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Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Odontogenic and Maxillofacial Bone Tumours

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Abstract

The 5th edition of the World Health Organization (WHO) Classification of Head and Neck Tumours (2022) comes out only five years after the previous edition, however it presents important updates that run in parallel with the rapid progression involving the increasingly sophisticated molecular investigation and its interpretation, some of which already have therapy-related impact. This manuscript provides an overview of the leading changes introduced in the classification of Odontogenic and Maxillofacial Bone Tumours that encompasses cysts of the jaws, odontogenic tumours, giant cell lesions and bone cysts, and bone and cartilage tumours. This is the first edition that Essential and Desirable Diagnostic Features were added for each entity, so that the most important clinical, microscopic and/or radiologic features were encapsulated and briefly highlighted. Surgical ciliated cyst was added to the group of odontogenic cysts, adenoid ameloblastoma was a newly recognized benign epithelial odontogenic tumour, and segmental odontomaxillary dysplasia was introduced in the group of fibro-osseous tumours and dysplasia. In addition, rhabdomyosarcoma with *TFCP2* rearrangement, was introduced into the group of malignant jawbone tumours. The unique genetic aberrations distinguish it from other types of rhabdomyosarcomas. On the other hand, melanotic neuroectodermal tumour of infancy and osteoid osteoma were deleted from the benign bone and cartilageneous tumours, as was the hematolymphoid tumour of solitary plasmacytoma of bone. We systematically reviewed each entity in this chapter and provided important updated findings for selected topics that can further aid in the diagnostic process for challenging cases, broaden insights on the logic of the present classification, and finally, emphasize the potential that some of the molecular results may have in the near future to set new treatment approaches.

Keywords Update · WHO Classification · Odontogenic cysts · Odontogenic tumours · Bone and cartilage tumours · Surgical ciliated cyst · Adenoid ameloblastoma · Segmental odontomaxillary dysplasia · Rhabdomyosarcoma with *TFCP2* rearrangement

Introduction

The 2022 World Health Organization (WHO) Classification of Odontogenic and Maxillofacial Bone Tumours (5th edition) [1] comes out only five years after its predecessor (4th edition, 2017) [2], while it took over a decade to update the edition published at the beginning of the twenty-first century (3rd edition, 2005) [3]. It is the fast pace of advanced and progressively changing molecular technology and its potential clinical relevance that was a major impetus for the WHO to reduce the time interval between new editions. Some of the ensuing novel molecular findings may have clinical application and can set the stage to the beginning of a new

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era of treatment approaches, different from the hitherto commonly accepted modalities.

There is little conceptually different between the new and latest editions but the new edition contains significant reorganization. There seems to be an effort to provide consensus definitions and more clearly articulated diagnostic features. In addition to the standard description of microscopic findings, every lesion contains Essential as well as Desirable Diagnostic Features. Despite the plethora of new molecular findings, only one new entity is defined in the 2022 edition by its molecular findings, namely a new rhabdomyosarcoma of bone with *TFCP2* rearrangement and a predilection for the jaws [1]. While the molecular findings in odontogenic cysts and tumours play a significant role in pathogenesis, at least for now, none are defining characteristics. Other notable changes included the addition of surgical ciliated odontogenic cyst, introducing a newly recognized benign epithelial odontogenic tumour – adenoid ameloblastoma, and adding segmental odontomaxillary dysplasia to the fibro-osseous tumours and dysplasia group of lesions. On the other hand, melanotic neurectodermal tumour of infancy and osteoid osteoma were deleted from the benign bone and cartilaginous tumours as was also the hematolymphoid tumour of solitary plasmacytoma of bone.

The following paragraphs highlight the main changes introduced in selected entities in the 2022 WHO classification of Odontogenic and Maxillofacial Bone Tumours. Table 1 presents odontogenic and maxillofacial bone tumours 2022 edition versus 2017.

