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REVIEW

Controversies in Odontogenic Tumours

Review

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جدل في الأورام سنية المنشأ

مراجعة

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ABSTRACT: Odontogenic tumours are lesions that occur solely within the oral cavity and are so named because of their origin from the odontogenic (i.e. tooth-forming) apparatus. Odontogenic tumours comprise a variety of lesions ranging from non-neoplastic tissue proliferations to benign or malignant neoplasms. However, controversies exist regarding the pathogenesis, categorisation and clinical and histological variations of these tumours. The recent 2017 World Health Organization classification of odontogenic tumours included new entities such as primordial odontogenic tumours, sclerosing odontogenic carcinomas and odontogenic carcinosarcomas, while eliminating several previously included entities like keratocystic odontogenic tumours and calcifying cystic odonogenic tumours. The aim of the present review article was to discuss controversies and recent concepts regarding odontogenic tumours so as to increase understanding of these lesions.

Keywords: Neoplasms; Oral Cavity; Odontogenic Tumors; Hamartomas; Classification; World Health Organization.

الملخص: الأورام سنية المنشأ هي آفات تحدث بالتحديد في جوف الفم وحسب التسمية تنشأ من الخلايا المنشأة للأسنان. تضم الأورام سنية المنشأ على العديد من الآفات تتراوح من تكاثر الأنسجة غير السرطانية إلى الأورام الحميدة والخبيثة. على الرغم من هذا، توجد إختلافات في الإمراض والتصنيف والتنوع الأكلينيكي والمجهري لهذه الأورام. شمل التصنيف الجديد 2017 للأورام سنية المنشأ لمنظمة الصحة العالمية على كيانات جديدة مثل أورام أولية سنية المنشأ، سرطانات مصلبة سنية المنشأ، وساركومة سرطانية سنية المنشأ، مع إستبعاد العديد من الكيانات المدرجة سابقا كأورام الكيسة الكيراتينية سنية المنشأ والأورام الكيسية المكلسة سنية المنشأ. تهدف هذه المراجعة إلى مناقشة هذه الإختلافات والمفاهيم الحديثة المتعلقة بالأورام سنية المنشأ لزيادة فهم هذه الأورام.

الكلمات المفتاحية: أورام؛ جوف الفم؛ أورام سنية المنشأ؛ أورام عابية؛ تصنيف؛ منظمة الصحة العالمية.

Many lesions, both intraosseous and extraosseous, can involve the maxillary and mandibular regions of the jaw; of these, odontogenic tumours are unique to the oral cavity and do not occur elsewhere in the body. These tumours originate from tissues involved in odontogenesis (i.e. tooth development) and include a wide variety of lesions ranging from hamartomas to non-neoplastic tissue proliferations and both benign and malignant neoplasms.[1,2] Due to this wide range of biological behaviour, there is currently much debate regarding the pathogenesis, classification and clinical and histological variations of odontogenic tumours.[1] The present review aimed to provide insight into different controversies and recent developments in this field, particularly with regards to the recent 2017 World Health Organization (WHO) classification of odontogenic tumours.[2] Awareness of such controversies may aid in a better understanding of these pathological entities as well as enhancing their diagnosis and management. A brief overview of the main controversies associated with different odontogenic lesions is shown in Table 1.

Classification

Odontogenic lesions were first classified by Broca in 1868.[3] In 1971, the WHO included these lesions in its first histological classification of such tumours and provided the clinicopathological criteria necessary for diagnosis.[1] Due to subsequent advancements in diagnostic immunohistochemistry, molecular biology and genetics, as well as clinical and epidemiological follow-up, modifications were made to the previous 2005 WHO classification in 2017 wherein some lesions were newly added, removed or reclassified; in addition, attempts were made to simplify the classification system, discarding subtypes or suffixes that lacked clinical relevance.[2,4,5] Table 2 provides a summary of the entities which were either newly included or excluded from the WHO 2017 classification.[2,4]

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Table 1: Key controversies in the pathogenesis, categorisation and clinical and histological variations of odontogenic tumours

