

Odontogenic tumors: a review

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Odontogenic tumors comprise a range of disorders of growth, from malignant and benign neoplasms, to malformations of dental tissues of self-limited growth. They are principally jaw lesions but some may present as localized gingival swellings, so-called peripheral odontogenic tumors. The majority of odontogenic tumors are benign; however, some, typically (but not exclusively) ameloblastomas, show locally infiltrative behavior. This review will incorporate an update on odontogenic tumors in the light of the 2005 World Health Organization (WHO) classification (3), which introduced some new nomenclature and, in the view of many specialists, more than a little confusion.

Classification

Table 1 shows of list of odontogenic tumors, based on the WHO classification. Where new nomenclature has been introduced, the previous names are included in parenthesis. The reader familiar with the earlier WHO classifications, of 1972 and 1991, will recall that these were based on an embryological framework dividing odontogenic tumors into two groups: those in which the tumor is largely epithelial; and those that are composed mainly of odontogenic ectomesenchyme (now known to be derived from neural crest cells) and in which the epithelium, if present at all, plays only a passive role in the tumor. The updated classification partially retains this conceptual framework, although several entities show features not found during normal odontogenesis and thus fall outside it. The reader is referred elsewhere for a recent, more detailed, account of odontogenic tumors also using the WHO nomenclature (4).

Benign odontogenic tumors

Epithelial – lacking evidence of inductive change

Tumors in this category do not show odontogenic mesenchyme or its principal product, dentine, and are represented by ameloblastoma, squamous odontogenic tumor, calcifying epithelial odontogenic tumor (Pindborg tumor) and adenomatoid odontogenic tumor. In the WHO classification, the odontogenic keratocyst, renamed the keratocystic odontogenic tumor, has been added to this group (discussed later).

Ameloblastoma

This is by far the most common unequivocal odontogenic neoplasm in all ethnic groups, representing about 1% of head and neck neoplasms in Europe and the USA, but has the highest incidence in Afro-Caribbean populations. Two main categories of ameloblastoma are now recognized: the conventional type, dominated by the solid/multicystic variant; and the unicystic variant whose clinical presentation, histopathology and behavior have led to its gradual recognition as a separate form of ameloblastoma, representing approximately 10% of the total.

Both types of ameloblastoma are benign and slow-growing neoplasms. The solid/multicystic variant shows a capacity for locally infiltrative behavior into adjacent bone marrow, and the gradually enlarging extensions of epithelium give rise to its typical multilocular radiolucency seen on imaging. Even large tumors are usually asymptomatic, any pain being caused by superimposed inflammatory changes subsequent to infection. The site of presentation is usually the mandible (80%) in the region of the third molar, although a more anterior

Table 1. Classification of odontogenic tumors (based on Barnes et al. (3)).

Benign	Odontogenic epithelial tumors	
	Ameloblastoma	
	Squamous odontogenic tumor	
	Calcifying epithelial odontogenic tumor	
	Adenomatoid odontogenic tumor	
	Keratocystic odontogenic tumor (odontogenic keratocyst)	
	Odontogenic epithelial/ectomesenchymal	
	Ameloblastic fibroma	
	Ameloblastic fibrodentinoma	
	Ameloblastic fibro-odontoma	
	Complex and compound odontomas	
	Odontoameloblastoma	
	Calcifying cystic odontogenic tumor (calcifying odontogenic cyst)	
	Dentinogenic ghost cell tumor	
	Odontogenic ectomesenchymal	
	Odontogenic fibroma	
	Odontogenic myxoma	
	Cementoblastoma	
	Malignant	Odontogenic carcinomas
		Metastasizing (malignant) ameloblastoma
Ameloblastic carcinoma		
Primary intraosseous squamous cell carcinoma		
Clear cell odontogenic carcinoma		
Ghost cell odontogenic carcinoma		
Odontogenic sarcomas		
Ameloblastic fibrosarcoma		

location in the premolar region or the midline is not unusual in Afro-Caribbean populations (Fig. 1). When presenting early, or at least as a small lesion, the solid/multicystic ameloblastoma may resemble an odontogenic keratocyst radiographically, but by the peak presenting age of the fourth or fifth decade of life, ameloblastomas have usually enlarged sufficiently to show significant buccal jaw swelling, unlike most keratocysts (discussed later). A layer of subperiosteal new bone and an often corticated outline on imaging are consistent with the slow rate of growth. In an assessment of the differential

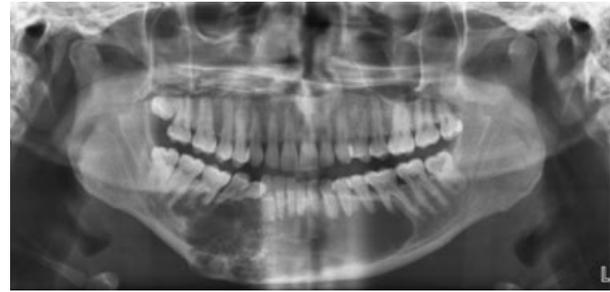


Fig. 1. Dental panoramic pantomogram showing a multilocular radiolucency that straddles the midline of the mandible, which exhibits swelling and tooth displacement on the right.

diagnosis, any radio-opacity seen within the lesion should be taken as evidence of mineralized tissue and is inconsistent with a diagnosis of ameloblastoma.

Incisional biopsy is mandatory for all odontogenic tumors unless they are very small or are mature odontomas where the procedure is usually impracticable, as well as unnecessary. It is important to seek any solid tissue to biopsy because a distended, cystic lining may provide insufficient material for a definitive diagnosis.

Histologically, the solid/multicystic variant has rather classical features, based upon two predominant cell populations (Figs 2 and 3). The first population is the peripheral basal cells that are often, but not always, elongate and palisaded and closely resemble the ameloblasts (or, more strictly the pre-ameloblasts) after which the tumor is named. These cells also show reversal of polarity, a feature reminiscent of the switch in the position of the nuclei and cytoplasmic organelles that their normal developmental counterparts display as a prelude to the start of enamel matrix secretion. However, the presence of any such protein in an odontogenic tumor is incompatible with the diagnosis of ameloblastoma. The second characteristic population consists of multilayered epithelium that has relatively few intercellular contacts and a conspicuous extracellular space. Centrally situated and often forming small cysts (microcysts), these cells also resemble a layer normally found in the developing enamel organ: the stellate reticulum. All epithelial cells of ameloblastomas have a bland cytological appearance (i.e. they lack chromatic variation in nuclear staining that usually indicates a malignant phenotype). Mitotic figures are sparse in most ameloblastomas, in keeping with their slow rate of growth.

The epithelial component is usually arranged in one of two principal patterns: islands or follicles apparently surrounded by connective tissue (Fig. 2);

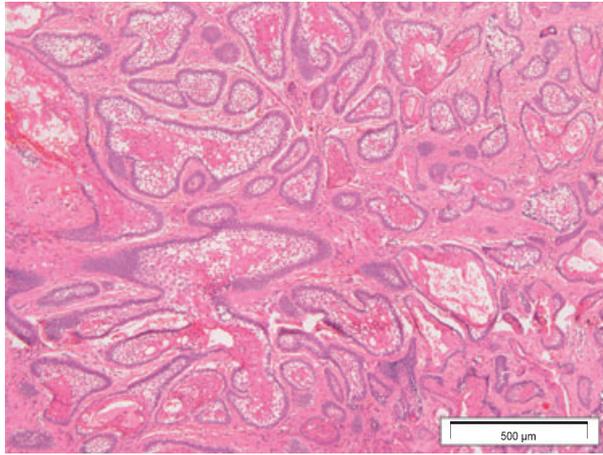


Fig. 2. Follicular variant of the conventional solid / multicystic ameloblastoma. The islands of epithelium have a peripheral layer of palisaded, elongate basal cells with a suprabasal 'stellate reticulum' zone. The central cells in many follicles are eosinophilic and more epidermoid in nature, an example of acanthomatous change.

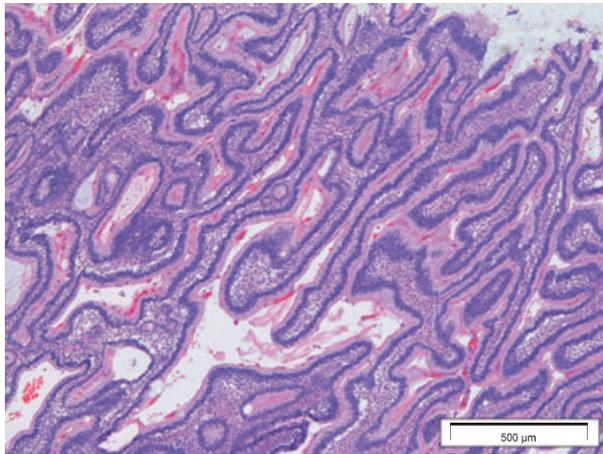


Fig. 3. Plexiform variant of a solid / multicystic ameloblastoma showing the same dual population of epithelial cells as in the follicular variant. The epithelial component consists of interlacing strands partially sequestering the connective tissue. The spaces shown represent stromal degeneration, although small blood vessels persist.

or an interlacing 'plexiform' network, the supporting connective tissue seemingly surrounded by epithelium (Fig. 3). These two patterns are referred to as follicular and plexiform, respectively, but there is no evidence that they differ in their natural history or in their response to treatment. Indeed, many ameloblastomas show both patterns in various proportions. No special features characterize the connective tissue stroma of ameloblastomas, which are thus neoplasms of the epithelium only. This essentially negative point provides an important distinction from several otherwise similar odontogenic tumors discussed later. Sometimes a thickened, hyalinized

basement membrane is present, but this does not progress to dentine formation as, for example, in the ameloblastic fibro-odontome. As ameloblastomas enlarge, most become increasingly cystic through the merging of intra-epithelial microcysts and through cystic degeneration in the connective tissue (stromal cysts), the latter particularly in the plexiform variant.

