histologically, the ODTx has a sponge-like architecture. The skeleton of the “sponge” is composed of thin tortuous walls of dentin, which irradiate from the center from which the ODTx started to grow (Fig. 46).
The walls of dentin contain a central pulpal space, which is slit formed and contains dental pulp-like ectomesenchyme. The walls are separated by narrow tortuous spaces, and enamel is formed on the surface of the walls, and in these spaces enamel epithelium, active or reduced is seen, and connective tissue with vessels are found (Fig. 47). At the periphery of the tumor various amount of soft tissue is observed depending on the developmental stage of the ODTx (Fig. 48). This tissue resembles the tissue of an AMF, but the strands of epithelium show a more organized pattern and can in some places be followed down in the ectomesenchyme in the clefts between the dentin walls. At the surface of the lesion a thin capsule of connective tissue is seen. It is difficult to envision this pattern from the study of two-dimensional histological sections. Only in areas where the clefts are cut longitudinally is the structure evident. In cross or tangentially cut areas the lesion presents as a mass of primarily tubular dentin with numerous oval or circular “holes,” some of which contain pulpal connective tissue (Fig. 49), while others show a coat of enamel on the surface of the dentin and contain enamel organ-like epithelium and strands of connective tissue with vessels in the center. If the ODTx is studied after decalcification—which is usually the case—empty spaces or enamel matrix is seen instead of enamel. Areas with tooth-like shapes, where the dentin has formed a root-like structure, which embraces a pulpal tissue and is covered by a crescent cap of enamel may be found mixed with the typical structure of the ODTx. Some odontomas show a less developed structure and present with a more irregular structure. The histology shows numerous variable details, areas of dentinoid (528,529) and dysplastic enamel (530,531) is usually found. Cementum is sparse in an ODTx, if tooth-like structures are seen it is found on the surface of the roots of these, but it may also be seen in
nontooth-like areas on the surface of the dentin where it is not covered by enamel. At the periphery of the hard tissue part of the lesion dentin and enamel may still be formed and the histological, but not morphological patterns, which characterize the normal odontogenesis are found. In the soft tissue in the clefts near the center of the lesion where enamel formation is completed reduced enamel epithelium is seen often with calcifications. Ghost cells may be found (532,533); Sedano et al. (534) detected ghost cells in 8 of 44 ODTx. Several authors reported ghost cells to be more common in complex than in ODTps, but Tanaka et al. (535) found ghost cells in 78.8% of 52 ODTps and in 29.4% of 17 ODTxs. If the odontoma has developed associated with a CCOT, it is located in the wall of a cyst covered with the epithelium, which shows the characteristics for that lesion. Sometimes hyaline deposits (536), or amyloid-like material as seen in the CEOT or small duct-like structures similar to those in the AOT are seen.

2.4.2 Compound Odontoma. The ODTp is a hamartoma composed of varying numbers of tooth-like elements (odontoides) (537).

ICD-O code 9281/0
Synonyms: Compound composite odontoma.

Clinical Features. The prevalence and incidences of the ODTp is not known. It is well-known fact that they are often diagnosed macroscopically by the oral surgeon and not submitted for histological examination or only the surrounding dental sac-like soft tissue is submitted.

The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 1.2% to 36.7% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of ODTp/\%.

Regezzi et al., Michigan, U.S.A. (31): 706/37/36.7%, Günhan et al., Turkey (32): 409/36/8.9%, Daley et al., Canada (33): 392/128/32.7%, Mosqueda-Taylor et al., Mexico (34): 333/63/18.9%, Ochsenerius et al., Chile (35): 362/71/19.6%, Fernandes et al., Brazil (37): 340/33/9.7%, Jones et al., England (2006, pooled figures from two studies) (39,40): 523/91/17.4%, Olga et al., Turkey (41): 527/42/8.0%, and Jing et al., China (42): 1642/20/1.2%. The discrepancies in the figures are most likely due to a variation in incentive to submit the lesion for microscopy.

In a review, which included an earlier review by Slootweg (437), Philipsen et al. (441) found the age range of 143 ODTp to be 6 months to 73 years. The mean age at time of diagnosis was 17.2 years. The mean age was about the same in a review by Ochsenerius et al. (35): 17.0 years (N = 71), but somewhat higher in two other studies Hisatomi et al. (503): 19.9 years (N = 62), and Fernandes et al. (37): 20.5 years (N = 33).

The gender ratio, males:females in three reviews of more than 50 cases has been almost 1:1, Philipsen et al.: 73:67 (N = 140), Hisatomi et al.: 33:29 (N = 62), and Ochsenerius et al.: 35:36 (N = 71). If the two studies by Jones et al. (39,40) are pooled, however the gender ratio was M:F = 39:51 (N = 91). In several reviews of smaller material the occurrence was equal in the two genders; so it is doubtful whether any difference exists.

The location of the ODTp has been studied in several reviews, and in all studies a predominant occurrence in the maxilla was found. In four reviews of more than 60 cases the distribution has been the following: Budnick et al. (505) maxilla: 48, mandible: 17; Mosqueda-Taylor et al. (34) maxilla: 46, mandible: 17; Ochsenerius et al. (35) maxilla: 48, mandible: 22; and Hisatomo et al. (503) maxilla: 32, mandible: 30. The ODTp may occur anywhere in the tooth-bearing regions of the jaws. In the majority of the reviews it has been revealed that within the maxilla the ODTp occurs primarily in the anterior region, and within the mandible it is most common in the anterior region as well (32,34,35,37,41,440,503–505).

Peripheral odontomas are very rare, but has been reported by Castro et al. (538) and Ledesma-Montes (539).

Multiple ODTps have been reported (510,511, 540–543), and have sometimes been termed odontomatosis. In the majority of cases they have been part of a syndrome.

The growth rate is slow and symptoms are rare, most compound odontomes are mature when they are diagnosed. Jacobs (544) reported five cases of ODTp in the mandible in three males and two females within an age range of 12 to 15.5 years. In all cases it was possible to retrieve previous orthopantograms taken at a time where there was no sign of the odontome. The radiograms were taken approximately 2, 3, 4, 5, and 5.5 years earlier. Although it was not possible to measure the exact time for the development of the odontomas, one of the cases suggested that an ODTp
may grow from a size where it is invisible on the radiogram to a size of about 1 cm at the longest diameter in less than two years. In all cases the patients reached the late mixed dentition stage before the lesions were diagnosed.

Clinical symptoms are similar to those of the ODTx, and in many reviews no subdivision of the odontomes has been made. In four studies the number of impacted teeth was considerably higher in the ODTp group than in the ODTx group (440,503, 512,517). Swelling and pain is less common in the ODTp variant (440).

In rare cases the ODTp may erupt into the oral cavity (545).

Imaging. Radiographically the ODTp presents as a densely opaque mass of small tooth-like structures (odontoides) surrounded by a narrow radiolucent rim within a hyperostotic linear border (Fig. 50). The odontoides are not always recognizable on the radiogram. Smaller ODTp may be situated between the roots of erupted teeth. Unerupted teeth are often seen; in a review of 62 cases of ODTp, Hisatomo et al. (503) found an unerupted tooth in 49 cases, a missing tooth in the region in five cases, and a supernumerary tooth in two cases. Resorption of neighboring roots was not seen. ODTp is almost never diagnosed at an immature stage (537).

Pathology. The etiology of the ODTp is unknown, but like the ODTx there are strong indications that genetic influence is an important etiological cofactor. Hereditary cases have been published (493,525).

The ODTp is primarily found in children and young adults and is believed to arise in remnant of odontogenic epithelium in the jaws from the dental lamina and from proliferations of odontogenic epithelium and ectomesenchyme close to the outer enamel epithelium in a dental sac (17), as it is seen in operculae (448,519). The tumors develop primarily in the odontogenic period (544), and it is likely that lesions diagnosed later in life have been present in the jaws for many years because of lack of symptoms.

Macroscopically the tumor presents as a number of miniature and/or misshapen teeth (odontoides), which may be fused into larger masses. They are all found within a single dental sac, which is thin if the ODTp has matured (Fig. 51). In most cases the final diagnosis can be made on the basis of macroscopic examination. The size and number of odontoides varies considerably, in a case reported by de Visscher (546) 112 odontoides were counted. The odontoides may be drop-shaped, irregular, or resemble a normal tooth; they rarely exhibit more than one root. The differentiation between an ODTp and supernumerary teeth is arbitrary, more than two odontoides within the same dental sac is usually considered an ODTp. Not all the elements in an ODTp are necessarily tooth-shaped; a few or many may be irregular and resemble the elements of an ODTx.

Sections of immature, developing ODTps show several dysmorphic tooth germs in a loosely textured connective tissue with cords and islands of odontogenic epithelium (22,537,547). Much of the enamel matrix is preserved in spite of decalcification.

2.4.3 Complex and Compound Odontomas.

Immunohistochemistry. In some of the immunohistochemical studies it has not been stated which type of odontomas was studied. Apparently no difference in immunoreaction has been found in the two types of odontomas.

Keratins were studied by Crevelini et al. (66) in three compound odontomes using monoclonal antibodies against CK-7, CK-8, CK-10, CK-13, CK-14, CK-18, and CK-19. Only CK-7 and CK-14 were detected. CK-7 and CK-14 were found in parts of the
epithelial strands and in stellate reticulum. CK-14 was negative in secretory ameloblasts. Also antibodies against vimentin was used, but with negative result.

Fujita et al. (422) studied the presence of nestin in 22 ODTx and 40 ODTps. Nestin is an intermediate filament of the cytoskeleton. Immunoreactivity was found in the odontoblasts adjacent to the dentin matrix, particularly in the compound odontomes. The dentinal fibers in the tubules of the dentin also showed immunoreactivity, and the pulp cells adjacent to the odontoblasts were positive in some cases. In ODTxs sparse flat cells adhering to the dentin and their processes were positive. A positive reaction was found in 16 of the ODTx and in 33 of the ODTps.

Growth factors were studied by So et al. (136), who used antibodies against the acidic FGF-1, basic FGF-2, and fibroblast growth factor receptors (FGFR2 and FGFR3) on sections from three AFODs and other odontogenic tumors. The staining pattern was similar to that of the AFOD. A significant immunoreaction to FGF-2 and FGFR2, but not FGF-1 and FGFR3 was found in the cytoplasm of the epithelial component and nuclear staining was seen in some epithelial cells sharing interface with the mesenchymal component. An intense staining for FGF-1 was found in ameloblasts. The authors concluded that the staining patterns in general were related to odontogenic differentiation rather than pathogenesis.

Tenascin, an extracellular matrix protein was detected in five ODTps by Mori et al. (70). A strong positive immunoreactivity was found in condensed connective tissue fibers, and was markedly concentrated in pulp-like tissue and odontoblasts, as well as in unmineralized dentinoid. No reactivity was found in calcified material.

The immunoreactivity to BMPs was investigated in two ODTps by Gao et al. (168). The reaction pattern was similar to that of normal tooth germs. Odontogenic epithelium including ameloblasts showed a strong positive reactivity. Predentin and odontoblast-like cells showed a weak positive reaction. Calcified material and dental pulp was negative. Fibrous tissue around the tooth-like structures was positive.

Enamel proteins have been studied. A strong expression for amelogenin was found in the enamel matrices in ODTxs by Abiko et al. (548). Well-calcified materials, such as enamel-, dentin-, and cementum-like structures did not show a positive reaction.

Takata et al. (160) found a strong positive reaction for enamelysin in immature enamel in odontomes, whereas dentinoid, dentin, and cementum as well as pulp tissue were devoid of immunoreactivity. Ameloblasts adjacent to enamel matrix showed moderate immunoreactivity. Ghost cells were found in some of the odontomes, and some of them were positive, especially in the periphery of clusters of ghost cells.

The presence of sheathlin was studied in 10 odontomas by Takata et al. (161). Immature enamel was strongly positive; dentin, cementum, and pulpal tissue were devoid of immunoreactivity. Cementum deposits on the surface of sheathlin-positive enamel were a common finding.

Tanaka et al. (535) used antibodies against human hair protein, β-catenin and lymphoid enhancer factor 1 (Lef-1) to study the presence of ghost cells, and the Wnt signaling pathway in 96 cases of odontomas, 17 complex and 52 compound. ODTps (78.8%) showed a higher incidence of ghost cells than ODTxs (29.4%). Human hair proteins are composed of hard keratins and matrix proteins, and it is believed that odontoma is a hard keratin-expressing tumor-like lesion, and that the Wnt-signaling pathway may be involved in the formation of ghost cells in odontomas.

Papagerakis et al. (461) studied late phenotype markers of ameloblasts and odontoblasts, such as amelogenin, keratins, collagen types III and IV, vimentin, fibronectin, osteonectin, and osteocalcin in odontomas and other odontogenic tumors. The patterns found in ODTxs showed similarities to those found in normal developing teeth. The authors suggested that the epithelial cells in the lesion are recapitulating genetic programs expressed during normal odontogenesis, but exhibit abnormal expression patterns for these genes.

Electron Microscopy. Sapp et al. (549) studied the ultrastructure of calcifications in COCs and odontomas, and found that spherical calcifications in the two lesions had a different ultrastructure although they appear similar in the light microscope. The epithelial cells in odontomas were separated from the calcifications by a basement membrane exhibiting a prominent lamina densa and lamina lucida and containing hemidesmosomes. In the peripheral cytoplasm of epithelial cells adjacent to calcifications prominent microvesicular activity was seen.

Marchetti et al. (531) investigated the enamel of decalcified samples of ODTxs using light microscopy and transmission electron microscopy and undecalcified samples using transmission electron microscopy. Simultaneous presence of prismatic enamel at varying maturing stages with different structural characteristics was observed. In some sites, the enamel did not present a prismatic structure, but appeared as clusters of unstructured material with abundant organic component.

Molecular-Genetic Data. No data are available.

Differential Diagnosis. As it is the case with any intrabony jaw lesion it is important that the pathologist gets access to the radiograms or other imaging of the tumor. The features of the border, the shape and the structure of the lesion often reveal important information. Differential diagnosis between odontoma and an ameloblastoma, even in cases of an immature odontoma dominated by soft tissue,
should not be difficult. The presence of dental hard tissues and a dental papilla–like connective tissue instead of a mature fibrous stroma excludes an ameloblastoma. If the epithelium of the odontoma is inflamed, in some areas a proliferation of the epithelium may be seen, which show some similarity to that of an ameloblastoma, but lacks stellate reticulum-like cells and the elongated peripheral cells with reverse nuclear polarity.

If the odontoma-like structure, complex or (more often) compound, is seen in the wall of a cyst, which exhibits the histomorphology of a COC, it should be classified as an OaCCOT.

Odontoma-like structures are seen in the exceedingly rare O-A. In the solid type of that tumor the dental hard tissue is found in minor areas scattered in the tumor. In the unicystic type of the tumor it is found in enclaves in various locations in the cyst wall in relation to dental papilla–like ectomesenchyme and dental lamina–like epithelium. The remaining part of the cyst is covered by an ameloblastoma-like epithelium, which, however, may exhibit many biminar epithelial strands, which are not usually seen in ameloblastomas.

The most difficult diagnostic problem is to distinguish an immature odontoma from AFOD, AFD, and AFOD. Initially the odontoma shows a histomorphology similar to that of an AFM (514). At a later stage the dental hard tissues have been formed and in cases where the lesion, particularly in a case of developing ODTx, is surrounded by a thick coat of soft tumor tissue, the differential diagnosis towards an AFOD may be difficult or even impossible. As indicated by Odell et al. (54) factors favoring one of the odontomas are a young (child) patient, a well-defined, often ball-shaped, unilocular lesion and a site overlying an unerupted tooth or replacing a tooth. Factors favoring AMF are a slightly older child or young adult, particularly if the patient is older than 22 years, and a multilocular lesion with progressive growth and displacement of teeth. The differential diagnosis between an AFOD and a large immature ODTx is particularly difficult. Factors favoring the AFOD are an irregularly shaped lesion with minor areas of irregularly shaped dental hard tissue scattered in the tumor, and indication of progressive growth. Factors favoring an immature odontoma are an oval or ball-shaped lesion, which contains a single mass of hard dental tissue in the center with irradiating radiopaque lines and is related to the occlusal surface of an impacted tooth. The irradiating structure is recognized in the microscope, as described above. Mature odontomas should not cause diagnostic problems; the ODTp in particular is often diagnosed macroscopically. The differentiation toward supernumerary teeth is arbitrary, more than two odontoides within the same dental sac is usually considered a ODTp. In the rare cases of multiple odontomas, and they are most often of the compound type, there is a high possibility that the odontomas are part of a syndrome.

**Treatment and Prognosis.** Conservative enucleation is adequate treatment for both types of odontomes, they usually cleave easily from the smooth surface of the bony cavity in which they are situated. The prognosis is excellent. Large odontomes may require special surgical considerations (550). Very often an impacted tooth is found below the odontome and in a large number of cases it is possible to save the tooth and bring it in situ by orthodontic management (551). Morning (517) reported follow-up of 42 cases of impacted teeth in relation to odontomas. The morphology of the impacted tooth was normal in 62% (26/42), in the remaining cases there was some root deviation. After removal of the odontoma the impacted tooth erupted in 45% (19/42) of the cases, 77% (13/17) of the remaining teeth erupted after a second operation. Overall, about three out of four of the impacted teeth erupted after removal of the odontoma. Recurrences are very rare and are probably only seen in cases of incomplete removal of immature odontomes (552,553).

2.5 Odonto-Ameloblastoma

**Introduction.** This rare composite tumor includes areas that resemble an ameloblastoma together with areas that correspond to AFOD or an immature odontoma (381,554).

ICD-O code 9311/0

Synonyms: Ameloblastic odontoma

**Clinical Features.** Little more than 12 cases of O-A have been published with sufficient documentation to prove that the description of the tumor complies with the diagnostic criteria suggested by the WHO working group (554). Epidemiological data are thus unavailable. Among 13 well-documented cases (417,555–562) [including two unpublished cases, IRC-226 and IRC-296 distributed by the International Reference Centre to Collaborating Centres for preparation of the first WHO classification of odontogenic tumors (22)] 4 were diagnosed in females and 9 in males. Age range was 2 to 53 years; mean age: 19.3 years; median age: 15 years. Three of the patients were in the first decade, six in the second, two were 25 years old, and one was 42, and one, 53 years old.

In six cases the tumor was located in the maxilla, and in seven cases, in the mandible. The anterior region was involved in one case, the anterior and posterior in one case, the remaining tumors were located posterior to the canine area, and some involved the mandibular ramus.

The size has varied from 1.5 to 7 to 8 cm at longest diameter; most have been large—between 4 and 6 cm at longest diameter.

The growth rate is difficult to estimate because of paucity of symptoms. A few patients have indicated pain and soreness, but in the majority of cases enlargement of the jaw caused by bony expansion has been the only symptom. Most patients have noticed the swelling for two to four months. In a few cases,
however, it has been possible to trace the lesion almost from the beginning, and the growth rate seems to be slow; the large lesions have existed for several years.

**Imaging.** Radiographically, the O-A has appeared as a unilocular radiolucency with a well-defined corticated margin unlike the conventional ameloblastoma. Often the lesion is less well demarcated in some areas, though. In some cases the dental hard tissue formed in the tumor has been so discrete that it is was undetectable on the radiogram. In most cases the lesion presented itself as a large radiolucent lesion with minor irregular radiopacities in the center or along the periphery. A few O-As showed abundant irregular radiopaque masses surrounded by a radiolucent zone. No “honeycombing” pattern as seen in ameloblastomas has been described. Better than radiograms, CT scans give detailed information about the border of the tumor.

Displacement of teeth has been observed in several cases (555,557,562), as well as resorption of roots of adjacent teeth (558,562,561).

**Pathology.** The etiology of the O-A is unknown. The most likely sources of tumor development are residues of the dental lamina and proliferations of odontogenic epithelium and ectomesenchyme adjacent to reduced enamel epithelium of unerupted teeth.

In six cases the removed specimen was a cystic lesion (Fig. 52) with a marked thickening of the wall and proliferation of tumor epithelium in various areas of the wall (555,557,558,560,561), including case ICR 226 contributed to the International Reference Center by Dr. Ishikawa, Tokyo, and illustrated in Figures 37 and 38, in the first WHO classification of odontogenic tumors by Pindborg and Kramer (22). It was a tumor in the left side of the mandible in a 13-year-old boy; it had been known for 10 years. In other cases an abundant amount of hard tissues has been more dominating.

Microscopically, the tumor consists of an ameloblastoma component admixed with an AFOD/immature odontoma component (555,557,561,562). Areas that are indistinguishable from ameloblastoma are seen (Fig. 53), demonstrating follicular and in particular plexiform growth pattern of odontogenic epithelium in a fibrous connective tissue stroma. In other areas several O-As have shown a different odontogenic epithelium, which looks somewhat like a plexiform ameloblastoma, but the strands are long and narrow (Fig. 54) and consist of only two layers of basal cells without stellate reticulum cells between them. The strands form loops and are intermingled with plates of epithelium consisting of small cells with sparse cytoplasm and round nuclei. These cells form “ball of yarn”-like nodules within the sheets. The pattern is very similar to that seen as part of the histomorphology of an AOT and is well illustrated by Matsumoto et al. (561) in Figures 2 and 4 and Jacobsohn et al. (557) in Figure 5. Groups of ghost cells may be encountered particularly in areas where dental hard tissue is seen. The dental hard tissue forming areas are in close contact with areas with ameloblastoma and AOT morphology (Fig. 55). They may be a minor or a more dominant part of the tumor. They show the pattern of an immature, complex (560) or, more often, compound odontoma with formation of many tooth-like elements (odontoids) (555,557,559). Sometimes only dentin and no enamel had been found (558,560,561). The soft tissue part involved in the formation of hard tissue has a morphology similar to that of an ameloblastoma.
to that found in an immature odontoma, and in some cases it is seen in such quantities compared with the hard tissue that it simulates an AFOD. Groups of ghost cells may be seen in several areas, particularly where the dental hard tissue is found (Fig. 55). In several of the cases consisting of one large cyst with proliferation of tumor tissue in various locations in the cystic wall, the border between the fibrous part of the cystic wall and the surrounding bone was well defined (555,557,558,560,561).

**Immunohistochemistry.** Only a single study has been published (417). The dental lamina–like epithelium in the soft part of the dental hard tissue forming areas reacted strongly to KL-1, a monoclonal marker for CKs-1, CK-2, CK-5-8, CK-11, CK-14, and CK-16-18 (563). The stellate reticulum-like epithelium reacted more weakly. The immature dental papilla–like ectomesenchyme around this epithelium was positive for tenascin and vimentin, while mesenchymal tissue showing myxomatous changes, and fibrous connective tissue was negative for tenascin, S-100 protein, and PCNA. A moderate amount of PCNA-positive cells were found in the dental lamina–like epithelium.

**Electron Microscopy.** No data have been published.

**Molecular-Genetic Data.** No data have been published.

**Differential Diagnosis.** Some authors (564) have found it impossible to distinguish between O-A and AFODs, but they concentrated primarily on clinical features. The diagnosis O-A should only be used for odontogenic tumors showing combined features of ameloblastoma and those of an immature odontoma or AFOD. Areas with loop-forming basal cell strands of epithelium and nodules with a swirling pattern like those seen as a part of the morphology of an AOT are also an important histomorphological hallmark. Such areas and those with ameloblastoma morphology are not seen in ameloblastic fibro-odontomes, which are the most important differential diagnosis.

**Treatment and Prognosis.** Most of the published cases were treated by curettage (417,555–562). In those with a unicystic appearance the tumor is found in a cavity with smooth walls. In one case hemimaxillectomy was done (558), other cases were treated by wide surgical resection and en-bloc resection (562). Follow-up for five years or longer has unfortunately only been reported in one case (555). The patient’s lesion appeared cystic and was treated by curettage; it recurred twice and both times as an ameloblastoma. The second time it was treated by en-bloc resection; the reported follow-up there after was only for 1 and a half years. Since the lesion possess the biological potential of an ameloblastoma, and recurrences have been reported after local curettage alone (555,565,561) the recommended treatment is excision in form of a marginal or bloc resection with long-term (at least 15 years) follow-up (381).

### 2.6 Odontogenic Ghost Cell Lesions

The term-odontogenic ghost cell lesions embraces a heterogeneous group of odontogenic lesions that histopathologically are cysts, solid benign neoplasms, solid malignant neoplasms, or a combination of these. They may be intraosseous or extraosseous. They share cytological and histomorphological features in terms of an epithelium, which is histomorphologically similar to that seen in s/mAM and UNAMs, but in contrast with ameloblastomas they show a conspicuous presence of ghost cells with tendency for calcification and...
they show formation of dentinoid (dysplastic dentin) in the juxtaepithelial connective tissue.

Although cases of odontogenic ghost cell lesions had been published under various titles since 1932 by Rywkin (566), Boss (567), Spirgi (568), and Lurie (569), it was not until 1962 that the lesion was recognized as a new entity by Gorlin et al. (570). It was described on the basis of 11 own cases and 4 from the literature. They were all cystic lesions; one of them was associated with an ODTx. The authors stressed their peculiar histological features that distinguish them from the CEOTs for which they were often mistaken. The similarities to the cutaneous calcifying epithelioma of Malherbe (pilomatrixoma) were also drawn attention to. For the lesion, the name “calcifying odontogenic cyst (COC)” was chosen, at least until its nature is clarified.

Further cases were published in the following years by Gold (571), Gorlin et al. (572), Abrams et al. (573), Chaves (574), Jones et al. (575), Ulmanský et al. (576), and Fejerskov et al. (577) among others. It became apparent that not all the COCs are cystic. The two cases published by Fejerskov et al. were a solid extraosseous tumor in the palatal gingiva and an intraosseous cystic lesion associated with an odontoma. The authors suggested that the name of the lesion be changed to “calcifying ghost cell odontogenic tumor.”

The COC was recognized in the first WHO classification of Odontogenic Tumours and Cysts (22) as a cystic nonneoplastic lesion, but classified among the benign odontogenic tumors. A malignant variant was recognized and illustrated in Figure 7.4 in the book as a carcinoma arising in a COC. The microphoto was taken from a case (IRC 58) contributed to the WHO International Reference Center for classification of Odontogenic Tumours by Dr. J. N. Astacio, El Salvador; it had been published in 1965 as a CEOT (578).

In the 1992 revision of the WHO classification (23) the COC was still classified among the benign odontogenic tumors. The contradictory term “nonneoplastic” was deleted. As pointed out by Li et al. (579), this classification implied that all COCs are neoplastic in nature, even though the majority may appear cystic and nonneoplastic. It was mentioned in the text of the classification that solid tumors had been described and termed “dentinogenic ghost cell tumor” (580) and “odontogenic ghost cell tumor” (581,582), but COC was still used as the general term to include all cystic and benign neoplastic variants. Consequently the term “calcifying odontogenic cyst” has been used in a number of publications in the last four decades as a common term to describe all the various variants of odontogenic ghost cell lesions (583–592), including two extensive reviews of the literature by Buchner et al. (593,594).

Pretorius et al. (580) suggested a classification, which classified cysts and neoplasms as two different entities. Hong et al. (582) studied 92 cases of COC from the files of Armed Forces Institute of Pathology (AFIP), Washington, DC, U.S.A., and found many variants that did not fit into the classification of Pretorius et al.; they suggested a classification with a main division in cystic and neoplastic lesions but with a more elaborated subdivision. Buchner et al. (594) in a review of 215 intraosseous cases from the literature suggested a classification with a main division of the lesions into intraosseous and intraosseous lesions and a subdivision into cystic and neoplastic lesions. Toida (595) reviewed the published classifications and suggested a classification dividing the lesions into cysts, neoplasms (benign and malignant), and combined lesions. In a study of 21 cases of odontogenic ghost cell lesions Li et al. (579) reviewed earlier classifications and suggested a revision. They divided the lesions into three groups: (i) developmental odontogenic cysts, (ii) benign odontogenic neoplasms, and (iii) odontogenic carcinomas (odontogenic ghost cell carcinoma). In the cyst group they placed the cystic COC with or without odontoma. The benign odontogenic neoplasm group was divided into odontogenic ghost cell tumor and combined lesions.

In the WHO classification of head and neck tumors published in 2005 (12), the benign and the malignant neoplasm was recognized as entities and named “dentinogenic ghost cell tumour” (596) and “ghost cell odontogenic carcinoma” (597), respectively. Cysts were excluded from the classification a priori, but with a view to the neoplastic potential of some COCs, the simple cysts and the cysts with a neoplastic potential were grouped together under the term “calcifying cystic odontogenic tumour” (598).

There are many good reasons (579), however, to keep the simple cysts separated from the cysts associated with odontomas or benign odontogenic neoplasms since many cystic lesions are nonneoplastic. It is therefore suggested to revise the classification of Toida and Li et al., as indicated in Table 4, where the terms accepted by WHO have been used and the lesions have been separated into simple cysts, combined lesions, benign neoplasms, and malignant neoplasms.

### Table 4 Suggested Classification of Odontogenic Ghost Cell Lesions

<table>
<thead>
<tr>
<th>Group 1. “Simple” cysts with or without limited proliferation of odontogenic epithelium in the cyst wall: Calcifying odontogenic cyst (COC)</th>
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<tbody>
<tr>
<td>Calcifying cystic odontogenic tumor (CCOT)</td>
</tr>
<tr>
<td>The following combinations have been published:</td>
</tr>
<tr>
<td>Solid/multicystic ameloblastoma associated CCOT</td>
</tr>
<tr>
<td>Unicystic ameloblastoma associated CCOT</td>
</tr>
<tr>
<td>Adenomatoid odontogenic tumor associated CCOT</td>
</tr>
<tr>
<td>Ameloblastic fibroma associated CCOT</td>
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<tr>
<td>Ameloblastic fibro-odontoma associated CCOT</td>
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<td>Odontoameloblastoma associated CCOT</td>
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<td>Odontoma associated CCOT</td>
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<td>Odontogenic myxofibroma associated CCOT</td>
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<table>
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<tr>
<th>Group 2. Cysts associated with odontogenic hamartomas or benign neoplasms:</th>
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<tr>
<td>Calcifying cystic odontogenic tumor (CCOT)</td>
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<tr>
<td>Odontogenic myxofibroma associated CCOT</td>
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<tr>
<td>Odontogenic fibro-odontoma associated CCOT</td>
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<td>Odontoameloblastoma associated CCOT</td>
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<td>Odontoma associated CCOT</td>
</tr>
<tr>
<td>Odontogenic myxofibroma associated CCOT</td>
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<tr>
<th>Group 3. Solid benign odontogenic neoplasms with similar cell morphology to that in the COC, and with dentinoid formation:</th>
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<tbody>
<tr>
<td>Dentinogenic ghost cell tumor (DGCT)</td>
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<tr>
<th>Group 4. Malignant odontogenic neoplasms with features similar to those of the dentinogenic ghost cell tumor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghost cell odontogenic carcinoma (GCOC)</td>
</tr>
</tbody>
</table>
neoplasms. This classification has served as a basis for the description of the various entities in the following.

2.6.1 Calcifying Odontogenic Cyst

Introduction. The COC is a developmental cyst with a particular epithelial lining that resembles the lining of a UNAM with a basal layer of columnar cells, and an overlying layer that resembles a stellate reticulum. Groups of epithelial ghost cells are seen in the epithelial lining or in the epithelial strands and islands in the fibrous capsule. Dysplastic dentin is often laid down adjacent to the basal layer of the cystic lining or of the epithelial islands in the capsule.