Entity	Controversy
Benign epithelial odontogenic tumours	
Peripheral ameloblastoma	This lesion may be either a hamartoma or a benign neoplasm
Peripheral ameloblastomas and intraoral basal cell carcinomas	These may be separate entities or variants of the same entity
Calcifying epithelial odontogenic tumour	The biochemical nature and origin of the amyloid-like material in this lesion is not yet understood
Keratocystic odontogenic tumour/ odontogenic keratocyst	There is debate as to whether this lesion is a cyst or tumour
Adenomatoid odontogenic tumour	This lesion may be either a hamartoma, cyst or neoplasm
Squamous odontogenic tumour	This lesion may be either a hamartoma or a neoplasm
Benign mixed epithelial and mesenchymal odontogenic tumours	
Complex and compound odontomas	There seems to be little clinical relevance in distinguishing these lesions as two separate entities
Ameloblastic fibroma	Both a neoplastic and hamartomatous line of development have been proposed for this entity
Primordial odontogenic tumour	There is doubt as to whether this is a new entity or a variant of ameloblastic fibromas, odontogenic fibromas or myxomas
Calcifying cystic odontogenic tumour/ calcifying odontogenic cyst	This lesion may be either a cyst or a tumour
Benign mesenchymal odontogenic tumours	
Odontogenic fibroma	There is doubt regarding the subcategorisation of this entity into epithelium-rich and epithelium-poor variants
Odontogenic myxoma	There is controversy regarding the pathogenesis of this lesion and whether it is truly odontogenic in nature
Cementoblastoma	This lesion may have either an odontogenic or osteogenic origin
Cemento-ossifying fibroma	This lesion may have either an odontogenic or fibro-osseous nature
Malignant odontogenic tumours	
Clear cell odontogenic carcinomas and clear cell ameloblastomas	These may be separate entities or variants of the same entity
Ghost cell odontogenic carcinoma	There is doubt as to whether the presence of ghost cells would cause malignancy
Sclerosing odontogenic carcinoma	There is as yet no confirmation of the metastatic potential of this lesion
Odontogenic carcinosarcoma	The existence of this lesion is questionable

Nevertheless, researchers have argued that classifying odontogenic tumours as either benign or malignant does not encompass the reported range of behaviours shown by these lesions.[6] As such, classifying these lesions in a manner similar to the WHO bone and soft tissue tumour classification—with the addition of intermediate (locally aggressive) and intermediate (rarely metastasising) categories—may be more appropriate.[6,7] In 2016, Singh *et al*. proposed a classification for odontogenic tumours based on histopathological patterns; unfortunately, some of the classified lesions had overlapping histological features, thus limiting their diagnostic utility.[8] The current review article categorises benign odontogenic lesions as either epithelial, mixed or mesenchymal lesions while malignant lesions are divided into carcinomas, sarcomas and carcinosarcomas.

Benign Epithelial Odontogenic Tumours

Due to their odontogenic potential, oral epithelial tissues may give rise to epithelial odontogenic tumours. These tumours can originate from the remnants of odontogenic epithelia such as reduced enamel epithelium and the respective epithelial cell rests of Malassez and Serres.[9]

Table 2: Summary of lesions either newly excluded, included or recategorised in the 2017 World Health Organization classification of odontogenic tumours[2,3]

Lesion	Reason
Entities excluded	
Keratocystic odontogenic tumour	Now considered an odontogenic cyst and renamed odontogenic keratocyst
Calcifying cystic odontogenic tumour	Now considered an odontogenic cyst and renamed calcifying odontogenic cyst
Primary intraosseous squamous cell carcinoma	Now considered a primary intraosseous carcinoma
Ameloblastic fibro-dentinoma and ameloblastic fibro-odontoma	Now grouped together under the category of ameloblastic fibroma and no longer considered separate entities
Newer entities included	
Primordial odontogenic tumour	This previously undescribed entity has been newly included as an odontogenic tumour following evidence that the periphery of the lesion resembles that of inner enamel epithelia (i.e. primordial epithelia)
Sclerosing odontogenic carcinoma	This tumour has been proposed to be a distinct entity from other odontogenic carcinomas due to its hyalinized or sclerosing *stroma*
Odontogenic carcinosarcoma	New research has reconfirmed the existence of this lesion
Cemento-ossifying fibroma	This lesion has been included due to its exclusive occurrence within tooth-bearing areas and probable periodontal origin
Changes in category	
Metastasising ameloblastoma	This lesion has been recategorised as benign due to its benign histopathology