Although not appropriate for expansive coverage here, several other histological subtypes of solid / multicystic ameloblastomas have been described. They include acanthomatous, granular cell, basal cell and keratopapillary ameloblastomas, although these are usually superimposed on one of the two main patterns and none appears to convey or reflect a difference in tumor behavior. However, there is some evidence, at least anecdotal, that the most recent variant to have been described, the desmoplastic type, may indeed be more aggressive (26). This ameloblastoma consists of densely collagenous stroma with a more spindle-cell epithelial component in place of the 'stellate reticulum', sometimes with prominent microcyst formation, and a basal cell layer that tends to be visible as a cuboidal or a flat profile rather than the classical palisaded form (Fig. 4). A further feature is that bone may form within the stroma, sometimes resulting in a misleading radiographic appearance. There are too few reports to confirm whether recurrence rates are higher in the desmoplastic ameloblastoma than in the conventional solid / multicystic type.

Although most ameloblastomas expand slowly, they do so by infiltrating into the adjacent bone marrow and, if allowed to grow until there is extensive jaw expansion, they may penetrate the cortex and extend into muscle and other local soft tissues. In developed countries it is uncommon to encounter such large ameloblastomas. Details of treatment of ameloblastomas are beyond the scope of this review, but in most cases surgical excision with an attempted clearance of 1 cm beyond the radiographic margin is the conventional objective. Such generous clearance is more of a challenge in young patients in whom ameloblastomas occasionally occur and in the maxilla where the more delicate bone texture provides less resistance to tumor expansion than does the mandible. Although benign neoplasms, ameloblastomas have a significant recurrence rate traditionally ranging between 5% and 30% over periods ranging from 5 to 15 years, thus necessitating resection. However, there is a current vogue in some centers for more conservative management, especially of mandibular lesions, and it remains to be seen whether recurrence rates start to return to earlier levels. The

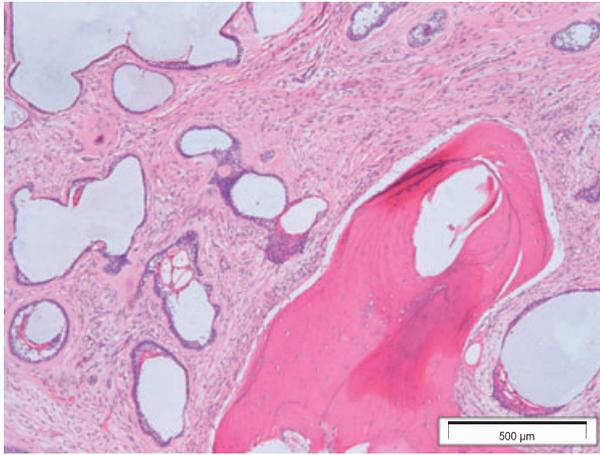


Fig. 4. Desmoplastic subtype of a solid/multicystic ameloblastoma. This example shows infiltration of bone marrow spaces by islands of odontogenic epithelium showing prominent microcystic degeneration and limited formation of elongate basal cells and stellate reticulum. The stroma is densely collagenous. Some authorities view the presence of any ameloblast-like cells and a stellate cell layer as evidence for a hybrid tumor between solid/multicystic and desmoplastic variants (Philipsen, 2001) but this is an over-rigorous application of diagnostic criteria. The site, the lower canine-premolar area, is typical of a desmoplastic ameloblastoma.

evidence base still favors definitive surgery that, in most cases, entails local resection (28); however, with better understanding of tumor growth pathways, alternative treatment strategies may emerge (31).

The unicystic variant of ameloblastoma is a distinct clinico-pathological entity, not simply a solid/multicystic type at the extreme of the cystic spectrum. It presents at a younger age, typically in the second or third decade of life, and is commonly in a dentigerous relationship with an unerupted tooth, raising the possibility that it develops from the dental follicle or from a pre-existing dentigerous cyst. Thus, they are most frequently located in the third molar region. On imaging, the unicystic ameloblastoma is a thinly corticated unilocular radiolucency involving an unerupted tooth and sometimes causing jaw expansion. At biopsy, attempts to find solid tissue generally fail and result in the recovery of membranous pieces of cystic wall only. These may provide a challenge for the pathologist as classical diagnostic features are often poorly displayed (Fig. 5). In the cystic lining, basal cells show limited elongation and nuclear palisading tends to be limited to small groups of cells. The suprabasal cells do stratify in the manner of stellate reticulum rather than of prickle cells, but interpretation requires some experience and may be further complicated if there is superimposed inflammation.

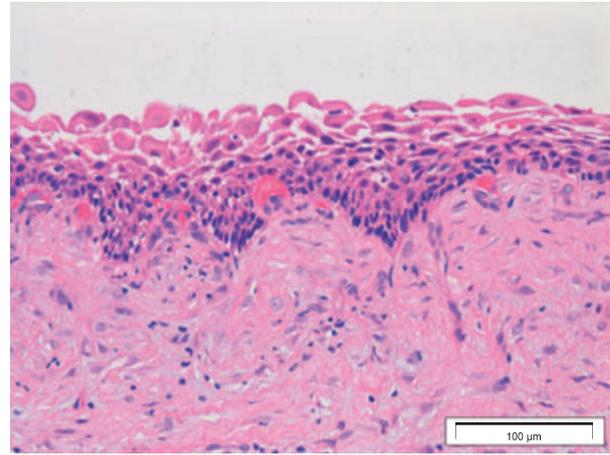


Fig. 5. Part of the wall of a unicystic ameloblastoma showing detail of the lining epithelium. Although more subtle than in solid/multicystic ameloblastomas, there is some basal palisading. The spiky rete processes and loosely attached suprabasal cells are further diagnostic aids in the appropriate clinical context. This is the luminal variant as neither intraluminal nor intramural ameloblastoma was present.

The unicystic ameloblastoma is split into three subtypes based upon the relationship of the tumor epithelium to the wall. If the wall forms a uniform sac lined by ameloblastomatous epithelium, this is known as the luminal variant (Fig. 5). If the wall forms thickenings containing ameloblastoma that invaginate into the lumen, this type is sometimes termed the 'intraluminal' variant, although the 2005 WHO classification combines these variants. In the mural variant, tumor islands infiltrate the fibrous wall much in the manner of a conventional ameloblastoma. Many unicystic ameloblastomas are only diagnosed as such after enucleation as supposed dentigerous cysts, so careful evaluation of the proximity of tumor islands to the excision margin is necessary in deciding between further surgery and careful regular review.

Mention should be made of peripheral ameloblastomas, especially as they may present to the periodontist as a painless, slow-growing gingival swelling, usually in an adult. Less common than their intraosseous counterparts, most resemble the basal cell variant although only produce a shallow depression in the underlying bone, rather than infiltration, as might be expected. A consequence of this is that peripheral ameloblastomas do not require further surgical treatment beyond curettage of the bone at the base that is likely to be a component of the initial excision. An origin from overlying gingival epithelium may be suspected, particularly when a transition is observed histologically (Fig. 6). Other odontogenic tumors may rarely present as peripheral variants, and

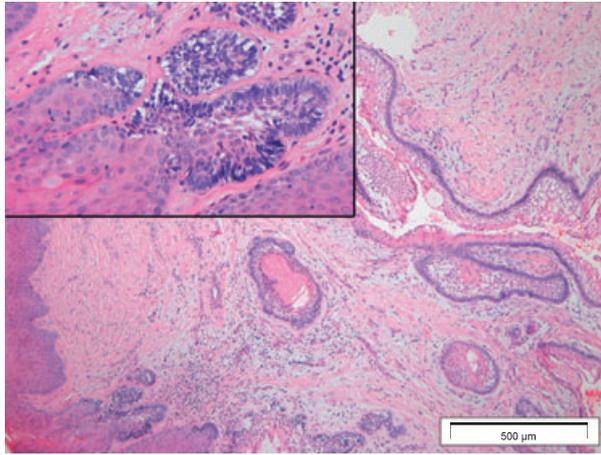


Fig. 6. Section from a gingival swelling that contained ameloblastoma confined to the mucosa. Part of the mucosal epithelium is visible to the left of the field. There is a transition from the stratified squamous epithelium to the biphasic ameloblastoma epithelium, highlighted in the inset, suggestive of a mucosal origin for this peripheral ameloblastoma.

their treatment is usually conservative excision (see below).

Squamous odontogenic tumor

Another benign odontogenic tumor in this category – that of neoplastic epithelium in the absence of odontogenic ectomesenchymally derived tissues – is the squamous odontogenic tumor. This rare tumor may present as a swelling and/or radiolucency, usually in the lower third molar region. It consists of strands and islands of epithelium (some of which are recognizably odontogenic) and yet, as its name indicates, is stratified squamous (Fig. 7). It is cytologically bland, lacks ameloblastic and stellate cell organization, and does not keratinize but often the islands show central microcystic degeneration. Mitoses are infrequent, yet normal. This tumor varies in its aggressiveness and is managed accordingly; however, local resection is necessary in most cases (11).

