Pitfalls in odontogenic lesions and tumours: a practical guide

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Abstract

Lesions arising from odontogenic tissues of the jaws vary from very common to very rare. Some, such as radicular cysts, form a routine part of the diagnostic workload for histopathologists who report specimens from the head and neck, but many other lesions are rarely seen and can cause significant diagnostic difficulty for the non-specialist. These issues are compounded by the vagaries of dental disease (and terminology used by dentists and oral surgeons) and issues in the interpretation of radiographic images, which can be crucial to making a correct diagnosis. In this review article, we will discuss a number of areas of diagnostic difficulty, largely based on the authors experience in receiving tertiary referrals. This will focus on practical advice to help avoid the pitfalls in the diagnosis of odontogenic lesions.

Keywords ameloblastoma; dental follicle; myxoma; odontogenic cyst; odontogenic tumour; odontome

Introduction

The pathology associated with the odontogenic tissues covers a wide range of lesions with varying aetiologies. Most lesions arise from the remnants of the tissues which give rise to the teeth, and an understanding of tooth development is often key to being able to reach a diagnosis. In some, epithelial and mesenchymal tissues remaining after completion of the dentition are subjected to the influence of inflammation, largely as sequelae to the dental caries − pulpitis − periapical periodontitis sequence. These lesions (apical granuloma and radicular cyst) are very common, and only infrequently cause diagnostic confusion. Other lesions, such as the developmental odontogenic cysts and odontogenic tumours are rarer (in some cases very rare indeed), and the varied clinical, radiological and histopathological features can lead to uncertainty in diagnosis. Much of this can be ameliorated by careful attention to appropriate clinical and radiological information (which can be hard to come by), but there are still a number of common areas of confusion with associated pitfalls.

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Based on the issues which commonly arise in referral cases, in this review we will outline a number of these, with practical advice on how to address them in the diagnostic process.

Pitfall 1: lesions in the immature dentition

Before we discuss the issue at hand, a quick review of tooth development is needed. The dentition starts to develop very early in intrauterine life, with the early stages microscopically evident by around week 6. The development of teeth requires both an epithelial component, which arises from a structure in the developing oral epithelium called the primary epithelial band (which gives rise to the dental lamina), and an ectomesenchymal component, originating from cells of the neural crest. The molecular interactions between these tissues are being progressively identified,[1] and these give rise to the enamel organ, which appears as an expansion of the dental lamina. This varies in shape throughout development (from bud to cap to bell shape) and progressively outlines the size and shape of the tooth crown (Figure 1). Further differentiation gives rise to formation of the hard tissues of the tooth: dentine secreted by odontoblasts derived from the mesenchyme of the developing dental pulp, and enamel secreted by ameloblasts derived from the inner layer of the dental lamina. Once the crown is complete, the root is outlined by an epithelial structure known as Hertwig's root sheath (HRS), which encompasses the ectomesenchymal component of the developing tooth, which then becomes the dental pulp. The developing tooth, prior to eruption, is surrounded by a band of fibrous tissue known as the dental follicle (Figure 2).

Once tooth formation is complete, the epithelial components are no longer required and the enamel organ undergoes atrophy and the dental lamina and Hertwig's root sheath fragment. However, epithelial remnants remain: Hertwig's root sheath gives rise to the cell rests of Malassez which are found in the periodontal ligament, and the dental lamina gives rise to the cell rests of Serres (Dental Lamina Rests: DLRs) which overlie an unerupted tooth, but also reside permanently in the superficial alveolar bone and gingival mucosa. The epithelium which covers the completed crown (Reduced enamel epithelium) remains until eruption, when it forms part of the developing gingival crevice epithelium. Mesenchymal components, largely dental follicle, can remain after the completion and eruption of teeth. These epithelial and mesenchymal remnants give rise to the full range of odontogenic lesions and tumours (Table 1).