Cysts of the Jaws

The post-surgical ciliated cyst, while not new, is new to the classification [1]. It is a rare cyst caused by the traumatic implantation of respiratory epithelium into the gnathic bones, most commonly diagnosed in the 5^{th}-6^{th} decades. It is entrapment of maxillary sinus or nasal mucosae that serves as the origin for the cysts and constitute the microscopic hallmark finding. The relatively few mandibular cases are assumedly caused during autologous nasal osteocartilagenous grafts for genioplasty or examples of other simultaneous maxillary and mandibular orthognathic surgical procedures [4] (Fig. 1). There is usually a long interval of up to 20 years between the causal surgery until diagnosis, although a considerable shorter interval has been reported in association with sinus floor augmentation prior to dental implant placement [5]. Cysts are usually asymptomatic; radiographically, they usually present as well-defined unilocular radiolucencies. Treatment consists of enucleation with no expected recurrence.

Definition of calcifying odontogenic cyst (COC) has been changed so that it currently refers only to the presence of characteristic ghost cells that may undergo calcification, while the ameloblastoma-like lining epithelium is a desirable diagnostic feature. In addition, those odontoma-associated COCs are no longer separated from the rest of COCs, despite the fact that they are separated by others, as 24% of COCs occur with odontomas and 3.5% with other odontogenic tumours [6]. The pathogenesis of COC has been linked to the identification of mutations in *CTNNB1* gene (Wnt molecular pathway) that encodes the beta-catenin protein product [7]. The *CTNNB1*/Wnt aberrations are shared with other head and neck, ghost cell-containing tumours, both non-odontogenic (i.e., adamantinomatous craniopharyngioma and pilomatrixoma) and odontogenic (dentinogenic ghost cell tumour, ghost cell odontogenic carcinoma and odontogenic carcinoma with dentinoid, the last not being included in the 2022 classification) [7, 8].

Glandular odontogenic cyst (GOC) is defined by epithelial lining that resembles glandular tissue [1]. In the 2017 edition, ten specific histopathological criteria were listed, with the concept that the fulfillment of seven of them could strongly support a diagnosis of GOC [2]. Two of these criteria were then considered to be present in all lesions, namely the thickness of the epithelium and the luminal layer of hobnail cells, present at least focally. In the 2022 classification, all histological features are characteristic but none are essential. Hob-nail cells are the only parameter considered to be the most characteristic finding of all GOCs, others being present with less consistency, therefore there is no reference to a specific number of criteria to support a diagnosis of GOC [1]. There is a certain extent of microscopic similarity and overlap between GOC and some central mucoepidermoid carcinomas (CMEC). *MAML2* gene rearrangements, once thought to be exclusively present in CMEC, have recently been reported also in one aggressive lesion that fulfilled the diagnosis of GOC [9]. As the knowledge is very limited so far, we only can hypothetically raise the possibility of a transition occurring in aggressive GOC to CMEC if *MAML2* rearrangements are identified. Clinical considerations and treatment decisions based on *MAML2* should be taken with caution.

Odontogenic keratocyst (OKC) maintains its status as a cyst in both 2017 and 2022 classifications [1, 2]. The most frequent genetic modification associated with OKC pathogenesis occurs in the *PTCH1* gene (Sonic Hedgehog (SHH) signaling pathway) and this has been identified in up to 93% of sporadic cases [10]. Interestingly, activating mutation in the *BRAF* p.V600E gene, mainly related to ameloblastoma, but not expression of its mutated protein product, has been reported in OKC [11, 12]. The molecular findings may open non-surgical, pharmaceutical options for treatment of OKCs, mainly large, destructive cysts, both sporadic and syndromic. Research is now focusing on small molecule selective inhibitors for SHH-related targets [13]. In addition, involvement

Table 1 WHO Classification of Odontogenic and maxillofacial bone tumours, 2022 versus 2017. Main headings are arranged in the order of the 2022 classification; within sub-headings, lesions are presented in the original order of each classification