Calcifying epithelial odontogenic tumor (Pindborg tumor)

The Pindborg tumor is a far rarer odontogenic tumor than the ameloblastoma and therefore few clinicians (including pathologists) have much first-hand experience of its presentation and behavior. Most common in men they present as a unilocular or multilocular radiolucent or mixed radiolucent/radio-opaque lesion in the lower premolar region, although a third of cases occur in the maxilla and the majority are associated with an unerupted tooth (25). When present, the radio-opaque component may be as dense as that of tooth enamel, marking it out from

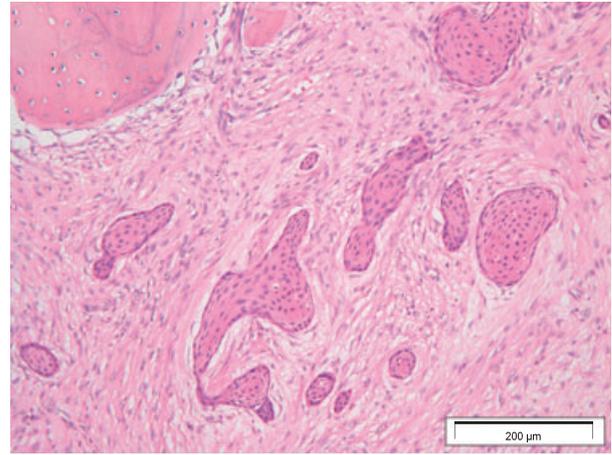


Fig. 7. The squamous odontogenic tumor is formed of bland-looking epithelial islands that vary in size and angularity, the smallest resembling odontogenic epithelial cell rests. In contrast to ameloblastomas, and indeed squamous cell carcinoma, the basal layer is inconspicuous. Nevertheless, the squamous odontogenic tumor can be quite infiltrative.

other mineralizing lesions of the jaws apart from odontomes (see below). The radiolucent component (Fig. 8) consists of sheets, strands or islands of epithelial cells with prominent intercellular junctions and that sometimes show a disconcerting degree of variation in nuclear size and staining. Particularly when mineralization is absent, this feature has led to a number of cases being mis-diagnosed as squamous cell carcinoma, with disastrous consequences for management. However, the epithelial cells in the Pindborg tumor show minimal proliferation, in keeping with such a slow-growing benign neoplasm. The mineralization is also centered on the epithelium, and builds up as ‘fossilizing’ cells with circular rings (so-called Liesegang rings) form the progressively enlarging aggregating masses (Fig. 9) that are conspicuous on imaging.

A further unusual feature of diagnostic importance is the presence, in the interepithelial stroma, of amyloid-like material (Fig. 8). This protein, in keeping with other forms of amyloid, consists of a beta-pleated sheet that rotates the plane of polarized light and thereby exhibits apple-green dichroism when stained with Congo Red. Whilst not quite unique amongst odontogenic tumors, in the appropriate context this is a reliable criterion for helping to diagnose Pindborg tumors.

Some behave in a manner similar to that of ameloblastomas, whilst others appear to be slowly expansile with minimal evidence of bone infiltration, especially in the mandible. In practice, each case tends to be treated on its own merits. Hence, the

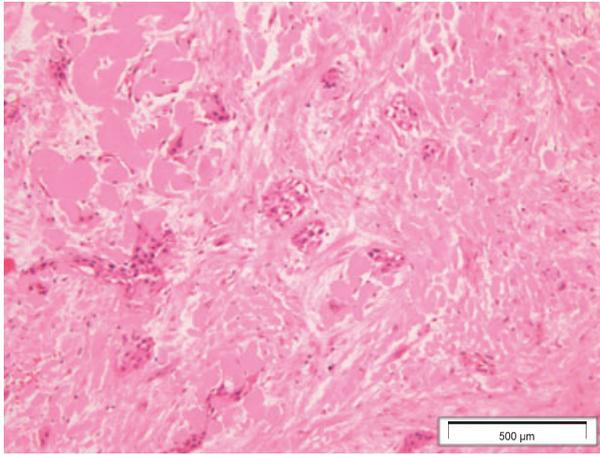


Fig. 8. Calcifying epithelial odontogenic tumor (Pindborg tumor). In this example there was very little mineralization and the small epithelial islands are scattered in fibrous tissue with deposits of eosinophilic material (upper left) that stains for amyloid. Such tumors have occasionally been misdiagnosed as squamous cell carcinomas.

need exists for a careful evaluation aided by quality imaging. The possibility of recurrence is present but unpredictable and certainly unquantifiable in view of the tumor's rarity.

Adenomatoid odontogenic tumor

One reason that the field of odontogenic tumors appears so esoteric to the nonexpert clinician or pathologist is that new entities appear and apparently standard well-understood names are jettisoned, as if on a whim. There are solid reasons for characterizing and renaming an entity, and foremost among these is when it can be established that it behaves

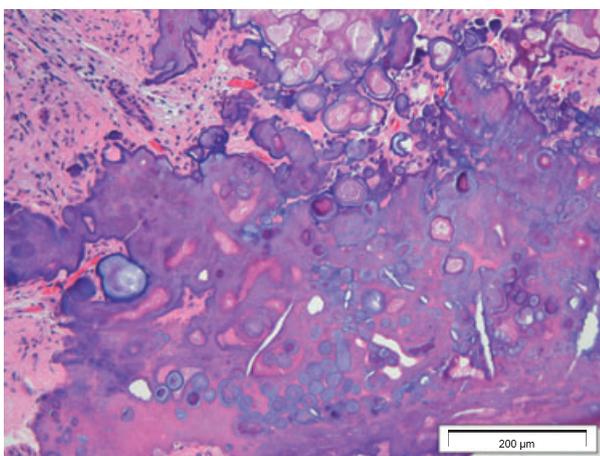


Fig. 9. A more heavily mineralized example of a Pindborg tumor. Individually mineralizing epithelial cells are coalescing with the main mass, a few recognizable islands being present (top left).

and can be managed differently from other members of its original group. In most cases it will be recognized as having distinguishable histopathological features also. Thus, it becomes a new clinico-pathological entity.

This was how the adenomatoid odontogenic tumor emerged from the then variants of ameloblastomas (23). As we shall see, several other entities in this group share some features with ameloblastomas but are distinguishable by various clinical and histopathological features. The adenomatoid odontogenic tumor is usually superimposed on a dentigerous cyst or, more descriptively, is a semi-cystic lesion lying in a dentigerous relationship with an unerupted tooth, usually an impacted upper permanent canine. An astute radiologist may distinguish it from a conventional dentigerous cyst if a radio-opaque component, similar to that of poorly mineralized dentine, is identified. It is a completely benign 'tumor' and in many authorities' view is a disorder of growth, rather than a true neoplasm. Adenomatoid odontogenic tumors rarely show continued growth and never infiltrate bone in the manner of ameloblastomas (20, 22, 24). The epithelial component can be markedly cellular: radially arranged pre-ameloblast-like cells are interspersed with whorled spindle-shaped cells (Fig. 10). In other areas the epithelial cells form thin, interlacing strands that are somewhat reminiscent of the plexiform ameloblastomas. Two types of secretory material may be found: thin deposits adjacent to the tips of the 'pre-ameloblasts' that have a deep hue with conventional hematoxylin and eosin staining, and broad bands of eosinophilic material in the subepithelial stroma. Either material may form the basis for mineralization. It is still a matter for speculation whether these truly represent enamel matrix and dentinoid, respectively. The remainder of the cystic wall is unremarkable and usually resembles a dentigerous cyst histopathologically. Most adenomatoid odontogenic tumors are removed as such with no adverse clinical consequences.

Keratocystic odontogenic tumor (odontogenic keratocyst)

No change in the nomenclature of odontogenic tumors and cysts in recent years has been more controversial than renaming the odontogenic keratocyst as the keratocystic odontogenic tumor. Previous generations of surgeons, radiologists and pathologists used the term 'primordial cyst' from the belief that it

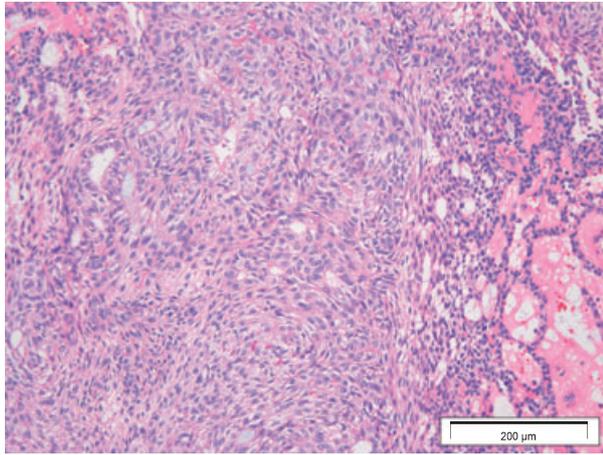


Fig. 10. The adenomatoid odontogenic tumor is typically composed of compact masses of epithelial cells that form whorls and duct-like structures with scattered foci (maroon colored) of secreted material that stain positively for glycoprotein. Hyaline or fibrillar material, such as that on the right, is sometimes mineralized.

developed from dental lamina in the absence of a tooth, usually the lower third molar. It was clear, however, that many such cysts developed in the presence of a complete dentition and that a more descriptive term would be more appropriate. Since the 1950s the term ‘odontogenic keratocyst’ has been the accepted terminology worldwide for this distinctive entity. It would therefore appear out of place to discuss this ‘cyst’ in a chapter on odontogenic tumors were it not for developments in molecular genetics during the 1990s.

The keratocystic odontogenic tumor (we shall use this name here) has long been an important clinicopathological entity of concern to clinicians because, unlike most other odontogenic cysts, it potentially has a higher recurrence rate following simple enucleation. Not only is this of significance but the cyst is one of a host of possible manifestations of naevoid basal cell carcinoma syndrome or Gorlin–Goltz syndrome. This is inherited in an autosomal-dominant manner and is strongly suspected clinically in a dental context when keratocystic odontogenic tumors form in children and/or are multiple. Keratocystic odontogenic tumors presenting in adults or which are sporadic (nonsyndromic) are usually symptomless, unilocular or multilocular radiolucencies that do not expand the jaws but grow at the expense of cancellous bone, looping between the roots of teeth and enlarging in the antero–posterior dimension rather than in the bucco–lingual dimension. Clearly, as well as dealing effectively with the cyst(s), it is essential for the clinician to ascertain the context

as other manifestations of naevoid basal cell carcinoma syndrome are potentially far more disabling.