Synonyms: Calcifying ghost cell odontogenic cyst, which may be a more precise term, but the term “calcifying odontogenic cyst” has been generally accepted for several decenniums.

Clinical Features. The prevalence and incidence of COC is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 1.0% to 7.2% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of COCs/%. Regezzi et al., Michigan, U.S.A. (31): 706/15/2.1%, Günhan et al., Turkey (32): 409/4/1.0%, Daley et al., Canada (33): 392/18/4.6%, Mosqueda-Taylor et al., Mexico (34): 349/24/6.8%, Oschnerius et al., Chile (35): 362/26/7.2%, Adebayo et al., Nigeria (36): 318/8/2.5%, Fernandes et al., Brazil (37): 228/12/3.5%, Ladeinde et al., Nigeria (38): 319/17/5.3%, Buchner et al., California (30): 1088/17/1.6%, Jones et al., England (2006, pooled figures from two studies) (39,40): 523/21/4.0%, Olgaç et al., Turkey (41): 527/29/5.5%, and Jing et al., China (42): 1642/36/2.2%. All these studies suffer from the bias that all COCs with epithelial proliferations in the cyst wall (31) have been pooled together. In all these series, however, the “simple” cyst, COC has accounted for the majority of cases. The percentage has been counted as the percent of ODOTs with an epithelial lining or of the epithelial islands in the capsule.

Shear (228) reported that only 30 examples accessioned as COCs were recorded in the archives of the University of the Witwatersrand, Department of Oral Pathology, South Africa, representing 0.9% of 3498 jaw cysts documented during the period 1958 to 2004 (46 years).

The age distribution of the COC is difficult to assess, again because other types of ghost cell lesions have been included in the surveys published. The OaCCOTs occur primarily in the second decennium and are very rare in patients older than 40 years. When this group is included, the age peak is moved markedly toward the younger age groups.

The line graph of ages of patients with COC without epithelial proliferations in the cyst wall (N = 35) in the study by Hong et al. (582) showed an age peak in the second and the eighth decade, the graph for COCs with epithelial proliferations in the cyst wall (N = 17) showed an even distribution over all decades. The mean age for all cystic variants was 33 years. In the review by Buchner (594) of 144 published cases of COC the age range was 5 to 82 years, 50 cases occurred in the second and 25 cases in the third decennium, making up 52% of the cases.

The COC does not seem to have any gender predilection. In a review of 88 published cases Shear et al. (228) reported a gender distribution of 44 COCs in men and 44 in women. In Buchner’s survey 105 patients were men and 110 women, but in the study by Hong et al., 47 were men and 31 women. These surveys all contain some cases, which are not simple cystic.

There seem to be an equal distribution between COCs located in the maxilla and in the mandible. In Buchner’s survey of all intraosseous histological variants 111 were in the maxilla and 104 in the mandible. The most common site of occurrence was the anterior parts of the jaws. Among 131 cystic lesions 62 were in the maxilla and 69 in the mandible. In the maxilla 71% were located in the incisor-canine region; in the mandible 55% were located in the incisor-canine region. Among 77 cases in the study by Hong et al., 67 occurred intraosseously, 30 in the maxilla, and 37 in the mandible. Ten cystic lesions were located extraosseously in the gingiva and were distributed evenly between maxilla and mandible. There was no significant preference for either maxilla or mandible among the cystic COCs except in the “ameloblastomatous” type, in which 9 of 11 cases occurred in the mandible. The “ameloblastomatous” type showed unilocular or multilocular intraluminal proliferative activity that resembled ameloblastoma, and thus resembled a UNAM. It corresponds to the “unicystic ameloblastoma-associated COT” in Table 4.

Clinically the extraosseous cases occur as firm or soft circumscribed, smooth-surfaced elevated masses on the gingiva or alveolar mucosa according to Buchner (593). The color is usually normal except for some lesions that are reddish. The size ranges from 0.5 to 4.0 cm, but most lesions are in the range from 0.5 to 1.1 cm in their greatest diameter. They are usually asymptomatic and detected during routine oral examination. The duration of the lesion has varied from 1 month to 15 years, but in half of the cases it ranged from one to eight months. Displacement of adjacent teeth has been reported.

In the review of 215 intraosseous ghost cell lesions by Buchner (594), which contained 72% COCs, 26% OaCCOTs, and 2% DGCTs, the lesions appeared as painless hard swellings. Expansion was recorded in 133 cases and perforation of bone in 10 cases. Early lesions did not exhibit expansion and were detected following radiographic examination, usually for the failure of tooth eruption. A few patients complained of tenderness or pain usually in association with a secondary infection. The time between the patient’s awareness of the lesion and consultation for treatment was recorded in 54 cases and ranged from three days to 9 years; the median duration was six months.

Imaging. The peripheral cases sometimes show a superficial resorption of the underlying bone, which is noted at surgery. In a few cases the resorption is so marked that it is visible in preoperative radiograms (593).
In Buchner’s review of intraosseous lesions (594) most of the lesions (156 cases) appeared radiographically as unilocular radiolucencies, only 12 cases were multilocular. The COCs usually have well-circumscribed borders, only in 10 cases they were poorly demarcated. The radiolucent lesion may show varying degree of scattered radiopaque material, ranging from tiny flecks to conspicuous masses, depending on the degree of calcification of the ghost cells in the lesion. Some of the maxillary COCs show antral involvement from encroachment to complete obliteration. Resorption of roots of teeth adjacent to the cyst has been reported in several cases (584,585), root diversion is less common (599). About one-third of the lesions are associated with unerupted teeth (Fig. 56), more common in the maxilla than in the mandible, in a few cases the cyst was associated with more than one unerupted tooth. The size of the cyst was known in 58 cases. It ranged from 0.5 to 12 cm. Almost 60% of the lesions were between 2 and 3.9 cm. The mean size was 3.3 cm.

In a study by Yoshiura et al. (600) it was shown that conventional radiography was adequate in most instances, but CT was useful as a means of identifying both desquamated keratin and peripheral calcification in COC.

Pathology. The etiology of the COCs is unknown. The peripheral cysts in the gingiva are believed to originate from remnants of the dental lamina and, less likely from the basal cells of the surface epithelium. The intraosseous cysts are believed to develop from reduced enamel epithelium of unerupted teeth or remnants of the dental lamina in terms of proliferating epithelium on the top of a dental follicle of an unerupted tooth.

On histological examination the lesion is characterized by a unicystic structure (23,54,228,570,601). Tangential sections of folded cysts may give a false impression of more that one lumen. However cases have been published in which, even on gross examination, the lesion appeared to be multicystic (594). The thickness and the morphology of the epithelial lining may vary from area to area, but at least in some areas the epithelium resembles that of an ameloblastoma with a well-defined basal layer of columnar cells with nuclei polarized away from the basal membrane (Fig. 57). Mitoses are rare. Generally the interface is flat without rete ridge formation. The overlying epithelium resembles the stellate reticulum of the enamel organ. Melanin is sometimes present in the epithelium, particularly in the stellate cells (602). Individual or more often clusters of ghost cells are seen in the epithelium (Fig. 58). They present as large, pale eosinophilic cells with a distinct outline and are considerably larger than the epithelial cells from which they seem to originate (Fig. 57). Some may contain remnants of the nucleus, but most cells show a well-defined, central empty space instead of a nucleus. Ghost cells are easily detected by means of trichrome staining (Fig. 59) or staining with rhodamine B and observed in fluorescent light (22,603,604). Some areas may show a flattened epithelium without ghost cells and with inconspicuous basal cells, others may show a narrow suprabasal epithelium with cuboidal basal cells with dark nuclei without polarization, and little or no stellate reticulum-like cells. Because of the size of the ghost cells the epithelium in areas with many ghost cells appear thicker than in other areas (Fig. 57). Most ghost cells are found in the upper layer of the epithelium. In areas where basal cells are transformed into ghost cells there is no distinct limit between the epithelium and the underlying connective tissue, and

![Figure 56](image1.png)  
**Figure 56** Calcifying odontogenic cyst. Radiograph of a COC simulating a dentigerous cyst around the crown of a left maxillary canine in a 14-year-old boy.

![Figure 57](image2.png)  
**Figure 57** Calcifying odontogenic cyst. Extensive formation of ghost cells is seen in the epithelial lining to the left. Some ghost cells show calcification. Apart from a few cells, the basal cell layer is still unchanged. Note to the right that parts of the cystic lining may be without any formation of ghost cells. H&E stain.
foreign body giant cells can be seen between the epithelial cells and in particular around ghost cells in the connective tissue. The ghost cells show an affinity for calcification (Fig. 57), initially as fine or course basophilic granules, but stacks of mineralized ghost cells may present as calcified sheets, which may be visible on a radiogram. Some epithelial budding may be seen from the basal cells and formation of individual strands or islands of epithelium or small daughter cysts in the adjacent connective tissue. They vary from a few strands to extensive proliferation (605). In their study of 79 COCs, Hong et al. (582) found 17 cases with marked proliferation of the cyst-lining epithelium and multiple daughter cysts of variable size. Some authors prefer to subdivide the COCs into nonproliferative and proliferative variants (582,606,607). Yoshida et al. (606) demonstrated that the mean Ki-67 L.I. was slightly greater in COCs and OaCCOTs with proliferative-type lining epithelium (vide infra). Cases with unifocal or multifocal intraluminal proliferative activity resembling UNAM are better classified as UNAM-associated CCOT (Table 4). Atubular dentinoid is often found in close contact with the epithelial lining (Fig. 59) or the epithelial islands (601). It is osteoid-like, but called dentinoid because it is only seen in contact with the odontogenic epithelium and resembles the dentin, which may be formed in teeth traumatized during development. The connective tissue is fibrous (Fig. 58); no cellular embryonal pulp-like odontogenic ectomesenchyme is seen, not even in areas with dentinoid formation. The dentinoid may contain entrapped cells including ghost cells (Fig. 59). Slight nonspecific inflammation may be seen in the connective tissue. A single case of COC with clear cells has been described by Ng et al. (608); the cells were located in the subepithelial connective tissue and may not be epithelia cells; the significance is unknown.

**Immunohistochemistry.** Immunohistochemical studies have usually been made on materials from COCs, OaCOCs, and DGCTs without a clear distinction between the entities. CKs have been studied by several authors (582,606,607,609–613). The results have been partly controversial. Antibodies against CK-19, which has been detected frequently in odontogenic epithelium, were used by Kakadu et al. (610), Yoshida et al. (606), and Fregnani et al. (607), with comparable results. A positive immunoreaction was found in the upper intermediate and superficial cell layers of the lining epithelium, but not in the basal layer, except the study of Fregnani et al. (607) who found a positive reaction in 6 of 10 cases. Murakami et al. (612) using monoclonal antibodies against CK-19 found a positive reaction in the basal layers, but negative in the suprabasal layers. In contrast, Yamamoto et al. (609) using PKK-1 against CK-8, CK-18, and CK-19 found essentially no reaction in the epithelium. They also used KL-1, a broad-spectred antibody against CK-1, CK-2, CK-5-8, CK-11, CK-14, and CK-16-18 and found a slightly positive reaction in the basal and suprabasal epithelium. Using the same antigens Kakudo et al. (610) found a positive reaction exclusively in the upper intermediate and the superficial layers. Fregnani et al. (607) detected expression of broad-spectred AE1/AE3 and 34βE12 (CK-1, CK-5, CK-10, CK-14) as well as monoclonal CK-8, CK-4, and CK-19.
in the suprabasal cells of the lining epithelium in all 10 of their cases, and they found CK-14 and AE1/AE3 keratins expressed in the basal cells in all cases.

Ghost cells gave a negative response to broad-spectrmed antibodies (TK, KL-1, AE1/AE3) in the studies by Yamamoto et al. (609), Kakudo et al. (610), Hong et al. (582), and Gordeeff et al. (611). Monteil et al. (604), however, detected a weak reaction to the antibody Dako K518, and Murakami et al. (612) detected a positive reaction to CK-13. Fregnani et al. (607) found immunoreactivity of ghost cells to 34E12 in 4 of 10 cases and to AE1/AE3 in 8 of 10 cases. Kusama et al. (613) raised three kinds of antibodies against hard \( \alpha \)-keratins in human hair and used them to investigate ghost cells in pilomatrixomas, craniopharyngiomas and 14 cases of COC. Positive reaction was found in all cases and in ghost cells exclusively. The CKs of ghost cells thus seem to be closely related to hard \( \alpha \)-keratins.

Involucrin was studied by Yamamoto et al. (609) who found that only few epithelial cells were positive. Kakudo et al. (610) detected involucrin in the upper intermediate cell layers exclusively. They studied filaggrin as well, only few epithelial cells reacted positively. Immunoreaction to vimentin in epithelial cells was moderate and only seen in individual cells.

HGF, TGF-\( \beta \), and their receptors were studied by Kumamoto et al. (134) in six cases of COC. The epithelial cells of COC showed reactivity for HGF, TGF-\( \beta \) and their receptors. High expression of receptors was noted in ghost cells. The authors concluded that the findings support the hypothesis that HGF and TGF-\( \beta \) act on epithelial cells via paracrine and autocrine mechanisms.

Tenascin, a multifunctional extracellular matrix glycoprotein, was investigated in four cases of COC by Mori et al. (70). Positive reaction was found exclusively in the connective tissue along the basement membrane of the epithelial cells.

Chen et al. (167) used ISH and immunohistochemistry on a case of COC to study BSP, a major noncollagenous protein synthesized and secreted by bone-, dentine-, and cementum-forming cells. Strong BSP signals were seen in epithelial cells surrounding nests of ghost cells with both methods.

Versican, a large chondroitin sulfate proteoglycan in extracellular matrix, was studied by Ito et al. (67) in one case of COC and several cases of other odontogenic tumors. Ghost cells and calcified matrix in COC were positive; the connective tissue was essentially negative.

The presence of enamel proteins (amelogenin, enamelin, sheathlin, and enamelysin) has been studied by several investigators (159–162,548,606,614).

Amelogenin was detected by Mori et al. (162) in eight COCs. The epithelial cells of the cysts were almost devoid of amelogenin staining, the ghost cells showed immunoreactivity at varying intensity; calcified ghost cells were negative. The results by Saku et al. (159) from a study of three COCs were different; they found a weak, diffuse reaction in the epithelial cells, no reaction in the ghost cells, and a strong reaction in the calcified globules. Takata et al. (614) studied the presence of amelogenin in ghost cells in six cases of COCs and three cases of pilomatrixoma. They found amelogenin located particularly to clusters of ghost cells, and sometimes exclusively to the periphery of the clusters. No amelogenin was present in the ghost cells of pilomatrixomas. In a study of two COCs Abiko et al. (548) confirmed that some ghost cells in the lining epithelium were strongly stained. Similar results were achieved by Yoshida et al. (606) in a study of 16 COCs among which 12 were OaCCOTs; amelogenin was expressed in the ghost cells, but not in the lining epithelial cells.

Enamelin was studied by Saku et al. (159) in three cases of COC. The reactivity was similar to that of amelogenin; in the lining epithelial layer, round mineralized material was diffusely positive for enamelin. The epithelial cells of the upper layers showed mild and diffuse immunoreaction in the cytoplasm. In the study of Takata et al. (614) enamelin was mainly expressed at the periphery of ghost cell clusters and not in centrally situated cells. The staining pattern in the individual ghost cell was often seen as linear fragments along the cytoplasmic membrane.

Sheathlin was studied in the same six cases of COC as mentioned above by Takata et al. (614) and a second time in 10 cases of COC (160). Although epithelial cells were generally negative for sheathlin, ghost cells in the epithelial lining showed distinct immunoreactivity, which was the most distinctive and frequent among the four enamel-related proteins examined. Dysplastic dentin was negative.

Enamelysin was studied in six COCs (614) and in 10 COCs (160) by Takata et al. by means of a monoclonal antibody (203-IC7). Although the epithelial cells surrounding the cysts were generally negative for enamelysin expression, selected ghost cells in the epithelial lining or in the connective tissue showed obvious immunoreactivity, especially at the peripheral areas of these cell clusters. Dysplastic dentin was negative.

The PCNA L.I. was assessed immunohistochemically in 12 cases of cystic COC and 9 cases of OaCCOT and compared to the index in ameloblastomas by Takata et al. (615). The COCs were divided into nonproliferative and proliferative according to the amount of epithelial proliferations in the connective tissue wall. The proliferative cystic COCs (\( N = 8 \)) showed a higher PCNA L.I. (mean 17.2 \( \pm \) 11.2, range 5.7–37.1) than the nonproliferative (mean 6.8 \( \pm \) 2.8, range 3.2–9.6). The PCNA L.I. for the proliferative COCs was almost equivalent to that of ameloblastoma (mean 18.3 \( \pm \) 13.3, range 5.1–40.8). Fregnani et al. (607) confirmed these results in a study of 10 cases, which consisted of five central cystic COCs, three OaCCOTs, and two peripheral DGCTs, which they considered “nonproliferative.” They found a mean L.I. of 10 (range <1–20) in the nonproliferative and a mean L.I. of 25 (range 10–50) in the proliferative. The L.I. for the five cystic COC (2 nonproliferative and 3 proliferative) was 20 (range <1–50).

Proteins produced by the proto-oncogene Bcl-2 suppress apoptosis. The protein was detected by Yoshida et al. (606) in a pool of 16 cases consisting of four cystic COCs and 12 OaCCOTs. Bcl-2 was
absent in two and present in two of the COCs. In the above-mentioned study by Fregnani et al. (607) all 10 cases expressed Bcl-2 in the basal and suprabasal cells, but ghost cells were negative in all cases.

An assessment of the Ki-67 L.I. was made by the same investigators as part of the study mentioned above (606,607). Yoshida et al. (606) found a mean Ki-67 L.I. of 1.45 ± 0.50 for the four cystic COCs. Ki-67-labeled cells were found in nuclei of lining epithelial cells, but not in the ghost cells. Among the five cystic COCs four expressed Ki-67 and one was negative. The mean L.I. was 2 (range 1-4). In the entire group the lesions with epithelial proliferations showed a three times higher L.I. than the nonproliferative.

Mel-CAM, a multifunctional heterophilic cell-to-cell adhesion transmembrane glycoprotein, was investigated by Fregnani et al. (607) in the same study where PCNA, Bcl-2, and Ki-67 were investigated. Mel-CAM was frequently expressed in suprabasal and ghost cells, but was practically absent in the basal-lining cells.

Mutations of β-catenin, a transcriptional activator of the Wnt-signaling pathway, was studied by Sekine et al. (156) in 20 cases of ameloblastoma and 10 simple cystic COCs by means of immunohistochemistry and genetic analysis. The results of the latter are discussed below. Monoclonal anti-β-catenin was used for immunohistochemical staining. All cases including two in which mutations were not identified showed similar β-catenin expression. The lining epithelium showed weak to moderate cytoplasmic staining. Cells around ghost cells tended to exhibit stronger nuclear accumulation. Peripherally palisading columnar cells showed somewhat stronger β-catenin expression in both the cytoplasm and the membrane. The study by Hassanein et al. (616) essentially confirmed these results. They found a strong nuclear and cytoplasmic staining in six of six COCs. The cytoplasmic staining was found in the basaloid and transitional cells. Ghost cells were negative in all cases.

Electron Microscopy. Donath et al. (617) published a detailed description of the ultrastructure of the COC. Basal cells were elongated and bordered on a conspicuous basement membrane. Desmosomes were seen and in the cytoplasm, a moderate number of tonofilaments, rough endoplasmatic reticulum, free ribosomes, mitochondria, and a small Golgi apparatus were detected. The nucleus was elongated and oval, had a small nucleolus and heterochromatin distributed ed at the periphery. The spinal cells had narrow intercellular spaces and abundant desmosomes. Intracytoplasmic tonofilaments irradiating from the desmosomes were poorly developed. Free ribosomes, RER, a well-developed Golgi apparatus, and enlarged cisternae were seen. Cells in the stellate reticulum-like areas showed large intercellular spaces partly empty and partly filled with fine granula and small vesicles. The cytoplasm exhibited laciniated extensions with desmosomes. The ultrastructure of the cytoplasm was similar to that of the spinal cells except that some cells contained lipid droplets, myelin figures, and large vacuoles.

Many variations in shape and size were seen in the ghost cells, they were generally larger than basal and spinal cells. The cytoplasm was packed with parallel bundles of tonofilaments with intermediate vesicles some of which were empty, and some filled with granular material. Cells were seen with RER, remnants of mitochondriae, and osmiophilic membranes or granula packed around the nucleus or along the periphery of the cell. Heterochromatin was irregularly dispersed along the inner nuclear membrane. Only few fragments of cellular membranes with desmosomes were seen, but clusters of disintegrated desmosomes were found. Membranes of spinal cells adjacent to ghost cells exhibited disintegration and vesicular transformation. In areas with coalescence of ghost cells two types of changes of tonofilaments were found, some were fused, and others—less frequently—were fragmented. Between the ghost cells remnants of cell organelles with needle-shaped calcifications were found. Completely calcified ghost cells were divided in zones.

Dentinoid (dysplastic dentin) showed a grid of filaments, which had an increased osmiophilia at the periphery. Embedded ghost cells were detected. Collagen fibrils could only be found in areas adjacent to fibroblasts.

Abaza (618) confirmed most of these findings and described a cell type, which unlike the ghost cells with thick uniform fibrils contained moderately densely packed and evenly distributed tonofilaments oriented in different directions and occasionally residue of organelles. Similar cells had been described by Chen et al. (619) in DGCTs and have been called “hornified cells.”

Mimura et al. (620) confirmed many of these findings and they also detected needle-like crystals around the epithelial cells. Many calcifications exhibited a distinctive ring formation around the periphery of an amorphous central core with no evidence of ghost cells. These calcifications were observed with necrotic remnants of nuclear material and many identifiable mitochondria, thin fibers, and epithelial cells. The cytoplasm of the ghost cells consisted of numerous short electron-dense tonofilaments bundles. In these calcification was observed. The needle-like structures were shown by X-ray diffraction analysis to be hydroxyapatite.

Molecular-Genetic Data. Somatic β-catenin mutations were found in 9 of 10 COCs analyzed successfully by Sekine et al. (156). All of the mutations caused amino acid substitution of serine/threonine residues of GSK-3β phosphorylation sites or residues flanking the first serine residue of the phosphorylation sites. The authors suggested that the results indicate that COC is caused by an activating mutation of β-catenin. Interestingly only 1 of 20 ameloblastomas showed β-catenin mutation, indicating that COC and ameloblastoma are two genetically distinct lesions, despite their histological resemblance.

Differential Diagnosis. If typical areas are present in the sample, differential diagnosis is usually not a problem. Ghost cells have been described in
eruption cysts, ameloblastomas, AMFs, ameloblastic fibro-odontomes, and particularly in odontomes, although usually in moderate amounts (534). The mere presence of ghost cells is therefore an insufficient criterion for the diagnosis of COC; stellate reticulum-like areas and elongated basal cells must be present. Differential diagnosis between COC and CCOT associated with odontoma or odontogenic tumors is not difficult if sufficient sampling and clinical information is available, except cases with marked proliferation of epithelium in the connective tissue wall. Some degree of epithelial proliferation is acceptable within the spectrum of COC, but in case of extensive luminal or mural proliferation, the lesion is better classified as UNAM-associated CCOT (Table 4). Borderline cases are difficult and the decision is arbitrary. It is important of course to distinguish the COC from the GCOC. The malignant tumor may have arisen in a COC and there may be benign areas in the operation specimen besides the carcinoma. While mitoses are very rare in COCs, they are numerous in the GCOC, which also show increased cellularity, some degree of pleomorphism, and areas with necrosis.

Treatment and Prognosis. The COCs are effectively treated by enucleation in most cases. Recurrence is rare, but has been recorded (570,585,617,621–625); according to Buchner (594) nine cases of recurrences have been reported, but among these DGCTs may be included. The case reported by Slootweg et al. (622) was a COC in the mandible, which recurred seven years after enucleation. One of the two cases of recurrence reported by McGowan et al. (585) recurred after four years, and the one by Daniels et al. (625) after eight years. A follow-up time of about 10 years seems required. Cystotomy is not recommended; case 3 reported by Donath et al. (617) recurred after cystotomy, and case reported by Praetorius et al. (580) was treated by cystotomy, with the consequence that the entire lumen became filled with COC tissue within the following months and protruded through the surgical window. Malignant transformation has been reported, the subject is discussed in the section “Ghost cell odontogenic carcinoma.”

2.6.2 Calcifying Cystic Odontogenic Tumor (Associated with Other Types of Odontogenic Tumors)

Introduction. As indicated above, the term “calcifying cystic odontogenic tumor (CCOT)” is used in this survey to designate a group of ghost cell lesions, which present as a calcified odontogenic cyst associated with an odontogenic neoplasm or an odontoma (Table 4). In rare cases, the cyst is associated with a malignant ghost cell containing tumor (581,626–631); these are called GGCs and are discussed below under the heading Malignant Epithelial Odontogenic Tumors.

ICD-O code 9301/0 The OaCCOT has been described in many reports, but only few cases of the other combinations are known. It is very unlikely that all these COC-associated tumors are collision lesions. It is far more plausible that the epithelial cells of the COC harbor genes that under favorable conditions initiate the development of an odontogenic tumor. Numerous COCs have shown various amounts of islands and strands of epithelium in the connective tissue wall, the differential diagnosis between extensive proliferations and an initial ameloblastoma may be arbitrary. The so-called “Vickers – Gorlin criterions” (270) are a useful guideline, but not a distinguishing mark; it must be borne in mind that many areas in a genuine solid/cystic ameloblastoma do not fulfill these criterions.

The question whether the cyst develops from a preexisting odontogenic tumor in a CCOT associated with an odontogenic tumor or the tumor develops from the wall of the cyst has been debated in the literature (228,580,605). There are convincing indications that the cyst is the primary lesion and the tumor develops from the cyst since the proliferations of the odontogenic epithelium in the wall of the cyst display such a vast spectrum, and many OaCCOTs have been published, which have shown a scale of development from small areas of formation of hard dental tissue in the wall of the cyst to large odontomas that fills most of the cystic space.

2.6.2.1 Solid/Multicystic Ameloblastoma–Associated CCOT. Three cases have been published of this variant. Hong et al. (582) described two cases. They occurred in a 10-year-old girl and in a 59-year-old man. Both tumors occurred in the posterior of the mandible and appeared as intraosseous, well-defined radiolucent lesions that produced progressive swelling. Few ghost cells and no dentinoid was seen in the ameloblastoma areas. Tajima et al. (632) reported a case in a 35-year-old man, which presented as a well-demarcated cystic lesion in the mandibular symphysis with slight enlargement of the overlying gingiva. Root resorption of the anterior teeth was observed. Besides the ameloblastoma-like appearance, the tumor contained dentinoid, and the epithelium showed a cribiform architecture, which is not usually seen in ameloblastomas. These cases should be treated as ameloblastomas.

2.6.2.2 Unicystic Ameloblastoma–Associated CCOT. Hong et al. (582) reported 11 cases of “ameloblastomatous calcifying odontogenic cyst.” The term is not felicitous since the epithelium of all COCs resemble that of an ameloblastoma, but the authors also described the lesions as resembling UNAMs except for the ghost cells and calcification within the proliferative epithelium. The tumor developed primarily in age groups between the second and sixth decennium, and 9 of the 11 lesions occurred in the mandible. Li et al. (579) reported a similar case (case 3) in the mandible of a 50-year-old woman. The tumor presented as a multilocular radiolucency from the right premolar to the left second incisor. It was treated by enucleation, and there was no sign of recurrence after six years. The authors mentioned that fewer ghost cells and less dentinoid were found in the ameloblastoma-like proliferations than in the cystic part of the lesion. Aithal et al. (633) reported a case in the left posterior region of the mandible of a 28-year-old woman. It presented as a well-defined, hard, nontender swelling,
which on the radiogram disclosed a multilocular radiolucency extending from the canine to the second molar. The case reported by Iida et al. (592) was diagnosed in a 17-year-old Japanese man who had a painful swelling (due to trauma) of the right mandibular body. The tumor showed a well-defined multilocular radiolucency from the right second molar to the right ramus with remarkable bony expansion toward buccal and lingual sides. It was treated with extirpation and curettage; there was no sign of recurrence after 13 years. Ide et al. (634) published a case, which was diagnosed in an edentulous posterior region of the right side of the mandible in a 79-year-old man. Radiograms showed a well-demarcated, multilocular mixed radiolucence–radiodense lesion; it was enucleated and no recurrence was recorded after five years. The lining showed typical COC features with dentinoid formation. Within the thick fibrous wall were many large follicles of ameloblastoma without formation of ghost cells or dentinoid.

The majority of these lesions seem to develop in the mandible. The same treatment modalities, which are used in the treatment of UNAMs should be considered in these cases.

_2.6.2.3 Adenomatoid Odontogenic Tumor-Associated CCOT._ No case of CCOT associated with a fully developed AOT has been published, but five cases have been described in which limited areas of the cystic wall or the epithelial proliferations show the architecture of an AOT. Freedman et al. (584) published a case (case 1 of 6) of COC in the molar region of the mandible of a 15-year-old girl. An area of the epithelium in the wall resembled an AOT (Fig. 8 in the report). A similar architecture with loop forming two-cell-layered strands is found in O-As. In a large COC from the right to the left premolar area in the mandible of a 35-year-old man Zeitoun et al. (635) found a minor area with pseudo-tubular structure characteristic of an AOT. Lukinmaa et al. (636) described a case with AOT-like areas in the lining of an otherwise simple cystic COC in the angle and ramus of the left side of the mandible in a 12-year-old boy. Furthermore there were minor areas in the wall, which were structured as an AMF. Buch et al. (637) found more extensive areas with AOT histomorphology in a CCOT in the premolar area of the mandible of an 11-year-old girl. In an AMF-associated CCOT, which occurred in the premolar–molar area of a six-year-old girl Lin et al. (638) observed sheet-like areas containing whorled masses of spindle-shaped cells and occasional duct-like structures, reminiscent of AOT.

The presence of AOT-like areas in a CCOT has no impact on the treatment.

_2.6.2.4 Ameloblastic Fibroma-Associated CCOT._ Four cases have been published of this rare lesion apart from the case (vide supra) published by Lukinmaa et al (636). Lin et al. (638) reported three cases. The first case was a six-year-old girl with a 3.8 × 2.0 cm cystic lesion in the right mandibular body. Some areas of the cystic wall were thickened and contained three nodules measuring up to 1.3 × 0.6 cm, which showed the histomorphology of an AMF. The lesion was enucleated and there was no sign of recurrence after 20 months. The second case was a 13-year-old boy with a large cystic lesion in the posterior area of the left side of the maxilla. One area of the wall was thickened and showed a rather large area in close contact with the lining epithelium with the histomorphology of an AMF. The lesion was excised through a Le Fort I osteotomy approach. The patient failed to return for follow-up. The third case was a cystic lesion around the crown of an impacted right third molar in a 22-year-old man. Slight nodular elevations were seen in the wall. The lining showed typical COC features in some areas and AOT-like structure in others, as mentioned above. In some of the nodular areas AMF-like structure was seen adjacent to the epithelial lining. The lesion was curetted; the patient did not show for follow-up. In all three cases the areas with AMF morphology were relatively large and without any sign of hard dental tissue formation, it is thus unlikely that they should represent initial odontoma formation. Yoon et al. (639) reported a case of cystic tumor, 3 cm in diameter in the right posterior maxilla of a 22-year-old woman. The cystic portion showed features characteristic of a COC with ghost cells and dentinoid. A solid portion of the tumor had characteristic features of AMF. Ghost cell masses were found in these areas as well. The lesion was excised, and no recurrence was observed at one-year follow-up.