2022 Classification	2017 Classification*	
Cysts of the jaws	Odontogenic cysts of inflammatory origin	Odontogenic & non-odontogenic developmental cysts
Radicular cyst	Radicular cyst	Dentigerous cyst
Inflammatory collateral cysts	Inflammatory collateral cysts	Odontogenic keratocyst
Post-surgical ciliated cyst		Lat. periodontal cyst and botryoid cyst
Nasopalatine duct cyst		Gingival cyst
Gingival cyst		Glandular odontogenic cyst
Dentigerous cyst		Calcifying odontogenic cyst
Orthokeratinized odontogenic cyst		Orthokeratinized odontogenic cyst
Lat. periodontal cyst and botryoid cyst		Nasopalatine duct cyst
Calcifying odontogenic cyst		
Glandular odontogenic cyst		
Odontogenic keratocyst		
Odontogenic Tumours	Odontogenic Tumours	
Benign epithelial odontogenic tumours	Benign epithelial odontogenic tumours	
Adenomatoid odontogenic tumour	Ameloblastoma	
Squamous odontogenic tumour	-Ameloblastoma, unicystic type	
Calcifying epithelial odontogenic tumour	-Ameloblastoma, extraosseous/peripheral type	
Ameloblastoma, extraosseous/peripheral	-Metastasizing ameloblastoma	
Ameloblastoma, unicystic	Squamous odontogenic tumour	
Ameloblastoma, conventional	Calcifying epithelial odontogenic tumour	
Adenoid ameloblastoma	Adenomatoid odontogenic tumour	
Metastasizing ameloblastoma		
Benign mixed epithelial and mesenchymal odontogenic tumours	Benign mixed epithelial and mesenchymal odontogenic tumours	
Odontoma	Ameloblastic fibroma	
Primordial odontogenic tumour	Primordial odontogenic tumour	
Ameloblastic fibroma	Odontoma	
Dentinogenic ghost tumour	-Odontoma, compound type	
	-Odontoma, complex type	
	Dentinogenic ghost tumour	
Benign mesenchymal odontogenic tumours	Benign mesenchymal odontogenic tumours	
Odontogenic fibroma	Odontogenic fibroma	
Cementoblastoma	Odontogenic myxoma/myxofibroma	
Cemento-ossifying fibroma	Cementoblastoma	
Odontogenic myxoma	Cemento-ossifying fibroma (discussed under the heading of Fibro-osseous and osteo-chondromatous lesions)	
Malignant odontogenic tumours	Malignant odontogenic tumours	
Sclerosing odontogenic carcinoma	Odontogenic carcinomas	
Ameloblastic carcinoma	- Ameloblastic carcinoma	
Clear cell odontogenic carcinoma	- Primary intraosseous carcinoma, NOS	
Ghost cell odontogenic carcinoma	- Sclerosing odontogenic carcinoma	
Primary intraosseous carcinoma, NOS	-Clear cell odontogenic carcinoma	
Odontogenic carcinosarcoma	-Ghost cell odontogenic carcinoma	
Odontogenic sarcomas	Odontogenic carcinosarcoma	
	Odontogenic sarcomas	
Giant cell lesions and bone cysts	Giant cell lesions and bone cysts	
Central giant cell granuloma	Central giant cell granuloma	
Peripheral giant cell granuloma	Peripheral giant cell granuloma	

Table 1 (continued)

2022 Classification	2017 Classification*	
Cysts of the jaws	Odontogenic cysts of inflammatory origin	Odontogenic & non-odontogenic developmental cysts
Cherubism	Cherubism	
Aneurysmal bone cyst	Aneurysmal bone cyst	
Simple bone cyst	Simple bone cyst	
Bone and cartilage tumours	Fibro-osseous and osteochondromatous lesions	
Fibro-osseous tumours and dysplasias		
Cemento-ossifying dysplasia	Ossifying fibroma	
Segmental odontomaxillary dysplasia	Familial gigantiform cementoma	
Fibrous dysplasia	Fibrous dysplasia	
Juvenile trabecular ossifying fibroma	Cemento-ossifying dysplasia	
Psammomatoid ossifying fibroma	Osteochondroma	
Familial gigantiform cementoma		
Benign maxillofacial bone and cartilage tumours	Benign maxillofacial bone and cartilage tumours	
Osteoma	Chondroma	
Osteochondroma	Osteoma	
Osteoblastoma	Melanotic neuroectodermal tumour of infancy	
Chondroblastoma	Chondroblastoma	
Chondromyxoid fibroma	Chondromyxoid fibroma	
Desmoplastic fibroma of bone	Osteoid osteoma	
	Osteoblastoma	
	Desmoplastic fibroma	
Malignant maxillofacial bone and cartilage tumours	Malignant maxillofacial bone and cartilage tumours	
Osteosarcoma of the jaw	Chondrosarcoma	
Chondrosarcoma family	-Chondrosarcoma, grade 1	
Mesenchymal chondrosarcoma	-Chondrosarcoma, grade 2/3	
Rhabdomyosarcoma with TFCP2 rearrangement	Mesenchymal chondrosarcoma	
	Osteosarcoma, NOS	
	-Low-grade central osteosarcoma	
	-Chondroblastic osteosarcoma	
	-Parosteal osteosarcoma	
	-Periosteal osteosarcoma	
	Haematolymphoid tumours	
	Solitary plasmacytoma of bone	