Keratocystic odontogenic tumors present across a wide age-range and predominantly in the posterior mandible, although presentation in the lower premolar region or in the maxilla is not unusual. Those that present as smaller radiolucencies tend to be unilocular. The surgeon is often the first to suspect the presence of a keratocystic odontogenic tumor as its wall is thin and more friable than other odontogenic cysts and disruption results in the extrusion of white, semisolid material (keratin) from the lumen.

The histopathological features are readily recognizable, even to the nonspecialist (Fig. 11). The wall is thin and composed of collagenous connective tissue, occasionally with subepithelial hyalinization but with no features suggestive of odontogenic mesenchyme. The epithelial lining ranges from about 8 to 12 layers in thickness, the basal layer typically showing elongation and palisading with a suggestion of reverse polarity reminiscent of the equivalent layer in ameloblastomas. Between the basal and parakeratinizing surface layers the prickle zone, usually three to four cells thick, retains a basaloid orientation before abruptly flattening at the point of transition with the parakeratin layer. The latter frequently, but not always, shows a corrugated profile (Fig. 11). Mitotic figures, unusually for odontogenic cysts and indeed for most benign odontogenic tumors, may be frequent as well as suprabasal. The epithelium–connective tissue interface is normally flat, the epithelium sometimes separating at the basement membrane, but in some cases may show a ‘budding’

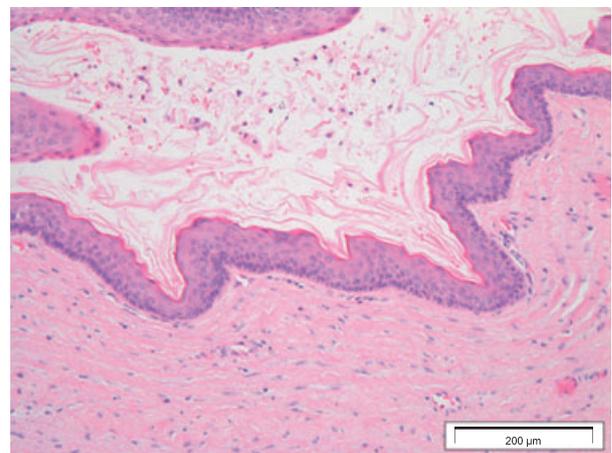


Fig. 11. Keratocystic odontogenic tumor (odontogenic keratocyst), now considered a neoplasm in the 2005 World Health Organization (WHO) classification, is characterized by a uniform parakeratinized epithelial lining with prominent, often columnar, basal cells showing reversed polarity, as seen in many epithelial odontogenic tumors.

pattern, occasionally associated with multiple odontogenic epithelial rests or satellite cysts in the wall. Some or all of these factors may contribute to recurrence in a proportion of cases.

There is now evidence that both syndromic and sporadic keratocystic odontogenic tumors contain mutations in the *PTCH* gene which normally functions as a suppressor of other genes that drive proliferation and are similar to those detected in basal cell carcinomas. These findings, which have been confirmed in subsequent publications, formed the basis for redesignating the odontogenic keratocyst an aggressive ‘tumor’ or ‘neoplasm’, although the precise sense in which these terms are to be applied is unclear. There are counter-arguments, not least the more recent reports that very large keratocystic odontogenic tumors not only respond to marsupialization (27) but may resolve completely, the characteristic ‘neoplastic’ epithelial lining being replaced by epithelium indistinguishable from that of oral mucosa. A fuller academic debate (21) on the neoplastic status of the keratocystic odontogenic tumor is beyond the scope of this review but few clinicians have taken up the new name, preferring to use ‘odontogenic keratocyst’, particularly because there is less danger of misunderstandings arising from the use of a new name in an unfamiliar context.

Epithelial odontogenic tumors that include a contribution from odontogenic ectomesenchyme (i.e. show histological evidence of inductive change)

Ameloblastic fibroma

This tumor, at least conceptually, forms one end of a spectrum at the other end of which is the compound odontoma and which also includes the ameloblastic fibrodentinoma, ameloblastic odontoma and complex odontoma (32). All show evidence of inductive interaction between odontogenic epithelial and ectomesenchymal components, but only the ameloblastic fibroma lacks hard tissue formation. The ameloblastic fibroma presents as a rare tumor in young people, in the first or second decade of life, as a jaw swelling and multilocular radiolucency in the lower premolar or molar region or, less commonly, in the maxilla. Its microscopic structure (Fig. 12), like its radiographic appearance, is reminiscent of that of the ameloblastoma, but with two major differences: the connective tissue component resembles dental papilla; and the stellate reticulum zone of the epithelium is poorly developed. However, both

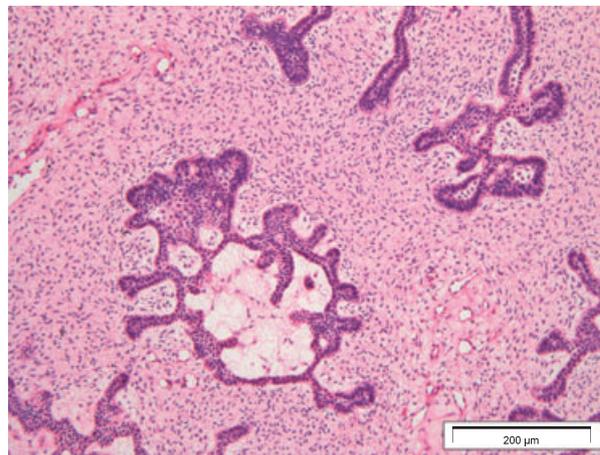


Fig. 12. The ameloblastic fibroma has a dental papilla-like stroma, within which are irregular strands and islands of odontogenic epithelium with a superficial resemblance to the cap stage of tooth development. The ‘stellate reticulum’ layer is inconspicuous, and the larger island, shown here, has central stromal cyst formation.

constituent tissues are considered neoplastic, making this a biphasic neoplasm that is unique amongst odontogenic tumors. Mitoses are usually frequent in both epithelium and connective tissue and they appear normal; abnormal mitoses in this context signify an ameloblastic fibrosarcoma, a malignant variant that follows a more aggressive course (discussed later).

The ameloblastic fibroma poses two further problems: for the histopathologist, it must be distinguished from a developing complex odontome; and for the surgeon, the requirement for complete excision must be weighed against the need to preserve the developing jaw bones and dentition. Even in a young child, a developing odontoma would be expected to show some evidence of hard tissue formation, or at least organization into incipient tooth germs. In ameloblastic fibromas the strands and islands of epithelium are randomly arranged in the cellular stroma and no predentine, dentine or enamel matrix are formed.

Ameloblastic fibrodentinoma and ameloblastic fibro-odontoma

Ameloblastic fibrodentinoma and ameloblastic fibro-odontoma represent, at least for didactic purposes, intermediate stages between the ameloblastic fibroma and the complex odontoma (32). They also represent the interface between hamartomas and neoplasms, and occur in late adolescence or in early adulthood. A classic site for the formation of an ameloblastic fibrodentinoma is within, or adjacent to, the follicle of an unerupted tooth, typically a lower third molar, in its path of eruption. Most often it

presents as a symptomless radio-opacity and may not be the cause of the failure of the underlying tooth to erupt.

Histopathologically, the ameloblastic fibro-dentoma consists of cellular stroma, probably formed of odontogenic ectomesenchyme, with variable amounts of dentine-like material containing sparse, irregular tubules and in the absence of enamel matrix or vestigial enamel organs. Any odontogenic epithelium present usually resembles cell rests rather than ameloblasts or pre-ameloblasts. To that extent its name is somewhat misleading and in early versions of the WHO odontogenic tumor classifications it was known as simply 'dentoma'.

These lesions are usually small, a few millimetres in diameter, and once removed, often as an accompaniment to the extraction of the adjoining impacted molar tooth, no further treatment is required.

The ameloblastic fibro-odontoma is a more variable entity and, as already noted, may be hard to distinguish, clinically, radiographically and histopathologically, from a developing complex odontoma or ameloblastic fibroma. The majority of ameloblastic fibro-odontomas are small, mixed radio-opaque/radiolucent lesions that occur across a similar age-range to the ameloblastic fibrodentoma, and most are small and unilocular with limited growth potential after completion of tooth formation. They show features that suggest the formation of tooth-like structures, complete with tubular dentine and varying degrees of enamel matrix calcification. That this is not a developing odontoma is suggested by its perceived continued growth potential (hence the belief that at least some are true neoplasms) and its presentation at an age when odontomes have normally 'matured' and become quiescent, as well as incorporating an extensive soft tissue (radiolucent) component (Fig. 13) that somewhat resembles ameloblastic fibroma. Occasionally they may run a more aggressive course, resorbing adjacent teeth and infiltrating bone to produce a multilocular expansion. There is no doubt that these are neoplasms which should be considered for treatment in the same way as ameloblastomas but they are of such rarity that no general rules for management can be advocated.