It is not possible on the basis of these few cases with short time or no follow-up to draw any conclusions regarding treatment and prognosis. Enucleation may be adequate, but long-time follow-up is recommended bearing in mind the tendency for recurrence and even malignant transformation of some AMFs.

_2.6.2.5 Ameloblastic Fibro-Odontoma-Associated CCOT._ Only two cases are known of this rare lesion. A case was included in a review by Prætorius et al. (580) and discussed by Shear et al. (228); it was a tumor, which presented as a multilocular lesion, which occupied almost the entire left side of the mandible of a 17-year-old man (Fig. 60). The tumor contained a single large cyst with a COC lining, and the remaining part was structured as an AMF apart from clusters of ghost cells and deposits of dentinoid (Fig. 61). In a few minor areas enamel was present adjacent to ghost cells (Fig. 62). Hemimandibulectomy was performed; no information on follow-up was available. A second case was reported by Matsuzaka et al. (495). The patient was a 23-year-old-man with a partly radiolucent, partly radiopaque lesion, which occupied the entire left mandibular ramus and the region around the third molar. It consisted of a cyst the size of a hen’s egg and covered with a typical COC lining; a thick wall was found on the outside, with the histomorphology of an AFOD. A segmental resection was done, there was no information on follow-up. The case was studied immunohistochemically with antibodies against CK-19, osteopontin, and osteocalcin. CK-19 was strongly immunoreactive in the epithelium of the lesion; osteopontin and osteocalcin reacted in the mesenchymal cells and weakly in the epithelial elements of the tumor.

Farman et al. (640) reported a case of “calcifying odontogenic cyst with ameloblastic fibro-odontome.”
The areas with AFOD-like features were very limited; the lesion is probably better classified as a CCOT with initial odontoma formation.

2.6.2.6 Odonto-Ameloblastoma-Associated CCOT.

This entity was reported briefly by Ledesma-Montes (641). It was diagnosed in the anterior maxilla of a 21-year-old man. It measured 4 cm at longest diameter and was clinically diagnosed as a dentigerous cyst.

2.6.2.7 Odontogenic Fibromyxoma-Associated CCOT.

A single case has been reported of this combination. Li et al. (579) described a tumor in the molar and ramus region of the right side of the mandible of a 15-year-old girl. The radiogram showed a large well-defined unilocular radiolucency associated with an unerupted third molar. The lesion consisted of a cyst with typical COC lining; adjacent to the cyst a tumor was seen with the histomorphology of an odontogenic fibromyxoma. The tumor made up the majority of the lesion. It was removed by enucleation, and there was no recurrence after one year.

2.6.2.8 Odontoma-Associated CCOT.

This combination is much more common than any of the other CCOT variants. As mentioned above, most surveys of COC have included more than one variant without clear distinction between them. From 17% to 75% of the published cases of COC have been associated with an odontoma in the reviews published with 10 cases or more, but in most reviews about 30% of the cases were odontoma associated (579,580,582,594,601,606,607,615,642).

Clinical Features. Hirshberg et al. (643) published a review of 52 OaCCOTs retrieved from the English language literature. It is the only review with focus on OaCCOTs exclusively. The authors suggested the name of the lesion changed to odontocalcifying odontogenic cyst.

The results of the review are basis for the following survey.

The age range was between 5 and 39 years, with a mean age of 16 years. The mean age at diagnosis is lower than that of the simple cystic COC (34.3 years), and very few cases have been diagnosed in persons who are less than 10 years old.
older than 30 years (594). About 60% were in their second decade. The gender ratio was 1:1.9; 18 were males and 34 females. A female predominance has not been found in the simple cystic COC where the gender ratio was about 1:1(228,594).

The most common location was the maxilla (32 cases; 61.5%), of which 24 (75%) were in anterior region (incisor-canine region), and 5 (15.6%) were in the posterior region. In three cases (9.4%), the lesion occupied both the anterior and the posterior regions. Twenty cases (38.5%) were located in the mandible, of which 11 (55%) were in the anterior region and 4 (20%) were in the posterior region. In five cases (25%), both regions were involved. The distribution of the simple cystic COCs is different, among 131 intraosseous cystic COC reviewed by Buchner et al. (594), the ratio between the maxilla and the mandible was more even, 62 cysts (47%) were located in the maxilla and 69 (53%) in the mandible. In the maxilla, 44 cases were found in the anterior and 18 in the posterior region. In the mandible, 38 cysts were found in the anterior and 31 in the posterior region.

A case of extraosseous OaCCOT has been published by Ledesma-Montes et al. (539).

The most common symptoms of the OaCCOTs were swelling (52%) and unerupted teeth (13.5%). Pain was noticed in 9.6% of the cases, and tenderness of the region caused by secondary infection was observed in 9.6% of the cases. In 19% of the patients the lesion was accidentally discovered during routine radiographic examination. The growth rate of the OaCCOTs is slow.

Imaging. In 29 of 36 cases (80.6%) the lesion was well-defined on the radiograms with a mixed radiolucent–radiopaque appearance (643). The radiopacities varied from minor flecks to well-defined tooth-like structures, which in a few cases dominated the lesion. In several cases the radiopaque particles are located at the periphery of the lesion. In four cases the development of the odontoma was initial and not visible on the radiogram. Impaction of teeth was observed in 20 cases (38.5%), most frequently the canine (11 cases) followed by the incisors (5 cases). Impaction of more than one tooth was observed in five cases.

Divergence of teeth is common (599) and resorption of the root of adjacent teeth has been reported in a number of cases (572,599,601,642,644–648). Exact figures are not available, because most reviews have not separated the various variants. Martin-Duverneuil et al. (648) showed the increase of information about the lesions, which is obtained if CT and MRI are applied.

Pathology. The etiology is unknown. Pathogenetically the dental hard tissue seems to develop from an odontogenic activity in the lining of a single large cyst with typical COC structure, as described above (Fig. 63). Various stages of odontogenesis may be seen from areas with embryonic pulp-like ectomesenchyme and dental lamina and enamel organ–shaped odontogenic epithelium to fully developed and mineralized tooth-like structures (odontoides) (579,580,606,636,649). When the formation of odontoides is more extensive, they protrude into the lumen of the cyst (Fig. 64), and in some cases fill out the cystic lumen completely. The structure of the dental hard tissue may be quite irregular, but in many cases it takes the shape of an ODTx (579,599,650) or apparently more often (Fig. 65) an ODTp (579,580,615,644,651,652,653). In some cases both morphologies are seen in the same tumor (599). The dental hard tissue formation is seen in close contact with the lining epithelium or deeper in the connective tissue. Variable amounts of dentinoid and
cluster of ghost cells with or without calcification may be seen (Fig. 66).

**Immunohistochemistry.** Most of the immunohistochemically studies on odontogenic ghost cell lesions have been performed on material, which have been a mixture of the variants, mostly COCs, OaC-COTs, and DGCTs. Possible differences in the findings in the variants have rarely been reported, so the results reviewed above for the COC are also valid for the OaCCOT, apart from obvious differences between lesions with and without embryonic pulp-like ectomesenchyme. In the study by Luukinmaa et al. (636) the expression of the glycoprotein tenasin-C was concentrated to the dental papilla-like regions and the pulp tissue of the odontoides. In a few cases differences have been stressed; Yoshida et al. (606) reported that Bcl-2 expression and the mean Ki-67 LI. in OaCCOTs were slightly higher than in simple cystic COC. However, these differences did not reach statistical significance.

**Electron Microscopy.** Fejerskov et al. (577) studied the ultrastructure of an OaCCOT in the maxilla of a 16-year-old female, and found that most ghost cells contained very thick electron-dense fiber bundles of relatively uniform size, which were sharply defined against large empty spaces in the cytoplasm unlike the even distribution of fine tonofilaments present in keratinizing cells of oral surface epithelia. Organelles could not be found in ghost cells.

In a study of the ultrastructure of two cases of OaCCOT, Eda et al. (654) observed that ghost cells contained abundant bundles of tonofilaments and that calcification seemed to start from the peripheries of the bundles. The calcified matrices had no clear structures. Sapp et al. (549) focused on the ultrastructure of the calcifications in OaCCOT. They observed three different types: (i) spherical calcifications, which form on ghost cells and which they interpreted as dystrophic; (ii) spherical calcifications, which appeared to be dysplastic enamel; and (iii) irregularly shaped, diffuse calcifications, which form on a collagenous matrix and appeared to be dysplastic dentin or cementum.

Satomura et al. (646) identified four types of cells in the epithelial layer of an OaCCOT. The basal cells were low columnar in shape and contained some intracellular organelles. Desmosomes attached to neighboring cells were seen on the cellular membranes, the basal cell layer resembled the inner enamel epithelium of the normal enamel organ. In the stellate reticulum-like layer the cells were polygonal and possessed desmosomes and many cytoplasmic projections. Some intracellular organelles and a few bundles of tonofilaments were observed in the cytoplasm. Cells in the vicinity of focal accumulations of ghost cells showed cell membranes that were discontinuous in parts and contained dilated membranous organelles and evenly distributed tonofilaments. In spite of discontinuous cell membranes the ghost cells, the fourth cell type, were attached to each other by means of desmosomes. The ghost cells contained many bundles of tonofilaments that were 60 to 240 nm in diameter and arranged in various directions. The cytoplasm did not contain intact intracellular organelles. A variety of vesicles, 90 to 450 nm in diameter, were scattered among the tonofilaments bundles. Some of the vesicles contained needle-like crystals, which were interpreted as initial calcification sites. These vesicles resembled matrix vesicles, and the authors suggested that matrix vesicle-like structures might be involved in the initiation of calcification of the ghost cells.

**Molecular-Genetic Data.** No data are available.

**Differential Diagnosis.** Previously the CEOT was sometimes confused with the COC, CCOT, or DGCT (570). With the accessibility of more precise
2.6.3 Dentinogenic Ghost Cell Tumor

**Introduction.** The DGCT is a slowly growing benign, but nonencapsulated and locally invasive, epithelial odontogenic tumor characterized by ameloblastoma-like islands in a fibrous connective tissue stroma. Clusters of ghost cells are seen in the epithelial islands and sometimes in the connective tissue. Various amounts of dentinoid (dysplastic dentin) are seen adjacent to the epithelium. Tumors without presence of dentinoid and with a limited amount of ghost cells are better classified as s/m ameloblastoma with ghost cells (596).

ICD-O code 9302/0

Synonyms: Odontogenic ghost cell tumor, calcifying ghost cell odontogenic tumor, epithelial odontogenic ghost cell tumor, dentinoameloblastoma, dentinogenic ghost cell ameloblastoma.

**Clinical Features.** Like most odontogenic tumors the DGCT occurs as an intraosseous and a less aggressive extraosseous variant. Judged from the published cases the extraosseous variant is far more common than the intraosseous. About 32 acceptable extraosseous cases have been published (579,580,582,585,588,591,593,607,636,658–668) and 14 intraosseous cases (579,580,582,669–676).

Among the 32 extraosseous cases the age range was 10 to 92 years, the mean age 57.6 years, and the median age 61 year. Apart from three patients who were 10 years old, all other patients were 33 years or older. It is tempting to speculate if the tumor in the three patients contained not only dentinoid, but also tubular dentin and were in fact initial OaCCOTs, rather than DGCTs. The gender ratio was almost equal, 18 males and 14 females. The age range in males was 10 to 82 years, mean age 53.0 years, and median age 57 years. In females, the age range was 10 to 92 years, the mean age 63.4 years, and median age 70 years.

The location was reported in 31 cases. The peripheral DGCT is more common in the mandible. Eight tumors were located in the maxilla, seven in the anterior region, one unspecified. Twenty-three tumors were located in the mandible; five in the anterior region, nine in the posterior, one in the anterior and posterior region, and eight unspecified.

It was reported in 18 cases that the tumor developed in an edentulous jaw or area, and several authors have suggested that traumatic influence from ill-fitting dentures could be an etiological cofactor (656). The lesions present as sessile, sometimes pedunculated nodules or irregular hyperplasias of the gingival or alveolar mucosa. They are usually slowly growing, have been observed for months or years, but in some cases recent rapid growth has been reported (658). Teeth in the affected area may be displaced. The tumors are otherwise symptomless, except when they become traumatized. The size was reported in 20 cases, it varied from 0.4 to 4 cm, but 14 of them measured 1 cm or less at longest diameter.

For the 14 intraosseous DGCTs the age range was 12 to 79 years, mean age 47.7 years, and median age 59 years. The gender ratio M:F was 1:0.3 (11 males and 3 females), there might be a male predilection, but the numbers are small. The age range for males was 12 to 79 years, mean age 50.9 years, and median age 59 years. The three females were 21, 24, and 63 years, respectively. The tumor was more common in the mandible; one was unspecified, but three were diagnosed in the maxilla, all in the posterior regions, and 10 in the mandible, two in the anterior, and seven in the posterior regions; the region was unspecified in one case. The most common symptom is bony expansion presenting as a slowly growing firm swelling, which may be soft in areas where the tumor has eroded the cortex and invaded the adjacent soft tissue (672,673,676). Tumors in the maxilla may obliterate the maxillary sinus. Pain is a rare symptom (669,670,672).

**Imaging.** The extraosseous DGCT may cause erosion of the underlying bone varying from a hardly visible change to a conspicuous bowl-shaped defect usually with well-defined smooth border. Several cases have been reported to be without bone involvement.

The intraosseous DGCT show a varying picture. Some have been radiolucent, unicocular, and well-defined (580). One was radiolucent with ill-defined borders; it had a rapid growth (671). Others have been described as radiolucent, multicocular, and ill defined (579,676). In three cases cortical erosion with tumor invasion of adjacent soft tissue was seen (673,675,676), a feature that is uncommon in solid/cystic...
ameloblastomas. Various amounts of scattered radiopaque material have been seen in the radiolucent areas in several cases. Teeth adjacent to the lesions may show root resorption (670), as it is seen in the COC and CCOT. In some cases impaction of teeth is seen. Tumors in the maxilla may encroach the maxillary sinus (582,673). CT scanning has been used in several cases and ameliorates the information on the borders of the tumor, particularly in cases with erosion of the cortical plates.

The size of the tumor has varied from 2 cm at longest diameter to a size where it has destroyed about 50% of the entire mandible (579). The majority have been within the range of 6 to 7 cm at longest diameter.

Pathology. The etiology of the DGCT is unknown. The extraosseous variant has been found in edentulous areas so often that is has raised the question whether a local trauma from ill-fitting dentures could be a cofactor. Pathogenetically the extraosseous lesions are supposed to arise in remnants of dental lamina in the gingiva.

The central tumors are likely to arise in reduced enamel epithelium or proliferation of remnants of odontogenic epithelium in the jaw.

Macroscopically the lesion has been described as a grayish mass with firm consistency (665) often with scattered foci of calcification. Some contain small multiple cystic cavities (673).

The overall microscopic impression of the DGCT is a tumor, which resembles the solid, intraosseous ameloblastoma in several aspects. The main difference is the presence of many clusters of ghost cells and of dentinoid in DGCTs (Fig. 67). The tumor is nonencapsulated. It presents as nests and sheets of odontogenic epithelium in a fibrous connective tissue stroma (596). The peripheral cells are cuboidal to columnar, with a central or reversely polarized nucleus, which is round or elongated. Mitoses are unusual and generally not present. The majority of the cells in the sheets and islands are stellate and morphologically similar to the cells in an ameloblastoma. The cytoplasm is pale eosinophilic. In some tumors foci of epidermoid differentiation with intercellular bridges may be encountered and in rare cases there may be keratinized foci in terms of horn pearls (670,674). Minor cysts may be seen in the epithelial islands, but no large unicystic structure unless the DGCT has developed from a COC. The most conspicuous cell type is the ghost cells. They are enlarged lightly eosinophilic epithelial cells, which may occur individually or more common in clusters. They seem to develop from the stellate cells. Some of them may contain central nuclear remnants, but most of them show a sharply defined empty space where the former nucleus was placed. Outlines of the individual ghost cells may be discerned. Where basal cells are transformed into ghost cells, the basement membrane disappears, and ghost cells extrude into the fibrous connective tissue and evoke a foreign body reaction. The ghost cells show a tendency for calcification, which appears as basophilic granules. The extent of calcification varies from tumor to tumor and may be related to the age of the lesion. Dentinoid is seen in the connective tissue stroma in intimate association with the epithelial islands (596,656) and is a hallmark, which separates the tumor from a conventional ameloblastoma (Fig. 68). It lacks the tubular structure of normal dentin; it resembles the dentin, which can be seen in teeth, which have been traumatized during development. It occurs as small or large irregularly shaped eosinophilic masses, which react as collagen with trichrome staining. It usually contains a few cells and some of them may be entrapped ghost cells. There may be some mineralization of the dentinoid. The stroma is composed of fibrous connective tissue; no embryonic pulp-like tissue is seen in relation to the dentinoid, as it may be the case in OaCCOTs.

Figure 67 Dentinogenic ghost cell tumor (DGCT). Segment of peripheral DGCT in the palatal gingiva of a 52 year-old man. Nearly all tumor cells are transformed into ghost cells. H&E stain.

Figure 68 Dentinogenic ghost cell tumor. From an intraosseous tumor in the posterior part of the mandible of a 63-year-old woman. For details see case No. 11 of Ref. 475. Numerous ghost cells (red) are seen in the irregular islands of tumor epithelium. Dentinoid (blue) is formed in the stroma in close contact to the epithelium. Masson trichrome.
In the peripheral DGCT (Fig. 69) the proliferation of the tumor epithelium may or may not be in continuity with the gingival or palatal surface stratified squamous epithelium, which seems stimulated to proliferate. Whether the tumor in some cases may arise from the basal cell layer of the surface epithelium is an unsolved question.

A single case has been published of an intraosseous DGCT with a conspicuous component of clear cells. The tumor caused destruction of the anterior part of the mandible and extended into the floor of the mouth (675). The presence of a prominent number of clear cells in an odontogenic tumor is considered a sign of malignancy (677). It is unknown how many clear cells are needed to create an impact on the prognosis of the tumor. The tumor had been growing slowly; it was treated by marginal mandibulectomy followed by an iliac bone graft. There was no evidence of recurrence or metastasis for three years and two months after surgery, but a follow-up of 15 to 20 years is needed for conclusions.

**Immunohistochemistry.** Several investigators have studied CK in DGCTs, extraosseous as well as intraosseous (607,636,666,668,673,675,676,678). The results from use of broad-spected CK-antibodies have been somewhat contradicting; Günhan et al. (678) used DAKO K-528 and detected a strong reaction from fragment of cells around ghost cells, and a questionable reaction in ghost cells. López-Tarruella et al. (673) used AE1/AE3 and tested CK-8 as well; all ghost cells were negative. All other investigators who used AE1/AE3 (607,666,668,675,676) found a strong, although not always homogeneous immunoreaction in tumor epithelium and a positive reaction from ghost cells in most cases.

Lukinmaa et al. (636) used high mw CK antibodies, 34BE12, and found a strong reaction in the tumor epithelium, while all ghost cells were negative; using the same antibodies on two peripheral DGCTs, five COCs, and three OaCCOTs, Fregnani et al. (607) confirmed the findings in the tumor epithelium but found positive reaction in ghost cells in some cases (the variants were unspecified).

Kusama et al. (613) created antibodies against hard α-keratins and tested pilomatrixomas, cranio-pharyngiomas, and COCs and detected consistent and strong reactions from all types of ghost cells. The fact that antibodies to most other CKs have been raised against soft keratins may explain the previous inconsistent results.

Antibodies against low mw CKs have been used in three studies (607,636,675). Lukinmaa et al. (636) used PKK-1 (CK-8, CK-18, CK-19); the reaction was strong in the tumor epithelium except ghost cells, which were negative as expected. Fregnani et al. (607) used several types of monoclonal antibodies against CKs. Tumor cells reacted positively to CK-8, CK-14, and CK-19 in all cases. Yoon et al. (675) confirmed the latter findings—a positive reaction was found in ameloblastic as well as in the clear cells, which were present in that particular tumor.

EMA and carcinoembryonic antigen (CEA) was studied by Mascrè et al. (588), with negative results. Günhan et al. (678) studied the same antigens and detected immunoreaction for both antigens in laminated fragments around ghost cell.

Studies of S-100 protein have yielded contradicting results. Günhan et al. (678) found a strong reaction in ghost cells; Yoon et al. (675) did not find any reaction from S-100 in tumor epithelium, including ghost cells.

Lukinmaa et al. (636) detected a prominent staining for tenascin in the connective tissue in a peripheral DGCT; the walls of the blood vessels were positive, the staining in the tumor epithelium was weak.

PCNA L.I. and Ki-67 L.I. were studied by Fregnani et al. (607) in two cases of extraosseous DGCT. One case was totally negative; in the other case the L.I. was low, about four times lower than in intraosseous COC. The PCNA L.I. (mean and range, %) was 5 (<1–10) and the Ki-67 L.I. (mean and range, %) was 0.5 (<1–1). Piattelli et al. (666) using Mib-1 reported a strong positive reaction (30–40%) in the basal and suprabasal cell layers of the tumor islands of an extraosseous DGCT, and some reaction in the stellate cells (5%). Ghost cells and dentinoid were negative. lezzi et al. (668) confirmed these results without indicating any L.I.

The antiapoptotic protein Bcl-2 was studied in four investigations (607,666,668,676). Piattelli et al. (666) detected a strong immunoreactivity in the basal and suprabasal cells and cells adjacent to ghost cells of tumor epithelium. Ghost cells and dentinoid were negative. These findings were confirmed by Fregnani et al. (607) and lezzi et al. (668). Kim et al. (676), however, did not find any reaction to Bcl-2 antibodies in an intraosseous DGCT.

In the same studies mentioned above Piattelli et al. (666) and lezzi et al. (668) investigated p53 proteins. In the former study a few positive cells were found between the odontogenic epithelium and...
the dentinoid. Ghost cells and dentinoid were negative. Iezzi et al. could confirm the latter findings, but detected a few positive cells in the tumor islands and in the dentinoid.

Kim et al. (676) studied β-catenin in an intraosseous DGCT by means of immunohistochemistry, TUNEL assay, and gene mutation analysis. A missense mutation of β-catenin was found (vide infra) and the TUNEL assay, which discloses fragmented DNA ends of apoptotic cells, showed positive signals in nucleated cells adjacent to the ghost cells. Immunohistochemistry showed nuclear, cytoplasmic, and membranous accumulation of β-catenin in the tumor cells.

Electron Microscopy. Chen et al. (619) studied the ultrastructure of an intraosseous DGCT in details. The basal cells were cuboidal or low columnar; they were attached to neighboring cells by a few desmosomes and to lamina densa by hemidesmosomes. At the interface toward the stroma a lamina lucida and a lamina densa was seen. Individual or small bundles of tonofilaments were seen in the cytoplasm, scattered or attached to desmosomes or hemidesmosomes. A moderate number of organelles in shape of mitochondria, RER, and ribosomes were present. The nuclei were irregularly ovoid with irregular clumped chromatin along the inner nuclear membrane. Nucleoli were small. The cells of the stellate reticulum-like layer were polygonal and had more desmosomes and more villous-like cytoplasmic projections than the basal cells. They were surrounded by prominently expanded intercellular spaces. Bundles of tonofilaments were scattered in the cytoplasm, and a few keratohyaline granules could be found and an infrequent Golgi apparatus. Ribosomes were clustered as polyosomes; mitochondria and endoplasmatic reticulum were moderately dilated. The nuclei were irregular circular with slightly condensed chromatin and a small nucleolus. The ghost cells were mostly anuclear and much enlarged compared with the stellate cells. Some contained pyknotic nuclei and residues of chromat in the nuclear zone. Thick electron-dense fibrils of uniform size were found in the cytoplasm outside the large empty space previously occupied by the nucleus. Small needle-like crystals could be found in the ghost cells. In most of the cells the desmosomes and the villous-like projections had disappeared, and some of them had plasma membranes, which were thickened and irregularly disrupted. A fourth cell type was described, the “hornified cells,” which in contrast to ghost cell contained evenly distributed tonofilaments oriented in different directions and occasional residues of markedly dilated organelles. The plasma membrane was thickened. These cells resembled those found in keratinized oral surface epithelium. They were seen scattered between ghost cells and stellate cells. Focal accumulations of ghost cells and hornified cells in the connective tissue were a frequent finding as well. Mineral crystals were deposited on bundles of tonofilaments of the ghost cells in the epithelium as well as in the connective tissue.

Molecular-Genetic Data. Kim et al. (676) investigated the β-catenin gene in a case of intraossseous DGCT with extensive destruction of the mandible and extension into the floor of the mouth. The tumor contained a missense mutation on codon 3 (ACT → TCT) of the β-catenin gene. Immunohistochemistry and a TUNEL assay were performed on the same tumor (vide supra). Mutations of the β-catenin gene were also found in COCs by Sekine et al. (156) but were rare in solid/cystic ameloblastomas.

Differential Diagnosis. The histomorphological pattern of the peripheral DGCT may resemble that of the PERAM, but the presence of clusters of ghost cells and dentinoid differentiates the DGCT from the ameloblastoma. The most difficult differential diagnosis may be the rare cases of multicystic COCs with some proliferation of odontogenic epithelium in the connective tissue. Sufficient information about clinical and radiographic features is crucial, particularly in case of intraosseous lesions. A COC is characterized by a rounded unicystic well-defined radiolucency. Microscopically the diagnosis of a DGCT requires a conspicuous amount of noncystic epithelial islands. The most important differential diagnosis is toward the GCOC. The clinical course of the GCOC is more aggressive. Microscopically the GCOC shows increased cellular density of small cells with sparse cytoplasm, darkly stained nuclei, and many mitoses as well as areas with necrosis. Mitoses are extremely rare in the DGCT. A GCOC may arise in a COC or DGCT, in such cases adequate sampling is extremely important since the lesion may contain benign-looking as well as malignant areas. The presence of islands of clear cells have been described (675). This cell type is considered a sign of malignancy when encountered in ameloblastomas (677), and may have a similar impact in a DGCT.

Treatment and Prognosis. Excision is an adequate treatment of peripheral DGCTs, recurrence has not been reported. Intraosseous DGCTs require wide marginal resection. Tumors that have been treated by enucleation have recurred, although it may take some years before the recurrence is evident. Li et al. (579) reported two cases, which were enucleated twice before they were resected. Both recurred twice. One case has been reported to recur five years after segmental resection. No other case has recurred after wide marginal resection, but the follow-up time has been limited in most cases. The longest have been 10 years (671), 4 years (674), and 3 years (675). A post-surgical follow-up time of 15 to 20 years is recommended.

Malignant transformation is a possibility, but seems to be extremely rare, although the number of published cases of GCOCs exceeds the number of DGCTs.

3. Tumors of Odontogenic Ectomesenchyme With or Without Included Odontogenic Epithelium

This group of tumors covers the following recognized entities: odontogenic fibroma, GCOT (or fibroma), ODOMYX/myxofibroma, and CEMBLA. None of them occur outside the jaws; they are believed to arise from odontogenic ectomesenchyme.
3.1 Odontogenic Fibroma

Introduction. The odontogenic fibroma is a rare, benign, expansively slowly growing, noninfiltrating odontogenic tumor composed of proliferating fibrous tissue containing various amounts of more or less inactive-appearing odontogenic epithelium. It is the most ill defined and least understood of the neoplasms of odontogenic origin. In the 1992 edition of the WHO classification of odontogenic tumors (23) it was stated: “Further subdivision of this group may become necessary, but at present criteria have not been agreed and differences in behavior have not been established.” Unequivocal criteria for the diagnosis of the lesion have still not been established, so the following description comprises tumors, which vary from radiologically rather ill-defined lesions to well-defined with a radiolucent border, from encapsulated to nonencapsulated lesions, from hypercellular fibrous tumors to some with moderate cellularity, from lesions with no odontogenic epithelium via some with moderate amounts of epithelium to tumors dominated by proliferating odontogenic epithelium.

In the WHO classification of 2005 (12), the tumor has been divided into two subtypes: epithelium poor type and epithelium rich type.

ICD-O code 9321/0
Synonyms: odontogenic fibroma simple type (without epithelium), odontogenic fibroma complex type, also called WHO-type (with epithelium). These terms are obsolete.

Like most odontogenic tumors the odontogenic tumor occurs as an intraosseous/central variant and an extraosseous/peripheral variant.

3.1.1 Central Odontogenic Fibroma.

Clinical Features. The prevalence and incidence of the tumor is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 1.4% to 4.9% in studies comprising more than 300 samples of odontogenic tumors. The reviews cited in the following are the few in which a subdivision between central and peripheral odontogenic fibromas has been made. The results are indicated as follows: number of odontogenic tumors/number of COFs/\%.

Daley et al., Canada (33): 392/19/4.9%, Mosqueda-Taylor et al., Mexico (34): 349/5/1.4%, Buchner et al., California (30): 1088/16/1.5%.

Approximately 60 cases of the COF have been published. The most recent reviews of the rare tumor have been published by Handlers et al. (679) and Kaffe et al. (680). Handlers et al. reviewed 39 cases, 19 from own files and 20 from the literature, Kaffe et al. reviewed 51 cases, 5 from own files and 46 from the literature, and focused on the radiology of the lesion. The COF may be seen at any age, but is discovered most frequently in the second to fourth decades. The age range among the 51 patients (680) was 4 to 80 years, with 55% of the patients between 11 and 39 years. The mean age was 34.4 years (33.5 years for males, and 33.8 years for females); the median age was 30 years (28 years for males, 33 years for females).

The tumor is primarily seen in females. Thirty-five (68.6%) of the tumors were diagnosed in females and 16 (31.4%) in males. The gender ratio M:F is thus 1:2.2.

The distribution between the jaws is almost equal. In the review by Kaffe et al., 23 (45%) were found in the maxilla and 28 (55%) in the mandible. In the maxilla the COF occurred mostly in the anterior area (65%), in the mandible it is most common in the premolar (32%) and the molar (54%) regions.

COF is a slowly growing tumor. Heimdal et al. 1980 (681) reported a case of recurrent COF in the mandible, where the recurrence was overlooked on a radiogram four years after removal, when it measured 7\times7 mm; it was diagnosed five years later when it measured 25\times25 mm; it thus took nine years to reach that size. Dahl et al. reported a case of a large COF in the posterior mandible of an 80-year-old man. The tumor was not removed because of the age of the patient. The tumor exhibited limited growth and few symptoms till the patient died four years later for other reasons.

Handlers et al. (679) reported the symptoms from a review of 39 cases. In 36 cases the tumor was asymptomatic, three patients experienced slight sensitivity, and in five cases—but none of them in the anterior regions—the tumor was associated with an unerupted tooth. Kaffe et al. (680) observed bone enlargement in 28 (55%) of 51 cases.

Three cases of a rare syndrome with multiple COF-like lesions combined with enamel dysplasia have been published (682).