*Original order of the main classes of lesions: Odontogenic carcinomas; Odontogenic carcinosarcoma; Odontogenic sarcomas; Benign epithelial odontogenic tumours; Benign mixed epithelial and mesenchymal odontogenic tumours; Benign mesenchymal odontogenic tumours; Odontogenic cysts of inflammatory origin; Odontogenic and non-odontogenic developmental cysts; Malignant maxillofacial bone and cartilage tumours; Benign maxillofacial bone and cartilage tumours; Fibro-osseous and osteochondromatous lesions; Giant cell lesions and bone cysts; Haematolymphoid tumours

of components from the connective tissue, i.e., fibroblasts [14], are also under investigation for the future development of possible therapeutic targets.

Odontogenic Tumours – Benign (Fig. 2)

Most (~ 70%) of sporadic adenomatoid odontogenic tumours (AOT) have been identified to carry mutations in *KRAS* gene (mitogen activating protein kinase, MAPK, pathway; p.G12V and p.G12R loci), but they have not been connected to their clinico-pathological features [15]. Multiple AOTs may be encountered in patients with neurocutaneous Schimmelpenning syndrome, which is caused by postzygotic mutations in the *RAS* gene (MAPK pathway) and is characterized by presence of nevus sebaceus, ophthalmic, neurologic, skeletal, urologic, and cardiovascular alterations. In addition to AOTs, other oral manifestations include dental defects,

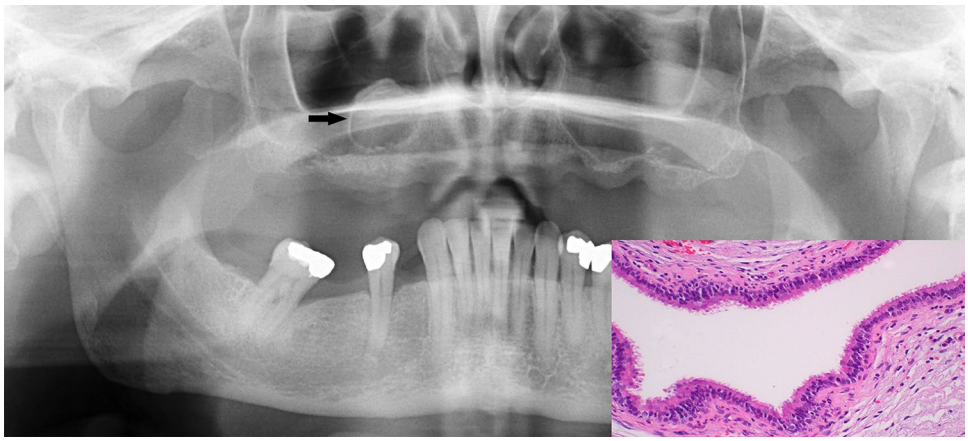

Fig. 1 Surgical ciliated cyst of the edentulous R maxilla (arrow) following sinus surgery, showing a unilocular, radiolucent, well-demarcated and corticated lesion located on the anterior floor of the maxillary sinus. Inset shows cyst lining entirely composed of upper respiratory epithelium. Courtesy of Dr. Maria A. Copete, MSc, DDS, Professor, College of Dentistry, University of Saskatchewan, Canada

	Radiolucent	Mixed Radiolucent-Radio-opaque	Radio-opaque
1st – 2nd decades	POT mand AF mand-post UAM 1st peak; mand-post OdM mand-post AOT max-ant		Cementoblastoma mand-post Odontoma cx-mand-post; cd-max-ant
3rd – 4th decades	SOT max-ant, mand-post UAM 2nd peak; mand-post MetAM mand OdF max-ant; mand-post COsF mand-post AdAM no site predilection CEOT mand-post AM mand-post DGCT mand/max-post		
5th – 6th decades			