As will be evident from what follows in later sections, many odontogenic hamartomas and tumours recapitulate the histological appearances of tooth development to some degree. The development of odontoma is a particular case in point, but ameloblastomas (most notably the follicular pattern) closely resemble the enamel organ, and odontogenic myxoma variable recapitulates features of the dental follicle or dental papilla. There is, therefore, potential for confusion of immature odontogenic tissues with odontogenic neoplasms, and this is a well-known pitfall in younger patients (<20 years), particularly before completion of the dentition.[2]

Care is required in a number of scenarios

- Dental lamina rests in tissues overlying unerupted teeth. DLRs are commonly found in gingival biopsies, particularly from the posterior mandible. They vary markedly in their appearance from small clusters of cells, very similar

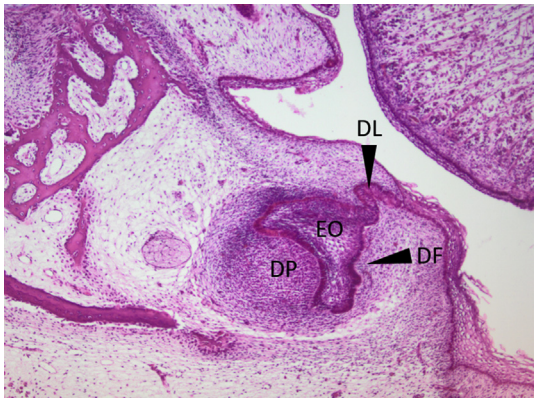

Figure 1 Developing tooth at 'cap' stage. Annotations: DL = dental lamina; EO = enamel organ; DF = dental follicle; DP = dental papilla.

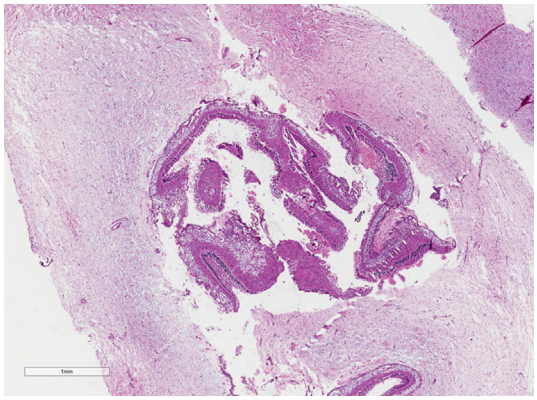

Figure 2 Dental follicle and enamel epithelium from a developing tooth, with crown development almost complete. The follicle comprises mature fibrous tissue.

The remnants of the tooth forming apparatus, and the lesions which arise from them

Originating structure	Lesions which develop
Dental follicle	Odontogenic myxoma?
Dental papilla	Odontogenic myxoma?
Cell rests of Malassez	Radicular cyst
Cell rests of Serres (DLRs)	Odontogenic keratocyst
	Ameloblastoma
	Other ODTs
Reduced enamel epithelium	Dentigerous cyst
	Paradental "cyst"
	Lateral periodontal cyst?
Overall enamel organ	Primordial odontogenic tumour?

Table 1

to the dental lamina, to larger islands of epithelium, which on occasion can show squamous metaplasia (Figure 3). There is potential, if the DLRs are extensive, for confusion with ameloblastoma (particularly peripheral type), but DLRs tend not to present with a follicular histological pattern, and the clinical and radiological features show no convincing lesion.

- Myxoid/fibromyxoid tissues overlying a tooth. Dependent on the stage of development, either the dental papilla or dental follicle can have similar histological features to an odontogenic myxoma (see later). As the dentition matures, the dental follicle can enlarge (often with a radiographic provisional diagnosis of a dentigerous cyst). If the biopsy consists of fibromyxoid tissue, the presence of other structures suggestive of a developing tooth, for example fragments of reduced enamel epithelium, can be helpful. However, in most cases, careful attention to the clinical details and review of the radiographs will resolve this issue.
- Developing odontome: this is an area of current controversy. Odontoma are hamartomatous lesions which arise from both odontogenic epithelium and mesenchyme and also contain dental hard tissues. However, as for the development of the dentition itself, these lesions initially develop without containing dental hard tissues. This mixture of disorganised dental epithelium and mesenchyme can cause confusion between a developing odontome and a number of true neoplastic lesions such as ameloblastic fibroma (AF) and ameloblastic fibro-odontome (AFO) (Figure 4). A number of authors consider all AFO to be developing odontome,[3,4] and this has been reflected in the 2017 WHO classification of Odontogenic Tumours, by the removal of AFO as a neoplastic entity in its own right.[5] It is the view of the current authors that this move is premature, as some AFO may reach large sizes, continue to grow and are obviously neoplastic.[6] Nevertheless, identification of such a histological differential diagnosis again requires careful consideration of the clinical (in particular, the age of the patient at presentation) and radiological features before arriving at a final diagnosis.