AMELOBLASTOMA

In the categorisation of conventional ameloblastomas in the 2017 WHO classification, solid/multicystic adjectives were eliminated as they were deemed to have no biological implications and could be confused with unicystic ameloblastomas.[4] Desmoplastic ameloblastomas, which had been sub-categorised under ameloblastomas in the previous 2005 WHO classification, were also removed as they were considered a histological variant similar to conventional ameloblastomas.[4,5] Metastasising ameloblastomas were reclassified as benign tumours rather than malignant odontogenic tumours as these tumours show benign histopathology in spite of their metastatic potential, rendering them difficult to differentiate histopathologically from conventional ameloblastomas.[2]

Based on the innocuous nature of peripheral ameloblastomas (PAs), Philipsen *et al.* questioned whether such lesions were analogous to solid multicystic ameloblastomas (SMAs) or hamartomatous lesions.[10] Indeed, the biological behaviour of a PA has been deemed more indicative of a hamartomatous proliferation or persistent hyperplasia than neoplasia.[11] Marx *et al.* defined a PA as a hamartomatous proliferation of odontogenic epithelia arising from the rests of Serres or perhaps from the basal cells of the oral mucosa.[12] However, the occurrence of intraoral basal cell carcinomas (BCCs) in the mucous membranes or tooth-bearing areas is not accepted by some investigators; thus, debate exists as to whether BCCs and PAs actually represent two distinct entities or the same lesion.[13] In spite of many histological similarities between PAs and BCCs, Reichart *et al.* and Sciubba have claimed that PAs deserved to be recognised as a separate entity.[9,14] In addition, Brierley *et al.* believed that while PAs may resemble BCCs histopathologically, a distinction was possible using immunohistochemical stains for BerEp4 and cytokeratin (CK) 19.[6]

CALCIFYING EPITHELIAL ODONTOGENIC TUMOUR

To date, the biochemical mechanism and the origin of amyloid material in calcifying epithelial odontogenic tumours (CEOTs) is still unknown. Immunohistochemical and electron microscope research has suggested a possible degenerative process involving CK intermediate filaments in tumour cells, while other investigators consider that the degeneration of type IV collagen associated with the basement membrane is responsible for amyloid derivation.[15] Murphy *et al.* determined through immunological and chemical analysis that amyloid associated with CEOTs is formed by the N-terminal fragments of a 153-residue protein coded by exons 5–10 of the odontogenic ameloblast-associated protein; this protein, along with green birefringent congophilic material, was detected in unerupted tooth follicles.[16]

KERATOCYSTIC ODONTOGENIC TUMOUR/ODONTOGENIC KERATOCYST

The renaming of odontogenic keratocysts (OKCs) as keratocystic odontogenic tumours (KCOTs) has been one of the most controversial changes in the nomenclature of odontogenic lesions in recent years.[17] This entity shows characteristics of both a cyst and a benign tumour and differs from other odontogenic cysts due to the appearance of mural growth with proliferation of the lining into the cancellous bone, instead of centripetal growth and expansion; thus, such lesions may reach a considerable size before the bony expansion becomes clinically apparent. Furthermore, the high recurrence rate suggests the aggressive

behaviour and inherent potential for growth of this lesion.[18] However, the association of KCOTs/OKCs with BCCs in nevoid BCC syndrome, along with the fact that a subset of OKCs have similar *patched homolog* (*PTCH*) gene mutations to those found in BCC cases, is suggestive of a neoplastic nature.[18] For this reason, in 2005 the WHO categorised OKC as a benign odontogenic neoplasm and changed the nomenclature of OKC to KCOT.[2] This classification was not fully accepted and many authors continued using the older terminology.[12,19,20]

Nevertheless, although *PTCH* gene alterations can be found in up to 85% of OKCs associated with nevoid BCC syndrome, they are only found in 30% of sporadic cysts.[21] In addition, such genetic alterations have been reported among several non-neoplastic lesions, including dentigerous and orthokeratinised odontogenic cysts, thus indicating that neoplasia cannot be defined on the basis of a single genetic event.[21] These molecular/genetic alterations may influence the biological behaviour of OKCs without the need to define the cyst as a neoplasm, particularly as the classification of a lesion as a cyst or tumour has a direct impact on its treatment.[21,22] For example, cystic lesions require more conservative management than neoplasms; as such, most KCOT/OKC cases are treated using marsupialisation and enucleation rather than surgical resection so as to reduce morbidity.[21] Even extensive KCOTs respond to marsupialisation and may resolve completely, with the characteristic neoplastic epithelial lining being replaced by epithelia similar to oral mucosa.[23] The resolution of such cysts following marsupialisation is not typical of neoplastic lesions.[21]