Fig. 2 Distribution of benign odontogenic tumours according to tissue of origin (epithelial, mixed epithelial and mesenchymal, mesenchymal), radiological appearance, peak age decade/s and frequent location. AdAM: adenomatoid ameloblastoma; AF: ameloblastic fibroma; AM: ameloblastoma; AOT: adenomatoid odontogenic tumour; CEOT: calcifying epithelial odontogenic tumour; COsF: cemento-ossifying fibroma; DGCT: dentinogenic ghost cell tumour; MetAM: metastasizing ameloblastoma; OdF: odontogenic fibroma; OdM: odontogenic myxoma; POT: primordial odontogenic tumour; SOT: squamous odontogenic tumour; UAM: unicystic ameloblastoma; mand-post: mandible posterior; max-ant: maxilla anterior; cx: complex odontoma; cd: compound odontoma

papillary lesions in the oral mucosa and giant cell lesions of the jaws [16].

Calcifying epithelial odontogenic tumour (CEOT) is now recognized to have three histopathological subtypes: clear cell, cystic/microcystic and non-calcified/Langerhans cell rich [1]. The latter is still disputed for the possibility of its being better classified as the amyloid sub-type of odontogenic fibroma, given that it shares microscopic and clinical properties more in common with odontogenic fibroma than with CEOT [17]. Areas with CEOT-like features may be seen in AOT and the diagnosis of these cases should be AOT. Mutations in tumour suppressor genes (*PTEN*, *CDKN2A*, *PTCH1*), oncogenes (*JAK3*, *MET*) have been identified in CEOT, however so far, these do not contribute to clinical properties or treatment decisions.

After being omitted in the 2017 edition as a descriptive term of ameloblastoma (AM) [2], the term "conventional" was re-introduced in the upcoming edition [1]. In the 2017 classification, the possibility of moving unicystic ameloblastoma (UAM) mural sub-type to conventional AM was raised, based on the need for aggressive surgical treatment for both tumours [2]. In the 2022 classification, UAM mural sub-type has been retained within UAMs [1]. As both conventional AM and UAM have been found to harbor *BRAF*p.V600E

mutations [18], aggressive and destructive tumours could be candidates for BRAF-targeted therapy that has the potential to reduce tumour size and ultimately enable a conservative surgical procedure [19]. Preliminary data of biological treatment show effectiveness in selected cases [20].

Adenoid ameloblastoma (AdAM) is a newly recognized entity separate from the AM group of tumours, defined as an epithelial neoplasm characterized by cribriform architecture and duct-like structures, with dentinoid being often present [1]. There are about 40 published cases, with a peak incidence in the 4th decade (age range 25-52y), a slight female predilection and demographically similar to conventional AM [21, 22]. It has a propensity for the mandible (64.7%) and usually manifests clinically as a painless swelling, occasionally with pain and paresthesia [21]. Radiologically, most (~82%) tumours present as radiolucencies with occasional radio-opaque foci with ill-defined margins and cortical perforation at time of diagnosis. The essential histopathological features of AdAM consist of an ameloblatoma-like component, duct-like structures, whorled cellular condensations reminiscent of morules and cribriform architecture (Fig. 3). About two-thirds of tumours contain varying amounts of dentinoid. There are overlapping microscopic features with AOT and dentinogenic ghost cell tumour (DGCT), but the combination of the essential features of AdAM are expected to distinguish it from these other entities. There is also considerable overlap between AdAM and odontogenic carcinoma with dentinoid, with limited current criteria to separate them [22]. Positively stained nuclear beta catenin colocalizes with the epithelial morules. Ki-67 proliferation marker is usually high. AdAM is characterized by an aggressive biological behavior with local infiltration and a recurrence rate that ranges between 45.5% [21] and 70% [22]. *BRAF*p.V600E mutations, usually identified in AM/UAM, are absent in AdAM. Whether AdAM is a unique standalone tumour or a histologic variant of AM will require further investigation.