Complex and compound odontomas

Complex and compound odontomas are best briefly described at this point as they are the result of disordered formation of teeth, conceptually the intermediate stage between ameloblastic fibro-odontoma and normal tooth development (7). Indeed, one could extend the spectrum to include other examples of

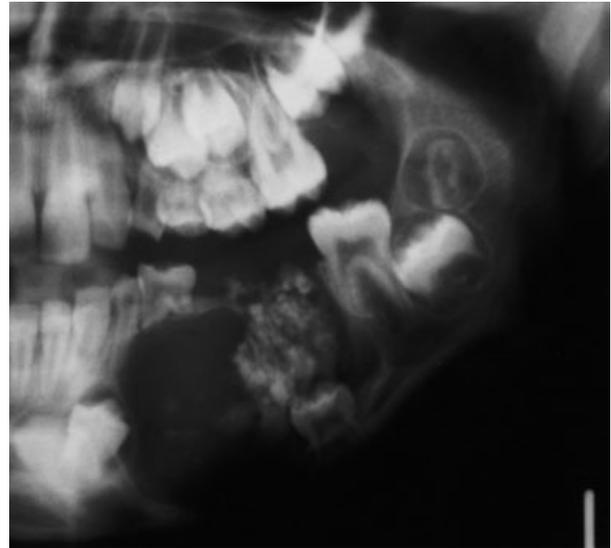


Fig. 13. Ameloblastic fibro-odontoma. This combines the radio-opaque component that resembles a complex odontoma with radiolucent soft tissue that histologically combines the features of ameloblastic fibroma with the early stages of tooth germ development.

disturbed tooth development, such as invaginated odontomes and 'dens-in-dente', although these are not usually classified as odontogenic tumors. To distinguish them from the latter entities, complex and compound odontomas were referred to in older texts as 'composite' odontomes (i.e. formed of multiple elements of odontogenic hard and soft tissues). Both are classical hamartomas in that they are formed of all the components of teeth, in different stages of development, but arranged in a disorganized manner. The somewhat arbitrary distinction between them is that compound odontomas contain recognizable tooth-like structures (denticles) but in complex odontomas the odontogenic tissues are arranged in a more haphazard manner (Fig. 14). As enamel-like radio-opacity is an obvious radiographic feature, and as the location (third molar, premolar or midline regions) and the age at presentation (first two decades) are so typical in most cases, histopathological analysis is usually quite perfunctory.

As should be apparent by this point, odontogenic tumors are no respecters of classifications, and there have been sporadic reports of tumors presenting usually in the posterior mandible and forming an irregular mass of tubular dentine and sometimes enamel matrix, but with a soft tissue component resembling the adenomatoid odontogenic tumor (2), and these were termed adenomatoid dentinomas. Although most have been symptomless and dentinoma/odontoma-like in their presentation, a more recently reported case presented with pain and

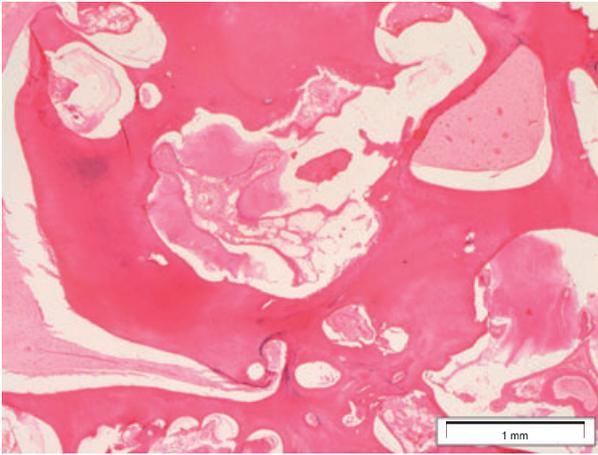


Fig. 14. Complex odontoma. The histological picture is dominated by an irregular configuration of dentine, which encloses dental follicle tissue and enamel matrix (as in the centre and bottom right of this field) or dental pulp (as in the top right). At the periphery one would expect to see evidence of a capsule of dental follicle origin.

swelling (17), thus leaving open the question of its hamartomatous or neoplastic nature.

Calcifying cystic odontogenic tumor (calcifying odontogenic cyst)

The calcifying odontogenic cyst is another entity or, as has emerged in recent years, a group of related entities, that was originally separated from ameloblastomas on the basis of both histopathological features and generally a less aggressive natural history. The WHO (2005) now terms the commonest and least aggressive variant the calcifying cystic odontogenic tumor but to most clinicians this is the classical 'calcifying odontogenic cyst'. It is usually a unilocular lesion radiographically and has a different site predilection from ameloblastomas, anteriorly in the mandible or maxilla. Under the microscope, tall columnar epithelial cells resembling pre-ameloblasts are evident but in place of a stellate reticulum-like layer the cells show expanded eosinophilic cytoplasm and, especially at superficial levels, an empty 'hole' in place of the nucleus. These are the characteristic 'ghost cells' that help to distinguish the calcifying odontogenic cyst from an ameloblastoma (Fig. 15). These cells are not unique to the calcifying odontogenic cyst and may be encountered in other epithelial odontogenic tumors (e.g. odontomas) and in the skin adnexal tumor, the pilomatrixoma. Sometimes, but by no means always, despite the name, the ghost cells mineralize and when they extend into the cyst wall they stimulate a foreign body giant cell reaction. A further feature of this tumor is the presence of osteodentine-like ('dentinoid') eosinophilic material

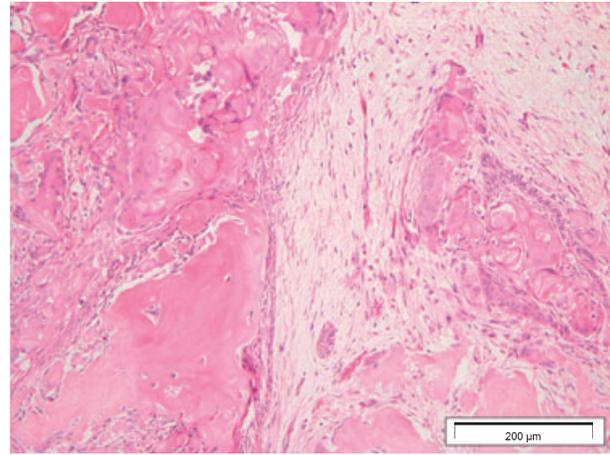


Fig. 15. The calcifying cystic odontogenic tumor (calcifying odontogenic cyst) is characterized by the presence of ghost cells (upper left and to the right), although the basal layer is usually palisaded, as in ameloblastomas (right side). Mineralized tissue considered by some to be dentinoid (lower left) is also usually present.

at the interface between the epithelium and the cyst wall (Fig. 15). Although by no means verified as such, this material is considered to be a result of tissue interaction analogous with early dentinogenesis in normal tooth development. Where epithelium lines a cystic space, ghost cells are less frequent or conspicuous, and its organization is therefore reminiscent of cystic expansion in ameloblastomas, so when taking a biopsy of such a cystic lesion an attempt should be made to sample any accessible solid area. However, diagnosis is usually made on the enucleated specimen and, in most cases, no further treatment is necessary as recurrence is rare.

Soon after calcifying odontogenic cysts were recognized as a group, reports emerged that some pursue a more aggressive course and that ghost cells may be found in association with other odontogenic tumors. A complex classification has been devised to accommodate these variants (4, 29) and a recent attempt made to clarify odontogenic tumors in which ghost cells predominate (18). The 2005 WHO classification now terms the more aggressive, and commonly solid, variant the dentinogenic ghost cell tumor. Despite the unique appellation, there are no clinical, radiographic or histopathologic features that consistently distinguish it from the calcifying cystic odontogenic tumor. Suggestive features are greater size (up to 5 cm maximum diameter) and consequent jaw swelling, multilocularity, resorption of adjacent teeth and a solid, rather than a cystic, histopathological presentation. In some respects this entity resembles an ameloblastoma with extensive ghost cell formation. Mineralization is variable.

Tumors considered to originate from odontogenic ectomesenchyme

This group of tumors is less controversial and reasonably straightforward in concept. They arise from the ecto-mesenchymal tissue that normally participates in tissue interactions leading to tooth development, but any epithelium present does not participate actively in the growth of these tumors. It should be restated that at present this is a working hypothesis from which to try and assemble a miscellany of odontogenic tumors into some order, but tools are becoming available with which to test it. The tumors in question are the odontogenic fibroma, the odontogenic myxoma and the cementoblastoma.

Odontogenic fibroma

Central odontogenic fibromas are encountered as unilocular radiolucencies that turn out to be solid, rather than cystic, following enucleation. They are rare, far rarer for example than ameloblastomas, and arise usually anterior to the molars, more commonly in the maxilla and mainly in women, as a small, well-circumscribed radiolucency that may cause resorption and/or displacement of adjacent vital teeth. A wide age-range is noted among the relatively few reported cases, and a scalloped radiographic margin may denote a more aggressive behavior pattern.

Histopathologically, the odontogenic fibroma consists of an unencapsulated mass of cellular fibrous or fibromyxoid tissue containing a variable component of odontogenic epithelium (Fig. 16). Even in epithelium-rich variants – that have, perhaps inevitably, formed the basis for further subclassification (10) – there is no organization into palisading columnar cells, and ‘stellate reticulum’ (the nests and strands of small cells much resembling cell rests of Malassez that are found in normal periodontal ligament and mitoses) are rare.

Following enucleation, most odontogenic fibromas do not recur, although there have been occasional reports of some following a more aggressive course; however, there seems to be little correlation with the histological pattern (12). The peripheral odontogenic fibroma is considered briefly below.