Pogrel found that initial decompression of a KCOT followed by aggressive curettage and peripheral ostectomy with methylene blue staining resulted in no recurrences of the lesion; however, the longest follow-up period in the study was only six years.[23] Similarly, Leung *et al.* concluded that enucleation of KCOTs along with the application of Carnoy's solution resulted in comparatively low rates of surgical morbidity and recurrence.[24] Hence, these lesions were reclassified as cystic lesions rather than odontogenic tumours in the 2017 WHO classification.[2,21] While both OKCs and orthokeratinised odontogenic cysts are considered developmental cysts, OKCs behave more aggressively.[20]

ADENOMATOID ODONTOGENIC TUMOUR

The true nature of adenomatoid odontogenic tumours (AOTs) has always been controversial, particularly as to whether these lesions should be considered hamartomatous growths, true benign neoplasms or cystic lesions. This may be due to difficulties regarding the precise definitions and overlapping features of hamartomas, cysts and cystic neoplasms.[25] An AOT is sometimes considered to be a hamartoma due to its limited size, occurrence at an early age (during the second decade of life) and lack of recurrence even following incomplete removal. However, the arrangement of odontogenic tissue within the lesional area is not in line with that of a developmental anomaly.[25] Researchers who consider AOTs to be non-aggressive non-invasive benign neoplasms claim that the limited size of most AOT cases is due to the fact that they are detected early and removed before reaching a clinically-noticeable size.[25]

In contrast, Marx *et al.* proposed that AOTs should not be considered tumours but cysts with a hamartomatous intraluminal proliferation of epithelial cells derived from the Hertwig epithelial root sheath.[12] However, Rick stated that AOTs were benign embryonal neoplasms; he disagreed with the change in terminology as the majority of lesions have a predominantly solid component instead of a fluid-filled cavity.[25] Similarly, Thakur *et al.* proposed that the term AOT was most apt for this entity.[26] A molecular study by Razavi *et al.* showed that the Ki-67 labelling index was lower in AOTs as compared to SMAs, signifying a hamartomatous nature.[27] However, using a *human androgen receptor* gene polymorphism assay, Gomes *et al.* found that AOTs are monoclonal and therefore neoplastic.[28]

SQUAMOUS ODONTOGENIC TUMOUR

The 2005 WHO classification defined squamous odontogenic tumours (SOTs) as locally infiltrative neoplasms;[5] however, Marx *et al.* considered them to be a hamartomatous proliferation of mature epithelial cells probably arising from the epithelial cell rests of Malassez.[12] The occurrence of multicentric SOTs may also be indicative of a hamartomatous nature, with Leider *et al.* reporting three cases of familial multicentric SOTs among siblings.[29]

Benign Mixed Epithelial and Mesenchymal Odontogenic Tumours

As the name implies, these tumours are composed of both epithelial and mesenchymal tissue.

ODONTOMA

Philipsen *et al.* suggested that complex and compound odontomas be regarded as two separate entities; this position is in contrast to that of Regezi *et al.*, who suggested that the classification of complex and compound odontomas should be combined

for therapeutic reasons.[30,31] Nonetheless, as these entities differ in their relative frequency, location and radiographical presentation, their separation as two distinct entities seems to be justified, regardless of the fact that both types of odontoma are treated conservatively.[9] Cases of odontomas have shown microscopic features of both types; however, clinical data and histological evaluations will, in most cases, lead to a diagnosis of either a complex or compound odontoma.[9] In general, however, there seems to be little clinical justification for differentiating these two entities.