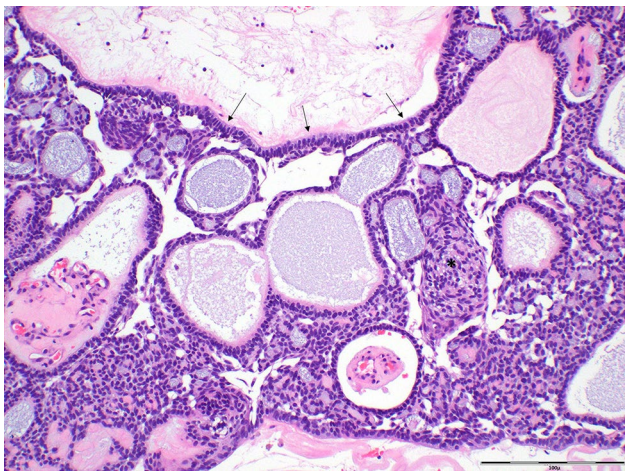

Fig. 3 Photomicrograph of a case of adenoid ameloblastoma highlighting the major histopathological features: cribriform architecture, ameloblastoma-like component (including basal palisading and reverse polarity) (arrows), duct-like structures and whorled cellular condensations reminiscent of morules (asterisk) (hematoxylin and eosin; scale bar 100μ)

Metastasizing AM is being currently considered in the AM group of benign epithelial tumours [1], similar to the 2017 classification [2]. In contrary, in the 2005 classification, it was regarded as a malignant odontogenic tumour [3]. Moving a neoplasm that metastasizes and has a 30% mortality rate into the benign category was and continues to be controversial [23, 24].

Odontomas are now considered as hamartomas and are currently the second most commonly accessioned odontogenic lesion after ameloblastoma, although their real frequency is probably higher as many of them are unreported [25]. WNT/beta-catenin pathway activation in embryonic SOX-2 positive dental stem cells can drive odontoma formation [26]. Developing odontomas may be comprised of soft tissue closely resembling dental papilla with prominent epithelial strands and limited or no evidence of dental hard tissue induction. These features overlap with ameloblastic fibroma (AF), sometimes causing a problem differentiating between them. Lesions previously diagnosed as ameloblastic fibro-dentinoma (AFD) and ameloblastic fibro-odontoma (AFO) have a soft tissue component that resembles AF, and a component of dental hard tissue matrix, which resembles but is less prominent and less well organized than odontoma. The status of AFD and AFO has been debated as they appear to be intermediate between AF and odontoma. Currently, AFD and AFO are classified as developing odontomas although presence of *BRAF* p.V600E mutations in AFD and AFO is similar to AF, but differs from odontoma, which lacks *BRAF* p.V600E mutations [27]. In addition, several AFO/AFD cases with locally aggressive biological behavior, large size and recurrence may better fit a neoplastic type of lesion rather than an odontoma/hamartoma, but these represent a minority overall of lesions diagnosed as AFD or AFO. Further molecular study is expected to clarify whether AFD and AFO are separate entities, intermediate lesions with a spectrum of behavior that ultimately result in formation of odontoma, or are a mixture of developing odontoma and AF.

Cemento-ossifying fibroma (COsF), which has already been defined as a benign mesenchymal odontogenic tumour in the 2017 classification, but was then detailed under the heading of Fibro-osseous and osteochondromatous lesions [2], has become an integral part of the benign mesenchymal odontogenic tumours in the 2022 classification [1] and is completely separated from the non-odontogenic juvenile trabecular and psammomatoid types. Pathogenesis of COsF in a minority of tumours is linked to inactivating mutations in the tumour suppressor gene *CDC73* (*HRPT2*), usually in

those cases that are part of hyperparathyroidism-jaw tumour syndrome [28]. COsF can also be part of gnathodiaphyseal dysplasia, which is characterized by *GDD1* gene mutations [27]. The microscopic features of sporadic and syndrome-related COsF are essentially the same, with a certain range of diversity between the fibrous and calcified components [29]. It should be emphasized that the peripheral ossifying fibroma should not be regarded as the peripheral counterpart of COsF, but rather a reactive gingival hyperplasia with mineralization [30].

Odontogenic myxoma with a greater amount of collagen was termed myxofibroma in the 2017 classification [2], while in the 2022 edition it is termed fibromyxoma [1]. Activating mutations in the MAPK/ERK signaling pathway have been identified in this tumour and as such, may serve as targets for pharmacologic therapy [31]. The microscopic differential diagnosis for odontogenic myxoma includes normal dental papilla, hyperplastic dental follicle, myxoid neurofibroma, chondromyxoid fibroma, odontogenic fibroma and low-grade fibromyxoid sarcoma, especially in the context of fibromyxoma [32].