Pitfall 2: incomplete/misleading clinical details or radiology

As in many other areas of histopathology, much of the information required to make the diagnosis comes in the form of clear and complete clinical information and correct interpretation of ancillary tests, such as radiological examination. It is difficult to over-emphasise how important the radiographs are in assessment of lesions in the jaws: an example is shown in Figure 5. For Oral and Maxillofacial Pathologists (OMFPs), this area is reasonably familiar, given the detailed training in radiology and radiography of the jaws which dentists receive. For many from a medical background, dental radiology is a bit of a "black box". Thus, it is important to build good relationships with radiology colleagues who are experienced in assessing jaw lesions. On occasion, it will be necessary for all pathologists to seek the specialist advice of a Dental and Maxillofacial Radiologist (DMFR). Problems with access to and interpretation of radiographs can be compounded by the use of dental jargon on pathology request forms and the frequent absence of important items of clinical information. The importance of this is illustrated in the following scenarios:

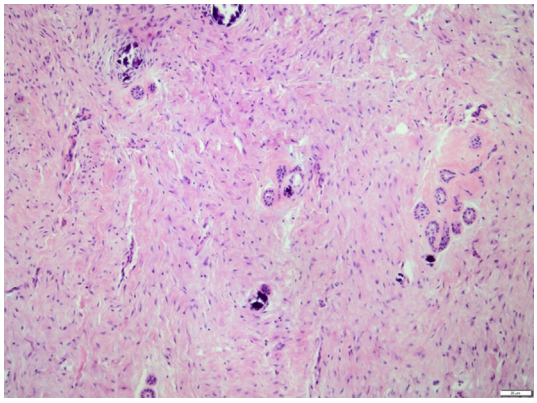

Figure 3 Inactive dental lamina rests in gingival tissue. Many have a rim of hyalinised surrounding tissue.

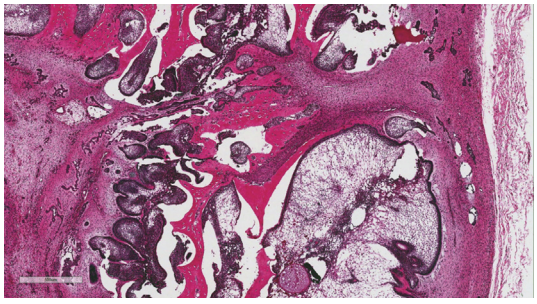

Figure 4 Ameloblastic fibro-odontome/developing odontome with arrays of ameloblastoma-like odontogenic epithelium and other smaller, scattered dental lamina remnants. There is dental hard tissue formation in the centre of the image.

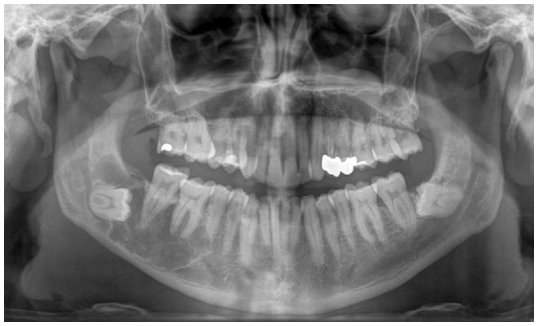

Figure 5 A representative panoramic radiograph from an adult patient. There is a well-defined radiolucency involving a displaced unerupted tooth, which has caused some resorption of the root of the second premolar tooth. On biopsy, the lesion was a calcifying epithelial odontogenic tumour (CEOT).

- A clear understanding of the clinical scenario is required when assessing inflamed lesions which contain squamous epithelium. Very often detail in the clinical history is lacking: for example, a history of a non-vital tooth and a periapical radiolucency makes assessment in this context much more straightforward. Similarly, in lesions most often associated with third molar teeth, defining whether the tooth is unerupted or partially erupted (or even if the follicle space is communicating with the oral cavity) gives useful information for refining a histological differential diagnosis.
- The importance of access to radiographs is very powerfully illustrated in the retrospective analysis of dentigerous cysts reported by Barrett et al.[7] Review of the clinical and radiological features of 101 dentigerous cysts prompted review of histology in 28 cases and identified 5 misdiagnoses: Four odontogenic keratocysts and one ameloblastoma. In view of this, the suggestion that review of the radiology should be undertaken in all cystic lesions of the jaws (and certainly in patients <20 years of age), is very reasonable.