AMELOBLASTIC FIBROMA

In agreement with the 1992 WHO classification, Philipsen *et al*. confirmed that ameloblastic fibromas (AFs)—in particular, those 22.3% developing after the age of 20 years—are true benign neoplasms.[30,32] Additionally, AFs which grow during the entire odontogenesis period of childhood and adolescence may represent non-neoplastic or hamartomatous lesions that develop into ameloblastic fibro-odontomas (AFOs) or odontomas. Both AFOs and odontomas go through stages of mineralisation and calcification; none of them arise *de novo* as calcified lesions.[9] On these grounds, Philipsen *et al*. proposed some hypothetical theories on the pathogenesis and relationship between mixed odontogenic tumours and odontomas and suggested that both a neoplastic and hamartomatous line of development should be considered to explain how mixed odontogenic tumours are formed.[30]

As the histopathological appearance of an AF in its neoplastic form is indistinguishable from that of a developing odontoma, Buchner *et al*. recommended the use of clinical and radiological features in distinguishing these lesions.[33] Large expansile multilocular lesions that exhibit extensive bone destruction and cortical perforation in young individuals are more likely to be of a neoplastic nature, while asymptomatic small unilocular lesions in children, when they lie directly over the crown of an unerupted tooth with no or minimal expansion of bone, are likely to be developing odontomas.[33] In the 2017 classification, the WHO ceased classifying ameloblastic fibrodentinomas and AFOs as separate entities, with only AFs considered a separate entity.[2]

PRIMORDIAL ODONTOGENIC TUMOUR

Mosqueda-Taylor *et al*. reported six cases of a previously undescribed odontogenic tumour that presented as well-circumscribed pericoronal radiolucencies with a dentigerous relationship.[34] Microscopically, the tumour was composed of immature loose fibrous connective tissue resembling dental *papillae* and the periphery was lined by columnar or cuboidal epithelia resembling the inner enamel epithelium of a developing tooth.[34] Due to the unique clinical, radiographical, histopathological and immunohistochemical presentation of primordial odontogenic tumours, this entity was included in the 2017 WHO classification.[2] However, Ide *et al*. questioned the exact nature of this tumour, particularly as to whether it was truly a newly recognised embryonal tumour of immature dental tissue exhibiting neoplastic characteristics of progressive growth or merely an architectural morphological variant of an AF or odontogenic fibroma (OF)/dentigerous myxoma arising during active dental development.[35] Future case reports may shed more light on this new lesion.

CALCIFYING CYSTIC ODONTOGENIC TUMOUR/CALCIFYING ODONTOGENIC CYST

Calcifying odontogenic cysts (COCs) were first identified as a specific type of odontogenic lesion by Gorlin *et al*.[36] However, controversy has since arisen regarding the association between non-neoplastic cystic lesions and solid tumour masses with similar cellular and histomorphological features. The 1971 WHO classification described COC tumours as a non-neoplastic cystic lesion, while the description was updated to state that "most lesions appear to be non-neoplastic" in the 1992 edition.[32,37] Reichart *et al*. theorised that the lesion had been wrongly classified as an epithelial-ectomesenchymal lesion because the *stroma* was not characterised by ectomesenchyme, but rather by mature collagenous connective tissue.[9]

The nature of the dentinoid material produced in COCs has not been fully clarified; however, its production is probably not the outcome of true induction via a sequence of reciprocal epithelial-ectomesenchymal interactions but rather as a result of the metaplastic process.[9] In 2005, the WHO grouped COCs with all of their variants as an odontogenic tumour rather than a cyst and defined it as a benign cystic neoplasm of odontogenic origin characterised by ameloblastoma-like epithelia with ghost cells that may calcify.[12] Dentinogenic ghost cell tumours were classified as a separate entity and defined as locally invasive neoplasms characterised by ameloblastoma-like islands of epithelial cells in mature connective tissue *stroma*.[5]

However, in a multicentre review of ghost cell lesions, Ledesma-Montes *et al*. found that over 85% of calcifying cystic odontogenic tumours were simple cysts occurring either alone (65%) or in association with odontomas (20%); only a few lesions showed ameloblastomatous proliferations, with merely 5%

of lesions found to be solid and described as true neoplastic dentinogenic ghost cell tumours.[38] Similar results were observed by Hong *et al*., who found that lesions which presented as simple cysts rarely recurred and had a completely benign course.[39] Martin *et al*. proposed that simple cystic lesions should be considered developmental cysts that may arise alone or in association with other developmental lesions, such as odontomas, whereas solid lesions showing ameloblastomatous proliferations should be regarded as neoplasms due to their high recurrence rates.[21] Subsequently, the WHO reclassified dentinogenic ghost cell tumours as odontogenic tumours in 2017, while excluding cystic lesions such as COCs.[2]

Benign Mesenchymal Odontogenic Tumours

These tumours are derived from mesenchymal tissue of dental origin, such as periodontal ligaments, dental *papillae* or dental follicles.[9]