Odontogenic myxoma

Despite the similarity of name, the odontogenic myxoma is quite a different entity from the odontogenic fibroma in almost all respects. Odontogenic myxomas occur in individuals over a wide age range, with a peak in the second to fourth decades of life,

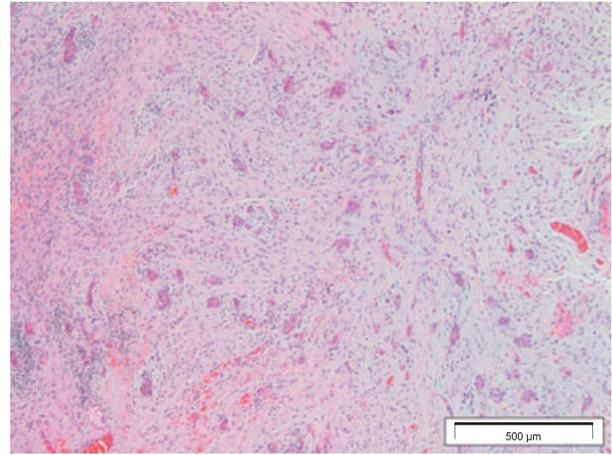


Fig. 16. Odontogenic fibroma. This example shows uniformly distributed epithelial islands within cellular fibrous tissue that is usually well-circumscribed. The epithelium rarely shows mitotic activity, and the small groups of cells resemble rests of Malassez.

but are more common and have a tendency to arise in the posterior region, usually in the mandible. Although small lesions may be unilocular, more typically they show some scalloping at the margin, with larger myxomas being more strikingly multilocular with numerous septa, resulting in a ‘soap-bubble’ appearance. As its name indicates, the key tissue is myxoid, giving a slimy consistency at macroscopic examination.

The histopathological appearance is of stellate and spindle-shaped fibroblasts dispersed within clear or finely fibrillar stroma (Fig. 17), as a result of the accumulation of glycosaminoglycans. These include, for example, heparan and chondroitin sulfates and are secreted by the fibroblast population. As with myxoid neoplasms elsewhere in the body, the fibroblasts often show minor degrees of nuclear atypia. Nuclei may be hyperchromatic, vary in size and show vacuolar inclusions, and occasional mitoses may be observed but are no clue to behavior. These features should not be misinterpreted as premalignant features but, as a range of benign and malignant non-odontogenic tumors may show myxoid change, there is potential for misdiagnosis. Even normal immature dental follicle, which is uniformly myxoid, may be mistaken for odontogenic myxoma if the clinical and radiographic context is not appreciated.

Epithelium is a variable component of odontogenic myxoma and is not essential for diagnosis. When present it consists of sparse islands or short strands of 4–6 cells that resemble rests of Malassez. Generally, odontogenic fibromas have more numerous epithelial islands than myxomas. Another variable component is collagen. Typically, odontogenic

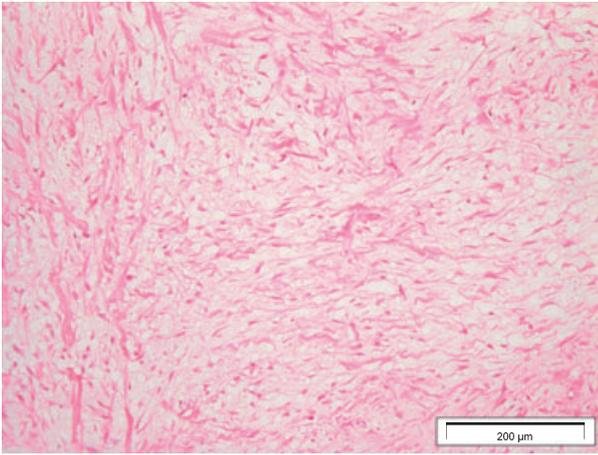


Fig. 17. The odontogenic myxoma contains more delicate, dispersed collagen fibers, between which is glycosaminoglycan, which gives the tumor its mucinous consistency. Epithelial cells may not be present, as in this example.

myxomas contain minimal collagen but those that are more collagenous are firmer and less mucoid in consistency macroscopically, and under the microscope the stroma stains more strongly pink with more distinct fiber bundles. As a result of a higher – but unspecified – collagen content, the tumor is sometimes termed ‘odontogenic fibro-myxoma’ but the prognostic significance of identifying a more collagenous variant is unclear.

Several factors combine to give odontogenic myxomas a significant recurrence rate (19): the gelatinous consistency can allow spilled tumor to seed readily, particularly in sites such as the maxillary complex; its growth pattern – tumor extending into marrow spaces at the periphery – determines that removal will be incomplete following enucleation or curettage; and, clearly, care must be exercised with incisional biopsies to prevent spillage into soft tissues.

Cementoblastoma

This uncommon neoplasm, formerly known as ‘benign cementoblastoma’, can be classified both as an odontogenic tumor (the third member of the mesenchymal group) and as a fibro-cemento-osseous lesion. It is generally considered to represent a true neoplasm of cementoblasts (5).

The cementoblastoma presents across a wide age-range in a fairly consistent manner: a gradually enlarging, bony swelling centered on a single molar tooth, usually the mandibular first permanent molar. The involved tooth is almost always vital. Radiographically, it is seen as a discrete, radio-opaque mass that has fused with the dentine of the root

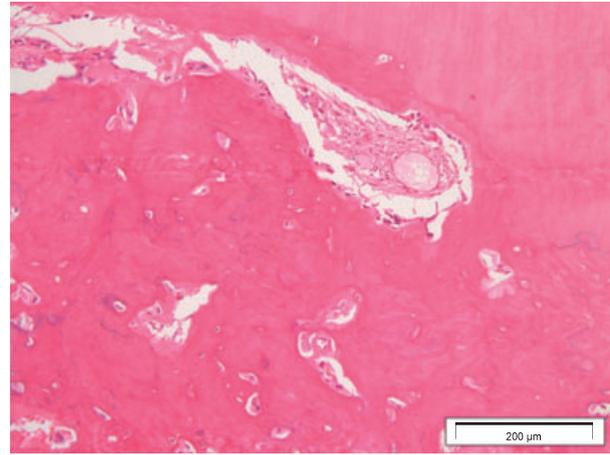


Fig. 18. Cementoblastoma. This view shows a union with dentine and cementum (top right part of the field). The neoplastic cementum contains an irregular network of resting and reversal lines reminiscent of those seen in Paget's disease of bone.

apices (Fig. 18), surrounded by an attenuated periodontal ligament space. With its characteristic radiographic appearance, preoperative diagnosis of the cementoblastoma is usually accurate.

At its periphery, the microscopic appearance of the cementoblastoma reveals bands of unmineralized matrix aligned in a broadly radial manner and lined, in most areas, by plump cementoblasts but with occasional osteoclasts (‘cementoclasts’) interposed. More centrally, where the cementum is mineralized, resting and reversal lines are more frequent and the union with the partially resorbed root of the involved tooth is complex (Fig. 18). The histological appearance of this part of the tumor has often been likened to that of mature Paget's disease of bone and the peripheral zone – hardly surprisingly – to osteoblastoma. However, more alarmingly and taken out of radiological context, especially in younger patients, the appearance may call to mind osteosarcoma.

Surgical removal of the cementoblastoma with the associated tooth is usually curative, although recurrences have been reported following incomplete excision.

Peripheral odontogenic tumors

As already mentioned in relation to ameloblastomas, odontogenic tumors are not all intraosseous and may arise solely within the gingival mucoperiosteum. The epithelial sources probably originate from down-growths from the elongate rete processes in the gingival mucoperiosteum. Histologically, these are

often indistinguishable from odontogenic epithelial cell rests and indeed the latter arise from oral epithelium, albeit in embryological development. When seen from this perspective it is perhaps not surprising that epithelial odontogenic tumors may, on occasion, form within the mucoperiosteum.

The peripheral ameloblastoma is the most commonly encountered epithelial odontogenic tumor and a number were described in earlier accounts as basal cell carcinomas, as a result of misinterpretation of their usually basaloid pattern. Basal cell carcinomas do not occur intra-orally. Peripheral calcifying epithelial odontogenic tumors (Pindborg tumors), adenomatoid odontogenic tumors, calcifying odontogenic cysts and a squamous odontogenic tumor (15) have all been described in the gingival tissues, often in the same general sites as their intraosseous counterparts (6).

The rare peripheral odontogenic fibroma, unlike its central equivalent, may be considered as a mixed odontogenic tumor because almost half of the reported cases include mineralized tissue resembling dysplastic dentine (30). Presenting across a wide age-range, they are gingival lesions and have a relatively high recurrence rate of 50% after surgical excision.

Malignant odontogenic tumors

Odontogenic malignancies may be encountered either as a clinically malignant lesion that turns out to be an odontogenic neoplasm on biopsy or through the identification of malignant cellular features in a tumor that has not yet demonstrated unequivocally malignant behavior. Given the capacity of some benign odontogenic tumors to show local infiltration, it is important to recognize the microscopic features that lead to a diagnosis of malignancy.

Metastasizing (malignant) ameloblastoma

The malignant or metastasizing ameloblastoma is an extremely rare entity consisting of a histologically benign ameloblastoma that demonstrates metastatic behavior to the lung or, less frequently, to bone marrow or brain. Some 70 cases have been reported in the world literature (4) although only about half have withstood the critical application of the criteria for diagnosis (33). In most cases there has been a long history of a large primary ameloblastoma in a conventional site but with multiple recurrences and sometimes extension into soft tissues. Malignant ameloblastomas reported hitherto have been of the solid/multicystic type, histologically indistin-

guishable from their conventional, nonmetastatic counterparts. It is therefore prudent to regard all ameloblastomas as potentially malignant when planning their surgical management, aiming for definitive excision rather than underestimating the significance of potential recurrences.