Pitfall 3: ameloblastoma: small biopsies and variable appearances

Ameloblastoma is the commonest odontogenic tumour and, in many cases, the classic histological appearances (follicular or plexiform patterns or both) provide little difficulty in diagnosis to those with some experience of the tumour. However, a number of issues arise in relation to diagnosing these in a general histopathology setting: even classic histology of a rare tumour can strike fear into an experienced pathologist. It is wise, in these circumstances to seek the opinion of colleagues who have more experience in odontogenic lesions, in order to improve confidence in their diagnosis. These difficulties are compounded by clinical and histological variations:

- A number of subtypes of ameloblastoma exist and, on occasion, these can cause difficulty, particularly in small biopsies. These include acanthomatous, granular and basaloid subtypes, with tumours containing clear cells and mucous cells also described. In desmoplastic ameloblastoma the islands of odontogenic epithelium can be very compressed and attenuated or irregular, pointed islands set in a hyalinised, active fibroblastic stroma (Figure 6). Myxoid changes may be present adjacent to the epithelial islands and metaplastic bone may be identified.
- Other odontogenic lesions may contain ameloblastoma-like epithelium, and these are shown in Table 2. In most cases, other histological features allow for distinction from ameloblastoma. Tumours which contain both odontogenic epithelium and mesenchyme include ameloblastic fibroma and ameloblastic fibro-odontome (also with dental hard tissue). In these cases, careful attention must be paid to the mesenchymal component. In ameloblastoma this is mature fibrous tissue, whereas in ameloblastic fibroma (and similar lesions), this is an immature cellular stroma, which resembles the dental papilla (Figure 7).
- Despite often being large lesions, biopsies can be very small. This is a particular issue with lesions which are predominantly cystic. Biopsies are usually taken in the most accessible site, which is commonly an area of expansion in the posterior mandible. Often this may only provide a small biopsy of cyst lining with features which are difficult to interpret. There are a number of pointers to

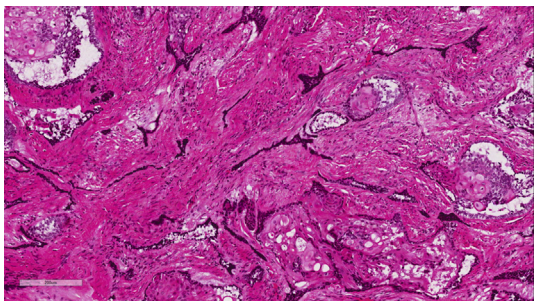

Figure 6 Ameloblastoma with a mixed histological appearance. Some larger islands are present, but most are very compressed and jagged strands of epithelium in an active, hyalinised fibrous stroma.

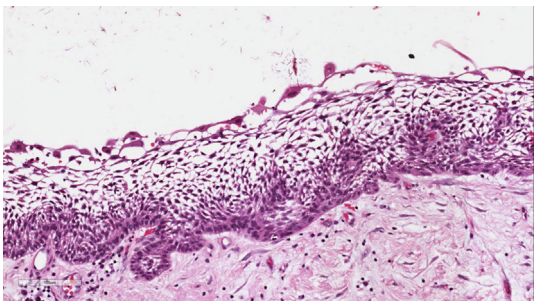

Figure 8 Unicystic ameloblastoma with the lining showing Stellate-reticulum-like appearance over basal cells. Some of the superficial cells have a "parachute" like appearance.