ODONTOGENIC FIBROMA

Due to their rarity and uncertainty regarding distinct types, OFs are often considered to be controversial.[9] It is worth mentioning that the current widely accepted terms—simple type or WHO type/complex central OFs—were not used in either the first or second editions of the WHO classification; both terms were proposed by Gardner.[40] Doyle *et al*. further recommended the term complex OF as an alternative to WHO type OF.[41] In 2005, the WHO divided OFs according to two histological types of lesions: epithelium-poor (formerly termed simple type OFs) and epithelium-rich (formerly termed complex or WHO type OFs) lesions.[5] In 2017, the WHO abandoned the epithelium-poor subtype as it was poorly defined and documented, with OF instead described as "a rare neoplasm of mature fibrous connective tissue, with variable amounts of inactive-looking odontogenic epithelium with or without evidence of calcification".[4]

ODONTOGENIC MYXOMA

Considerable confusion exists regarding the pathogenesis of jaw myxomas and whether they are odontogenic (i.e. derived from odontogenic mesenchyme) or osteogenic (i.e. presumably derived from primitive bone tissue).[19] While myxomas do occur in the long bones, they are rare and are thought to arise from the pluripotent mesenchymal stem cells. The jaws also contain a small population of non-odontogenic pluripotent mesenchymal stem cells that may generate myxomas.[12,42] Although it is as yet unproven, jaw myxomas are thought to originate from the odontogenic rather than somatic mesenchyme.[12] On the other hand, myxomas have been reported in non-odontogenic sites, such as the sinonasal tract, facial bones, extracranial skeleton, upper *ramus* and the condyle of the mandible.[42] According to Johnson *et al*., true myxoid tissue is a specific fundamental primary tissue in humans and not merely an embryonic connective tissue as it performs many functions, is an essential component of the mucoperiosteum of the paranasal sinuses, cranial sutures and dental *papillae* and may also be responsible for the development of myxomas.[43] Subclassifying myxomas derived from the facial skeleton into odontogenic myxomas (OMs) and true osteogenic myxomas may therefore better reflect their histogenesis.[42]

The dental *papillae*, dental follicles and periodontal tissues have been implicated as possible germ centres of OMs.[1] However, OMs differ from dental *papillae* or dental follicle lesions due to differences in the amount and types of proteoglycan present. Hyaluronic acid concentrations in OMs have been found to be four times higher than other glycosaminoglycans, such as chondroitin sulphate.[1] This finding is contrary to those of mesenchymal tissues from dental pulp, the *gingivae* and the periodontal ligament.[1] Adekeye *et al*. suggested that the characteristic histopathology of this neoplasm could be due to myxoid changes within a pre-existing mesenchymatous lesion or that it may represent a degenerative form of OF.[44]

CEMENTOBLASTOMA

Cementoblastomas are considered the only true neoplasms of cemental (odontogenic) origin.[9] However, some researchers have pointed out that the histopathological features of jaw cementoblastomas are identical to those of osteoblastomas.[19] The only differentiating feature seems to be that a cementoblastoma is attached to the *apex* of a tooth and grows in an expansile pattern with radiating osteoid columns growing outwards.[18,19]

CEMENTO-OSSIFYING FIBROMA

In the 2005 WHO classification, ossifying fibromas were incorporated under bone-related lesions; however, the 2017 WHO classification included this entity under the category of mesenchymal odontogenic tumours instead.[2,5] This may be because their exclusive occurrence within the jaws and probable periodontal origin are suggestive of an odontogenic nature. Despite the fact that definitions of cementum include its anatomical association with tooth roots, Wright *et al*. proposed that cemento-ossifying fibroma was the best name for this entity because it is a well-understood term and laboratory

evidence indicates that periodontal ligament stem cells can produce both bone and cementum.[22] Morover, the term cemento-ossifying fibroma also emphasises that the lesion occurs exclusively within the tooth-bearing areas of the jaws. However, confusion may still arise when differentiating cemento-ossifying fibromas from ossifying fibromas of other bones.