Ameloblastic carcinoma

Ameloblastic carcinomas are rather more common than malignant ameloblastomas and most are readily distinguishable histologically from conventional ameloblastomas. There should be correlation with clinical and radiographic evidence of malignant behavior – for example, pain and/or paraesthesia with poorly delineated bone destruction (1) – although sometimes diagnosis can be problematic.

The ‘ameloblastic’ element usually consists of islands (follicles) of epithelial cells showing a variable resemblance to those of benign ameloblastomas, including a palisaded basal cell layer (Fig. 19) and sometimes a more stellate suprabasal zone centrally. However, hypercellularity and a relatively high rate of mitosis, and the presence of apoptotic cells and occasionally necrosis, indicate malignancy. Cytological atypia and a frankly malignant pattern of invasion are variable features and, where present, facilitate diagnosis. Diagnostic difficulties may arise in respect of maxillary solid/multicystic ameloblastomas, which are often more highly cellular than mandibular ameloblastomas and may demonstrate faster growth, the bone texture of the maxilla providing less resistance than that of the mandible. In such cases reliance has to be placed on a combination of clinical, radiographic and histological criteria.

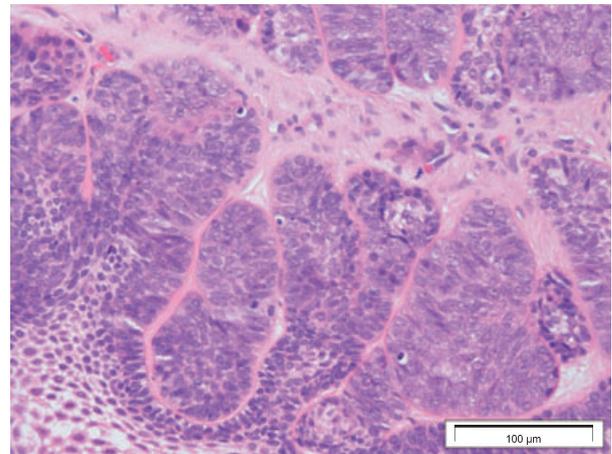


Fig. 19. Ameloblastic carcinoma, showing hypercellularity of basal cells accompanied by mitoses and apoptoses, all pointers to malignancy. Adjacent areas have the features of conventional solid/multicystic ameloblastoma (see the bottom of the field of view).

Approximately 25% of ameloblastic carcinomas are reported to metastasize (35), usually to regional lymph nodes, when a combination of surgical resection, neck dissection and radiotherapy may be required. Too few cases have been published to provide reliable data on prognosis.

Variants of ameloblastic carcinomas that arise from pre-existing benign intraosseous ameloblastomas (16) and from peripheral ameloblastomas are recognized but reports are in single figures and may hardly justify their status as a secondary subcategory.

Primary intraosseous squamous cell carcinoma

The 2005 WHO classification (3) divides primary intraosseous squamous cell carcinoma into three subcategories: those arising *de novo*; those arising from pre-existing odontogenic cysts; and those arising from pre-existing benign odontogenic neoplasms. Most arise in the posterior mandible and in older patients, about 10% arising in the maxilla, almost exclusively in the anterior segment. Criteria for their diagnosis must be stringent to exclude metastatic carcinomas from, for example, lung, as well as carcinomas derived from intraosseous salivary tissue and maxillary antral carcinomas. All three entities are rarer than ameloblastic carcinomas and in practice it is not always easy to distinguish between them. Like the far more common oral mucosal squamous cell carcinomas, they are aggressive tumors and tend to overgrow a cystic or a benign neoplastic precursor lesion, although remnants may be identified if the whole tumor is inspected carefully. Sometimes there may be circumstantial evidence: for example, an unerupted tooth may be engulfed by the carcinoma, indicating probable derivation from a dentigerous cyst (Figs 20 and 21), or earlier radiographs may reveal the presence of a circumscribed, presumably benign, lesion in the same location.

While contained within the jaw, these tumors are likely to have a more favorable prognosis than if they have extended into the soft tissues, but clinical data are limited in view of their rarity. Radical surgery with radiotherapy and/or chemotherapy has been advocated (34). In the experience of the author, several cases had been initially diagnosed and treated in dental practice as odontogenic infections: an important differential clinical diagnosis, but a cause of delay in appropriate management.

Clear cell odontogenic carcinoma

Normal odontogenic epithelial cell rests often show clear cytoplasm, as do some cells in a number of benign odontogenic tumors. Also, metastatic deposits

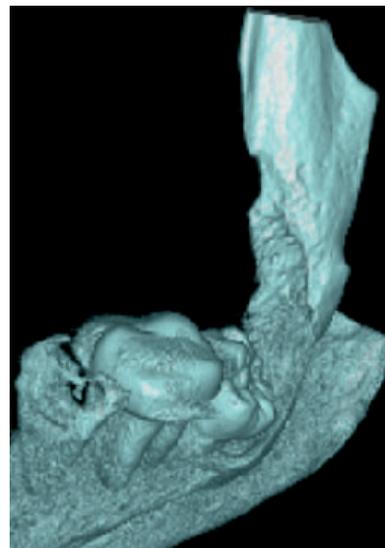


Fig. 20. Cone beam computed tomography reconstruction of part of the resection specimen of a primary intraosseous carcinoma, possibly having arisen from a dentigerous cyst around the unerupted lower third molar. Note the irregular pattern of bone destruction on the anterior aspect of the ramus. (Courtesy of Dr. Jonathan Davies, Dental Radiology, King's College London and Guy's & St. Thomas' NHS Foundation Trust.)

in the jaws from malignancies elsewhere (e.g. renal, lung or thyroid carcinomas) may exhibit clear cells. Distinct from all of these is an odontogenic carcinoma that shows a preponderance of clear cells and was first recognized as a separate entity in 1985 (13) but was not immediately considered malignant. Since then, some 50 cases have been described in the world literature, from which it has emerged that the tumor is usually a low-grade malignancy with a potential to metastasize. Most clear cell odontogenic carcinomas present clinically as rapidly growing intraosseous lesions, mostly in the mandible, and mostly in women older than 60 years of age. They are varying well defined radiographically and often associated with loosening of teeth.

Histologically it is a solid tumor, composed of variably sized islands and strands of small, round or polyhedral cells with clear cytoplasm as a result of the accumulation of glycogen (Fig. 21). The cells are usually uniform but occasional cases may show cytological atypia. Mitoses also vary in number, but in most cases they are infrequent. In some tumors a proportion of cells have pink, rather than clear, cytoplasm, giving rise to a biphasic pattern. The stroma consists of strands of fibrous tissue that may show hyalinization adjacent to the tumor islands. In those cases where metastases have been examined, the tumor in lymph nodes has the same features as

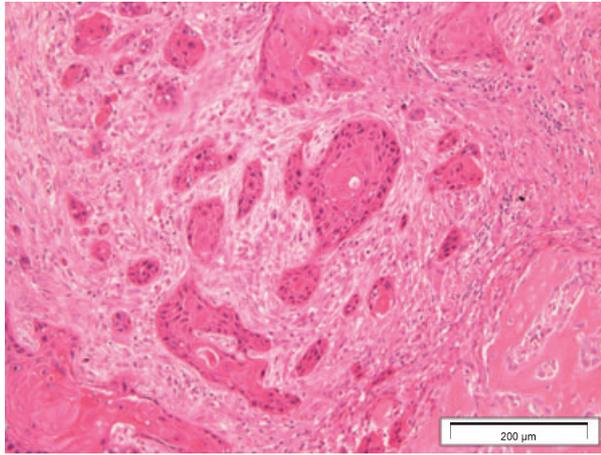


Fig. 21. Primary intraosseous squamous cell carcinoma. This tumor presented clinically as a pathological fracture of the mandible. A radiograph of the region taken several years previously showed a (probable) dentigerous cyst associated with an unerupted premolar.

in the primary site, perhaps with higher mitotic activity.

The clear cell odontogenic carcinoma is an unpredictable tumor with a high recurrence rate that requires definitive resection once diagnosed (9). Simple excision is almost inevitably followed by local recurrence and a propensity to metastasize, either to regional lymph nodes or further afield to the lungs or even to the liver.

Ghost cell odontogenic carcinoma

This very rare tumor is the malignant counterpart of the calcifying cystic odontogenic tumor (calcifying

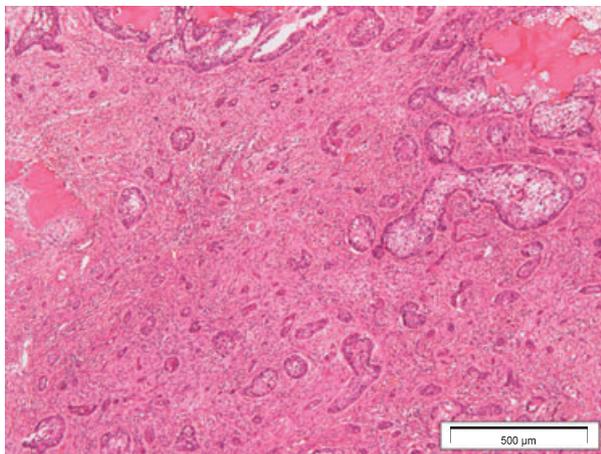


Fig. 22. Clear cell odontogenic carcinoma. This presented as an irregular radiolucency posterior to an impacted lower third molar. There are variably sized epithelial islands with clear cells centrally, and at the top of the field the tumor is in intimate contact with resorbing bone. This particular carcinoma behaved aggressively and metastasized widely within 2 years of the jaw resection.

odontogenic cyst) and combines the features of that tumor, the presence of ghost cells and sometimes dysplastic dentine, with the clinical and cytological features of malignancy (18).