Imaging. The COF exhibits a great variation in radiological appearance. Some are small and unilocular (Fig. 70), others are large and multilocular; the latter

Figure 70 Central odontogenic fibroma between the first and second left mandibular incisor in a 9-year-old boy. The tumor was well delineated.
may resemble ameloblastomas or myxomas (683). Kaffe et al. (680) reviewed the radiographic features of 51 cases. The majority of COFs were unilocular with well defined, sometimes sclerotic borders, some were multilocular, some had poorly defined and some had diffuse borders. A few exhibited some radiopacity. The size varied from less than 1 cm to more than 5 cm at longest diameter. The unilocular tumors were below 4 cm, most were below 3 cm. A few of the multilocular were small (1-2 cm), but most were more than 3 cm. The tumor was radiolucent in 45 of 51 cases; 6 (3 in the maxilla, 3 in the mandible) showed a mixed radiolucent–radiopaque appearance. Border definition was mentioned in 45 cases, 33 were well defined, 5 were poorly defined, and 7 were diffuse. Among the 51 cases, the COF was associated with the crown of an unerupted tooth in 14 cases (27%), usually the incisors in the maxilla, and the third molars in the mandible. In six cases (12%) the tumor was found associated with roots of teeth, and in five cases (10%) it presented as a periapical lesion. Further more 15 (29%) were not tooth associated and 3 (6%) were located in edentulous areas. Tooth displacement was found in 25 of 45 cases and root resorption of adjacent teeth in 13 of 45 cases.

**Pathology.** The etiology of the COF is unknown. It is believed to arise from odontogenic ectomesenchyme, from the periodontal membrane in the cases that develop around the roots of teeth, and possibly from the dental sac in cases where the tumor is associated with the crown of an unerupted tooth. Wright et al. (684) demonstrated oxytalan fibers in the calcified material of periapical odontogenic fibromas, which supports the assumption that these lesions are of periodontal ligament origin.

Macroscopically, the COF is tan (685) or white, homogeneous, and glistening (686) in color and has a rubbery texture and a slightly hemorrhagic appearance. The cut surface may have a gritty consistency.

The WHO 2005 classification of odontogenic tumors (12) recognized two histological variants of COF, an epithelium-poor type and an epithelium-rich type. Variants of COFs exist, however, which exhibit a very well-demarcated, smooth surface covered with a thin fibrous capsule and contain no odontogenic epithelium at all (Figs. 71, 72). They exhibit a connective tissue with moderate cellularity; the fibroblasts are seen in clusters surrounded by bundles of collagen with a slightly whorled and interlacing pattern. Such a tumor should not be classified as myxofibroma, which is an invasively growing tumor and requires more radical surgery. The histopathology of the epithelium-poor type (687) resembles that of a dental follicle. Moderate cellularity is seen, fibroblasts with primarily ovoid nuclei exhibiting finely dispersed chromatin, and distinct small nuclei are uniformly distributed between delicate collagen fibers and a considerable amount of ground substance. The nuclei may be plump and stellate. There is no mitotic activity. Scattered inactively-looking islands of odontogenic epithelium with various shapes are seen (Fig. 73). They do not exhibit peripheral cylindrical and palisading cells nor do they contain stellate reticulum-like cells. Various forms of calcifications may be seen.

The epithelium-rich type (687) is characterized by a cellular fibroplastic connective tissue interwoven with less cellular and often vascular areas. Some have a “pushing border,” but many show an irregular border. The fibroblasts are elongated, spindle-shaped with dense nuclei. The cytoplasmic membranes are indistinct. There is no mitotic activity. The collagen is organized in parallel bundles of fibers, which show an interlacing pattern, and sometimes form a “herringbone pattern” (22). Islands and strands of inactively-looking odontogenic epithelium are an integral component. They contain cuboidal cells with uniformly stained predominantly round, but sometimes polygonal nuclei. In some tumors the epithelium exhibits long narrow strands of cells with a lightly stained
cytoplasm (679). Periepithelial hyalinization is usually not seen. Foci of calcified material are often seen with varying histomorphology resembling dysplastic cementum (Fig. 74), osteoid or dentinoid, the latter in particular is seen in close contact with the odontogenic epithelium. The epithelial component may be so abundant that it is tempting to consider the lesion an epithelial tumor. The demonstration of abundant proliferating epithelium and the induction of dentinoid suggest that the epithelium has more than a casual role (688). Ide et al. (465) published two cases of this variant, which they called ameloblastomatoid, central odontogenic fibroma. One of them contained a markedly cellular fibromatous connective tissue with numerous strands and islands of active-looking odontogenic epithelium (Fig. 75). The connective tissue had no similarity to the dental papilla. No mineralized matrix was seen. Large epithelial sheets exhibited palisading of the peripheral cells, with the nuclei showing reversed polarity and apical vacuolization. In the larger islands many glycogen containing clear cells were seen. A hyalinized cuffing was present adjacent to the epithelium. The epithelium thus showed some features common with an ameloblastoma, but at the same time showed a tumor-like highly cellular connective tissue. It is difficult to consider such a tumor a variant of a COF.

Allen et al. (689) reported three cases of epithelial-rich COF with features of a central giant cell granuloma. Fowler et al. (690) reported three additional cases, and Odell et al. (691) published eight cases of this variant, two of which recurred after curettage, one case with cortical perforation. The recurrent lesion showed the same hybrid pattern as the initial lesion. The behavior of this variant is thus more like a central giant cell granuloma than like that of a COF.

**Immunohistochemistry.** Few histochemical studies of the tumor have been performed. Gao et al. (168) used antibodies against morphogenetic proteins in two cases of COF. The cells of the tumor were almost negative, except for some weak positive reaction in some odontogenic epithelial cells. In the unusual ameloblastomatoid cases of COF published by Ide et al. (465), the epithelial cells were strongly positive for broad spectred CK (AE1/AE3) and focally positive for CK-19.

**Electron Microscopy.** The ultrastructure of the COF was studied by Wesley et al. (686) and Watt-Smith et al. (692). Wesley et al. found fibroblast-like cells surrounded by numerous wavy collagen bundles. The cells were elongated with large central nuclei with an irregular nuclear membrane and a narrow band of peripherally clumped heterochromatin and uniformly distributed euchromatin. Dense small intranuclear inclusions were seen in some cells. The cytoplasm exhibited a prominent Golgi complex and large number of microfilaments. No tonofilaments were seen. Small amounts of RER were seen, some with dilated cisternae containing amorphous material. Small numbers of free ribosomes, empty vacuoles, and occasional lysosomes were present as well. Watt-Smith et al. (692) found that the fibroblastic cells exhibited features of myofibroblasts, they showed characteristics of both smooth muscle cells and fibroblasts.

**Molecular-Genetic Data.** No data are available.

**Differential Diagnosis.** The differential diagnosis is difficult and depends primarily on exclusion of other lesions (54). The diagnosis should be based on the overall histomorphology combined with the radiographic appearance of the lesion.

If the tumor does not contain odontogenic epithelium the following differential diagnoses should be considered: hyperplastic dental follicles, ODOMYX/myxofibroma, desmoplastic fibroma, (cemento-) ossifying fibroma, neurofibroma, and low-grade histiocytical sarcoma. In absence of odontogenic epithelium the majority of the epithelial islands are small, narrow and elongated and consist of small polyhedral or cubic cells. Myxoid changes (right) were seen in many areas, the tumor could be termed myxofibroma. van Gieson–alcin blue stain.
the diagnosis of COF should be made with caution (23). Lack of odontogenic epithelium does not preclude the diagnosis of odontogenic fibroma, but if the tumor does not have a rim of reactive bone at the border or exhibits a capsule, the diagnosis is likely not to be COF.

Hyperplastic dental follicles show a histomorphology, which may be indistinguishable from a COF. Evaluation of the size, location, and radiographic features should make it easy to exclude dental follicles.

The myxoma is characterized by a conspicuous myxoid component with scattered spindle, stellate, or rounded fibroblasts in contrast to the fibrous component of the COF. The myxofibroma is more fibrous and may be more cellular in areas, but show marked myxoid areas, which are not seen in the COF. Since both these tumors are growing invasively it is important to include the radiographic or other imaging features in the diagnosis.

The desmoplastic fibroma contains neither odontogenic epithelium nor hard tissue formation. It is characterized by mature fibroblasts exhibiting plump ovoid or long slender nuclei and prominent collagen-whorled bands, often broad bands. Like the COF it may resorb the roots of neighboring teeth. It is an invasively growing tumor. Few COFs are highly collagenous.

The (cemento-) ossifying fibroma shows a prominent hard tissue formation, which matures toward the center of the lesion.

The neurofibroma, the myxofibroma, and the low-grade histiocytic sarcoma should be differentiated on their histological features and immunohistochemical reactions.

If epithelium is present the following lesions must be excluded: hyperplastic dental follicles, myxoma/myxofibroma, AMF, AFD, and ameloblastoma.

The dental follicles may contain reduced enamel epithelium and hyperplastic odontogenic epithelium besides a histomorphology similar to that of COF. The size, location, and radiographic features of the lesion should make it easy to exclude a dental follicle.

A few scattered islands of odontogenic epithelium may be seen in myxomas and myxofibromas. The differential diagnosis is made on basis of a combined evaluation of the radiograms and the mesenchymal component of the tumor.

The epithelial component of the AMF and the AFD differs from that of the COF by forming bilaminar ramificating strands with formation of buds, which show cylindrical basal cells and may contain stellate reticulum-like cells. The ectomesenchymal component may focally be slightly fibrous, but overall it resembles the dental papilla.

Apart from the above-mentioned rare cases of ameloblastomatoid COFs the differential diagnosis toward the invasively growing ameloblastoma should be straightforward. The ameloblastoma always exhibits a fibrous, vascular stroma with moderate cellularity.
Treatment and Prognosis. The required treatment is enucleation and vigorous curettage and the prognosis is very good. Dunlap et al. (693) reported two cases, which were followed for 9 and 10 years without recurrence. Recurrence has been reported in a few cases (681, 694). Kinney et al. (685) reported a thought-provoking case of aggressive epithelium-rich COF with ill-defined margins around the roots of a mandibular right second molar. It measured 2.5 cm and was asymptomatic apart from a slight buccal expansion. It was enucleated and separated easily from the adjacent bone. Histology was compatible with a COF, no clear cells were observed in the epithelium. One year later it recurred with marked expansion, painful swelling, and paresthesia of the lower right lip and chin. The lesion encompassed the entire right mandible with buccal and lingual erosion and perforation. Histological examination showed CCCG.

3.1.2 Peripheral Odontogenic Fibroma.

Introduction. The peripheral odontogenic fibroma (POF) is a benign, slowly growing, exophytic lesion occurring on the gingiva or the attached alveolar ridge mucosa in edentulous areas. Histologically it consists of an unencapsulated, focal mass of hypercellular fibrous and sometimes myxoid connective tissue that contains varying numbers of odontogenic epithelial islands or strands (444, 695). The tumor was recognized in the 1971 and the 1992 WHO classification of odontogenic tumors (22, 23), but only digressively mentioned in the 2005 edition (687).

ICD-O code 9322/0

Synonyms: There are no synonyms, but cases have been published under diagnoses like “odontogenic gingival epithelial hamartomas,” “hamartoma of the dental lamina,” “peripheral ameloblastic fibrodentinoma,” and “peripheral ameloblastoma” (695). The term “hamartoma” was introduced to designate a tumor-like but nonneoplastic malformation or inborn error of tissue development characterized by an abnormal mixture of tissues indigenous to the part with excess of one or more of these tissues (15). Odontomes are hamartomas, they develop during the odontogenic period, which ceases about the age of 22 years, but the term cannot be legitimately used for tumor-like lesions of odontogenic tissue with self-limiting growth potential, which primarily occur in patients past that age.

Clinical Features. The prevalence and incidence of the POF is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years was 3.1% and 8.9% in two studies comprising more than 300 samples of odontogenic tumors and in which a subdivision between the central and the peripheral odontogenic fibroma has been made. The results are indicated as follows: number of odontogenic tumors/number of POFs/%. Daley et al., Canada (33): 392/35/8.9%, Mosqueda-Taylor et al., Mexico (34): 349/11/3.1%.

The POF seems far more common than the COF. Somewhat more than 120 cases have been reported. Several reviews have been published (212, 444, 688, 695–697). Daley et al. reviewed 36 cases from own files and 73 from the literature including cases from earlier reviews; operculae were not included. The age was indicated in 103 cases; the age range was 2 to 80 years, but there were few children below 10 years and few adults over 70 years. There was an age peak in the third decade and a somewhat lower, but almost equal number of patients in the fourth, fifth, sixth, and seventh decades. Siar et al. (696) reported 46 cases in Malaysians and calculated the mean age to be 32 years.

The gender distribution in the review by Daley et al. was quite different from that of the COF; the ratio was more balanced, among 107 cases 48 were males and 59 females.

In the same review the anatomic site of the lesion was stated in 59 cases. All sites and both buccal and lingual gingiva were affected. In the maxilla there was a predilection for the anterior region, in the mandible there was a predilection for the cuspid/premolar region. Garcia et al. (697) reported 17 cases of which 68% was found in the posterior region of the mandible.

Clinically the POF usually presents as a pedunculated or sessile, firm, non tender gingival mass of normal color. The size varies from 0.3 to 2.0 cm, with mean size of 1.0 cm (695). Occasionally displacement of teeth is seen. If traumatized by occluding teeth, the lesion may be inflamed or even ulcerated. Bleeding on tooth brushing was reported in 13 of 46 cases (28%) by Siar et al. (696). In the same review duration of symptoms in general ranged from one week to 10 years.

Imaging. De Villiers Slabbert et al. (688) reviewed 30 cases of POF from own files and reported that radiograms frequently showed calcified material inside the COFs.

Pathology. The COF shows a wide histological spectrum (688). All are nonencapsulated and most are poorly delineated. In all of them odontogenic epithelium is present (Fig. 76). In a review of 30 cases from...
Figure 77 Peripheral odontogenic fibroma with hard tissue formation. Numerous strands and islands of odontogenic epithelium as seen in a cellular mesenchymal connective tissue. The hard tissue is formed in close contact with the epithelium, histomorphologically it resembles cementum. H&E stain.

own files, de Villiers Slabbert et al. (688) found that the odontogenic epithelium was sparse in 15 cases, in 9 it was moderate, and in 6 it was exceptionally abundant, with little fibrous tissue between the islets. Most epithelial islands were small. In a few cases the odontogenic epithelium was intimately associated with hard tissue, which was recognized as dentinoid on basis of its histomorphology (Fig. 77). The connective tissue component varied; in most cases it presented as a cellular fibrous tissue with streaming and whirling, in some cases it was relatively acellular with abundant collagen. Myxomatous areas could be encountered. Buchner (695) described a pattern of markedly cellular strands of mesenchymal tissue interwoven with less cellular areas and occasionally observed cuffing of epithelial cells around mineralized material. In the review of POF he reported mineralized or unmineralized hard tissue in 20 (57%) of 35 cases; it was absent in 15 lesions. De Villiers Slabbert et al. (688) observed calcified material with great morphological diversity in 22 (73%) of 30 cases. They also noticed elongated rete ridges from the surface epithelium in 8 cases (27%) and inflammation due to trauma in all 30 cases.

Immunochemistry. Daley et al. (444) used high and low mw CK antibodies and detected a positive reaction in the odontogenic epithelium. Immunohistochemical studies have mainly concentrated on POFs with granular cells, which are discussed in the section on GCOT.

Electron Microscopy. The ultrastructure of the POF has been studied by Daley et al. (444) in two cases with a moderate cellular connective tissue and numerous islands and thin strands of odontogenic epithelium with hyaline cuffing. The epithelial cells exhibited desmosomes and tonofilaments that were focally prominent. The cytoplasm contained numerous polyribosomes, but a poorly developed endoplasmatic reticulum. The nuclei were round to oval; frequently they showed indentations and often a well-developed nucleolus. Occasionally epithelial cells with clear cytoplasm was seen, they had an organelle-poor cytoplasm. The fibroblastic cells were spindle- to kite-shaped and had oval nuclei. The cytoplasm contained a RER, which was more developed than in the epithelial cells. Collagen fiber bundles were seen in the extracellular matrix but they were not abundant. The hyaline cuffing adjacent to the epithelial islands consisted of condensations of collagen fibers, which were orientated more or less parallel to the cell membrane.

Molecular-Genetic Data. No data are available.

Differential Diagnosis. Several so-called peripheral ossifying fibromas have been misdiagnosed as POF. It is totally different lesion. It is unrelated to the central ossifying fibroma and is probably better termed “peripheral granuloma with ossification/calcification” or “calcifying fibroblastic granuloma.” The main histological difference is that it is highly cellular, does not contain odontogenic epithelium, and does not exhibit a pattern of cellular areas interwoven with relatively less cellular areas.

POFs should be differentiated from peripheral AMF and peripheral AFD; both these neoplasms seem to develop as intraosseous lesions exclusively. A case reported as a peripheral AMF in a 40-year-old women (443) did not contain dental papilla-like connective tissue and is better classified as a POF. A case published as peripheral AFD (476) should also be considered a POF for the same reasons.

Differential diagnosis toward PERAM may be very difficult. The connective tissue in the ameloblastoma is a fibrous vascularized stroma with relatively few cells and the morphology of the epithelium is different and shows at least in some areas cylindrical peripheral cells with hyperchromatic nuclei with reversed polarity and a cytoplasm with vacuoles. The stroma of the ameloblastoma has a much lower cellularity than the connective tissue component of the POF.

The POF should also be differentiated from peripheral CEOT, which is characterized by islands composed of strongly eosinophilic polygonal cells and presence of hyalinized material, which stains positively with stainings for amyloid.

Treatment and Prognosis. The adequate treatment is local surgical excision. Recurrences are not uncommon. Among 30 cases de Villiers Slabbert et al. (688) reported a case of a 1.5 cm POF in the palatal gingiva in a 44-years-old man, which recurred after 14 months. Among 18 cases with sufficient follow-up information Daley et al. (444) reported recurrence in seven cases. Two cases recurred within a year, five cases recurred one to four years after treatment. The follow-up period in the 11 cases that did not recur was 10 months to 11 years. Malignant transformation has not been reported.

3.2 Granular Cell Odontogenic Tumor

Introduction. The GCOT is a rare, benign, slowly growing, noninvasive, but unencapsulated odontogenic neoplasm composed of connective tissue with varying cellularity and a varying amount of...
odontogenic epithelium. Most characteristic are clusters of granular cells in the connective tissue. The tumor shares clinicopathological features with the odontogenic fibroma, but there are indications that the granular cells do not derive from fibroblasts, but rather from a histiocytic cell line.

ICD-O code: None; the tumor was described briefly in the 1992 WHO classification (23) as a variant of the odontogenic fibroma. It was disregarded in the 2005 edition (687).

Synonyms: Granular cell odontogenic fibroma, granular cell tumor of the jaw.

Clinical Features. The tumor is rare. The prevalence, incidence, and relative frequency is unknown.

Brannon et al. (698) published a review of 30 cases of central GCOT. Since then two cases of central GCOT (699,700) and one case of peripheral GCOT (701) have been published. In the review by Brannon et al. the age range was 16 to 77 years (N = 30), the mean age for both gender was 45.4 years; 53.3% of the patients were in the sixth decade. The patients were thus generally older than the patients with COF.

Like the COF the gender ratio showed female dominance. Among 29 cases 7 (26.7%) were males and 22 (73.3%) were females.

The site of the tumor was reported in 29 cases, 7 GCOTs were located in the maxilla and 23 in the mandible, and they were most common in the premolar and molar region.

The duration of symptoms varied from 5 months to 19 years (N = 4). Expansion of bone was recorded in nine cases (N = 22). Facial swelling, intraoral ulceration, maxillary sinus involvement, and cortical perforation were seen (1 case each).

Four peripheral (gingival) lesions have been published. They all occurred in women. The patients were 16-years-old (site not specified) (444), 34-years-old (maxillary premolar area) (457), 40-years-old (maxillary third molar area) (702), and 58-years-old (mandibular incisor area) (701), respectively.

Imaging. In the review by Brannon et al. (698) radiological features were recorded in 22 cases, among these 19 were radiolucent, 2 had mixed density, and 1 was radiopaque. The patterns ranged from unilocular to multilocular, often with sclerotic border. Displacement of teeth was seen in two cases, and displacement of the mandibular canal in one case. The size (N = 12) varied from 0.5 to 8.0 cm, the average was 2.8 cm.

Pathology. The etiology of the tumor is unknown. The pathogenesis is poorly understood, and the nature of the granular cells has not been established with certainty.

The histopathology resembles the odontogenic fibroma apart from sheets and clusters of round to polygonal cells with abundant eosinophilic, finely granular, lightly PAS-positive diastase-resistant cytoplasm (Fig. 78) and an eccentric round to ovoid nucleus (698). The size of the cells ranges from 20 to 50 μm. No mitoses are seen. Lobules of granular cells are separated by thin, fibrous connective tissue septae containing small thin-walled vessels. Cords and islands of odontogenic epithelium are seen scattered in the connective tissue and bordered with low columnar or cuboidal basal cells. No stellate reticulum-like cells are seen in the islands. Epithelial cells with clear cytoplasm are not unusual (698). If the pattern is lobular the epithelium is usually found in the center of each lobule (54). Small oval, basophilic islands of cementum-like tissue are often seen, and dystrophic calcifications may be seen, some with a concentric pattern. Calcifications may be intimately associated with granular cells (698). The periphery of the tumor is generally well demarcated, and in some cases a pseudocapsule is seen.

Two cases of malignant central GCOT (granular cell odontogenic sarcoma) have been published (109,703). The tumor described by Piattelli et al. (703) occurred in the maxilla of a 40-year-old man where it encroached the maxillary sinus and protruded toward the oral cavity. Strands of benign inactive-looking epithelium were scattered in the neoplastic component, which consisted of fibroblast-like spindle cells with slight nuclear pleomorphism and hyperchromatic and pleomorphic granular cells with frequent mitoses. Necrosis was absent.

The peripheral tumors show a similar histopathology. The tumor may extend to the covering gingival epithelium, and extensions from the basal layer of that epithelium may be seen in the tumor as double-stranded prolongations with morphology-like the epithelium deeper in the lesion (457,702).

Immunohistochemistry. Several investigators have tried to disclose the function of the granular cells by immunohistochemical technique on sections of central and peripheral GCOT (698–700,704–711) as well as peripheral GCOT (444,701).

Broad spectred CK antibodies (AE1/AE3) yielded a positive immunoreaction in the cells of the odontogenic epithelium (444,698,701); a strong reaction to CK-14 was detected by Machado de Sousa et al. (711). Meer et al. (700) detected immunoreactivity to CK-marker MNF116 in the epithelial cells. The granular
cells are nonepithelial, they were negative to CK antibodies in all assays (698,700,701,704–706,710,711).

Granular cells were vimentin-positive in most investigations (444,698,700,701,705,706,710,711). Epithelial cells have been invariably negative.

A negative immunoreaction to antibodies against S-100 protein was found in all investigations (444,698–701,705,707,709,710).

Granular cells have also been detected negative to actin, desmin, muscle-specific antigen, neurofilaments, and NSE (700,705,707,709,710).

CD1a, a marker for Langerhans cells could not be detected in granular cells by Brannon et al. (698) and Meer et al. (700). The cells have been tested positive for lysozyme/muramidase, α-1-antitrypsin, α-1-antichymotrypsin, carcinogenic embryonic antigen, and CD68. The latter is a marker for macrophages.

Meer et al. (700) used antibodies against the proliferation marker Ki-67, and the antia apoptotic protein Bcl-2. Granular cells as well as the cells of the odontogenic epithelium were tested negative for Ki-67. Both cell types were positive for Bcl-2.

The immunohistochemical results suggest that the granular cells are mesenchymal in origin and derived from a histiocyteic cell line (700).

Piattelli et al. (703) studied a case of malignant central granular cell tumor. The tumor cells exhibited vimentin and CD 68 immunoreactivity and showed a high Ki-67 L.I. (21%) compared to less than 1% for the epithelial odontogenic cells. The tumor cells were negative for CKs.

Electron Microscopy. The ultrastructure of the GCOT has been studied by Wesley et al. (686), Mirchandani et al. (706), Chen et al. (708), Yih et al. (710), Brannon et al. (698), and Meer et al. (700). The peripheral variant has been studied by Takeda et al. (457). Epithelial cells are attached to each other by desmosomes. Tono filaments, ribosomes, and mitochondriae are scattered in the cytoplasm. The Golgi apparatus is observed in small numbers. Numerous glycogen particles are found. Abundant intercellular collagen fibers are present. The granular cells are large cells with an irregularly curved cell membrane. No desmosomes are seen. The nucleus is ovoid in most cells with an irregularly indented nuclear membrane. The chroma tin is evenly distributed in the nucleus, the nucleolus is moderately large (700,708). Well-preserved mitochondriae and profiles of RER are seen in most cells. The granular cells contain many primary lysosomes, autophagic vacuoles, and phagocytic vacuoles. Numerous intermediate filaments are scattered throughout the cytoplasm, and microtubules are frequently observed (710). Phagocytosis of collagen fibrils have been observed. No Birbeck’s granules have been found, nevertheless it was stated by Chen et al. (708) that the granular cells resembled Langerhans cells more than macrophages and that they were distinct from myofibroblasts and fibroblasts morphologically. They suggested that the granular cells may be immediate precursors of Langerhans cells. Meer et al. (700) found that the ultrastructural findings supported the hypothesis that the granular cells of the central GCOT are of mesenchymal origin with a possible histiocytic cell lineage, and they expressed the opinion that both ultrastructural and immunohistochemical evidence suggest a phagocytic function for the granular cells.

The ultrastructure of the peripheral GCOT was similar to that of the central variant (457).

Molecular-Genetic Data. No data are available for benign GCOT. The genetic portrait of a malignant GCOT (granular cell odontogenic sarcoma) was studied by Carinci et al. (109). By using cDNA microarray they identified several genes, which were significantly differentially regulated when compared with nonneoplastic tissues. The cancer-specific genes included a range of functional activities like transcription, signal transduction, cell-cycle regulation, apoptosis, differentiation, and angiogenesis.

Differential Diagnosis. The differential diagnosis must include the granular cell type of the s/mAM. The granular cells in ameloblastomas are epithelial. The epithelial islands are much larger, are a dominant component of the neoplasm, and in most cases some of them will show stellate reticulum-like cells in the center and cylindrical peripheral cells with hyperchromatic nuclei with reverse polarization and intracytoplasmic vacuoles. The connective tissue in ameloblastomas is a fibrous vascularized stroma with moderate cellularity.

In some GCOTs the granular cells are so sparse that they are easily overlooked, or it seems more reasonable to use the term “epithelium-rich odontogenic fibroma with granular cells.” In neither case does it have any impact on the treatment and prognosis.

Treatment and Prognosis. The central GCOT is easily enucleated and has a tendency to encapsulate. Most tumors have been treated by conservative surgical removal, mostly enucleation and curettage. The peripheral GCOT is adequately removed by surgical excision. The prognosis is good. The cases reported have been entirely benign, except for a case in the maxilla of a 40-year-old man reported by Piattelli et al. (703), and the one studied by Carinci et al. (109). Recurrence is rare and metastases have not been reported (700).

Brannon et al. (698) reviewed 12 cases with adequate follow-up data; in 11 cases with follow-up from 2 to 15 years there was no recurrence. One case in the posterior maxilla of a 19-year-old woman recurred 13 years after curettage, it had increased in size; it showed the same histological features as the primary tumor, except that the granular cell component encompassed numerous medium-sized peripheral nerves.

3.3 Odontogenic Myxoma and Myxofibroma

Introduction. The ODOMYX is a benign, but locally invasive intraosseous neoplasm characterized by spindle, rounded or stellate cells embedded in an abundant myxoid or mucoid extracellular matrix. When a relatively greater amount of collagen is evident, the term myxofibroma may be used (712).

ICD-O code 9320/0.

Synonyms: Odontogenic fibromyxoma
Clinical Features. The prevalence of ODOMYX is unknown. A prospective study over a four-year period was carried out in Tanzania by Simon et al. (713) who calculated the annual incidence to be 0.07/ million. Although it is a rare tumor, it is the third-most common odontogenic tumor after the odontomes and the ameloblastomas in most surveys. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 2.2% to 17.7%, in studies comprising more than 300 samples of odontogenic tumors. In the following the results are indicated as follows: number of odontogenic tumors/number of myxomas/% of all cases. Regezzi, Michigan, U.S.A. (31): 706/20/2.8%, Gümhan, Turkey (32): 409/20/5.6%, Daley, Canada (33): 392/ 24/5.1%, Mosqueda-Taylor, Mexico (34): 349/62/ 17.7%, Ochsenius, Chile (35): 362/32/8.8%, Adébayo, Nigeria (36): 318/38/11.9%, Fernandes, Brazil (37): 340/31/9.1%, Ladeinde, Nigeria (38): 319/21/6.5%, Buchner, California (30): 1088/24/2.2%, Jones, England (2006, pooled figures from two studies) (39,40): 574/25/4.4%, Olgac, Turkey (41): 527/83/ 15.7%, and Jing, China (42): 1642/76/4.6%. The differences in frequency are conspicuous, but may only reflect differences in the type of lesions, which are considered necessary to send for histological diagnosis.

The age range is difficult to estimate because in a number of studies the age is indicated as the number of patients in decennia only. The range seems to be about 5 to 72 years, if the cases of infantile extraosseous paranasal myxomas are excluded (714). A number of such cases have been published as maxillary myxomas (715–719); they are not odontogenic. Jing et al. (42) found a mean age of 25.3 ± 13.2 years in 76 patients. Ochsenius et al. (35) found a mean age of 24.3 ± 14.5 in 32 patients. The mean age of 448 cases from the literature was 28.9 years (720). In most studies the majority of patients occurs in the second and third decennium. Kaffe et al. (721) found 75% of 164 patients in the age groups between 11 and 40 years, and 49% between 20 and 39 years, other findings for the latter age groups have been 53.1% (442), 54.2% (41), and 44.7% (42).

The gender ratio has varied in the studies published; but in most cases it has been close to 1:1. In 213 cases from the literature, Farman et al. (722) found an M:F ratio of 1:1.3, Kaffe et al. (721) found an M:F ratio of 1.15 (N = 164), and MacDonald-Jankowski et al. (720) found 229 males and 335 females in 564 reported cases of 1:1.5. In four publications, which comprise more than 50 cases of ODOMYX the M:F ratio has been as follows: an exceptional 1:2.1 in a study of 61 cases from Mexico by Mosqueda-Taylor et al. (34); 1:1.1 (N = 83) in a study from Turkey (41), and 1:1.1 (N = 76) in a study from China (42). In general ODOMYX seems to be a slightly more common in women than in men.

ODOMYX may be present in any area of the jaws. It is striking that tumors are more common in the mandible than in the maxilla in three studies, which are mainly based on collected cases from the literature than in four studies based on cases from the archives of one or a few diagnostic services. Farman et al. (722) found a maxilla:mandible ratio of 1:1.6 in 176 cases from the literature, Kaffe et al. (721) found 55 in the maxilla and 109 in the mandible, a ratio of 1:2 in 109 cases, and MacDonald-Jankowski et al. (720) a ratio of 1:1.3 in 536 cases.

In the studies from the diagnostic services the ratios were 1:1 (N = 50) (34), 1:1.1 (N = 64) (442), 1:1 (N = 83) (41), indicating an almost equal occurrence in the two jaws.

In most studies the majority of ODOMYXs have been located in the posterior part (including the premolar area) of the maxilla or the mandible with very few cases located in the anterior areas (34,42,442). Large tumors often comprise the posterior as well as the anterior region (720).

A few cases of peripheral ODOMYXs have been published. Some of these are better diagnosed as oral fucinclusion (723,724). Others are myxomas, which present with a gingival swelling together with a conspicuous destruction of the underlying bone making it difficult to decide if the center of origin was intra- or extraosseous (725). No case of extraosseous myxoma in a tooth-bearing area with only slight erosion of the underlying bone has been published.

The rate of growth is generally slow, but unpredictable. Some undergo periods of rapid growth where they give rise to suspicion of malignancy, while others remain almost static in size despite repeated recurrence (720). Lesions of the maxilla, which involve the maxillary antrum, show a tendency for rapid growth (54).