Lesions containing ameloblastoma-like epithelium

Lesion	Distinguishing features
Ameloblastic fibroma	Uniform, cellular stroma, resembling dental papilla
Ameloblastic fibro-odontome/dentinoma/ developing odontome	Similar stroma to ameloblastic fibroma; formation of dental hard tissues
Calcifying odontogenic cyst	Ghost cells extensively within the cyst lining, some of which may calcify. Dentine-like material may also be present in the cyst wall.
Dentinogenic ghost cell tumour	Extensive collections of ghost cells within the epithelium, dentine/ dentinoid formation
Ameloblastic carcinoma	Cytological atypia; frequent mitotic figures; Ki67 >20% of cells

Table 2

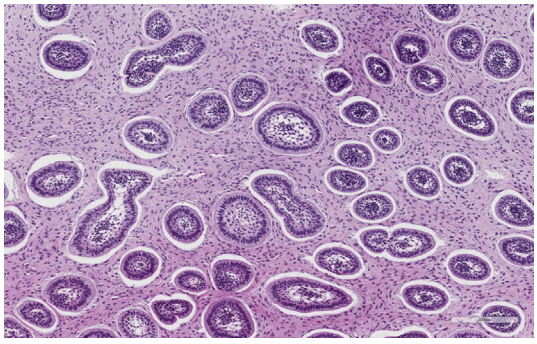

Figure 7 Ameloblastic fibroma, with island of ameloblastoma-like epithelium in a cellular stroma, which resembles the dental papilla.

ameloblastoma, including eosinophilic "parachute" or "umbrella" cells at the luminal surface of the epithelial cyst lining, palisading and reversed nuclear polarity of the basal ameloblast-like cells and crowding of the parabasal cells (Figure 8). On occasion it is not possible to definitively resolve a differential diagnosis of a developmental cyst (e.g. dentigerous cyst or odontogenic keratocyst) or ameloblastoma on a small biopsy and it is then reasonable to request a further, larger biopsy.

- Care must be taken before arriving at a final diagnosis of a unicystic ameloblastoma. This variant, which comprises a single cyst space (often unilocular on radiology), with or without proliferation into the cyst lumen, probably has a much lower recurrence rate than conventional ameloblastoma, albeit the support in the literature for this is somewhat sparse.[8] The pitfall comes in misdiagnosing a predominantly cystic conventional ameloblastoma, where very little solid component is present, or, indeed if the solid component has been missed in the biopsy. Great caution should be taken in using the term unicystic ameloblastoma in this context. In order to arrive at this final diagnosis, the whole specimen should be examined for the absence/presence of solid islands of tumour in the cyst wall. It is not possible to make a definitive diagnosis on an incisional biopsy!

Pitfall 4: cysts/tumours with overlapping histologic features

A further area of challenge is in the diagnosis of odontogenic lesions which have overlapping/common features with other lesions (in addition to the array of lesions with ameloblastoma-like epithelium). Common histological features in this regard are the presence of mucous cells and keratinisation in cystic lesions. Both are common, and raise a number of interesting differential diagnoses. Ghost cells are also seen in a range of odontogenic lesions, but these are much less frequent.

Mucous cells are a common finding in a range of odontogenic lesions: in some, they are a key diagnostic feature, whilst in others they are a metaplastic phenomenon, further illustrating the plasticity of odontogenic epithelium. The main lesion that is characterised by mucous cells is the glandular odontogenic cyst (GOC). This cyst, has overlapping features with other developmental cysts of the jaws, including the lateral periodontal and botryoid cyst, but does on occasion raise a differential diagnosis with a central/intra-osseous mucoepidermoid carcinoma (IOMEC). GOCs present variable histologic features, including cilia, "hobnail" surface cells and plaque-like thickenings of the cyst lining (Figure 9), but it is the presence of mucous cells and multiple cystic spaces which overlap with IOMEC and may raise concerns. Assessment of MAML2 gene rearrangement has been suggested as a possible tool for differentiating these lesions. However, whilst the presence of MAML2 rearrangement allows the diagnosis of IOMEC to be

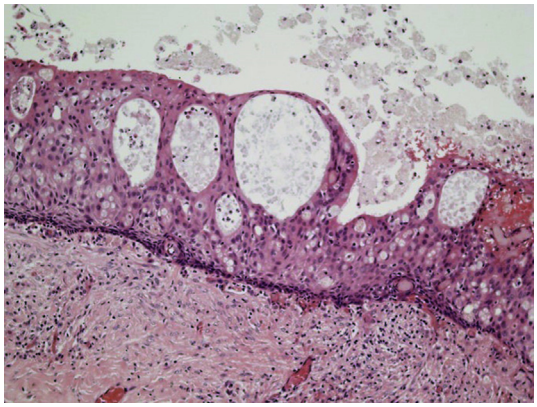

Figure 9 Glandular odontogenic cyst, with numerous mucous cells and lumen-like spaces within the cyst lining.

made, the converse is not necessarily true: absence of the translocation does not exclude a diagnosis of IOMEC.[9] In such cases, arriving at a definitive diagnosis can be very challenging: the distribution of lesions can be helpful (GOC often anterior jaws; IOMEC more common in posterior jaws), and the presence of symptoms (much more common in IOMEC) may be useful, but a range of experienced opinion should be sought in such cases.