Odontogenic Tumours—Malignant

Ameloblastic carcinoma (AMCa) is defined in the 2022 WHO as a primary odontogenic carcinoma histologically resembling AM [1] and not as the malignant counterpart of AM, as it has been in the 2017 classification [2]. AMCa, although rare, constitutes 30% of the malignant odontogenic tumours [1]. Most of them occur de novo, but some might arise in pre-existing longstanding, untreated or recurrent AM. Microscopically, AMCa essentially resembles AM with variable features of malignancy, however the threshold for diagnosis is still poorly defined. AMCa should show at least moderate cellular or nuclear atypia, nuclear hyperchromatism, increased mitotic activity, crowding of basal cells with their expansion into the other epithelial layers; central necrosis, if present, can support the diagnosis. The 5-year survival after complete surgical removal is ~ 70%, irrespective of the microscopic findings or presence of a pre-existing AM; local recurrence is ~ 40%, distant metastases (mainly lungs) have been found in ~ 33% of cases, far higher than in regional cervical lymph nodes (~ 13%), with novel treatment modalities being pursued [33]. The differential diagnosis includes entities in keeping with the predominant microscopic findings in AMCa, so that tumours with predominant presence of basaloid cells should be differentiated from tumours such as basal cell AM, basaloid squamous cell carcinoma and adamantinoma-like Ewing tumour [34]; true spindle cell AMCa should be distinguished from spindle cell/sarcomatoid squamous cell carcinoma, and tumours with clear cells should be differentiated from clear cell odontogenic carcinoma (COdC).

COdC is characterized by *EWSR1* gene rearrangement in about 80% of cases [reviewed in 35]. Recurrence rate is as high as 40%, regional lymph node metastases are more common than distant ones and death rate is about 11% [35]. Differential diagnosis includes jawbone clear cell-containing tumours, such as CEOT, amyloid-rich odontogenic fibroma, odontogenic carcinoma with dentinoid, primary or metastatic tumours of salivary glands (e.g., mucoepidermoid carcinoma, clear cell carcinoma, epithelial myoepithelial carcinoma), and metastatic tumours (i.e., renal cell carcinoma, melanoma).

Giant Cell Lesions and Bone Cysts (Fig. 4)

Central giant cell granuloma (CGCG) is now defined as a lesion comprised of osteoclasts [1], while in the 2017 classification these were termed osteoclast-type giant cells [2]. It is now believed that the mononuclear stroma harbors osteoclast precursors that mature and differentiate into osteoclasts following different molecular inductions. In about 70% of sporadic CGCGs, mutually exclusive somatic mutations in *KRAS*, *FGFR1* and *TRPV4* genes were identified that all lead to the activation of the MAPK signaling pathway [36]. Interestingly, the *TRPV4* gene encodes for a calcium channel that was found to be mutated in hereditary channelopathies, which are characterized by peripheral nervous system and skeletal changes. Recently, CGCG-like lesions have been described as part of a syndrome caused by germline *TRPV4* mutation [37], further enhancing the apparent *TRPV4* gene mutations-calcium channels-CGCG interconnections. *H3F3A* mutation characteristic of giant cell tumours of long bones, has not been identified in CGCG [36]. Multiple giant cell lesions that microscopically are indistinguishable from CGCG, occur in several syndromes, most of which are known to be caused by mutations in the MAPK pathway [38]. Peripheral giant cell granuloma (PGCG), a reactive gingival/alveolar lesion, is now also defined as osteoclast-containing [1], and not as osteoclast-type giant cell-containing, as was in the 2017 classification [2]. Like in CGCG, about 70% of cases of PGCG harbor mutations in the *KRAS* gene, including those lesions associated with dental implants [36].

In spite of the ongoing use of the term aneurysmal bone cyst (ABC), it should be emphasized that this lesion has been recognized as a neoplasm already in the 2017 classification [2]. The leading genetic aberration identified in about 70% of ABCs is the *USP6—CDH11* fusion [39]. ABC-like cystic haemorrhagic areas may be part of the microscopic features in various lesions but these do not show the genetic mutations characteristic of true ABCs (Fig. 4).