Small ODOMYXs are asymptomatic; eventually they cause progressive swelling. MacDonald-Jankowski et al. (720) made a systematic review of the literature and found that only about one-third of the reports presented clinical details. The mean duration of symptoms before diagnosis was 2.0 years. In 5 of 14 cases (36%) where the information was given the tumor was symptom free or found incidentally. Swelling was reported in 76% of 155 cases, signs of pain in 14% of 159 cases, loosening of teeth in 22% of 41 cases, and displaced teeth in 53% of 49 cases. Tumors in the maxilla with encroachment on the maxillary sinus may cause nasal obstruction or exophthalmus. Paresthesia has been reported in a few cases of ODOMYX in the lower jaw (713). Ulceration of the overlying oral mucosa is seen when the swelling of the tumor brings the surface in contact with teeth.

Imaging. The radiographic appearance of ODOMYX varies and ranges from small unilocular lesions between roots of teeth and large multilocular tumors, which may displace teeth and less frequently resorb roots of teeth (726). The borders of the lesion may be well defined with sclerotic margins or ill defined with diffuse margins (Fig. 79). The interpretation of the radiogram is challenging, because the radiographic features overlap with those of other benign and malignant neoplasms like ameloblastoma, central giant cell granuloma, central hemangioma, aneurismal bone cyst, and metastatic lesions to the jaws (727). An analysis by MacDonald-Jankowski et al.
(720) of the radiological features of reported cases revealed that among 55 cases 47% were unilocular and 53% multilocular, among 117 cases 55% had margins with good definition, and 45% with poor definition. Kaffe et al. (721) found 34 (35.4%) unilocular, 53 (55.2%) multilocular, and 9 (9.4%) not loculated myxomas among 96 cases; regarding borders 63 (65.6%) were well defined, 16 (16.7%) were poorly defined, and 17 (17.7%) were diffuse.

Noffke et al. (727) have published a detailed analysis with well-defined criteria of radiograms from 30 cases of ODOMYX, 11 from the maxilla, and 19 from the mandible. They found expansion of the mandible in 18 cases, and perforation of the mandibular cortex in 7 cases. In 11 of the maxillary cases invasion of the sinus was detected, and in two of these the tumor had also invaded the nasal cavity. They defined a unilocular lesion as a single radiolucent lesion that could include internal calcifications but no compartments. Unilocular lesions were small; they varied from 30 to 55 mm (mean, 42.5 mm). The presence of locules was indicative of septa. The term multilocular was used if the septa divided the radiolucent internal structure into at least two compartments. Multilocular lesions varied in size from 15 to 130 mm (mean, 70.7 mm). To describe the radiographic patterns created by the septa the following terms were used: soap bubble appearance represented large spaces surrounded by round or curved bony septa, honeycomb appearance represented small angular spaces, tennis racket appearance was represented by crossed straight septa resembling the strings of a tennis racket, and ground glass appearance described the visual effect of many, fine, poorly calcified trabeculations being superimposed on each other and without organized arrangement. Among the 30 tumors 6 were unilocular and 24 multilocular; 7 showed soap bubble, 13 tennis racket, 4 honeycomb, and 2 ground glass appearance. Calcifications were found in nine cases.

When the radiographic pattern of the septa was compared with the histomorphology of the tumor it could be shown that the coarse well-defined peripheral septa were reoriented residual lamellar cortical bone, while most of the delicate internal septa were found to be dense fibrous partitions that divided the tumor in myxomatous lobules. Impaction of teeth was found in 3 cases, extrusion and mobile teeth in 9 cases, tooth displacement in 22 cases, and root resorption in 13 cases. In two cases a widening of the periodontal ligament space was seen, mimicking an osteogenic malignancy. In other studies a few tumors have demonstrated a sunray or sunburst appearance mimicking an osteosarcoma (728,729).

It has been demonstrated that while tooth displacement and root resorption is better observed on conventional radiographs, the use of CT and MRI is superior when establishing the intracortical extent of the tumor, cortical perforation and soft tissue involvement, and the extent of the tumor (720,727,730–733).

Pathology. The etiology of the ODOMYX is unknown. The tissue of origin is believed to be the odontogenic ectomesenchyme of a developing tooth or undifferentiated mesenchymal cells of the periodontal ligament. The odontogenic origin of the neoplasm is supported by some histological similarity to embryonic pulpal ectomesenchyme and particularly to the dental follicle, its rarity in nontooth-bearing areas although it does occur in the upper part of the mandibular ramus, its frequent occurrence in adolescence, its association with missing and unerupted teeth, and the sporadic presence of nonproliferating odontogenic epithelium within the neoplastic, myxomatous tissue.

Macroscopically the margins of the ODOMYX may be lobulated and well defined in some cases, but are usually ill defined. On cut section the surface may be homogeneous and slightly translucent. Gelatinous tumors tend to collapse or become fragmented; more heavily collagenous lesions tend to be firm and cohesive (24).

Histologically the tumor is nonencapsulated and composed of randomly orientated stellate, spindle-shaped, and round cells (Fig. 80) with long, fine, anastomozing pale or slightly eosinophilic processes extending from the centrally placed nucleus (712). The cellularity is relatively low. The tumor cells, which have been called myxoblasts (726,734) are almost evenly dispersed in an abundant myxoid stroma that contains only a few fine collagen fibers (Fig. 81). The amount of collagen may vary within a tumor and may be more prominent in some tumors, which are then usually called fibromyxomas, when the myxomatous component is dominating, and myxofibromas, when the collagenous part is dominating. In some tumors collagen is very scarce (735). Binucleated cells, mild pleomorphism (Fig. 80), and mitotic figures may occur (736). Areas with increased cellularity may be found. Nests or islands of odontogenic epithelium may be present, but is rarely seen (735,737,738) and are not necessary for the diagnosis (726); they may be surrounded by a hyalinized zone. Vascularity is generally minimal and inconspicuous (738) but some tumors may exhibit delicate capillaries (737).
The intercellular matrix contains acid mucopolysaccharides, primarily hyaluronic acid and to a lesser degree hyaluronic acid (739). It stains strongly with alcian blue pH 2.5 (738) and reacts metachromatically to toluidin blue (Fig. 81). It usually stains faintly with periodic acid–Schiff reagent or not at all (740). Mori et al. (741) detected a high alkaline phosphatase activity in the anastomozing processes of the tumor cells, but the ground substance was devoid of activity.

**Immunohistochemistry.** CK has been demonstrated with broad spectred antibodies (AE1/AE3), and CK-19 was detected in the epithelial islands found in two myxomas by Li et al. (738); no other cells contained CK. CK-19 is often found in odontogenic epithelium.

Fujita et al. (422) studied the immunoreactivity to nestin antibodies in nine cases of ODOMYX. Four of the nine cases displayed round, angular, or reticular neoplastic cells that were positive for nestin. Tumor cells were homogeneously stained in positive cases.

Vimentin has been detected in the tumor cells by several investigators (738,742–746).

Muscle specific actin was found by Moshiri et al. (745), Lo Muzio et al. (746), and Li et al. (738), but only in a fraction of the tumor cells. On the basis of such findings and results from ultrastructural studies (vide infra) it has been suggested that the majority of tumor cells are myofibroblasts (745,746).

Desmin could not be detected (738,744).

S-100 protein-positive tumor cells were found in ODOMYX in two investigations (742,743), but these findings could not be confirmed by others (738,742–746).

The presence of growth factors have been studied by Heikinheimo et al. (130,133). The expression of EGF, TGF-α, and EGF-R was studied by means of RT-PCR and Southern blotting, ISH, and immunocytochemistry in two cases of ODOMYX. TGF-α and EGF-R are overexpressed in several neoplasms. No EGF-R transcripts were detected by ISH nor was immunoreactivity observed. A low number of TGF-α mRNA was observed in the mesenchymal tissue. Spindle-shaped tumor cells and capillaries were immunopositive for TGA-α (130).

TGF-β2, a modulator of cell growth and differentiation, was studied by means of RNA extraction and Northern blotting, RT-PCR and Southern blotting, ISH, and immunocytochemistry in two cases of ODOMYX (133). None of the tumors were associated with TGF-β2 mRNA and protein expression.

The immunoreactivity of some extracellular matrix proteins, collagen type I, procollagen type III, collagen type VI, undulin, tenascin, and fibronectin in tissue from four cases of ODOMYX was studied by Schmidt-Westhausen et al. (747). The tumor stroma showed a pronounced reaction for collagen type I. The myxoblasts displayed an intense intracytoplasmatic reaction for procollagen type III and collagen type I, which was not found in the fibroblasts of the adjacent normal oral mucosa. In contrast to the surrounding connective tissue, label for collagen type VI was weak, as was the reaction for fibronectin and tenascin. Undulin was almost undetectable.

Glycosaminoglycans in the extracellular matrix of a jaw myxoma were analyzed biochemically by Slootweg et al. (748) and compared with known data on glycosaminoglycans from the normal dental pulp and periodontal ligament. Glycosaminoglycans formed approximately 1% of the total tumor weight and 17% of the dry weight. Hyaluronic acid formed 72.4% of the glycosaminoglycans fraction. Neither the high glycosaminoglycans-content nor the high fraction of hyaluronic acid was found in the normal dental tissues.

Martins et al. (736) determined the cell-proliferating index in 10 cases of ODOMYX and 6 cases of AMF by means of the AgNOR technique. The mean AgNOR counts were higher in the epithelium and
mesenchyme of the AMF than in the mesenchyme of the ODOMYX; the differences between the mesenchymal components of the two tumors were statistically significant \((p < 0.05)\).

Bast et al. (749) studied the expression of apoptotic proteins and matrix metalloproteinases in tissue from 26 ODOMYXs. They evaluated the expression of cell cycle protein Ki-67, apoptosis-regulating proteins Bcl-2, Bcl-XL, Bak, and Bax, and matrix metalloproteinases MMP-2, MMP-3, and MMP-9. The myxoblasts did not show an increase in cell division. Less than 1% of tumor and control cells were positive for Ki-67. The myxoblasts showed increased expression of antipapoptotic proteins (Bcl-2 and Bcl-XL) and the matrix metalloproteinase MMP-2. The tumor cells were negative for the proapoptotic proteins (Bak and Bax) and for the matrix metalloproteinases MMP-3 and MMP-9. The authors suggest that the production of antipapoptotic proteins and the secretion of matrix metalloproteinases are involved in progression of the disease.

Activated RAS genes have been found in both benign and malignant tumors. Using an immunohistochemical assay Sandros et al. (105) evaluated the expression of the HRAS- and KRAS-encoded gene products p21(ras) in two cases of ODOMYX and compared the findings with those in ameloblastomas, AMFs, and normal human developing teeth. The epithelium of the ameloblastomas and the AMFs showed the highest immunoreactivity. The two myxomas displayed different staining patterns. In one of them nearly all the tumor cells stained weakly positive for p21, while in the other tumor less than 5% of the cells were positive. The immunoreactive cells were evenly distributed throughout the tissue sections. The sparse amounts of odontogenic epithelium present in both cases were negative.

**Electron Microscopy.** The ultrastructure of the myxoma has been studied by several investigators (734,745,746,748,750–754,618). The main tumor cell type has been described as elongated and spindle-shaped or triangular with an irregular cellular outline with several invaginations and surface projections (734,745,746,748,753) and has been characterized as fibroblastic. The cell is round in cross sections. The nuclei are prominent with irregular contour, pores in the nuclear membrane, margination of condensed heterochromatin, and with one to two nucleoli. The cytoplasm is rich in organelles. The RER is well developed; a Golgi complex is invariably present. Mitochondria, glycogen particles, lipid vacuoles, vesicles, and polysomes are seen. Dense packed microfilaments are found throughout the whole cytoplasm. Goldblatt (734) identified two cell types. Type I was a spindle cell identical to the one described above; the author considered it a secretory cell. Type II was generally a round to ovoid cell with an abundant granular matrix, which was virtually devoid of RER, but contained free ribosomes. A few mitochondria were noted, but Golgi complex, if present, was inconspicuous. The nucleus was round, with mainly peripherally disposed heterochromatin and a less prominent nucleolus. Cell type II was considered nonsecretory. Lo Muzio et al. (746) identified cells with several morphological variations, but considered them one cell type. Like Moshir et al. (745) they found that several of the cells were very similar to myofibroblasts, a suggestion that was supported by immunoreaction to muscle-specific antigen in many of the cells \(\text{(vide supra)}\).

The matrix background has been described as fine granular with sparse collagen fibers.

**Molecular-Genetic Data.** To investigate the role of the stimulatory Gs alpha \((\alpha_g)\) gene as a potential candidate oncogene in ODOMYX, Boson et al. (755) used polymerase chain reaction (PCR) to amplify the appropriate genomic fractions extracted from 23 biopsies followed by denaturing gradient gel electrophoresis (DGGE) analysis. Although \(\alpha_g\) gene mutations have been demonstrated in other neoplasms, they could not be demonstrated in any of the tumors analyzed.

Myxomas of bones and other sites occur as part of the Carney complex (CNC), a multiple neoplasia syndrome caused by mutations in the \(\text{PRKARIA}\) gene, which codes for the regulatory subunit of protein kinase A (PKA). Perdigao et al. (756) screened 17 ODOMYXs for \(\text{PRKARIA}\) mutations by DNA analysis and for \(\text{PRKARIA}\) protein expression by immunohistochemistry. Mutations of the coding region of the \(\text{PRKARIA}\) gene were identified in two tumors; both these lesions showed no or significantly decreased immunostaining of \(\text{PRKARIA}\) in the tumor compared with that in the surrounding normal tissue. Of the remaining tumors, 7 of the 15 without mutations showed almost no \(\text{PRKARIA}\) in the tumor cells, whereas immunohistochemistry showed that the protein was abundant in nontumorous cells. The authors concluded that \(\text{PRKARIA}\) may be involved in the pathogenesis of ODOMYX.

**Differential Diagnosis.** ODOMYXs may be confused microscopically with nonneoplastic normal tissue and with benign and malignant neoplasms (726). Most enlarged dental follicles are myxoid and may easily be misdiagnosed microscopically as ODOMYX (757). Accurate clinical and radiographic information should exclude this possibility. If the lesion submitted for diagnosis is radiologically confined to the crown of an unerupted tooth and a few millimeters around it, then an enlarged follicle is almost certainly the diagnosis (54). The appearance of such a follicle under a high-power objective may be identical to that of a myxoma. Kim et al. (758) found that among 847 dental follicles and/or dental papillae referred to the AFIP, Washington, DC, about 20% were misdiagnosed. The dental follicle is usually more collagenous than myxomas and may contain reduced enamel epithelium and numerous islands of odontogenic epithelium, some of which may be calcified. ODOMYX rarely contains islands of odontogenic epithelium, and if so usually few. The formative dental pulp, the dental papilla may be separated from a developing tooth during surgery and may be included within a surgical specimen separate from any formed tooth elements (381). Kim et al. (758) quote a 5.8% incidence of misinterpretation of dental follicles and/or papillae for ODOMYX. Macroscopically the dental papilla is a...
doughnut-shaped or flattened sphere of gelatinous tissue up to 12 mm in diameter. Usually a few odontoblasts remain in the tissue close to the surface and a narrow cell-free zone is seen below them and along the margin elsewhere (54), a histological feature that distinguishes it from ODOMYX. Among odontogenic neoplasms the odontogenic fibroma may cause differential diagnostic problems. Other myxoid neoplasms to consider are myxoid neurofibroma, myxoid lipoma, low-grade myxoid fibrosarcoma, and liposarcoma, mesenchymal chondrosarcoma, chondromyxoid fibroma, and in the maxilla, chordoma, and nasal polyps. These can usually be ruled out by good sampling, characteristic light microscopic features, and immunohistochemistry (54,726).

**Treatment and Prognosis.** Smaller ODOMYXs have been treated successfully with curettage, but in general, conservative treatment has resulted in unacceptable high recurrence rates. In the literature, recurrence rates range from 10% to 33%, with a reported average of 25% (721,746). Although a slow-growing neoplasm, it is never encapsulated, but infiltrative and may be aggressive. For larger lesions radical surgery in terms of resection is the treatment of choice, especially in maxillary lesions, and they require subsequent reconstruction of the jaw. Complete removal can be difficult. Among 25 cases Li et al. (738) reported 5 cases to be treated by enucleation followed by curettage. Four patients showed no signs of recurrence after being followed 7 to 11 years. One patient with a maxillary tumor exhibited recurrent tumor six months after surgery. The majority of the patients (17 cases) were treated by radically radical procedures (segmental resection, partial, or complete maxillectomy); follow-up data ranging from 2 to 12 years (mean, 3.9 years) were available for 12 patients, and none of them developed recurrence. Although the majority of recurrences are diagnosed within two years after surgery, some tumors recur after many years. One case, followed for 35 years, recurred after prolonged remissions after 20, and then 10 years (759). MacDonald-Jankowski et al. (720) recommended lifelong or at least long-term follow-up.

Malignant transformation (odontogenic myxosarcoma) is extremely rare; only four cases have been reported (760–762).

### 3.4 Cementoblastoma

**Introduction.** The neoplasm (CEMBLA) is characterized by the formation of sheets of cementum-like tissue containing a large number of reversal lines developing on the surface of a root of a tooth, and being unmineralized at the periphery of the mass or in the more active growth areas (23,763). A simultaneous resorption of the root takes place.

**ICD-O code 9273/0**

**Synonyms:** Benign CEMBLA, true cementoma.

**Clinical Features.** The prevalence and incidence of the CEMBLA is unknown. The relative frequency of the tumor in material received for histological diagnosis in services of diagnostic pathology in various countries for various amounts of years ranges from 0.1% to 4.2% in studies comprising more than 300 samples of odontogenic tumors. The results are indicated as follows: number of odontogenic tumors/number of CEMBLAs/%. Regezzi et al., Michigan, U.S.A. (31): 706/1/0.1%, Daley et al., Canada (33): 392/7/1.8%, Mosqueda-Taylor et al., Mexico (34): 349/3/0.8%, Ochsenius et al., Chile (35): 362/6/1.7%, Fernandes et al., Brazil (37): 340/8/2.3%, Ladeinde et al., Nigeria (38): 319/2/0.6%, Buchner et al., California (30): 1088/10/0.9%, Jones et al., England (2006, pooled figures from two studies) (39,40): 523/22/4.2%, Olge et al., Turkey (41): 527/10/1.9%, and Jing et al., China (42): 1642/33/2.0%. The data are skewed; however, the figures reflect regional differences in type of lesions sent for histopathological confirmation rather than effects of genetical or environmental factors.

Only about 120 cases have been published (764,765). In a review of 44 cases of CEMBLA from AFIP, Washington, DC, and 74 cases from the literature the gender distribution was: males: 58.1% and females: 41.9% (765). The ratio 1.4:1 may not be statistically significant since the material is likely to be biased. Caucasians made up 65.7% of the patients.

The tumor occurs primarily in teenagers and young adults, age range is 6 to 71 years, with a mean age of 21.3 years (764–766).

The lesion has a predilection for the mandible molars, particularly the mandibular first molar, 20.5% were located in the maxilla, and 79.5% in the mandible; in 47% of the cases the tumor was attached to the mandibular first permanent molar. Only two cases of incisor involvement have been reported (767,768). Involvement of deciduous teeth have been documented, but is an infrequent finding (769–773). A patient with bilateral mandibular CEMBLAs has been reported (774).

The growth rate is estimated to be 0.5 cm/yr (775,769). The average duration of clinical symptoms before treatment in 44 patients was found to be 12.4 months (765). The following symptoms were registered: 10 patients were symptom free; swelling accompanied by pain was seen in 17 patients, swelling alone in 8 patients, pain alone in 3 patients. The swelling may be considerable, and manifested as buccal and lingual/palatal expansion of the bony cortical plates. The pain in seven cases was described as severe or “worsening.” It may simulate pulpitis making the diagnosis difficult without a radiogram in early cases. The tooth may be sensitive to percussion, and tooth mobility has been noted in some cases. Despite the root resorption the pulp is usually vital, unless it has been endodontically treated or died for other reasons.

**Imaging.** Radiographic examination is crucial in establishing the diagnosis. The typical finding is a well-defined, circumscribed, radiopaque mass fused to the root of a tooth and surrounded by a narrow radiolucent zone of uniform width (381,764,765). A variable degree of root resorption is present but may be obscured by the density of the tumor, and the periodontal ligament space may be obliterated. If the tumor is diagnosed within the initial phase, the lesion is radiolucent or has a mixed density; the radiographic

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*Prätorius*
appearance depends on the degree of mineralization. In such cases a vitality test of the pulp is particularly important for differential diagnostic reasons. Occlusal radiograph may be useful to evaluate the expansion of the tumor; CT or MRI is usually not indicated (766). The size of the lesion has ranged from 0.5 to 5.5 cm, with an average of 2 cm (765,774). Fusion to adjacent teeth, displacement of adjacent teeth, and external resorption of adjacent tooth roots may be seen in rare cases. Recurrent CEMBLAs consistently showed radiographic evidence of a locally destructive neoplasm characterized by somewhat irregular margins with radiopaque foci (698).

**Pathology.** The etiology of the CEMBLA is unknown and difficult to study, since the lesion is rare and experimental studies have been unfeasible. A further complication is that specific cementum markers are not yet available. In earlier classifications of odontogenic tumors (9,22,23) the lesions, which are now considered osseous dysplasias in the 2005 WHO classification (12), were included in the group of cementum producing tumors. They have been excluded as a consequence of the lack of a specific cementum marker and the unreliability of histomorphology as a mean of differentiating between pathological bone and cementum. There are conspicuous physiological differences between normal bone and cementum, however, the most important being a different reaction to physical pressure. Orthodontic treatment is based on the fact that mild physical pressure to a tooth causes resorption of the surrounding bone without resorption of the cementum of the root. The availability of a reliable specific cementum marker may well change our concept of cemento-osseous lesions.

The tumor is considered a neoplasm with unlimited growth potential. It is supposed to arise from the ectomesenchymal cells of the periodontium and is initially characterized by periapical osteolysis and beginning resorption of the surface of the root of the tooth. Eventually increasing formation of hard tissue takes place together with root resorption and later stages are dominated by calcified hard tissue (776).

Macroscopically, the CEMBLA appears as a hard, rounded, or nodular mass fused to the apical part of one or more teeth roots (Fig. 82) and surrounded by a grayish layer of irregular soft tissue. The lesion may be submitted in fragments. Tissue from recurrent tumors have been described as “poorly calcified chalklike tissue,” “gritty,” and “irregular-shaped calcifications” (765,777).

Histologically the tumor is composed of irregular cementum-like trabeculae with numerous basophilic reversal lines. The hard tissue is attached to the resorbed surface of the root of a tooth (Fig. 83), and this is the main feature that distinguishes the lesion from an osteoblastoma or osteoid osteoma, which may have a similar histomorphology. The root of the associated tooth is usually shortened by resorption, and the tumor may involve the pulp. In more mature parts the hard tissue contains entrapped cells. In numerous places the trabeculae are rimmed with large, plump cementoblasts, which may exhibit some degree of pleomorphism (Fig. 84). At the periphery and in other areas of active growth, extensive sheets of unmineralized tissue may be seen, which show no remodeling (23). At the periphery radiating columns of unmineralized matrix is typically seen. There is no permeation of the surrounding bone; often a capsule-like layer of fibrous tissue is seen at the border of the

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Figure 82  Cementoblastoma. The tumor developed around the mesial root of a left first mandibular molar of a 14-year-old boy. It is fused to the surface of the root and causes resorption of cementum and dentin. The pulp of the root was vital. The hard tissue shows varying degree of calcification and is mixed with areas composed of soft tissue. H&E stain.

Figure 83  Cementoblastoma. High-power view of an area with cementogenesis, they are primarily found in the periphery of the tumor. Cementoid is seen lined by numerous large cementoblasts with darkly stained nuclei. H&E stain.
lesion. The soft tissue component consists of vascular, loose-textured fibrous tissue containing large, deeply staining cells with a single nucleus and multinucleated cells. Mitotic activity has not been reported (23,381,765,766). Recurrent lesions have shown multiple small foci of cementum between trabeculae of normal bone. The cemental foci frequently exhibit radiating columns of partly calcified matrix at their periphery (765).

**Immunohistochemistry.** A CEMBLA-conditioned medium-derived protein has been purified and corresponding antibody used in a study of human periodontal tissue with a positive reaction from cementoblasts, cementocytes, and acellular and cellular cementum throughout the cementoid phase (778). However, no immunohistochemical studies of CEMBLA with cementum markers have been published to date. Monoclonal antibody against bovine morphogenetic protein (BMPMcAb) has been used on sections from five cases of CEMBLA. Both cementoblast-like tumor cells and connective tissue matrix showed a positive reaction to BMPMcAb, but no staining was found in the calcified cementum-like tissue (168).

**Electron Microscopy.** No studies have been published.

**Molecular-Genetic Data.** No studies have been published.

**Differential Diagnosis.** The most obvious differential diagnosis is the osteoblastoma, which has a similar histomorphology. If sufficient clinical information including radiograms is available or the removed specimen is received with the tumor attached to the tooth, the diagnosis is uncomplicated. Osteoblastomas do not fuse with the surface of tooth roots and CEMBLAs remain separated from bone (765,779,780). The CEMBLA’s fusion to the surface of a tooth root is not a fortuitous event; it is a morphological expression of a specific property of the cells, which produce the neoplasm.

In some cases the lesion may show a slight pleomorphism of the cementoblasts, which make it resemble an atypical osteosarcoma, but malignancy has never been reported, and its distinctive relationship to the root of a tooth is unique. Diagnosis should not be made on the basis of biopsy material alone.

In case of a recurrent CEMBLA the pathologist may be dependent on sufficient clinical information.

**Treatment and Prognosis.** Until recently the CEMBLA has been considered a slowly growing neoplasm, which is readily enucleated and does not recur (766). Due to the capsule and the unmineralized margins the removal is usually uncomplicated. The studies of Brannon et al. (765) have shown, however, that recurrence of the tumor is more common than previously reported. The recurrence rate was 37.1% in 44 own cases, and 21.7% for 118 cases, which included 74 cases from the literature. The recurrence is primarily caused by incomplete removal of tumor tissue. Residual tumor cells will continue to grow (781); hence appropriate treatment should consist of removal of the lesion, including the affected tooth or teeth, followed by thorough curettage or peripheral ostectomy (782). If less than half of the root of the tooth is resorbed by the tumor, it is technically possible to remove the tumor and retain the tooth by amputation of the root in conjunction with endodontic therapy. However, most attempts to retain the tooth by means of this therapy have ultimately ended with subsequent extraction of the tooth (764). Malignant development of the neoplasm has not been reported.

## II. MALIGNANT ODONTOGENIC TUMORS

### 1. Odontogenic Carcinomas

Odontogenic carcinomas include METAM, AMCA, PIOSCC, CCOC, and GCOC.

#### 1.1 Metastasizing Ameloblastoma

**Introduction.** A METAM is an ameloblastoma that metastasizes in spite of a benign histological appearance (783).

ICD-O code 9310/3

**Synonym:** Metastasizing, malignant ameloblastoma

Per definition the histopathological features of the METAM do not differ from those of ameloblastomas that do not metastasize. An ameloblastoma with histological sign of malignancy should be classified as an AMCA. Therefore the diagnosis of a METAM can only be made in retrospect, after the occurrence of metastatic deposits (783). It is thus its clinical behavior and not the histopathology that justifies a diagnosis of METAM. Despite suggestions from Elzay (784), Slootweg et al. (785), and Waldron et al. (786) to change the classification of odontogenic carcinomas and separate the two entities, it was first done in the 2005 WHO classification (12). This lack of distinguishing between the two entities has caused much confusion; cases

![Figure 84](Image)
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published as malignant ameloblastoma, METAM, or atypical ameloblastomas have been METAMs as well as AMCAs, resulting in a grouping of entities showing considerable differences in clinical course and histological appearance (785). Furthermore reviewing the literature on the subject is made complicated; reviews where the entities are not separated have become obsolete.

Clinical Features. METAM is a rare tumor; only about 70 cases have been reported. In a Chinese review (42) of cases received for diagnosis from 1952 to 2004 a total of 1642 odontogenic tumors were diagnosed; 50 cases were malignant (3.0%); none of these were METAM.

It has been estimated that approximately 2% of ameloblastomas do metastasize, but the estimate is probably too high (787). In a long-term follow-up on recurrence of 305 ameloblastoma cases, Hong et al. found one case (0.3%) with metastasis. Reviews of reported cases have been published by Slootweg et al. (785), Kunze et al. (788), Laughlin (789), Ueda et al. (790), Ameerally et al. (791), and Henderson et al. (792). Reichart and Philipsen (793) pooled the data from the 43 cases published by Laughlin, the 7 cases by Ueda, 11 cases by Ameerally, and single cases reported by Duffey et al. (794), Sugiyama et al. (795), Weir et al. (796), and Witterick et al. (797).

Among the 65 pooled patients 35 were males and 30 females, the male:female ratio was thus 1:0.86.

The data showed an age range of 5 to 74 years, and the mean age was 34.4 years. There was an age peak in the fifth decade, though.

The location of METAM does not differ significantly from that of non-METAM (789,792); about 80% of ameloblastomas, s/m type occur in the mandible, primarily in the posterior region.

A case of peripheral METAM was published by Lin et al. (798).

No differences in clinical signs between the primary tumor in METAM and non-METAM has been found, but multiple recurrences evidently increase the probability of malignant behavior (55,788).

The metastases seem to grow slowly in most cases. The time between operation of primary tumor and diagnosis of metastasis is long. The data differ somewhat in the reviews of published cases. On the basis of 31 cases Ueda et al. (790) found a range of time to be 0.25 to 31 years, with a mean time of 10.3 years. Eleven metastases (35.5%) were diagnosed within the first five years. Ameerally et al. (791) reviewed 28 cases and found a time range from seven weeks to 38 years between primary tumor and metastases; the mean time was 13.5 years. In five cases (17.9%) the metastasis was diagnosed within the first five years.

The most common site of metastases is the lung (785,788,789). Ameerally et al. (791) reviewed 28 cases from 1965 to 1995; 75% of the cases had lung metastases, including hilar lymph nodes; 25% involved bones, including skull, vertebrae, and femur; 18% cervical lymph nodes; 11% liver; 10% brain, and 3.5% other lymph nodes, spleen, and kidney. Pulmonary metastases are most commonly found bilaterally and with multiple nodes (792). Metastasis to cervical lymphnodes from METAM are usually diagnosed many years after first operation (799); Duffey et al. (794) analyzed published cases of METAMs with metastases to cervical lymphnodes and found nine cases to which they added their own case. The range of time from first presentation to the detection of metastases was 2 to 24 years (7 cases), with a mean of 11.7 years.

Several factors appear to contribute to the development of metastatic disease, inclusive the size and duration of the initial tumor, multiple local recurrences, inadequate surgical procedures, radiotherapy, or chemotherapy (792). The exact importance of each parameter has not been unraveled.

Ameerally et al. (791) put attentions to the fact that there has been a propensity to unrestrained soft tissue invasion in several cases of METAM. Ameloblastomas are usually confined to bone.

Imaging. The primary tumor of METAM presents as a typical ameloblastoma, and its radiological features do not differ from those of the non-metastasizing counterpart.

Pathology. The etiology of the tumor is unknown. It is suspected that the ameloblastoma possess an inherent low-grade malignancy, which is stimulated by multiple recurrences (788). It shares many features with the basal cell carcinoma of the skin, in terms of histopathology as well as behavior. Like ameloblastomas basal cell carcinomas usually do not metastasize; the frequency is less than 1% (800).