Mucous cells are also identified in a number of other lesions[10]: focally in dentigerous cysts (Figure 10), radicular cysts (more so in residual radicular cysts, where the originating inflammatory focus has been removed), and even on occasion in ameloblastoma.[11] These are most likely metaplastic in origin and are part of the spectrum of appearances in theses lesions. Their significance is not known and they require no further attention unless extensive, when other differential diagnoses come into play.

Keratinisation is also very common in odontogenic lesions. This is most obvious in the odontogenic keratocyst (OKC) with its characteristic parakeratinised lining and basal cell palisading. This rarely causes diagnostic difficulty, except when there is coincident inflammation: in this situation the characteristic features of the lining are lost, and may only be present focally, with the rest resembling an inflammatory odontogenic cyst. This may require careful examination of a whole specimen if OKC is a consideration clinically. Other cysts are orthokeratinised, and whilst this was once considered part of the spectrum of OKC, such cysts are now termed orthokeratinised odontogenic cysts, and have sufficiently distinctive clinical and histological features to warrant a separate entry in the 2017 WHO classification.[5] However, in practice, focal keratinisation in a range of other odontogenic lesions probably causes more diagnostic uncertainty than these entities.[12] Keratinisation may be present focally in about one third of odontogenic cysts, including dentigerous cysts and radicular cysts. Keratinisation is almost never present in very inflamed cysts, but is relatively common in residual radicular cysts where inflammation has markedly reduced.

Pitfall 5: myxoid lesions

A myxoid histological appearance in tissues can arise for a number of reasons and a myxoid extracellular matrix (ECM) has been recognised in reactive and neoplastic lesions. Such an appearance may be due to an accumulation of glycosaminoglycans and hyaluronic acid, and in many body sites, this is considered a degenerative phenomenon.[13] Staining characteristics in H&E are a loose, pale staining eosinophilic to grey colour in the connective tissues. Classically, this appearance is seen in odontogenic myxoma (OM), a rare mesenchymal tumour of the jaws, most common in the mandible. The radiological appearance is variable, but is more often multilocular than unilocular. Despite arising in the jaws, there is not universal agreement that this tumour arises from dental mesenchyme as the ultrastructural links to immature odontogenic tissues are somewhat tenuous. The characteristic histological appearances are shown in Figure 11, but are also variable in terms of the extent of fibrous component and odontogenic epithelial content (some contain no odontogenic epithelium). The appearances are, however, not specific and full attention to the clinical, radiographic and histological features is required. Myxoid change in the dental follicle overlying unerupted teeth is relatively common: clinical and radiological information is very useful in this distinction, but no good histological features or markers have been shown to robustly separate these entities: a lack of small nerves, common in dental follicles, and highlighted by S100 staining, may be

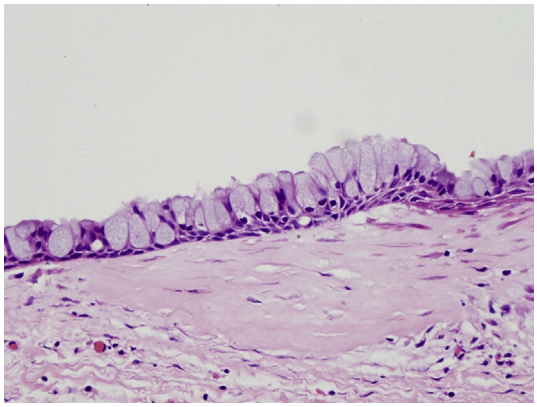

Figure 10 Mucous prosoplasia in the lining of a dentigerous cyst. Such changes are common and focal in nature.