Malignant Odontogenic Tumours

These lesions are extremely rare as the majority of odontogenic tumours are either completely benign or only locally aggressive.[22]

ODONTOGENIC CARCINOMA

In the 2017 WHO classification, carcinomas derived from the odontogenic epithelia have been categorised in a number of ways, including as ameloblastic carcinomas (ACs), primary intraosseous carcinomas, sclerosing odontogenic carcinomas, clear-cell odontogenic carcinomas (CCOCs) and odontogenic ghost cell carcinomas.[2] Metastasising ameloblastomas, which were previously considered to be malignant odontogenic neoplasms in the 2005 WHO classification, are now designated as benign odontogenic tumours (i.e. ameloblastomas).[2,5] The practice of subtyping carcinomas as ACs or primary intraosseous carcinomas has been abandoned as there seems to be no advantage to dividing these rare lesions.[4] However, some researches have highlighted the difficulty in differentiating these two entities because of their overlapping histopathological and clinical features.[22,45,46]

CLEAR CELL ODONTOGENIC CARCINOMA

The existence of a relationship between clear-cell ameloblastomas (CCAs) and CCOCs is an interesting proposition which has yet to be fully elucidated. Piattelli *et al.* were the first to postulate that CCOCs are a distinct and separate entity of ameloblastomas and not simply a clear cell variant, whereas Waldron *et al.* maintained that CCOCs and CCAs were part of the same histopathological spectrum.[47,48] Slater also regarded CCA to be a synonym for CCOC, although Reichart *et al.* believed that these lesions should be differentiated as two different entities based on their distinct demographic, clinical and histological features.[9,49] Future studies with large sample sizes may reveal whether these lesions should be viewed as separate entities or variants along a spectrum.

ODONTOGENIC GHOST CELL CARCINOMA

These lesions have been described in a variety of ways, including as malignant COCs, odontogenic ghost cell carcinomas, carcinomas arising in COCs, aggressive epithelial odontogenic ghost cell tumours, dentinogenic ghost cell ameloblastomas and malignant calcifying ghost cell odontogenic tumours.[9] Slater considered this entity to be a variant of an AC with evidence of ghost cell keratinisation.[49] However, the mere presence of ghost cells does not necessarily dictate the biological behaviour of a lesion; prognosis is determined by the tissue that surrounds the ghost cells. For example, a benign lesion containing ghost cells will exhibit benign biological behaviour, while a carcinoma containing ghost cells will behave malignantly.[49]

SCLEROSING ODONTOGENIC CARCINOMA

These tumours were not included in the 2005 WHO classification of odontogenic carcinomas and were first proposed as a distinct entity by Koutlas *et al.*[5,50] The characteristic histopathology includes infiltrating 'single file' thin cords and strands of polyhedral neoplastic cells within a *stroma* of dense sclerosis. Koutlas *et al.* described the tumour as having an odontogenic origin, as the immunohistochemical profile of the tumour cells exhibited positive CK markers (CK5/6, CK19 and weak CK7 stains).[50] Despite its bland cytological features, the tumour exhibits extensive local infiltrative growth into the muscles and nerves.[51] This newer entity has been included in the 2017 WHO classification; however, metastasis has not been reported in any of the seven cases described to date.[2,51] Hence, further study of its biological behaviour is required to confirm its placement within the category of odontogenic carcinomas.

ODONTOGENIC SARCOMA

The 2005 WHO classification made a distinction between odontogenic sarcomas with (i.e. amelo-blastic fibrodentinosarcomas and ameloblastic odontosarcomas) and without (i.e. ameloblastic fibrosarcomas) formation of dental hard structures, which is useful when making a histopathological diagnosis.[5] However, this concept has been questioned as the biological profile and prognosis of ameloblastic fibrodentinosarcomas, ameloblastic odontosarcomas and ameloblastic fibrosarcomas appear to be identical.[52] In the 2017 WHO classification, only odontogenic sarcomas were mentioned, thereby simplifying this category.[2]

ODONTOGENIC CARCINOSARCOMA

This entity was excluded from the 2005 WHO classification as evidence supporting its inclusion was questionable; however, recent research has reconfirmed its existence and it was once again incorporated in the 2017 WHO classification.[4,5,53–55]

Conclusion

There are a number of controversies currently under debate within the field of odontogenic tumours, particularly regarding their nomenclature, incidence, pathogenesis and histopathological characteristics. It is hoped that the elucidation of key controversies and recent concepts regarding odontogenic tumours presented in this article may help to enhance the understanding, diagnosis and treatment of these unique lesions.

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