The histopathological features of the METAM are the same as those of the non-METAM. There is no cytological atypia or other indication of ability to metastasize. Among the different cell types encountered in ameloblastomas, Hartman (59) found that the granular cell type of ameloblastoma demonstrated a marked tendency to recur following conservative therapy. This finding has been partly confirmed; in a long-term follow-up on recurrence of 305 ameloblastoma cases with statistical analysis (55) it was found that the histopathology of an ameloblastoma is significantly associated with a recurrence. The follicular growth pattern and the granular and anachomatosus cell types have a relatively high likelihood of recurrence. However, the recurrence of an ameloblastoma in large part reflects the inadequacy or failure of the primary surgical procedure. The majority of patients with METAMs have a history of multiple recurrences (788).

All METAMs have originated from solid/cystic ameloblastomas. Metastases from desmoplastic, peripheral, or UNAMs have not been reported.

The metastases of some METAMs show histomorphological signs of malignancy (785). Some authors require that both the primary and metastatic foci lack any features of malignancy (793,800). However, the primary tumor in such cases cannot be classified as AMCA; if it can be established that a metastasis with histomorphological sign of malignancy has derived from the benign looking ameloblastoma, it is meaningful to classify the lesion as METAM.

Immunohistochemistry. Kumamoto et al. (163) used antibodies against amelogenin and CK-19 on sections from a case of METAM. The immunoreactivity for amelogenin and CK-19 was similar to that of
the non-METAMs, which showed expression of amelogenin in peripheral columnar or cuboidal epithelial cells and some central polyhedral cells. Immunoreactivity for CK-19 was diffusely present in neoplastic cells. There was no distinct difference in amelogenin or CK-19 expression between the primary and recurrent ameloblastomas.

Kumamoto et al. (178) investigated the immunoreaction of extracellular matrix-degrading serine proteinase in odontogenic tumors and detected expression of urokinase-type uPA, uPAR, PAI-1, and maspin in two cases of METAM.

To evaluate roles of the Akt-signaling pathway in oncogenesis and cytodifferentiation of odontogenic tumors, Kumamoto et al. (250) investigated the expression of phosphorylated Akt, P13K, and PTEN in two cases of METAM, which both reacted positive.

The roles of MAPKs in oncogenesis and cytodifferentiation of odontogenic tumors were investigated by Kumamoto et al. (78), who detected expression of p-p38 MAPK, and p-ERK5, but not p-JNK in two cases of METAM.

To clarify the roles of rat sarcoma (Ras)/MAPK-signaling pathway in oncogenesis and cytodifferentiation of odontogenic tumors, K-Ras status and expression of Ras, Raf1, MAPK/ERK, kinase (MEK), and ERK 1/2 proteins were analyzed in two cases of METAM together with other odontogenic tumors, and were compared with the reactivity in human tooth germs by Kumamoto et al. (801). The reactivity for K-Ras, Raf1, MEK1, and ERK 1/2 was detected chiefly within odontogenic epithelial cells neighboring the basement membrane. The reactivity was lower than that in dental lamina of tooth germs.

Miyake et al. (157) detected β-catenin (CTNNB1), but no mutation of the corresponding gene in a case of METAM. CTNNB1 is believed to play an important role in promoting tumor progression by stimulating tumor cell proliferation.

To clarify the roles of the p53–MDM2–p14arf cell cycle regulation system in oncogenesis and cytodifferentiation of odontogenic tumors frozen sections from a case of METAM (and 10 benign ameloblastomas) were used for direct DNA sequencing by Kumamoto et al. (116). No alterations of the p53 gene exons 5–8 in a case of METAM (and 10 benign ameloblastomas).

The metastases in the majority of cases are diagnosed several years after the removal of the primary tumor, and the growth rate seems to be slow and constant during long periods (790), Goldberg et al. (802) recommended that patients with ameloblastoma be followed serially and for a long time; they recommended annual chest radiographs to evaluate the most likely site for distant metastasis.

The metastases have been treated in various ways depending on their location and how advanced the disease is at the time of diagnosis. Regarding metastases to the lungs significant resection with preservation of as much viable lung tissue as possible has been the treatment of choice, as this is the only way to offer a significant disease-free survival (803).

Radiation therapy and chemotherapy is recommended as palliative care for inoperable cases only (792). The response to radiation therapy cannot be predicted (789) and the recurrence rate is high. Chemotherapy is not curative (804), but has been shown to have a palliative effect on patient’s symptoms, and in a limited number of cases it has shown a reduction in the size of the metastasis (792).

The median survival time after treatment of the primary tumor has ranged from 11 to 14 years; however, the median survival time after the appearance of metastatic disease has ranged from three months to just five years (792). Nineteen (44.2%) of the forty-three patients reviewed by Laughlin (789) died of tumor and/or metastasis. The longest-reported survival time after the appearance of metastatic disease has been 25 years (787).

1.2 Ameloblastic Carcinoma

1.2.1 Primary.

Introduction. The term “primary type of ameloblastic carcinoma” covers a rare malignant odontogenic tumor that combines the histological features of ameloblastoma with cytological atypia. The diagnosis is used whether the tumor has metastasized or not (783).

ICD-O code 9270/3

Clinical Features. The incidence and prevalence of AMCA is unknown. In a Chinese review (42) of cases received for diagnosis from 1952 to 2004 a total of 1642 odontogenic tumors were
diagnosed; 50 cases were malignant (3.0%); 27 (1.6%) of these were AMCA.

About 80 cases have been published, all subtypes (primary, secondary, peripheral) included. The relative frequency of AMCA in material received for histological diagnosis in services of diagnostic pathology for varies amount of time has been recorded in four studies, which comprise more than 300 cases of odontogenic tumors. The figures have varied from 0.3% to 2.2% in different countries; the numbers in square brackets are the total number of odontogenic tumors in the study. Brazil 0.3% [340] (37), Turkey 0.4% [527] (41), China 1.6% [1642] (42), and Nigeria 2.2% [319] (38).

Slootweg et al. (785) reviewed the cases published from 1927 to 1983. Akrish et al. (805) have reviewed the cases published from 1984 to 2004. Since then five reports of single cases have been published (806–810). Furthermore Hall et al. (811) have published 14 cases, among which 9 contained clear cells, and might be classified as CCOC by others, but 5 of the AMCA did not contain clear cells. Slootweg et al. (785) reviewed 9 cases of AMCA with metastases and 14 cases without. Among these 23 patients 13 (56.5%) were males and 10 (43.5%) were females (ratio 1:0.8). The age range was 4 to 62 years, with a mean age of 34.4 years. Regarding location of the tumors 19 were diagnosed in the mandible and 4 in the maxilla, with a ratio of 4.8:1. Akrish et al. (805) reviewed 37 cases from the literature and added one case of their own. Four of them were secondary, dedifferentiated tumors, i.e., they developed in benign ameloblastomas. Their results differ from those of Slootweg et al. Among the 38 patients 25 (66%) were males, and 13 (34%) were females (ratio 1:0.5). The age range was 15 to 84 years, the mean age: 52 years, and median age 59 years. The mean age of males (54 years) was five years higher than that of females (49 years).

The locations of the tumors were as follows: 25 (66%) in the mandible, and 13 (34%) in the maxilla, the ratio was thus 2:1. The location within the jaws was reported in 29 cases. Among 17 tumors in the mandible, 3 were in the posterior region, 11 extended from the posterior region to the ramus, and 3 involved the anterior and posterior region extending to the ramus. Twelve of the lesions were located in the maxilla, eleven in the posterior, and one in the anterior and posterior region.

The most reported symptom (N = 22; 58%) was swelling (“expansion” or “hard mass”), followed by pain or discomfort (N = 12; 31%), and tooth ache or tooth mobility (N = 7; 18%). Other less commonly reported symptoms were a nonhealing extraction site, ulcer or fistula, facial asymmetry, and trismus. Perforation of the cortex is a very unusual symptom in benign ameloblastomas; it was reported in 12 (31%) cases. Parasthesia of the lower lip is an important symptom; it was reported in six cases (16%).

The growth rate was rapid in eight (21%) of the cases; the mean duration of symptoms to initial diagnosis was 11 months. For ameloblastomas the mean duration of symptoms has been calculated to be 27 months.

Imaging. Since many of the AMCA have perforated the cortex, CT and MRI are important tools to establish the borders of the tumor. In the review by Akrish et al. (805) the locularity of the lesions on radiograms was described in 15 cases; 10 (76%) were multilocular, and 5 (33%) were unilocular. Border information could be obtained in 13 cases; six (46%) were well defined and seven (54%) were ill defined.

Pathology. The etiology of the AMCA is unknown. Per definition the tumor is a de novo neoplasm, if areas of ameloblastoma are present together with malignant features, the tumor is considered a secondary (dedifferentiated) type. Resemblance to an ameloblastic phenotype together with cytological features of malignancy is crucial to establishment of the diagnosis. The growth pattern may be follicular, or pleomorphic, or both. The cytology may vary, but peripheral palisading of tall columnar cells must be present in some areas, and inverted nuclear polarity may also be evident (224). A stellate reticulum-like structure in the epithelial islands and strands will usually be discernable, but may be absent, and basaloid cells may dominate in the centermost areas of the tumor islands (Fig. 85). Criteria for the malignant features have been suggested by Hall et al. (811) to include hypercellularity, hyperchromatism, loss of ameloblastic differentiation, spindling, more than two mitotic figures per high-power field, vascular invasion, and neural invasion. No single of these features is by itself a determinant of malignancy, and there is no single definitive microscopic criterion for AMCA. Pseudosarcomatous areas with a storiform pattern may be seen, which may require detection of CKs to disclose their epithelial origin. Areas may be encountered, which are undifferentiated to the extent that those areas alone are not recognizable as ameloblastic in origin. Necrosis may be seen as focal areas of

Figure 85 Ameloblastic carcinoma. Section of a peripheral primary AMCA which developed in the gingiva around the extraction wound of a newly extracted right third mandibular molar in a 60-year-old man. Numerous mitotic figures are seen and several were abnormal. Some central areas are stellate reticulum-like and the peripheral cells are columnar with distinct reverse polarity of the nuclei. H&E stain.
subtle necrosis to more obvious central, comedo necrosis-like areas (783). Hall et al. (811) have suggested the presence of clear cells (Fig. 86) as a criterion for AMCA if there are other features of malignant ameloblastoma in the tumor; such neoplasms have hitherto been classified as clear cell carcinomas (812). Keratin production and clusters of ghost cells may be seen (811).

The stroma is collagenous with a moderate cellularity. Focal areas of dense hyaline matrix was observed in five (35.7%) of the cases studies by Hall et al. (811); two cases showed dentinoid/osteoid formation, and small dystrophic calcifications was seen in one case, an unusual feature of an ameloblastoma.

**Immunohistochemistry.** Zarbo et al. (813) detected CK (CK types not specified) in the tumor cells of a spindle-cell variant of AMCA. Datta et al. (814) used antibodies against pancytokeratin (AE1/ AE3) and CK-8 and CK-18 (CAM 5.2) and found a strong immunoreactivity. Kumamoto et al. (163) used antibodies against CK-19, which was expressed diffusely in neoplastic cells of both well- and poorly differentiated cases. There was no distinct difference among the primary, recurrent, and metastatic lesions. Monoclonal antibodies against CK (33βE12), against EMA, and against vimentin were used by Kawauchi et al. (815) on sections from a spindle-cell AMCA. The epithelial carcinomatous cells were positive for CK and EMA, whereas few cells were positive for vimentin. Spindle-shaped sarcomatous cells were stained positively for vimentin, but only occasional cells were positive for CK; spindle-shaped cells were negative for EMA.

Basement membrane–related molecules were studied by Sauk (816) who used antibodies against type IV collagen and laminin. The AMCA and its metastases showed only scattered foci of extracellular staining of both these basement membrane proteins, only in the most differentiated portions of the neoplasm could some focal linear staining be seen. These findings are in agreement with those of Nagatsu et al. (75) who found that collagen IV α chain staining in the AMCA demonstrated an irregular and disrupted expression pattern with specific loss of α1(IV)/α2(IV) chains. Poorly differentiated tumor nests showed complete disappearance of α1(IV) chain expression. In well-differentiated areas the basement membranes demonstrated a discontinuous and fragmented expression pattern for α5(IV)/α6(IV) chains.

Ito et al. (67) detected versican in two cases of AMCA. Versican is a large aggregating chondroitin sulfate proteoglycans, which might be involved in epithelial growth. The reaction was strong and located to the tumor nests. Kumamoto et al. (178) investigated the immunoreaction of extracellular matrix-degrading serine proteinase in odontogenic tumors, and detected expression of urokinase-type uPA, uPAR, PAI-1, and maspin in three cases of AMCA.

To evaluate roles of the Akt-signaling pathway in oncogenesis and cytodifferentiation of odontogenic tumors Kumamoto et al. (250) investigated the expression of phosphorylated Akt, P13K, and PTEN in three cases of AMCA, which all reacted positive.

The roles of MAPKs in oncogenesis and cytodifferentiation of odontogenic tumors were investigated by Kumamoto et al. (78), who detected expression of p-p38 MAPK, and p-ERK5, but not p-JNK in three cases of AMCA.

The tumor cells do not react with S-100 protein antibodies (815). Amelogenin expression in peripheral cuboidal cells in well-differentiated areas of AMCA was detected by Kumamoto et al. (163). Poorly differentiated areas reacted sporadically and faintly. Lo Muzio et al. (121) studied expression of the TP63 gene (a member of the TP53 gene family) in odontogenic tumors. Reactivity for p63 was detected in the epithelial cells of all odontogenic tumors, and was only nuclear. In sections from three AMCAs p63 was found in more than 50% of the tumor cells. The expression was significantly higher than in benign nonaggressive odontogenic tumors, but did not differ significantly from the expression in benign, local aggressive tumors with high risk of recurrence.

Kim et al. (79) studied the occurrence of PCNA in sections from a case of AMCA. The reactivity showed a variable pattern, but the fraction of positive cells was remarkably high with a mean score of 379.1, compared with a mean score between 70 and 78 in benign ameloblastomas.

**Electron Microscopy.** Kawauchi et al. (815) studies the ultrastructure of a case of spindle-cell AMCA. The finding of desmosomes and perinuclear aggregates of tonofilaments confirmed the epithelial character of the spindle-shaped sarcomatous cells. The epithelial ultrastructural phenotype was compared with genomic analysis (vide infra).

**Molecular-Genetic Data.** DNA ploidy was studied by means of image and flow cytometry in 22 ameloblastomas and 5 AMCAs by Muller et al. (817).
Aneuploidy was found to be significantly more common in AMCs than in primary and recurrent ameloblastomas and was considered a strong predictor for malignant potential.

Kawauchi et al. (815) used CGH to study the chromosomes of tumor cells from a spindle-cell AMCA. Gains of 5q and 6q and amplification of 5q13 were shown in the tumor as chromosomal imbalances. No loss of chromosomal fragments was detected.

DNA microarray technology was used by Carinci et al. (806) to detect possible upregulated or downregulated genes in a case of AMCA. Several genes were found to be differentially expressed, and they covered a broad range of functional activities: (i) transcription, (ii) translation, (iii) signaling transduction, (iv) cell-cycle regulation, and (v) differentiation.

Nodit et al. (110) used tissue from 12 ameloblastomas and 3 AMCs to study for loss of heterozygosity of tumor-suppressor genes on chromosomes 1p, 3p, 9p, 10q, and 17p (L-myc, HOGG1, p 16, pten, and p53). The rate of allelic loss in the three AMCs was similar to that seen in benign tumors. The authors concluded that since tumors that behaved aggressively did not harbor more allelic losses, it is likely that DNA damage in ameloblastomas and AMCs is sporadic and cumulative; other genetic or epigenetic mechanisms may be responsible for malignant behavior in AMCs.

**Differential Diagnosis.** The differential diagnosis includes other odontogenic carcinomas and ameloblastomas. Occasional mitoses, keratinization, and formation of hyaline material adjacent to the epithelium in ameloblastomas are not signs of malignancy (811). If areas of cytological benign ameloblastoma are present in a tumor, which otherwise shows signs of malignancy with ameloblastic feature, the tumor is an AMCA ex ameloblastoma, and should be diagnosed as a secondary type. If the malignant part is a squamous carcinoma, the diagnosis is intrasosseous squamous carcinoma ex ameloblastoma, and not AMCA. Carcinomas metastatic to the jaws should also be considered, but they do not show ameloblastic features (783).

Some AMCs have been reported to contain clear cells. If the presence of clear cells is conspicuous, most pathologists will classify the tumor as a clear cell carcinoma (812). Hall et al. (811) have suggested they should be regarded as clear cell type of AMCA and have demonstrated that those with a significant amount of clear cells have a worse prognosis, than those without.

AMCs may be dominated by spindle cells and areas with sarcomatoid proliferation. Pancytokeratin and vimentin stainings are useful means to establish the epithelial quality of the tumor cells. Cases have been reported with such a histomorphology and been considered carcinomasarcomas or AMCA with development of sarcoma (818,819). No immunohistochemistry was done to clear up the origin of the tumor cells.

**Treatment and Prognosis.** Patients with AMCA have been treated with curettage, resection, irradiation, and chemotherapy (805,811). Patients treated with radical surgical removal early in the course of the disease had the fewest recurrences and were apparently cured (811). Resection in terms of complete removal of the tumor with a wide margin of clinically uninvolved tissue is the treatment of choice. The study of Hall et al. (811) comprising 14 cases from the Mayo Clinic, Rochester, 9 of which contained clear cells, showed that surgical resection was more successful in eradicating disease earlier in the course of the disease than later, and after multiple recurrences it was not successful. Eight patients were cured by surgical intervention. All tumors treated with irradiation or curettage recurred. Primary radiotherapy may be considered when an adequate surgical intervention is impossible. It is doubtful whether chemotheraphy has any effect on AMCA or metastases from AMCA.

In their review of 30 cases, mainly from the literature Akrish et al. (805) found a history of metastatic tumor in 8 (28%) patients, all with the primary tumor located in the mandible. All metastases were diagnosed within 1.5 years after the initial treatment. Follow-up information on recurrence was available for 29 patients. Seven (24%) of these had a history of recurrent tumor. The time span from initial surgery to recurrence was three years for one patient and within 1.5 years for six patients. Four of the patients were reported to have died from the disease, either because of uncontrollable local tumor or metastasis.

**1.2.2 Secondary (Dedifferentiated), Intraosseous (Arising in a Preexisting Benign Ameloblastoma).**

**Introduction.** AMCA may arise in a preexisting benign ameloblastoma. The term “dedifferentiated ameloblastoma” has been applied when morphological features of typical ameloblastoma were noted (783).

ICD-O code 9270/3

Synonym: Carcinoma ex intraosseous ameloblastoma.

**Clinical Features.** Seven cases of secondary, intraosseous AMCA have been published (785,810,814,820-823). All cases have been located in the mandible. In two of these, areas of ameloblastoma and AMCA were found in the tumor at the first operation, one patient was a 22-year-old man (814), the other was a 74-year-old-man (810). In the remaining cases the AMCA occurred after one or more recurrences often after many years: 5 years (M 65 years at diagnosis of ameloblastoma/70 years at diagnosis of AMCA) (822), 12 years (F 32years/44years) (823), 18 years (M 25years/43years) (821), 19 years (F 33years/52years) (785), and 25 years (F 36years/64years) (820) after the diagnosis of the primary ameloblastoma. The patients’ gender and age at diagnosis of the primary tumor and at the diagnosis of the AMCA is indicated in the parentheses.

The clinical symptoms of ameloblastomas, which dedifferentiate to AMCA over time do not differ from those of ameloblastomas. In most of the cases the tumor has been very large when it was diagnosed. The course of the disease has varied considerably in the reported cases; no general conclusions can be drawn.
Imaging. At the time of malignant transformation an increased growth rate can be expected with more rapid destruction of bone with ill-defined borders and cortical destruction with invasion into the soft tissue, a feature that is not typically found in an ameloblastoma.

Pathology. The etiology of the tumor is unknown, as is the reason for the malignant transformation, although previous radiotherapy has been suspected in some cases (814).

Macroscopically the tumor has been described as a firm, homogenous, ivory-colored mass with an ill-defined border with respect from the surrounding bone (814).

Per definition the primary tumor must contain at least some areas histologically compatible with a benign ameloblastoma. In the majority of cases the primary tumor and sometimes even the first recurrence (820) has shown ameloblastoma without signs of malignancy. The malignant features have appeared in the first, second, or third recurrence.

Immunohistochemistry. In a case of AMCA, which showed dominating cytological malignancy in the primary tumor with areas of ameloblastoma, Datta et al. (814) detected CKs (with AE1/AE3 and Cam 5.2) and vimentin. Epithelial cells do not usually react with antibodies against vimentin. The reaction to a number of other antibodies including muscle-specific actin, desmin, S-100, and neurofilament was negative. Glycogen was found in the tumor cells.

A histochemical study of tissue from the first, second, and third recurrence and the metastases of an AMCA was performed by Hayashi et al. (820). At first recurrence the tumor was an ameloblastoma, at second recurrence the tumor was partly ameloblastoma, partly AMCA. At third recurrence the tumor disclosed a poorly differentiated squamoid pattern. Tissue from first recurrence, second recurrence, benign as well as malignant areas, and the third recurrence all stained positively for a cocktail of antibodies against CK-1, CK-5, CK-10, and CK-11, but none of them reacted to CK-1 alone, nor to EMA or vimentin. CK-7 was detected exclusively in benign areas of the second metastasis and the squamoid areas of the third metastasis. CK-8 was detected in the first recurrence, the benign areas only in the second metastasis, and in the squamoid tumor epithelium of the third metastasis. A dedifferentiated metastasis to the orbital area without features of typical ameloblastoma was negative to all the antibodies used.

Kumamoto et al. (178) investigated the immunoreaction of extracellular matrix-degrading serine proteinase in odontogenic tumors, and detected expression of uPA, uPAR, PAI-1, and maspin in three cases of AMCA.

To evaluate roles of the Akt-signaling pathway in oncogenesis and cytodifferentiation of odontogenic tumors Kumamoto et al. (250) investigated the expression of phosphorylated Akt, P13K, and PTEN in three cases of AMCA, which all reacted positive.

The roles of MAPKs in oncogenesis and cytodifferentiation of odontogenic tumors were investigated by Kumamoto et al. (78), who detected expression of p-p38 MAPK, and p-ERK5, but not p-JNK in three cases of AMCA.

Abiko et al. (810) stained sections of an AMCA ex ameloblastoma using anti-p53 antibodies. No staining was observed neither in the benign nor in the malignant areas. The study was made in connection with a genetic analysis (vide infra).

Electron Microscopy. In a case of secondary AMCA Datta et al. (814) described rare tight cell junctions, well-defined basal lamina, numerous glycogen granules, and abundant mitochondriae in the tumor cells.

Molecular-Genetic Data. Abiko et al. (810) extracted DNA separately from cytological benign and malignant areas in an AMCA ex ameloblastoma. The isolated DNA was separately amplified for exons 5 to 8 for the p53 gene with PCR and sequenced in a genetic analyzer. Direct sequencing showed no genetic mutation of exons 5 to 8 of the p53 gene. Hypermethylation of CpG islands of the p16 gene was detected in the malignant parts of the tumor. It was concluded that hypermethylation of p16 may have been involved in the malignant transformation of the ameloblastoma.

Differential Diagnosis. To fulfill the requirements suggested in the definition by WHO 2005 (783) there must be evidence of a preexisting benign ameloblastoma. If the tumor is a recurrence, which does not show areas of ameloblastoma together with malignant ameloblastic tumor epithelium, there must be evidence that a previous metastasis or primary tumor was indeed an ameloblastoma. Otherwise the differential problems are similar to those of a primary AMCA.

Treatment and Prognosis. Radical surgical resection with clear margins of uninvolved surrounding tissue as early as possible is undoubtedly the treatment of choice. It appears from the case reports, however, that the tumor is likely to have eroded the cortical bone and invaded the surrounding soft tissue sometimes making a radical surgical removal technically impossible. In some of these cases and in cases that have been considered intractable, radiotherapy has been used postoperatively or alone. The course of the disease in the reported cases have differed considerably and the follow-up time after the last treatment been short. As with de novo AMCA, prognosis must remain guarded over an observation period of several years.

1.2.3 Secondary (Dedifferentiated) Peripheral (Aris-
ing in a Preexisting Benign Ameloblastoma).

Introduction. The term covers a preexisting peripheral (extraosseous) ameloblastoma with transformation to a malignant cellular phenotype. Prior cases of so-called intraoral basal cell carcinomas (gingiva) may, in retrospect be considered in this category as well (783). Basal cell carcinomas develop from the annexes of the skin and do not occur in the jaws or the oral mucosa.

ICD-O code 9270/3
Synonym: Carcinoma ex PERAM
Clinical Features. In a review of 160 published cases of PERAM Philipsen et al. (192) found six cases of malignant PERAM. Another three cases have been published (195,824,825). Six have occurred in men and three in women. Nearly all patients have been past 50 years. The age range is 40 to 83 years, the mean age 65.1 years, median age is 71 years. A possible case has been published by Dufau et al. (826) as a peripheral AFS, which developed in a recurrent PERAM in an 89-year-old man. No immunohistochemistry was done.

The gingival soft tissues are the sites of the transformed PERAM. The tumors may present with variable surface alterations including irregularity, concavity, sessile, and pedunculated features as well as resorption of the underlying bone (783). They are generally nontender. Four of the peripheral AMCAs occurred in the upper jaw, one in the left canine area (220), one in the left premolar area, and two in the left tuber area (219,827). Five tumors were diagnosed in the mandible, one in the left lateral incisor area (824), one in the right premolar area extending to the floor of the mouth (828), two in the left third molar or retro-molar area (825,829), and one extending from the right third molar to the right canine area (798).

Imaging. Radiograms may disclose erosion of the underlying bone (195,219,824,829,827). In one case occurring in the maxillary premolar area all bone between the roots of the premolars was resorbed, but no resorption of the teeth was seen (195). In some cases the bone is not involved (220,798,825), even in a case that has metastasized (798).

A CT scanning is often more informative than radiograms in these cases (219,827).

Pathology. The etiology of the tumor is unknown. The origin of the tumor is believed to be from remnants of the dental lamina in the gingival submucosa. It has also been suggested that the tumor may develop from the basal cell layer of the surface epithelium, but the question is controversial. The amalgamation of the tumor with the surface layer, which is seen in some cases (195,219,825,827,829), may represent fusion of tumor from below with surface epithelium. In the majority of cases the primary tumor shows areas of PERAM together with cytologically malignant areas. In two cases the AMCA did develop in a recurrence and was not present in the primary tumor (219,825). The tumor is usually characterized by an extensive network of strands and islands of recognizable ameloblastoma-type histology with peripherally located columnar cells and centrally located stellate reticulum-like areas, which may show variable degree of squamous differentiation. To fulfill the criteria for the diagnosis of AMCA some areas must show signs of cytological malignancy in terms of cellular and nuclear pleomorphism, invasion of alveolar bone, or the sheets of abnormal mitotic figures, invasion of alveolar bone, and round and spindle neoplastic cells. Neither CK-18 nor CK-19 was present in the gingival epithelium. CK-19 is usually present in odontogenic epithelium.

Putzke (824) studied the proliferation activity in a case of peripheral AMCA by measuring the Ki-67 L. I. In the central areas of well-differentiated follicular ameloblastoma the index was 4.9% and in the peripheral cylindrical basal cells 10.4%. In contrast an index of 43.6% was found in the dedifferentiated areas. The tumor had metastasized to regional lymph nodes where indexes varying between 18.9% and 41.1% were found.

Electron Microscopy. Edmondson et al. (829) studied the ultrastructure of a peripheral AMCA, in which they diagnosed as an intraoral basal cell carcinoma. Tumor cells contained scattered mitochondriae, tonofilaments, and free and polyribosomes. Occasionally endoplasmic reticulum was present. The nuclei contained one or two discrete nucleoli. The plasma membranes were generally smooth, containing few microvilli and scattered desmosomes. At the periphery of tumor islands there was a lamina-densa and scattered hemidesmosomes.

Molecular-Genetic Data. No data published.

Differential Diagnosis. Proliferation of hyperplastic odontogenic epithelium in the gingival submucosa may be difficult to diagnose. To fulfill the criteria for the diagnosis of AMCA some areas must show signs of cytological malignancy in terms of cellular and nuclear pleomorphism, in combination with the histological patterns of an ameloblastoma. Lesions that, besides the odontogenic epithelium, show cell-rich embryonic pulp-like tissue can easily be excluded. The epithelial-rich type of the peripheral odontogenic fibroma (830) may be difficult to distinguish from a PERAM but not from an AMCA because of its lack of features of malignancy. Similar considerations are valid with regard to the rare peripheral variant of the SOT.

Treatment and Prognosis. Wide local excision with en bloc resection of the involved segment of the affected jawbone is the indicated treatment (783). None of the reported cases contain long-term follow-up. Experience from other types of AMCAs and from METAMs underlines the importance of long-term follow-up.

1.3 Primary Intraosseous Squamous Cell Carcinoma

PIOSCC is a central jaw carcinoma having no initial connection with the oral mucosa and is presumably originating from residual odontogenic epithelial elements. To fulfill the criteria for this lesion there must be no evidence to suggest metastatic tumor and tumors originating from salivary gland tissues are excluded (831,832). Invasion from an antral primary carcinoma must also be excluded.

ICD-O 9270/3

Synonym: Primary intra-alveolar epidermoid carcinoma of the jaw (833).
With regard to the pathogenesis three subcategories of PIOSCC are recognized (832): (i) a solid tumor that invades marrow spaces and induces osseous resorption, (ii) as SCC arising from the lining of an odontogenic cyst, and (iii) a SCC arising in association with a benign epithelial odontogenic tumor (832,834). When the tumor destroys the cortex and invades the surface mucosa it may be impossible to distinguish a PIOSCC and a carcinoma arising from the oral mucosa (832).

Other classifications have been suggested previously (784–786).

1.3.1 Solid Type ( ARISING DE NOVO).

Introduction. A primary intraosseous SCC arising from a noncystic source like remnants of odontogenic epithelium, reduced enamel epithelium (835) or from a benign odontogenic tumor (836,837).

Clinical Features. The prevalence and incidence of this rare tumor is unknown. The relative frequency was indicated in a Chinese review (42) of cases received for diagnosis from 1952 to 2004; a total of 1642 odontogenic tumors were diagnosed; 50 cases were malignant (3.0%), 14 of these (0.9%) were PIOSCC, subtypes were not specified.

About 51 cases of this rare lesion have been published. Reviews have been written by Elzay et al. (784): 12 cases, Ohtake et al. (838): 28 cases including cystogenic types, Suei et al. (839): 39 cases, Kaffe et al. (840): 24 cases, Thomas et al. (841): 35 cases. Eight cases have been published later or were not included (315,835,837,842–846).

There is a male predominance, with a male:female ratio higher than 2:1 (839,841). The age range is 4 to 81 year, and the mean age about 50 to 53 years (839,841), it is about three years higher for women than for men. More than 60% of the patients have been older than 50 years.

Only 10% of the lesions have been located in the maxilla, and all in the anterior part. The posterior mandible is the predominant site; 80% of all PIOSCC, solid type, have been located in that region.

Swelling of the mucosa at the affected site is a common symptom (81%), as well as pain (74%) (839). Sensory disturbances (numbness or paresthesia of the mandibular nerve), an important symptom, were found in 9 of 15 cases in which this data was available (839).