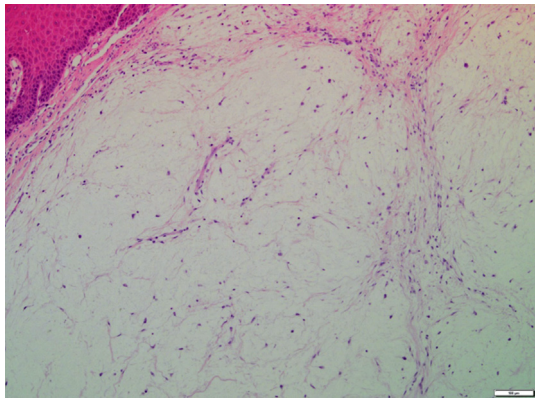

Figure 11 Peripheral extension of an odontogenic myxoma, with poorly defined nodules of sparsely cellular myxoid tissue. Some contain scattered dental lamina rests.

useful, but this has not been widely assessed. Myxoid degeneration in other tumours, such as those of nerve sheath origin must also be considered. This can be problematic because a proportion of odontogenic myxomas do express S100[13]. Other markers such as αSMA are widely expressed in a range of myxoid lesions. On occasion a myxoid appearance can be seen in a reactive gingival lesion (fibrous epulis): this presents a differential diagnosis which includes peripheral extension of OM, other differential diagnoses as above, and other phenomena, such as focal oral mucinosis. Careful clinical and radiological correlation may help in distinguishing these cases.

Pitfall 6: tumours containing clear cells

Clear cells may be identified in a wide range of odontogenic lesions and are mostlyregarded as a degenerative phenomenon. A number of tumours contain a significant proportion of clear cells, with a range of biological behaviours, albeit most clear cell lesions in the jaws do not demonstrate significant cytological atypia, even if malignant. The most significant diagnoses are the malignant ones: clear cell odontogenic carcinoma (CCOC; Figure 12), and clear cell variants of intraosseous mucoepidermoid carcinoma and ameloblastic carcinoma. Clear cell odontogenic carcinoma most commonly occurs in the posterior mandible. These tumours often recur locally and can metastasise.[14] In addition, it is important in these circumstances to consider a number of other metastatic tumours which may contain clear cells, such as renal cell carcinoma, other salivary gland tumours and melanoma. Clear cell variants of the calcifying epithelial odontogenic tumour (CEOT) have been reported and these present an often troublesome differential diagnosis with odontogenic malignancies containing clear cells. Thus, it is important to work through the differential diagnosis systematically: PAS with and without diastase and pre-treatment and a mucin stain (alcian blue or mucicarmine) are the starting point, to rule out mucin or glycogen accumulation. Immunohistochemistry can be used to address other elements of the differential diagnosis, such as RCC and CD10 for renal cell carcinoma and S100 and Melan A in melanoma.

Clear cell malignancies from many parts of the body have been demonstrated to contain EWSR1 gene re-arrangements, and this has been demonstrated in clear cell odontogenic carcinoma.[15] Thus, assessment of EWRS1 rearrangements by FISH can be very useful in distinction of CCOC from clear cell CEOT.

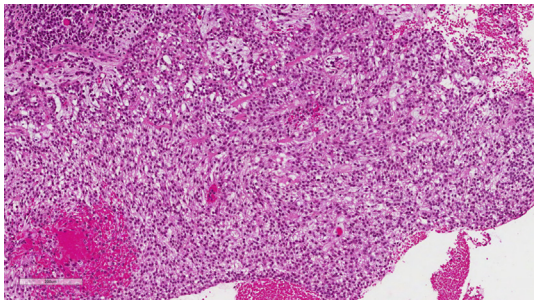

Figure 12 Clear cell odontogenic carcinoma comprising sheets of cells with cytoplasmic clearing. In many tumours there is a biphasic appearance with smaller darker staining cells also present.

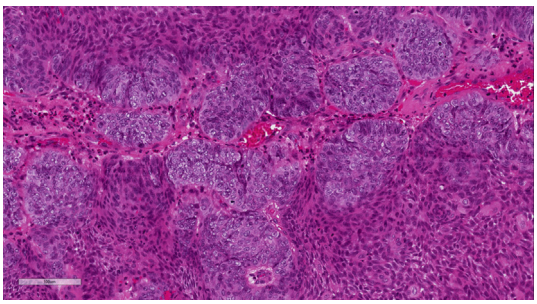

Figure 13 Budding growth with crowding and cytological atypia in an ameloblastoma with transformed to ameloblastic carcinoma.