Ameloblastic fibrosarcoma

Most malignant odontogenic tumors are carcinomas, but a rare sarcoma, the malignant counterpart of the ameloblastic fibroma, has long been recognized. This arises, usually in the mandible in teenagers or young adults, as a localized radiolucency accompanied by swelling and low-grade pain. The ameloblastic fibrosarcoma may well be diagnosed initially as an ameloblastic fibroma, either because the pathologist is unfamiliar with the entity and diagnoses the benign tumor, or because the sarcoma develops from the fibroma. Both scenarios are discernible from the literature. The tumor is aggressive and tends to recur locally, but distant metastasis is rare. Prompt and definitive local resection is the preferred treatment.

Small numbers of other sarcomas – malignant variants of ameloblastic fibro-odontomas and fibro-dentinomas – have been reported, but are exceedingly rare.

A research perspective on odontogenic tumors

Odontogenic tumors have been largely the domain of oral and maxillofacial surgeons and pathologists, the former relying upon the latter for guidance on treatment, as few clinicians in Europe and the USA can claim extensive experience in this field, compared, for example, with oral cancer. For similar reasons, research on odontogenic tumors is limited to what can be performed on relatively small numbers of fixed and processed excision specimens. Fortunately, however, the range of research techniques that can be applied to fixed tissue is broadening and in recent years many more immunohistochemical and molecular genetic studies have been published, mostly on ameloblastomas and keratocystic odontogenic tumors, but also on other tumors (4). The successive WHO classifications have attempted to impose clinico-pathological order on what might seem a bewildering diversity of entities, but this has not yet been joined by a biological order, in terms of similarities/dissimilarities in gene expression. However, gene-expression profiling in odontogenic tumors is in its relative infancy (8, 14) and histopathological diagnosis is still based very much on pattern recognition, with few markers available compared, for

example, with those employed in the diagnosis of lymphomas. Odontogenic epithelium, in all its manifestations, may be distinguished from other epithelia, with some provisos, through its expression of cytokeratin 19, and assessment of proliferation may be greatly aided by use of the KI-67 or proliferating cell nuclear antigen (PCNA) antibodies. These have useful laboratory applications but it is hoped that tumor-specific markers will be developed to find uses in better defining the structure and biological behavior of odontogenic tumors, as well as their likely response to treatment.

References

- Akrish S, Buchner A, Shoshani Y, Vered M, Dayan D. Ameloblastic carcinoma: report of a new case, literature review, and comparison to ameloblastoma. *J Oral Maxillofac Surg* 2007; **65**: 777–783.
- Allen CM, Neville BW, Hammond HL. Adenomatoid dentinoma. Report of four cases of an unusual odontogenic lesion. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; **86**: 313–317.
- Barnes L, Eveson JW, Reichart P, Sidransky D. *Pathology and genetics of head and neck tumours*. Lyon: IARC Press, 2005.
- Barnes L. *Surgical pathology of the head and neck*. Pittsburgh: Informa Healthcare, 2009: 1201–1337.
- Brannon R, Fowler C, Carpenter W, Corio R. Cementoblastoma: an innocuous neoplasm? A clinicopathologic study of 44 cases and review of the literature with special emphasis on recurrence. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 311–320.
- Buchner A, Sciubba JJ. Peripheral epithelial odontogenic tumors: a review. *Oral Surg Oral Med Oral Pathol* 1987; **63**: 688–697.
- Budnick SD. Compound and complex odontomas. *Oral Surg Oral Med Oral Pathol* 1976; **42**: 501–506.
- Carinci F, Francioso F, Piattelli A, Rubini C, Fiorini M, Evangelisti R, Arcelli D, Tosi L, Pezzetti F, Carinci P, Volinia S. Genetic expression profiling of six odontogenic tumors. *J Dent Res* 2003; **82**: 551–557.
- Ebert CS, Dubin MG, Hart CF, Chalian AA, Shockley WW. Clear cell odontogenic carcinoma: a comprehensive analysis of treatment strategies. *Head Neck* 2005; **27**: 536–542.
- Gardner DG. Central odontogenic fibroma current concepts. *J Oral Pathol Med* 1996; **25**: 556–561.
- Goldblatt LI, Brannon RB, Ellis GL. Squamous odontogenic tumor. Report of five cases and review of the literature. *Oral Surg Oral Med Oral Pathol* 1982; **54**: 187–196.
- Handlers JP, Abrams AM, Melrose RJ, Danforth R. Central odontogenic fibroma: clinicopathologic features of 19 cases and review of the literature. *J Oral Maxillofac Surg* 1991; **49**: 46–54.
- Hansen LS, Eversole LR, Green TL, Powell NB. Clear cell odontogenic tumor – a new histologic variant with aggressive potential. *Head Neck Surg* 1985; **8**: 115–123.
- Heikinheimo K, Jee KJ, Niini T, Aalto Y, Happonen RP, Leivo I, Knuutila S. Gene expression profiling of ameloblastoma and human tooth germ by means of a cDNA microarray. *J Dent Res* 2002; **81**: 525–530.
- Hietanen J, Lukinmaa PL, Ahonen P, Krees R, Caloniuss PE. Peripheral squamous odontogenic tumour. *Br J Oral Maxillofac Surg* 1985; **23**: 362–365.
- Karakida K, Aoki T, Sakamoto H, Takahashi M, Akamatsu T, Ogura G, Sekido Y, Ota Y. Ameloblastic carcinoma, secondary type: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110**: e33–e37.
- Kemp S, Gallagher G, Kabani S, Todd R. Adenomatoid dentinoma: case report and review of a rare odontogenic lesion. *J Oral Maxillofac Surg* 2008; **66**: 1489–1491.
- Ledesma-Montes C, Gorlin RJ, Shear M, Prae Torius F, Mosqueda-Taylor A, Altini M, Unni K, Paes de Almeida O, Carlos-Bregni R, Romero de León E, Phillips V, Delgado-Azañero W, Meneses-García A. International collaborative study on ghost cell odontogenic tumours: calcifying cystic odontogenic tumour, dentinogenic ghost cell tumour and ghost cell odontogenic carcinoma. *J Oral Pathol Med* 2008; **37**: 302–308.
- Leiser Y, Abu-El-Naaj I, Peled M. Odontogenic myxoma – a case series and review of the surgical management. *J Craniomaxillofac Surg* 2009; **37**: 206–209.
- Leon JE, Mata GM, Fregnani ER, Carlos-Bregni R, de Almeida OP, Mosqueda-Taylor A, Vargas PA. Clinicopathological and immunohistochemical study of 39 cases of adenomatoid odontogenic tumour: a multicentric study. *Oral Oncol* 2005; **41**: 835–842.
- Li TJ. The odontogenic keratocyst: a cyst, or a cystic neoplasm? *J Dent Res* 2011; **90**: 133–142.
- Mohamed A, Singh AS, Raubenheimer EJ, Bouckaert MMR. Adenomatoid odontogenic tumour: review of the literature and an analysis of 33 cases from South Africa. *Int J Oral Maxillofac Surg* 2010; **39**: 843–846.
- Philipsen HP, Birn H. The adenomatoid odontogenic tumour. Ameloblastic adenomatoid tumour or adenoameloblastoma. *Acta Pathol Microbiol Scand* 1969; **75**: 375–398.
- Philipsen HP, Reichart PA, Zhang KH, Nikai H, Yu QX. Adenomatoid odontogenic tumor: biologic profile based on 499 cases. *J Oral Pathol Med* 1991; **20**: 149–158.
- Philipsen HP, Reichart PA. Calcifying epithelial odontogenic tumour: biological profile based on 181 cases from the literature. *Oral Oncol* 2000; **36**: 17–26.
- Philipsen HP, Reichart PA, Takata T. Desmoplastic ameloblastoma (including “hybrid” lesion of ameloblastoma). Biological profile based on 100 cases from the literature and own files. *Oral Oncol* 2001; **37**: 455–460.
- Pogrel MA, Jordan RC. Marsupialization as a definitive treatment for the odontogenic keratocyst. *J Oral Maxillofac Surg* 2004; **62**: 651–655. discussion 655–656.
- Pogrel MA, Montes DM. Is there a role for enucleation in the management of ameloblastoma? *Int J Oral Maxillofac Surg* 2009; **38**: 807–812.
- Praetorius F, Hjorting-Hansen E, Gorlin RJ, Vickers RA. Calcifying odontogenic cyst. Range, variations and neoplastic potential. *Acta Odont Scand* 1981; **39**: 227–240.
- Ritwik P, Brannon RB. Peripheral odontogenic fibroma: a clinicopathologic study of 151 cases and review of the liter-

- ature with special emphasis on recurrence. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110**: 357–363.
31. Sauk JJ, Nikitakis NG, Scheper MA. Are we on the brink of nonsurgical treatment for ameloblastoma? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110**: 68–78.
 32. Slootweg PJ. An analysis of the interrelationship of the mixed odontogenic tumors – ameloblastic fibroma, ameloblastic fibro-odontoma, and the odontomas. *Oral Surg Oral Med Oral Pathol* 1981; **51**: 266–276.
 33. Van Dam SD, Unni KK, Keller EE. Metastasizing (malignant) ameloblastoma: review of a unique histopathologic entity and report of Mayo Clinic experience. *J Oral Maxillofac Surg* 2010; **68**: 2962–2974.
 34. Yamada T, Ueno T, Moritani N, Mishima K, Hirata A, Matsumura T. Primary intraosseous squamous cell carcinomas: five new clinicopathologic case studies. *J Cranio-maxillofac Surg* 2009; **37**: 448–453.
 35. Yoon HJ, Hong SP, Lee JI, Lee SS, Hong SD. Ameloblastic carcinoma: an analysis of 6 cases with review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; **108**: 904–913.