Many of the cases were diagnosed during the course of routine dental examination or in patients presenting with persistent symptoms from dental disorders (847). The diagnosis of PIOSCC was delayed in such patients, because the dental problem was given prior attention.

Metastases to regional lymph nodes were confirmed histologically in 13 of 33 cases (839).

Imaging. Radiograms have shown osteolytic bone changes in all cases, and only a few with mixed radiopaque areas. Among 22 cases (839) the margins were diffuse, irregular or ill defined in 16 cases, and well defined in 6. Among 23 cases 15 were unicocular, 1 multilocular, and 7 not loculated (840). The lesions extended into the alveolar bone and/or the body of the jaw and the mandibular ramus. Root resorption was only reported in two cases (839). The supplementary use of CT examination has proved to increase the level of image information considerably (840).

Pathology. The etiology of the tumor is unknown. It is presumed to arise within the jawbones from periradicular rests of the epithelial root sheet (Malassez) or from the reduced enamel epithelium (835,843). A few cases have developed in benign ameloblastomas (837,848) or SOT (315).

The histomorphology of the PIOSCC is similar to the conventional SCC (849) with islands of neoplastic squamous epithelium in a fibrous connective tissue with varying degree of diffuse infiltration of lymphocytes (Figs. 87, 88). The extent of keratinization varies;
Chapter 19: Odontogenic Tumors

Introduction.

The lesion is defined as a SCC arising within the jaws in the presence of an odontogenic cyst and without connection to the oral mucosa. Evidence of dysplastic or malignant transformation of the squamous epithelium in a cyst wall is essential for the diagnosis of PIOSCC ex odontogenic cyst (855).

Molecular-Genetic Data. Alevizos et al. (852) performed a cytogenetic analysis on 120,000 keratinocytes harvested from 5 μmol cryosections of a moderately to poorly differentiated PIOSCC associated with a displaced mandibular third molar. There were no odontogenic cyst remnants in the area. Functional genomic analysis of about 6800 human sequences was performed, and the database generated was compared with the gene expression demonstrated in four oral mucosa SCC databases generated in a similar fashion. Comparison of the databases revealed numerous, verifiable upregulated (N = 102) and downregulated (N = 99) genetic events unique to PIOSCC. On the other hand 1340 genes appeared to be commonly expressed between all five tumors. There were eight PIOSCC genes, which had a more than threefold upregulated expression and 20 genes with a more than threefold downregulated gene expression, among these 10 ribosomal protein genes and 4 CK type genes. Thus only a small subset of genes seemed to distinguish this PIOSCC from oral mucosal epithelial carcinoma.

Differential Diagnosis. The diagnosis of PIOSCC is not possible without supporting clinical and radiographic information. A distant primary site can only be excluded about six months after treatment. To distinguish a solid PIOSCC from a PIOSCC derived from an odontogenic cyst may be impossible; a PIOSCC in an advanced stage may have obliterated any residual tissue of origin. Histologically differential diagnosis should include a central mucoepidermoid carcinoma in which epidermoid cells predominate (54) and an acanthomatous ameloblastoma and a SOT, which may be misdiagnosed as SCC (853).

Treatment and Prognosis.

Patients with PIOSCC have been treated with radical surgery, radiotherapy, and chemoradiation, and combinations of these treatment modalities (841,847). Partial to hemimandibulectomy is appropriate when the tumor is located in the maxilla depending on the size of the lesion with postoperative radiation as an elective option (849). Hemimandibulectomy may be required for extensive mandibular lesions; involved lymph nodes require block dissection. Postoperative radiation therapy is an elective option.

The prognosis is difficult to determine because of the paucity of cases reported and the very few cases with a follow-up period of five years or more, but it seems quite poor. Shear (833) estimated a five-year survival rate between 30% and 40%. This estimate was confirmed by To et al. (854); in a group of 29 patients 11 died within a year, 4 died within two years, 3 were alive and well for two to five years, and 11 survived more than five years.

Metastases at the time of presentation were seen in 31.4% of the cases analyzed by Thomas et al. (841), but they did not find any significant effect of lymph node involvement on survival time. In an analysis of 35 cases Thomas et al. found an overall survival rate at one year, two years, and three years to be 75.7%, 62.1%, and 37.8%. Only 29.8% were disease free after three years.
from the COC and the KCOTs are excluded, data from a total of 43 cases of PIOSCC derived from radicular, residual, and dentigerous cysts give the following information about age at time of diagnosis and location. Among the 43 cases 30 were males, and 13 females; the male:female ratio is thus 2.3:1. The age range is 22 to 90 years (for males: 22–75 years, for females: 30–90 years), the mean age is 56.7 years (for males: 54.8 years, for females: 61 years); the median age is 57 years (for males: 57 years, for females: 67 years). Thirty of the forty-three patients (58.9%) were older than 50 years.

Like the solid type of PIOSCC the carcinomas derived from odontogenic cysts are more common in the mandible than in the maxilla. Among the 43 cases, 13 were located in the maxilla (10 males, 3 females) and 30 in the mandible (20 males, 10 females); the ratio maxilla:mandible being 1:2.3.

Regarding PIOSCC derived from the KCOT about 26 cases have been published, six of them in the Japanese or Korean language (860). Data from 20 cases published in English (861–879) show that 13 of the 20 patients were males and 7 were females, making the male:female ratio 1.9:1. The age range is 18 to 81 years (males: 25–79 years, females: 18–81 years). The mean age is 51.3 years (for males: 51 years, for females: 51.7 years). The median age is 54 years (for males: 46 years, for females: 54 years).

The tumor is more common in the mandible, where it was located in 14 cases (9 males and 5 females), than in the maxilla: 6 cases (3 males and 2 females). The ratio maxilla:mandible is 1:2.3. Among the six tumors in the maxilla, three were located in the anterior region and three in the posterior. None of the tumors in the mandible were located in the anterior region, apart from two cases where the tumor occupied the entire left or right side of the jaw. The remaining 12 cases were located in the posterior region.

There are no obvious differences in the data from patients with PIOSCC ex KCOT and PIOSCC from other types of odontogenic cysts except that the mean and median age in patients with PIOSCC ex KCOT is somewhat lower, but the number of patients is small, so the difference may not be significant.

Since more than 50% of the KCOT and more than 50% of the dentigerous cysts are diagnosed in the posterior part of the mandible, and the majority of the radicular and residual cysts occur in the anterior part of the maxilla (228), a difference in the prevailing locations between PIOSCCs derived from various types of cysts could be expected, but the study has not been done.

Irrespective of the source of the tumor there is an absence of any indication of malignancy in most cases, even at the time of biopsy or enucleation. The diagnosis of PIOSCC derived from a cyst is often made on the basis of a histological examination. When symptoms are present they are mainly nonspecific, including swelling and pain. In a review of 56 cases Schwimmer et al. (858) found enlargement in 58.9%, pain in 19.6%, and painful swelling in 21.5% of the patients. In a review of 39 cases Suei et al. (839) recorded swelling in 64.1%, pain in 64.1%, sensory disturbance in 23%, and local lymph node metastasis in 33% of the cases. Significant symptoms apart from swelling of lymph nodes are paresthesia or anesthesia, rapid, firm nontender enlargement of the jaw, and failure of an extraction alveolus to heal.

**Imaging.** In the majority of cases the lesion presents itself on the radiogram as a round to ovoid unilocular, sometimes multilocular radiolucency with well-defined, sometimes ill-defined margins. Early lesions are diagnosed as cysts; in more advanced stages at least some parts of the border is indistinct and may be jagged with indentations, thus distinguishing the cyst-derived PIOSCC from a benign odontogenic cyst (856). Thinning of the cortex of the jaw may be seen, and resorption of roots of teeth adjacent to the radiolucency has been observed.

**Pathology.** The etiology is unknown; there are no predisposing factors (832). It has been noted that a surprising amount of cysts in which PIOSCC developed, and which were not KCOT showed some keratinization (880,881,863), a feature that could be related to the carcinomatous potential.

Histopathologically, the tumor is characterized as a cyst in association with a SCC. The histomorphology of the lining of the cyst depends on its type, radicular/residual, dentigerous, COC, or keratinizing cystic odontogenic tumor. The latter is usually parakeratinized, but it may be orthokeratinized (870,875). The diagnosis requires documentation in the microscope of transition from a benign cyst with its characteristic epithelial lining to an invasive carcinoma (849). The transition may be abrupt or gradual in terms of various degrees of epithelial dysplasia in the epithelial lining (Fig. 89). The SCC extends from the epithelial lining of the cyst into the connective tissue wall accompanied by chronic inflammation. The carcinoma is well differentiated in most cases, but a case of spindle cell carcinoma arising in an odontogenic cyst has been published (882). Sawyer et al. (883) published a case in which they observed hard tissue

**Figure 89** Primary intra-osseous squamous cell carcinoma, cystogenic type. Carcinoma in situ is seen in this part of the lining of a cyst, which in other areas showed invasive carcinoma. The tumor developed in a large cyst in the left mandible of a 76-year-old woman. H&E stain.
formation in the PLOSCTC; it was interpreted as dysplastic dentin (dentinoid).

**Immunohistochemistry.** McDonald et al. (884) studied the expression of p53-protein with a monoclonal antibodies in a SCC derived from a cyst around the crown of a mesially impacted lower right molar. An overexpression of p53 was found in the nuclei of tumor cells, but not in the cystic epithelium.

**Electron Microscopy.** Herbener et al. (870) studied the ultrastructure of a SCC juxtaposed to a KCOT. Dysplasia in the cyst epithelium could not be found, the ultrastructure of the cystic lining was in accordance with other similar studies (228). The tumor cells were loosely bound to one another and had a tortuous outline. The nuclei had an irregular outline and contained multiple prominent nucleoli. The cytoplasm was rich in mitochondria, contained a dilated RER, and inclusions that resembled lysosomes. Occasionally Golgi apparatus, vacuoles, and glycogen were found. Some cells contained irregularly distributed bundles of tonofilaments throughout the cytoplasm. The authors stated that some of the cells had a remarkable resemblance to the ameloblasts of developing teeth and ameloblast-like cells in the ameloblastoma.

**Molecular-Genetic Data.** By means of flow cytometry, High et al. (864) studied the DNA of cells from a keratinizing cystic odontogenic tumor (odontogenic keratocyst) with epithelial dysplasia, which underwent subsequent malignant transformation. The cells from the cyst showed a type of DNA-aneuploidy, which was found in the subsequent SCC as well.

**Differential Diagnosis.** Any connection with a mucosal surface SCC as well as a metastatic must be excluded. The main differential diagnosis should include a central mucopeidermoid carcinoma dominated by epithelial cells, and SOT-like proliferations in the cyst wall (315). In the latter case there will be no epithelial dysplasia in the cyst lining.

**Treatment and Prognosis.** In the few cases where the malignancy was detected before the initial treatment, aggressive resection like a bloc resection, hemimaxillectomy, and hemimandibulectomy have been performed (315). In the latter case there will be no epithelial dysplasia in the cyst lining.

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data separated for the variants CCOC and CCAM (898,899). The latter (899) in particular is detailed, and the authors use stringent criteria for separation of the two variants; the following description of clinical features is based on that review.

Among 27 cases of CCOC, 8 were males and 19 females, with a male-to-female ratio of 1:2.4. Among eight cases of CCAM there were five males and three females (ratio 1.7:1).

Age at the time of diagnosis ranged from 17 to 89 years in CCOC with a mean age of 59 years and a median age of 61 years. The mean age of females was eight year higher than that of men (61 and 53 years, respectively). Regarding the eight cases of CCAM, age ranged from 14 to 71 years, with a mean age of 44 and a median age of 46 years. The mean age of females was about the same as that of the males, 45 and 43 years, respectively.

CCOC and CCAM are primarily intraosseous neoplasms. A single case of PERAM with clear cells has been published (903); the amount of clear cells was very limited and it was apparently a benign lesion. No case of multiple lesions has been published. The CCOC is by far most often located in the mandible. Among 29 cases, 3 were in the maxilla (2 anterior, 1 posterior) and 24 in the mandible (12 anterior, 11 posterior, 1 unknown). The eight cases of CCAM were distributed with two in the maxilla (both posterior) and six in the mandible (4 anterior, 2 posterior).

The size of the neoplasm has varied considerably. A few were small, about 2 cm at longest diameter, many were about 5 cm, and some have been very large, about 10 cm. The growth rate seems to be fast; the time from first symptom to diagnosis is generally short, often between two and six months. In some cases it was two years or more, but in such cases the tumor has often developed in continuation of or as recurrence of another lesion. Very few, and they were all small tumors, were diagnosed during routine examination.

Swelling and expansion are the most common symptoms in CCOC as well as in CCAM. A few have complained of mild pain or a dull ache. Among 27 cases of CCOC tooth mobility was found in seven cases, and tooth displacement in six cases. Among eight cases of CCAM tooth mobility was found in one case, and tooth displacement in 2 cases (899).

**Imaging.** The information on radiographic characteristics have been incomplete in many reported cases (899). The lesions have been described as radiolucent; nine cases of CCOC as unilocular and four as multilocular. The lesions had well-defined borders in 5 cases and poorly defined borders in 9 cases; root resorption has been reported in 1 case and cortical destruction in 11 cases. Among the CCAM lesions all eight were radiolucent; five of them were unilocular and one multilocular. Well-defined borders were seen in two lesions, and one was poorly defined. Root resorption occurred in one case. Cortical destruction was seen in five of seven cases in which this data was available. CT scanning has proven to be very useful in tracing the extension of the lesion (888,904,895).

**Pathology.** The etiology and pathogenesis of the CCOC and the CCAM are unknown. Since they are both exclusively intraosseous, they arise most likely in residues of the dental lamina and proliferations of odontogenic epithelium adjacent to reduced enamel epithelium (448), although histological similarities to tissue in the developing tooth germ are lacking in the CCOC (800). Clear cells have been found in the wall of gingival cysts of the adult, in the wall of the lateral periodontal cyst, and in rests of dental lamina in the gingival, and in operculae, but not in radicular or dentigerous cysts (228,905,906). Some tumors seem to arise in preexisting recurring ameloblastomas (cases 2 and 3) (894,907).

Macroscopically the tumor has been described as a white or pinkish-gray, solid mass with (908) and without (886) necrosis.

Histologically, the CCOC is composed of irregular bands and islands of relatively uniform, round to oval epithelial cells with abundant clear cytoplasm and round, lightly stained vesicular nuclei (Fig. 90). Other islands may consist of smaller polygonal cells with an eosinophilic, faintly fibrillar cytoplasm and monomorphic hyperchromatic nuclei. The two cell populations may exist in the same tumor island (biphasic pattern), and transition to clear cells may be observed (849,886,898,908). Strands of small eosinophilic cells may be present. Neither nuclear pleomorphism nor mitotic activity is necessarily present, but moderate nuclear pleomorphism is not uncommon (Fig. 91). Mitotic activity is usually rare (886), but in some cases mitoses are frequent (891) or numerous (909). No squamous, glandular, or ameloblastoma-like features are seen. The tumor islands are separated by narrow bands of mature, fibrous, sometimes hyalinized connective tissue with few cells. There is no encapsulation, and the tumor invades the surrounding medullary bone and sometimes even dental pulp (831). Cortical destruction with growth into the

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**Figure 90** Clear cell odontogenic carcinoma. The tumor is composed of oblong, rounded epithelial islands with many clear cells and moderate pleomorphism. The histology shows no resemblance to an ameloblastoma, no palisading columnar cells are seen in the periphery, and no stellate reticulum-like epithelium is present in the islands. H&E stain. Source: Section by courtesy of Professor G. Bang, Bergen.
The CCAM variant is characterized by a histomorphology, which is in some aspects similar to that of an ameloblastoma with follicular growth pattern, but often with cuboidal central cells with vesicular nuclei and abundant eosinophilic, slightly granular or fibrillar cytoplasm instead of a stellate reticular pattern. Together with this pattern a prominent clear cell component is present within the follicular nests with areas showing transition between the two patterns (biphasic pattern). Squamous cells may be seen, particularly in the central areas of the islands. A few mitoses may be observed. However, if signs of malignancy are present, like hypercellularity, hyperchromatism, loss of ameloblastic differentiation, spindling, more than two mitotic figures per high power field (40×), vascular invasion or neural invasion, the tumor should be classified as AMCA (811).

The stroma consists of dense fibrous, connective tissue with hyalinized areas. The stroma is often more abundant than in tumors with the CCOCC pattern. A few ghost cells may be seen, which is not unusual for many odontogenic tumors. In very few cases a formation of dentinoid or even canicular dentin has been observed (891,910). Similar findings have been described in AMCAs (811). While the case reported by Ariyoshi et al. (910) is likely to be a DGCT with clear cells, other cases published by Miyauchi et al. (891) and Kumamoto et al. (911) are more difficult to explain, since no odontogenic ectomesenchyme was detected in the tumors. Small cystic spaces with amorphous, eosinophilic, Congo red negative content has been described (900,911,912).

Immunohistochemistry. A considerable amount of histochemical and immunohistochemical studies have been published; it remains unclear if differences exist between the CCOCC and the CCAM.

Figure 91  Clear cell odontogenic carcinoma. Higher magnification of another area of the tumor seen in Figure 90. The tumor islands show a moderate, but distinct pleomorphism in a mixed population of clear cells and eosinophilic polyhedral cells. The histology differs clearly from that of an ameloblastoma. H&E stain. Source: Section by courtesy of Prof. G. Bang, Bergen.

Glycogen (diastase-digested, PAS-positive granules) in the cytoplasm of the clear cells is a common finding (891,900,913). The cells are consistently negative when stained with mucicarmine and alcin blue, thus excluding glandular activity (563,900,914,915).

Intracellular enzymes have been detected: acid phosphatase in lysosomes (909,913), nonspecific esterase and NADH diaphorase, while alkaline phosphatase, which is related to mineralization is absent (913).

Most investigators have found the tumor cells S-100 protein-negative (891,900,911,912,914,916,917). EMA has been detected (891,915,917,918), but the tumor cells do neither contain involucrin (563,911), smooth muscle actin (891,900,911,914,916,917) nor vimentin (891,900,914–918).

Filagrin has been detected (911), as well as various types of CK. Tumor cells have reacted positively to pankeratin antibodies (AE1/AE3, KL1) sporadically in clear cells, invariably in eosinophilic cells (563,891,900,907,909,917). Reaction to CK-10, which is found in keratinized squamous epithelium has been negative (563). CK-5, CK-6, CK-13, and CK-14, which are usually found in lower or middle layers of squamous epithelium have been detected in tumor cells (889,912,916). CK-14 is a common finding in ameloblastomas. Among the CKs usually found in simple epithelium, CK-8 has been found by some (891,900,912,916). Investigations of CK-18 have given contrasting results, some were negative (916), some found weak focal reactions (912,918). CK-19 is a constant finding in odontogenic epithelium and has been detected in the tumor cells repeatedly (163,891,900,907,912,916,917). CK-20 could not be detected (563).

Amelogenin, an enamel protein has been disclosed in the tumor cells (163).

An overexpression of MDM2, an oncogene product has been detected in the tumor cells as well.

Electron Microscopy. Ultrastructural studies have shown nests of epithelial cells surrounded by a continuous basement membrane (909,914,915). The islands are surrounded by fibrous stroma of collagen and fibroblasts (913). No glandular or luminal structures are seen. The plasma membrane is often very convoluted (913) and the cells tightly interdigitated by microvillus projections (891,914). Desmosomes are small (891,915,914). Basal lamina-like deposits between the tumor cells have been observed (891,913). Palisading cubic or elongated basalt cells are found in some places in the CCAM variant (914). The clear cells show an abundant clear cytoplasm with a paucity of cell organelles. Organelles are more numerous in the eosinophilic cells (914). Mitochondria that appear normal are sparsely dispersed or clustered in one end of the cell (913,914); some are swollen. Glycogen rosettes are commonly found, sometimes in accumulations (891,919). Lysosomes are present (913), and sometimes abundant (909). Short segments of RER have been detected and annulate lamellae are frequently seen in the cytoplasm, often adjacent to cell nucleus (913). No well-developed Golgi apparatus or secretary granules are found (913,914). A concentration of microfilaments may be seen, particularly in eosinophilic cells (915). Many cells have centrioles or
microtubule organizing centers adjacent to the nuclei (913). Large empty or clear areas in the cytoplasm may be seen. The nuclei have complex invaginations and one or two nucleoli (891, 914). Many nuclei look pycnotic.

The fibroblasts of the stroma are elongated, with a rough endoplasmatic reticulum, which appears swollen (913, 914).

**Molecular-Genetic Data.** Flow cytometry DNA-analysis has disclosed a polyploid tumor cell population with DNA-index 1.93 and an S-phase of 10.2% (920).

CGH analysis of tumor cell chromosomes have disclosed aberrations in terms of gains for chromosomes 19 and 20, and the long arm of chromosome 14, as well as loss for chromosomes 6 and 9 (916). DNA-microarray has been used to detect gene expression changes in CCOC compared with reference tissue (921). Several genes were found whose expression was definitely upregulated or downregulated. The genes were found to be differently expressed over a broad range of functional activity: transcription, signaling transduction, cell cycle regulation, apoptotic stimulation, and differentiation.

Tumor suppressor genes have been studied (5); a high expression of p63—a member of the TP53 gene family—was found in peripheral as well as in central epithelial cells (121).

The cell proliferation marker Ki-67 has been studied in sections of CCOC. The activity was conspicuously increased (40% positive nuclei) (909).

**Differential Diagnosis.** Differential diagnosis from other tumors of the jaws with a prominent clear cell component may be very difficult. They include primary odontogenic, primary intraosseous salivary gland, and metastatic neoplasms. A detailed setting up of differential diagnostic features of head and neck tumors with clear cells has been published by Eversole (677) and by Brandwein et al. (915).

CEOT with clear cells is a very rare tumor; about 15 cases have been published (332). Most CEOTs will show typical sheets of polygonal epithelial cells some of which are transformed into eosinophilic material that stains for amyloid and eventually calcifies. They should be easy to identify. Even in absence of these features the differential diagnosis should not be too difficult, since the clear cell nests are usually small and form clusters, and the cytomorphology of the CEOT cells differs conspicuously even from the eosinophilic polygonal cells of the CCOC.

S/mAMs may contain areas with clear cells. The only difference to the CCAM variant of the CCOC with absence of mitoses and cellular atypia may be the proportional amount of clear cells in the tumor. While the CCAM has been documented to be a malignant tumor, it is unknown whether a limited amount of clear cells in an s/mAM does influence its pathogenesis.

Salivary gland neoplasms arising within the jaws are extremely rare, but may cause differential diagnostic problems particularly if the CCOC is monophasic, consisting entirely of clear cells. Mucoepidermoid carcinomas are usually biphasic with a squamous cell and a mucous cell component. The latter is stainable with mucicarmine and alcian blue in contrast to CCOC clear cells. Sometimes the mucoepidermoid carcinoma may be composed almost exclusively of clear cell sheets, but this clear cell variant is distinctive (677).

About 6% of acinic cell carcinoma irrespective of location contain clear cells with a cyttoplasm that is nonreactive with a PAS staining (922), but they usually contain some areas with serous acinar cells with zymogen-like granules, which are PAS-positive and resistant to diastase. Ultrastructural examination will demonstrate evidence of glandular differentiation, which is absent in CCOC.

The most difficult differential diagnosis is CCOC versus an intraosseous hyalinizing clear cell carcinoma (HCCC), a very rare salivary gland tumor (922). Histochemistry is not useful. Berho et al. (923) argue that the cells of the CCOC are S-100 protein-positive, and those of the HCCC are negative. However, later investigations have invariably shown the CCOC to be S-100 protein-negative (*vide supra*). The most conspicuous difference is the stromal component, which is less prominent and less hyalinized in CCOC than in HCCC, which may show a heavy hyalinized stroma almost completely obliterating the epithelial elements (915, 923, 924).

Metastases to the jaws with clear cell features are primarily of renal origin. Histologically the differential diagnosis to CCOC may be difficult, but renal clear cell carcinoma tends to be composed of smaller islands of clear cells, and the capillary septa are more extensive. Furthermore the renal carcinoma cells are vimentin-positive; the CCOC cells are vimentin-negative. Careful physical examination of the patient and meticulous metastatic work-up should contribute to solve this issue (923).

**Treatment and Prognosis.** The treatment of choice for CCOC as well as the CCAM variant is resection with at least 1 cm tumor-free margins, and long-term follow-up (10–15 years or more). Adjvant radiotherapy is a rational option in case of eroded cortical bone and invasion into soft tissue (915). Patients treated with local enucleation and curettage have eventually developed multiple recurrences, metastasis and died of the tumor (899–901, 902, 915). Recurrences and/or metastases may occur even despite aggressive surgery. There is no obvious difference in the prognosis of CCOC and CCAM, although the mean time between diagnosis and appearance of metastasis was three years for CCOC patients and 13 years for CCAM in the cases published. More CCAM patients (38%) than CCOC patients (13%) died of their tumor (899). It is worth noting in this context that in a study of 14 cases of AMCAs, with clear cells present in nine of the tumors, Hall et al. (811) observed that three of four patients who died of or with the tumor had a substantial amount of clear cells in the tumor.

1.5 Ghost Cell Odontogenic Carcinoma

**Introduction.** GCOC is the malignant counterpart of the calcifying odontogenic cyst CÔC, CCOT, and the DGCT. It is characterized by cell-rich usually large
islands of various shapes consisting of small round epithelial cells with hyperchromatic nuclei and numerous mitoses admixed with ghost cells and sometimes calcification (597).

ICD-O code 9302/3

Synonyms: Odontogenic ghost cell carcinoma; calcifying GCOC; malignant epithelial odontogenic ghost cell tumor; malignant calcifying ghost cell odontogenic tumor.

Clinical Features. The prevalence and incidence of GCOC is unknown. The relative frequency was indicated in a Chinese review (42) of cases received for diagnosis from 1952 to 2004, a total of 1642 odontogenic tumors were diagnosed; 50 cases were malignant (3.0%), 5 of these (0.3%) were GCOC.

Only about 29 cases of this rare tumor has been reported in the English and Spanish language literature (142,578,581,626–631,935), some others have been published in Chinese and Japanese (657). The first case was published in Spanish in 1965 as “Tumor odontogenico epithelial calcificante” (578).

On the basis of the reviewing of the 29 published cases the following data could be extracted. All cases have been intraosseous, but several have invaded the surrounding soft tissue. There is a male predominance; 24 males versus 5 females. The age range for both genders is 13 to 72 years, for males 17 to 72 years, for females 13 to 72 years. Mean age at time of operation is 37.7 years; for males 36.4 years, for females 44.0 years. The median age is 38 years; for males 38 years, for females 48 years. Nineteen patients (65.5%) have been between 30 and 48 years.

The tumor occurs primarily in the maxilla; 21 cases have been diagnosed in the maxilla (16 in males, and 5 in females), and 8 cases have been diagnosed in the mandible (all in males). The ratio maxilla:mandible is 2.6:1.

The tumors have been large, five of them involved the region of two to four teeth only, but eight of them have involved the entire left or right side of a jaw; four have crossed the midline, and one case (578) developed in the left mandible, but eventually invaded the left maxilla via the soft tissues after several recurrences. The size of the tumors has varied, but most have been larger than 5 cm at the longest diameter at the time of operation.

The growth rate is fast, but in several cases the tumor has arisen in, or in association with a COC, CCOT, or DGCT, which has been present as a painless swelling for years. Many patients have experienced even the malignant tumor as a painless swelling; pain has been reported in seven cases and paresthesia of the mandible in one case (628). Some patients have had symptoms related to the invasion of the tumor into the nasal cavities, maxillary sinuses, or the orbit.

Imaging. The typical radiographic picture shows a poorly demarcated osteolytic radiolucency with radiopaque foci (597); only five cases have been reported to be exclusively radiolucent (631). The lesion may be unilocular or multilocular. Supplementary CT and MRI scanning is recommended (936). Displacement of roots of teeth has been described in five cases and root resorption in six cases (631).

Although the specific diagnosis is difficult to make on the basis of the imaging, it does indicate a malignant tumor.

Pathology. The etiology of the tumor is unknown. It seems to arise either de novo or from, or at least in association with, a COC, CCOT, or the more rare DGCT, and sometimes in connection with recurrence of one of these entities. These benign lesions may be part of the operation specimen besides the malignant tumor mass; the malignant component may be separated from or admixed with the benign lesion. Some tumors are completely solid, but when it is associated with a COC or CCOT it consists macroscopically of a well-circumscribed cystic portion and a solid portion with gritty consistency on cut surface (597).

Histologically the tumor consists of rounded, irregularly shaped, varying-sized islands of closely packed, small epithelial cells with a sparse eosinophilic cytoplasm and with rounded, dark, moderately pleomorphic nucleoli (Fig. 92). Numerous mitoses are found. Admixed with the tumor cells varying-sized islands of ghost cells are seen; they present as large polygonal cells with a homogeneous pale eosinophilic cytoplasm (Fig. 93). The nuclei have disintegrated and left a rounded empty space, in some of these remnants of chromatin may be seen. Distinctly atypical ghost cells with retention of nuclei may also be seen as described by Ellis et al. (581) (case 1). Where ghost cell masses are in contact with the connective tissue stroma, a foreign body giant cell reaction is visible. There may be various amounts of calcification in the ghost cells. Clear cells or vacuolated cells may be admixed with the ghost cells. Necrosis within the central area of tumor islands is common and may be marked. Dysplastic dentin (dentinoid) has only been observed in cases admixed with an original COC.
CCOT, or developed from a DGCT (930). The tumor invades surrounding bone and adjacent soft tissue.

Immunohistochemistry. Tumor cells have reacted positively to antibodies against high mw CKs (CK-1, KL-1, AE3, 34βE12) as well as low mw CKs (Cam 5.2, NCL-5D3, AE1). They have been strongly and uniformly positive for high mw CKs and more weakly and focally positive for low mw CKs (628,926,931). Kim et al. (142) used antibodies against low and high mw CKs (AE1/AE3) and found that the tumor cells were focally positive for both antibodies. Nucleated cells adjacent to the ghost cells were positive as well; ghost cells were not stained. The positivity for CKs and involucrin in the nucleated cells adjacent to the ghost cells appeared to disappear as the nuclei disappeared.

Results of reactions to antibodies against vimentin, CEA, S-100 protein, and p53 have been controversial (628,931,935).

Lu et al. (628) detected immunoreaction to NSE in tumor cells; these findings were confirmed by Sun et al. (935).

Takata et al. (615) assessed the proliferative activity of GCOC tumor cells by measuring the PCNA L.I. in four cases of GCOC and compare the results with the findings in 25 cases of COC. The PCNA L.I. of GCOC (65.2 ± 5.6% and 65.9 ± 7.3%) was significantly higher (p = 0.002) than that of the COC (29.3%) and the DGCT (45.8%). The authors concluded that the PCNA L.I. seems to be a possible parameter in differentiating the GCOC from its benign counterparts.

Overexpression of Mi-1, which detects the epitope of Ki-67 was found in three cases of GCOC by Lu et al. (628). In the same investigation an overexpression of p53 was found.

Electron Microscopy. Ultrastructural studies of a GCOC have been performed by Ikemura et al. (626). The high nucleocytoplasmic ratio of the tumor cells, which is clearly seen in the light microscope, was confirmed. The cells have a prominent nucleus in a polygonal nucleus and a well-developed RER with dilated cisternae, some free ribosomes, and numerous mitochondria. The cells have numerous microvilli on the surface; they are arranged in a pavement pattern and connected with a few desmosomes, which form poorly developed intercellular bridges. The loss of cohesion between many tumor cells was observed by Folpe et al. (931) who also described condensation of keratinfilaments around the nuclei.