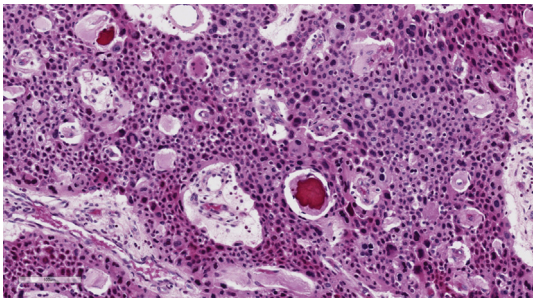

Figure 14 Extensive nuclear and cellular pleomorphism in a CEOT. Note that mitoses are absent.

Pitfall 7: assessment of malignancy in odontogenic tumours

The assessment of malignancy in odontogenic tumours is, in some cass, straightforward if a destructive tumour shows the classic histological features of malignancy: nuclear and cellular pleomorphism, a high mitotic rate with abnormal mitoses and areas of necrosis (Figure 13). In many cases these features are not so clear cut: in particular, solid ameloblastomas in the maxilla tend to show increased, and in some cases rather worrying, cell crowding, overlapping and budding, and these are not necessarily indicators of malignancy in this context. The clinical features that have been associated with development of malignancy in ameloblastoma are not surprising: namely older patients, sited in the maxilla and larger tumours,[16] but these features are of limited use in the assessment of malignancy in individual cases. Ancillary tests to help in this distinction are lacking, however on occasion, use of ki67 to assess the proliferation fraction may help. This has been demonstrated as significantly higher in ameloblastic carcinoma than in ameloblastoma.[17] Conversion of this into a practically useful cut-off has not been robustly tested, but the current authors' view is that ki67 expression in more than 20% of cells is very suggestive of malignancy. Other biomarkers such as high expression of SOX2 and OCT-4 have been suggested for use in distinguishing solid ameloblastomas and ameloblastic carcinoma, but these require to be tested in a larger patient cohort.[18]

As a caveat, there are other tumours, which on occasion present with prominent nuclear pleomorphism. Most notably this is seen in the calcifying epithelial odontogenic tumour (CEOT)

where extensive, and on occasion rather bizarre, atypia are often identified (Figure 14). This feature has been long recognised as part of the histological spectrum of appearances of CEOT,[19] and as other malignant features, such as increased mitoses and abnormal mitoses are absent, this is not considered as an indicator of malignant behaviour.

Conclusion

Due to their relative rarity, odontogenic lesions, whether reactive, developmental or neoplastic can cause diagnostc uncertainty. In many cases, taking the time to explore the clinical and radiological features of the lesions will be very helpful in arriving at a diagnoses. We hope that the other practical suggestions in this review may be of help in negotiating these difficulties and also allow the reporting pathologist to provide useful comment to the referring practitioners. ◆

Practice points

- Be very cautious in making a diagnosis of an odontogenic tumour in a patient whose dentition is still developing. Clinical and radiographic information must be carefully reviewed before arriving at such a diagnosis.
- It is very important to have access to the radiographs when reporting lesions in the jaws: seek specialist help in interpretation if this area is not familiar. Clinical and radiological correlation within the whole team (including the surgical team) is required.
- Do not hesitate to ask for a further biopsy of a cystic lesion in the jaws if the biopsy is small and the histological features are equivocal or do not agree with the clinical or radiological impression.
- Mucous cells and keratinisation are often focally present in odontogenic cysts: unless prominent, these form part of the usual histological spectrum of such lesions and only require further work up if further features suggest other differential diagnoses.
- Diagnosis of myxoid lesions requires a careful approach, including clinical, radiological and histological features. OM is most often a diagnosis of exclusion.
- Identification of clear cell in lesions of the jaws presents a differential diagnosis which must be worked through: in some cases other histological clues are present, but in others special stains and cytogenetics may be required to arrive at a diagnosis.
- Assessment of malignancy in destructive odontogenic lesions is challenging. The specimen should be widely sampled with assessment of proliferation as a useful aid in the overall consideration of malignancy.

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