Molecular-Genetic Data. Kim et al. (142) studied the possible involvement of apoptotic processes in the formation of ghost cells, which has been considered an abnormal form of keratinization. They performed immunohistochemical stains for Bcl-2 and Bcl-XL, which prevent apoptotic cell death and for Bax, which induces apoptotic cell death. No cells had a positive response for Bcl-2, whereas Bcl-XL was demonstrated in the pleomorphic tumor cells and in nucleated cells adjacent to the ghost cell areas. Some ghost cells were faintly positive for Bcl-XL. Bax was expressed in ghost cells and in nucleated cells adjacent to ghost cells, but it was not found in the tumor cells, except for some nests of ameloblastoma-like cells, which were positive for Bax and Bcl-XL. Furthermore a terminal deoxynucleotidyl transferase (Tdt)-mediated dUTP nick-end-labeling (TUNEL) assay was used to detect cells undergoing apoptosis. On the basis of the results the authors suggested that the ghost cells might result from abnormal terminal differentiation toward keratinocytes or from the process of apoptosis of the poorly differentiated odontogenic cells.

Differential Diagnosis. The histological picture of the tumor is quite distinct with an admixture of small cells with hyperchromatic nuclei and many mitoses and with areas of necrosis and clusters of ghost cells. Since some of the neoplasms develop in association with a COC, it is important that representative areas of the often large operation specimen are examined. In almost all cases the clinical picture has clearly indicated a malignant tumor, but a preoperative biopsy may not necessarily produce tissue from the malignant part of such a process.

Treatment and Prognosis. Twelve of twenty-six patients from the published cases had recurrence after operation; most of them had multiple recurrences, and often despite aggressive surgery. Two had metastases and died because of the metastases. Four patients died from local tumor extension. Many cases have been reported with no or short-time follow-up, some were lost for follow-up, one refused treatment, and one died for other reason. Two patients have been reported to be tumor free after more than 5 years, one after 7 years (927), the patient was treated with hemimaxillectomy, and one after 10 years (627); this patient was treated with enucleation and postoperative irradiation. GCOC is obviously an aggressive tumor and radical surgery with clear margins is required. Postoperative irradiation may be indicated in some cases. It is unknown whether chemotherapy has any effect.
2. Odontogenic Sarcomas

This group of malignant ectomesenchymal odontogenic neoplasms comprises tumors named ameloblastic fibrosarcoma (AFS), ameloblastic fibrodentinosarcoma (AFDS), and ameloblastic fibro-odontosarcoma (AFOS). To this group belong as well very rare malignant counterparts to the odontogenic fibroma and the ODOMYX or fibromyxoma called odontogenic fibrosarcoma and odontogenic myxoma (or fibromyxoma) sarcoma, respectively. None of the latter was included in the WHO classification 2005 of odontogenic sarcomas (937).

The term “ameloblastic sarcoma” is used as a collective name for AFS, AFDS, and AFOS (938); somewhat confusing it is also used as a synonym for AFS, mainly because some authors consider it unnecessary to subdifferentiate into variants without and with dental hard tissue. For therapeutic purposes there seems to be no reason for separating the three variants. Those containing hard dental tissue are extremely rare, and regarding clinical aspects, treatment, and prognosis they do not seem to differ significantly from the AFS. They do represent a higher level of histodifferentiation, though (937), which is the main reason for keeping the separate terms.

The ameloblastic sarcomas all contain benign odontogenic epithelium; they represent the malignant counterparts of the so-called mixed odontogenic tumors, which reflect the normal odontogenesis in the way that they contain odontogenic epithelium and odontogenic ectomesenchyme with mutual inductive effects similar to some of the interactions, which take place during normal odontogenesis. The AFS contains soft tissue exclusively; the AFDS contains additional hard tissue in terms of dentin or dentinoid, and the AFOS contains furthermore some enamel or enamoid.

A review of the literature of this group of tumors reveals a very inconsistent use of nomenclature; like lesions have been published under different terms.

2.1 Ameloblastic Fibrosarcoma

Introduction. AFS is an odontogenic tumor with a benign epithelial and a malignant ectomesenchymal component. The epithelial component is identical to that of the AMF, and the tumor is regarded as the malignant counterpart of the AMF (937,849). This malignant neoplasm may arise de novo or from a preexisting AMF. ICD-O code 9330/3

Synonym: Ameloblastic sarcoma

Clinical Features. The tumor is rare; no data about prevalence and incidence are available. The relative frequency was indicated in a Chinese review (42) of cases received for diagnosis from 1952 to 2004; a total of 1642 odontogenic tumors were diagnosed; 50 cases were malignant (3.0%), 2 of these (0.1%) were AFS.

Detailed reviews of cases from the literature have been published by Leider et al. (939), Yamamoto et al. (940), Muller et al. (941), and Carlos-Bregni et al. (942). The latter reviewed the literature and found 60 cases, including cases with formation of dentin/dentinoid and enamel/enameloid. They presented two cases, and since then three cases have been published (943–945). The total amount of published cases is thus about 66. In the review by Carlos-Bregni et al. (942) the gender was known in 60 cases, 37 (59.6%) were males and 23 (37.1%) were females, giving a male:female ratio of 1.6:1. The age range was 3 to 83 years for 62 cases, and the mean age at time of diagnosis was 27.3 years.

If the cases were divided in AFSs, which had arisen de novo (64.2%), and AFs derived from malignant transformation of an AMF (35.8%), the mean age was 22.9 years for the former and 33.0 years for the latter group, this is a confirmation of the findings by Muller et al. (941).

The tumor was diagnosed in the mandible in 49 cases (79%) and in the maxilla in 13 cases (21%), with a ratio of about 5:1. The exact location was reported in 46 cases; the majority of the tumors were located in the posterior part of the mandible; 34 lesions were located in the mandible (32 posterior and 2 anterior), 9 were located in the maxilla, all in the posterior region.

A single case of peripheral AFS has been published (826). The diagnosis is controversial; the tumor was highly unusual; it developed in a recurrent PERAM in an 89-year-old man.

Various kinds of symptoms have been reported. Among the most constant findings are swelling and pain (938,939,941,946–949). Mobility of teeth was seen in some cases and paresthesia in a few cases (939,948). Growth may be rapid; some tumors have been more than 10 cm at longest diameter (942).

The potential for metastasis is low. It has been reported in one case (950) in which pleuropulmonary metastases and later hepatic metastases were diagnosed 10 years after the first symptoms of the tumor and without any local recurrence.

Imaging. Radiographically, a uni- or multilocular radiolucent area with indistinct margins is characteristic (Fig. 94). The margins may be partially distinct (951). Penetration of the cortex and extension into the surrounding soft tissue is not uncommon (467,939,952). Intralesional septa and peristeal new bone formation has been detected (951). Impaction of teeth has been described in several cases (942,951,953,954), and displacement of teeth is common (951,955–958); resorption of teeth has rarely been reported (959).

CT and MRI are important tools for evaluation of tumor extension and bone destruction (467,947,960).

Pathology. The etiology of the tumor is unknown. Pathogenetically it may develop de novo (958,961,962) or from malignant transformation of a preexisting AMF. About 36% of the reported AFSs developed from an AF, and the average age of these patients is higher (33.0 years) than that of patients with AF, which arose de novo (22.9 years) (941,942).

Macroscopically, the tumor was described as tender but solid and whitish at the cut surface by Eda et al. (963), as tough and rubbery with some
calcified spicules of bone by Dallera et al. (951), and as soft and pale with a few hemorrhagic areas by Yamamoto et al. (940).

The histomorphology of the AFS may resemble that of the AMF in many aspects (937,964,965). The tumor is composed by strands and slender branching cords of odontogenic epithelium with formation of buds imitating the formation of enamel organs from a dental lamina. No malignant features are detected in the epithelial component (Fig. 95). The basal cells are cubic or columnar with darkly stained nuclei, which are polarized away from the basement membrane when the basal cells are palisaded, columnar-shaped cells (Fig. 96). The epithelium also presents as small rounded or irregularly shaped islands with basal cells of similar morphology and a central network of interconnected stellate-shaped cells with a clear or faintly stained, eosinophilic cytoplasm (Fig. 96). Mitoses are rare or nondetectable, the histomorphology of the epithelium may be indistinguishable from that of an AMF. The epithelium is growing in an abundant hypercellular ectomesenchymal tissue, which takes up about three-fourth of the tumor area (951).

Cytological features of malignancy are found in this connective tissue, which shows a marked increase in cellularity. The cells are polygonal, rounded, or fusiform and closely packed. The cytoplasm is scanty, and the nuclei are hyperchromatic, and may show moderate variation in nuclear size and shape, but in some cases cellular and nuclear pleomorphism are prominent dominated by bizarre and hyperchromatic nuclei (Fig. 96). Mitoses are frequent and may be abnormal. In cases derived from AMFs (458,467,946,952,954,957,966,967), areas without cytological features of malignancy may be found. Correct evaluation of the histology may require extensive sampling. Collagen may be seen in some areas, like in AMFs, but is usually only present in small amounts. The vascular component is inconspicuous. Variations in the cellularity may be seen. In some areas the greatest density of sarcomatous cells is seen in zones surrounding benign epithelial islands (964), but in other areas these zones may show conspicuously less cellular density than the main part of the tumor (937). AFS with areas with an Antoni A neurilemmoma-like pattern has been described (964), but the finding is quite unusual. Several authors have described a greater stromal cellularity and increased mitotic rate in recurrent tumors, and a decrease in the amount of the epithelial component, which after several recurrences may disappear completely (458,954,939,966).

**Immunohistochemistry.** Compared with other types of fibrosarcomas of the head and neck,
Chomette et al. (950) found a higher level of alkaline phosphatase and adenosinetriphosphatase (ATPase) in the ectomesenchymal tissue of three cases of AFS.

Several authors have detected CK in the epithelial component of the AFS (467,940,944,968). Yamamoto et al. (940) detected CK in the columnar and polyhedral cells of the ameloblastic epithelium. The intensity of the staining reaction was not uniform, and the polyhedral cells were more intensely stained. Lee et al. (944) found a positive immunoreactivity for pancytokeratin (AE1/AE3) in the ameloblastic epithelium, and Williams et al. (467) detected a uniformly positive reaction for pancytokeratin and CK-5 and CK-6 in the epithelial component in the benign areas of a recurrent AMF with malignant transformation. The reaction to CK-7, CK-19, and CAM 5.2 was negative.

Tajima et al. (968) found the epithelial cells of an AFS slightly positive to monoclonal EMA. S-100 protein in AFS was investigated in two studies (944,968); both tumor component were negative.

Vimentin antibodies were used in two studies (940,944), the malignant fibroblastic spindle-shaped cells were positive in both investigations.

Fujita et al. (422) detected nestin in the ectomesenchymal tumor cells of two cases of AFS; the epithelium was negative. Nestin is an intermediate filament constituting the cytoskeleton, and is related to tooth development and repair of dentin; it is considered a useful marker for ectomesenchyme and odontoblasts in odontogenic tumors.

Lee et al. (944) detected CD34 in the malignant spindle-shaped cells in an AFS. The antigen is a transmembrane glycoprotein, which is considered a leukocyte antigen. It is usually found on the surface of some bone marrow and blood cells. They also used antibodies to CD117 and found all tumor cells to be negative in contrast to Williams et al. (467) who found that the sarcomatous component of a recurrent AMF with malignant transformation was strongly positive for c-KIT (CD117). No expression of the antigen was present in either the stroma or in the epithelial cells of the AMF areas. CD177 is a leukocyte differentiation antigen frequently found on early normal and leukemic hematopoietic cells.

The presence of p53 protein was investigated in three studies (943,467,969). They all detected the protein in the nuclei of the mesenchymal sarcomatous cells, but not in the epithelial cells and not in AMFs or the benign component of a recurrent AMF with malignant transformation (467). No overexpression of MDM2, a regulator of p53, was detected in either the benign or sarcomatous component.

Huguet et al. (969) used PCNA and Ki-67 in a study of AFS and AMF. The sarcomatous component of AFS was positive; AMFs were negative. Sano et al. (463) counted the L.I. of the monoclonal MIB-1 antibody in tissue from two AMFs, two AFODs, and one AFS. The antibody recognizes the epitope of Ki-67 antigen. Positive reaction for MIB-1 was observed in the nuclei of tumor cells in both the epithelial and mesenchymal components. The labeling indices were higher in the mesenchymal components than in epithelial ones in an AMF with late recurrence and in the AFS. The highest label in the mesenchymal component was observed in the AFS. The authors concluded that the findings suggest that evaluation of the growth potential in AMFs and related lesions by means of proliferation-associated nuclear antigens could be of help in estimating the tumor’s aggressiveness.

**Electron Microscopy.** The ultrastructure of the AFS have been described in several publications (940,946,949,950,963,970).

The epithelial nests were lined with columnar or more often cuboidal cells and had a core of stellate cells with large intercellular spaces; the cells were intermingled with epidermoid cells containing loosely arranged tonofilaments. On the whole these epithelial nests were poorly differentiated (950). Takeda et al. (946) found a stratum intermedium-like layer between the peripheral cells and the innermost cells. Various results have been reported from the study of the cytoplasm of the peripheral cells. According to Chomette et al. (950) the peripheral cells contained few organelles, they detected some mitochondriae, rare lysosomal bodies, poorly developed rough endoplasmatic reticulum and Golgi apparatus. Eda et al. (963) on the contrary found many organelles in the peripheral cells. Glycogen granules and tonofilaments were generally well preserved. A basal lamina around the peripheral cells was clearly seen. Their case contained minor areas of primitive dentin and enamel.

The malignant tumor cells of the ectomesenchymal connective tissue have been described by Chomette et al. (950) and Yamamoto et al. (940). The latter described spindle-shaped fibroblasts with large irregularly shaped nuclei with one, two, or more nuclei and a variable amount of chromatin. Mitotic figures were present. In some cells bizarre mitochondria were observed and the Golgi fields were well preserved. A dilated smooth and rough endoplasmatic reticulum could be detected, as well as glycogen granules. Polyribosomes were scattered throughout the cytoplasm. Collagen was relatively scarce in the matrix. Chomette et al. (950) detected various cell types in the connective tumor tissue. Closely packed clear round cells with numerous delicate, short filaments were detected, as well as more differentiated oval or spindle-shaped cells with well developed Golgi-apparatus and secretory vacuoles. Numerous microfilaments were present parallel to the plasmatic membrane. Other cells were of the granular type, they contained a vast number of osmiophilic heterophagosomes. Some well-differentiated fibroblasts and myofibroblastic cells with distinct myofilaments could also be identified.

**Molecular-Genetic Data.** Muller et al. (941) compared nuclear DNA content of five AFSs and three AMFs by image analysis of Feulgen stained nuclei by means of an image cytometer. A DNA index was generated for each tumor. The three AMFs were diploid, whereas 1 of 5 AFSs was aneuploid. There was no correlation between aneuploidy and the histological grade of malignancy. Williams et al. (467) analyzed an anaplastic AFS for genetic mutations in exons 9, 11, 13, and 17 of the c-KIT gene; a proto-oncogene located in chromosome 4, but found no mutations.
Differential Diagnosis. The differentiation of an AFS from an AMF with high cellularity and presence of mitoses may be a difficult decision. Mitosis may occur in the epithelium and in the ectomesenchymal tissue of an AMF, but should be normal. More than a few mitoses and any atypia seen should provoke the suspicion of malignancy in the appropriate clinical setting (54). The patient’s age may be taken in consideration as well, AMFs rarely occur in patients older than 30 years. After recurrence, in particular multiple recurrences, the epithelial component of the tumor may decrease or disappear so traces of the odontogenic origin may eventually be lost (939, 954, 962); such cases risk to be diagnosed as conventional fibrosarcomas, unless the pathologist had access to sections of the tumor from earlier operations.

Treatment and Prognosis. The AFS is a locally highly aggressive neoplasm with a very low potential for distant metastasis (937), only one of the published cases has been reported to metastasize (950). Lymph node metastases with histological documentation have not been reported (941), and are rare in any type of sarcoma of the head and neck (971). En bloc resection with wide margins and follow-up for at least 10 years is the recommended treatment. Postsurgical radiotherapy (952) or adjuvant chemotherapy has been used in some cases. Goldstein et al. (966) reported curative effects from the use of Actinomycin D, Vincristine, and Cytoxane. Others have reported unsatisfactory results from the use of chemotherapy (947); chemotherapy may be indicated as an adjuvant with radiotherapy to surgical resection, where a wide margin of resection is difficult to achieve (971).

The prognosis for the AFS is apparently better than for other fibrosarcomas of the orofacial region, but recurrences are common. One, two, three, or multiple recurrences were reported in 20 of 49 cases reviewed by Muller et al. (941), and 20.4% of the patients with AFS died within 2 to 19 years. Takeda et al. (946) reviewed eight fatal cases, where the patients died from uncontrollable local infiltration.

2.2 Ameloblastic Fibrodentinovo-Odontosarcoma

Introduction. The AFDS and the AFOS combine the histological features of AFS with dysplastic dentin (AFDS) and dentin or dentinoid together with enamel or enamelled (AFOS) (937).

ICD-O code 9290/3

Synonyms: Ameloblastic dentinosarcoma; ameloblastic odontosarcoma; ameloblastic sarcoma; odontogenic sarcoma.

Some have found the terms disturbing (964) since “ameloblastic odontosarcoma” evokes the notion of a “malignant tooth.” The term is based on the knowledge that some of the tumors have developed from malignant transformation of an AFOD (950, 480, 501).

Clinical Features. The tumors are exceedingly rare, and the exact amount of published cases is difficult to estimate because of inconsequent use of nomenclature. Some authors find it unnecessary to distinguish these tumors from the AFS (54, 941, 951, 964, 968, 972). Cases of AFDS and AFOS (950, 956) have thus been published under the term “AFS” or “ameloblastic sarcoma,” and a case, which contained dentinoid, but no enamel, has been published as an ameloblastic odontosarcoma (973). According to Carlos et al. (937) 14 cases of these tumors were published before 2003; nine cases occurred in men and four in women. The age range was 12 to 83 years, with a peak in the third decade. Most of the cases have been found in the mandible. The clinical findings have been similar to those present in the AFS, swelling and pain being the most common symptoms, and sometimes mobility of teeth.

Imaging. In the majority of cases the amount of dental hard tissue in the tumor is so limited that it does not show on a radiogram. In cases of AFOS developed in an AFOD (950, 480, 501), the dentin and enamel produced by the benign tumor before the malignant transformation will be detectable on the radiogram. The use of CT and MRI increases the information about the borders of the tumor considerably.

Pathology. The etiology is unknown.

The resection specimens are usually large. Macroscopically, Forman et al. (956) described the tumor as fleshy and lobulated; the cut surface had a firm gelatinous appearance.

The major part of the tumor is histomorphologically indistinguishable from an AFS. In the AFDS scattered areas of dentinoid is found; such cases have been reported and well illustrated by Tahsinoglu et al. (974) [supplementary illustrated in *Thoma’s Oral Pathology* (63)], Altini et al. (972), and Altini et al. (938). Eosinophilic hyalinized zones in the connective tissue without a cellular border, seen around the epithelial islands, are not regarded as dentinoid (938). Areas of benign ectomesenchymal tissue may be present (938, 972), suggesting malignant development in an AMF or an AFD. The formation of dentinoid and dentin is dependent on complex interchange of signals and substances between the odontogenic epithelium and the odontogenic ectomesenchyme (975, 976). The gene expressions necessary for this process seems conserved to some degree in these sarcomas, since the dentinoid can be found in areas with conspicuous polymorphism in the ectomesenchyme. Cases compatible with the definition of an AFOS have been reported by Chibret (977), the clinical features were described by Polaillon (978); and by Forman et al. (956), Eda et al. (963), Howell et al. (480), Chomette et al. (950), Takeda et al. (979), and Herzog et al. (501). In nearly all cases the amount of dentin and enamel has been very limited (963), and rather (Figs. 97, 98) dentinoid and enamelled (501, 979, 980). In Chibret’s case though, formation of canalicular dentin was reported.

Immunohistochemistry. Nagatsuka (75) included a case of AFOS in a study of differential expression of collagen IV α1 to α6 chains in basement membranes of benign and malignant odontogenic tumors. A moderate immunoreactivity of α1(IV)/α2 (IV) and α4(IV) chains was found along the basement membrane of ameloblastic epithelium. Chains of α5 (IV)/α6(IV) were strongly codistributed as continuous...
linear patterns demarcating the benign epithelial tumor nests from the surrounding sarcomatous stroma. These α(IV) chains also randomly stained the tumoral and stromal cells. In the inductive dental hard tissue areas; no reactivity was found.

Electron Microscopy. Eda et al. published an ultrastructural study of a case of AFOS, but concentrated on the soft parts of the tumor, which showed changes similar to those described for the APS apart from a higher concentration of organelles in the peripheral cells of the epithelial islands (950).

Molecular-Genetic Data. No data are published.

Differential Diagnosis. The amount of dental hard tissue in AFDS and AFOS is usually scarce, so its detection may depend on extensive sampling from a large tumor. It has no therapeutic consequences, however, to diagnose an AFDS or an AFOS as an APS, which is the main argument for using the common diagnosis “ameloblastic sarcomas” for all three tumors. As it is the case with the APS, the most difficult diagnostic problem is to decide if a large, fast-growing highly cellular AFDS or AFOS show histomorphological signs of malignancy. Any signs of pleomorphism and the presence of more than a limited amount of mitotic figures should be regarded as signs of malignant transformation in the appropriate clinical settings.

Treatment and Prognosis. The AFDS and the AFOS are highly locally aggressive neoplasms with a very low potential for distant metastases and should be treated with wide margin en bloc resections. In cases where complete surgical removal is impossible, adjuvant radiotherapy is indicated, but may not be curative as reported by Howell et al. (480) (case 1). In another case (case 2) reported by Howell et al. (480) an adjuvant-combined chemotherapeutic regimen of Cytoxan, Actinomycin, and Vincristine gave a favorable result.

The prognosis is difficult to assess. The two cases of AFDS reported by Altini et al. (1976 and 1985) (938,972) were cured after resection, but the follow-up time was short. In the case of AFOS (case 1) and in two other reported cases the patients were cured after hemimandibulectomy (956,963), but the follow-up time was relatively short.

A long-time follow-up is indicated, as clearly illustrated by the case of Herzog et al. (501). A 14-year-old girl had an AFOD removed from the angle of the left side of the mandible by means of curettage. The tumor recurred five years later, and was again treated by curettage. Twelve years after the first symptoms, the tumor recurred again and microscopy showed an AFDS. It had invaded the adjacent soft tissue, including the parotic gland. It was treated by extensive surgery and Cobalt 60. Two years later metastases to lymph nodes in the neck were diagnosed.

2.3 Odontogenic Fibrosarcoma

As pointed out by Slater (964) the cases reported as APS by Tajima et al. (968) and by DeNittis et al. (960) contained slender cords of odontogenic epithelium more closely resembling those seen in odontogenic fibroma than those in AMF (454,687). Both tumors were fibrosarcoma de novo and both were characterized by short collagenous fibers and did not resemble the embryonic pulp-like tissue, which is typical for AMFs. They were both highly cellular with conspicuous pleomorphism and numerous mitoses. One of them contained some dentinoid or rather cementoid (968). Chan et al. (981) reported a case of COF in the premolar region of the mandible of a 34-year-old man. Radical resection was not possible for cardiac reasons, the tumor was enucleated and recurred 10 months later. It was now diagnosed as a low-grade odontogenic fibrosarcoma. A second recurrence was diagnosed 15 months later, and a hemimandibulectomy
was performed. The mesenchyme was unchanged, the odontogenic epithelium had disappeared. There were no symptoms till eight years later when a lung metastasis measuring 60 mm was diagnosed. Chemotherapy was used without response. The patient died 20 months later from brain metastasis and hemoptysis. The authors recommended chest X rays every six months for prolonged periods of time after initial surgical resection.

The tumor reported by Tajima et al. (968) occurred in the right maxillary molar region of a 14-year-old male. Hemimaxillectomy was performed; the tumor recurred two months later with involvement of the maxillary sinus and with subsequent invasion of the orbital base. The patient died six months after the operation. Immunohistochemistry was done on sections from the operation specimen. The odontogenic epithelium reacted strongly to antibodies against wide spectrum CKs, and faintly to EMA. The sarcomatous cells reacted strongly to vimentin, but were negative to desmin, smooth muscle actin, neurofilament, and S-100 protein.

The case reported by DeNittis et al. (960) was a tumor in the molar area of the maxilla in a 32-year-old man; it had eroded the bone and infiltrated the adjacent soft tissues. An extended maxillectomy was done, which removed all tumor tissue except for a focus in the right maxillary sinus and with subsequent invasion of the orbital base. The patient died two months after the operation. Immunohistochemistry was done on sections from the operation specimen. The odontogenic epithelium reacted strongly to antibodies against wide spectrum CKs, and faintly to EMA. The sarcomatous cells reacted strongly to vimentin, but were negative to desmin, smooth muscle actin, neurofilament, and S-100 protein.

The odontogenic fibrosarcomas were not classifiable in the 2005 WHO classification of tumors of the head and neck (982).

2.4 Odontogenic Myxosarcoma

Very few cases of odontogenic myxosarcomas have been published (760–762). Lambeg et al. (761) reported a maxillary myxoma in a 40-year-old man, which recurred three weeks after surgery. The tumor had infiltrated the adjacent soft tissues. Repeated biopsy as well as reassessment of the removed tumor lead to the diagnosis myxosarcoma. Microscopy showed a tumor composed of pleomorphic, stellate cells with bizarre mitotic figures surrounded by an amorphic myxoid matrix. Electron microscopy showed that the tumor cells were similar to fibroblasts. Radiotherapy was unsuccessful, so the left part of the maxilla was removed with orbital exenteration. The patient died accidentally three years later. At autopsy no signs of recurrence or metastasis were found.

The tumor reported by Pahl et al. (762) was an ODOMYX with an aggressive clinical course, which developed in the maxilla of a 53-year-old man. Nuclear MRI was used to determine the extension of the tumor, which invaded the sinuses and the nasal cavity. The tumor recurred twice after extended maxillectomy and ultimately caused the patient’s death by uncontrollable local disease with infiltration of the cranial cavity. Microscopy showed a low grade myxosarcoma. A cytogenetic analysis revealed an unexpectedly aberrant hypertetraploid chromosome complement, which was considered as incompatible with the usual karyotypic patterns of benign tumors. Mosek et al. (760) described sarcomatous changes in ODOMYX in two cases that resulted in death.

3. Odontogenic Carcinosarcoma

The odontogenic carcinosarcoma (ODCASA) was defined in the second edition of the WHO “Histological Typing of Odontogenic Tumours” (23) as “a very rare neoplasm, similar in pattern to AFOS, but in which both the epithelial and the mesenchymal components show cytological features of malignancy.” The entity was not included in the year 2005 edition of the WHO classification of head and neck tumors (12) because of the paucity of published cases and because of controversial opinions regarding the definition of the tumor (831, 964, 983).

Three acceptable cases have been published (964, 980, 984).

Phillips et al. (980) reported a case in a 29-year-old man. Ten months after the removal of an inflamed partly unerupted lower left third molar the patient presented with a fast growing, large, firm swelling extending from the lower left first molar to the coronoid process of the left mandible. The radiogram showed a radiolucency, which was scalloped and multilocular, relatively well circumscribed from the first molar and into the ramus. There was erosion of the base of the mandible and both the facial and the lingual plate. The left part of the mandible from the premolar area to the condyle was resected. The follow-up time was 13 months without sign of recurrence or metastasis. Microscopy showed a neoplasm with a histomorphology compatible with an AFOS, with small areas of dysplastic dentin and enamel. In some areas the odontogenic epithelium was pleomorphic, showed hyperchromatic nuclei, and mitotic figures.

The case reported by Slater (964) was a 55-year-old man with an 8 × 6.2 × 5 cm large tumor in the right mandibular body and ramus. A hemimandibulectomy was done. There was no follow-up information. Microscopically, the tumor showed at low magnification architecture similar to a cell-rich AMF. At higher magnification the mesenchymal component presented signs of sarcoma with closely packed mitotically active polygonal cells showing hyperchromatic nuclei and moderate nuclear polymorphism. The ameloblastic epithelial component showed epithelial dysplasia with peripheral large cells with crowded large hyperchromatic nuclei and mitotic figures. The central stellate reticulum showed high cellularity and plump cells.

Kunkel et al. (984) reported a tumor in the right posterior mandible of a 52-year-old man with a large swelling in the retromolar area and numbness of the right lower lip. There was no regional lymphadenopathy. Radiography showed an ill-defined radiolucency.
extending from the third molar to the coronoid process. A segmental resection of the mandible including adjacent soft tissue was performed. All margins were free of tumor. Two years later local recurrence occurred with infiltration of the condyle and the parotid gland. A second extensive resection was done. Three years later a second recurrence was diagnosed. The patient was treated with extended surgery, including exenteration of the infratemporal fossa and the pterygoid region, resection of the zygomatic arch, the lateral zygoma, and the infiltrated skin area. Twelve months later mediastinal and pulmonary metastases were diagnosed, but there was no local recurrence. Chemotherapy involving Adriamycin and Ifosfamid gave no response. Temporary reduction of pulmonary mass was recognized on administration of Etoposide and Cisplatin. After further spread of metastases to ribs and pelvis and development of an acute myelocytic leukemia the patient died 64 months after the initial surgical treatment. Sections from primary tumor and the first and second recurrence showed well-demarcated islands and cords of malignant epithelial cells embedded in hypercellular mesenchymal tissue with pleomorphic cells. Similar changes were found in the metastasis from the lung. The epithelium stained positively for CK-5, CK-6, CK-8, and CK-17 and the mesenchymal component reacted strongly to vimentin antibodies. A Ki-67 labeling indicated a high proportion of proliferating cells in both of the tumor components.

It is unknown if the primary tumor had an architecture similar to an AFS, it was neither described nor illustrated, but it seems reasonable to classify an odontogenic tumor consisting of malignant ameloblastic epithelium and malignant ecomesenchyme as an ODCASA.

Two cases have been published as ODCASA, which are better classified as biphasic AMCAs (985,986). None of these showed an AFS-like pattern, they consisted of an epithelial component resembling an AMCA and a sarcomatous component of spindle cells, which is sometimes seen in biphasic AMCAs. No immunohistochemical stainings for CK and vimentin to determine the nature of the tumor cells were done in the two cases. These stainings are mandatory for the differential diagnosis.

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ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFD</td>
<td>Ameloblastic fibrodentinoma</td>
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<td>AFDS</td>
<td>Ameloblastic fibrodentinosarcoma</td>
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<td>AFOD</td>
<td>Ameloblastic fibro-odontoma</td>
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<td>AFOS</td>
<td>Ameloblastic fibro-odontosarcoma</td>
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<td>AFS</td>
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<td>AMF</td>
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<td>CCAM</td>
<td>Clear cell ameloblastoma</td>
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<td>CCOC</td>
<td>Clear cell odontogenic carcinoma</td>
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<td>OaCCOT</td>
<td>Odontoma-associated calcifying cystic odontogenic tumor</td>
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<td>ODCASA</td>
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<td>UNAM</td>
<td>Unicystic ameloblastoma</td>
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IX. GIANT CELL ANGIOFIBROMA