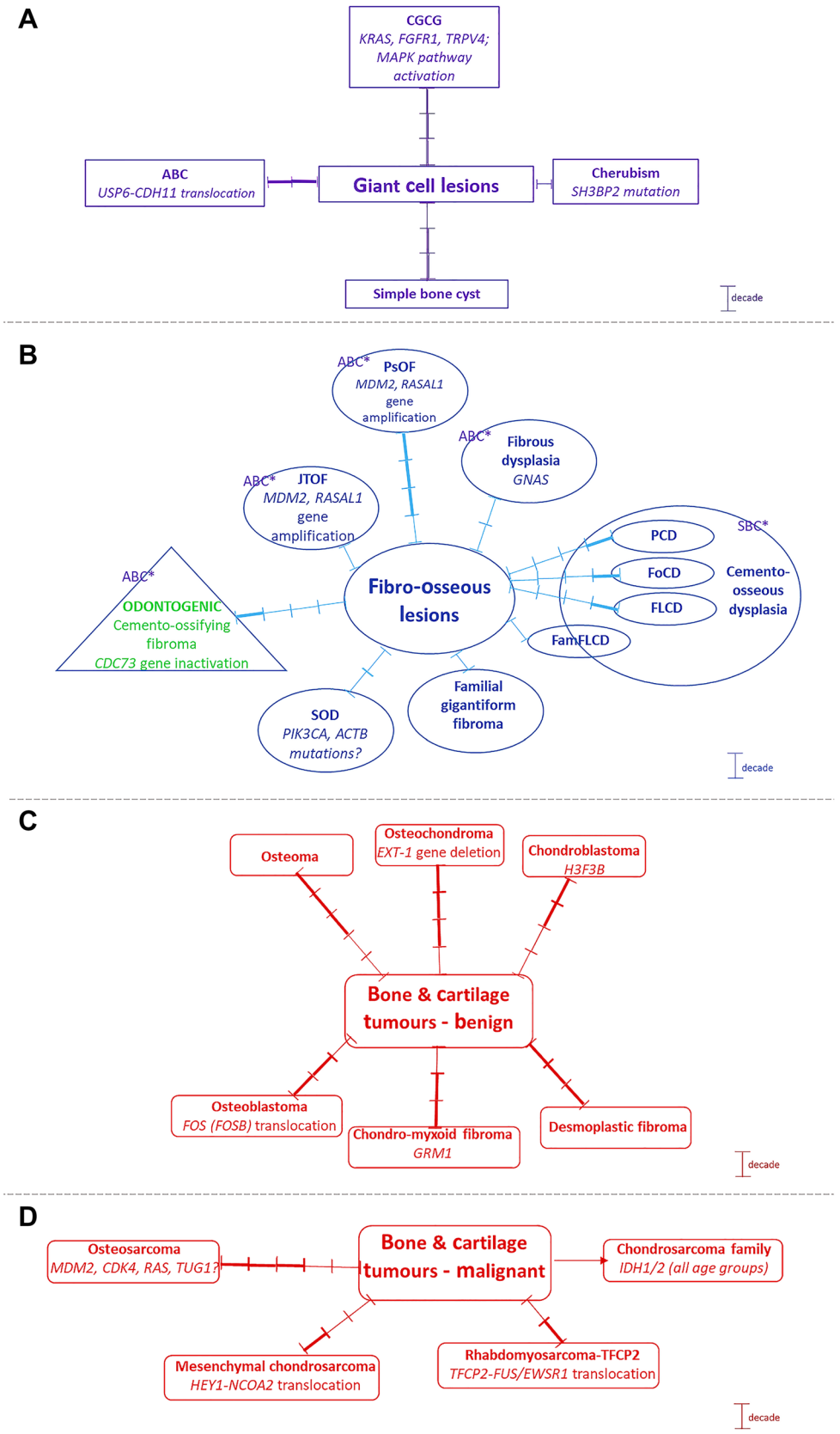

Fig. 4 Giant cell lesions, Fibro-osseous lesions and bone and cartilage benign and malignant maxillofacial lesions with emphasis on peak age decade/s (each scale bar = 1 decade; thick scale/s = peak frequency) and leading genetic aberrations. ABC: aneurysmal bone cyst; ABC*: secondary aneurysmal bone cyst; CGCG: central giant cell granuloma; JTOF: juvenile trabecular ossifying fibroma; FoCD: focal cemento-ossifying dysplasia; FamFLCD: familial florid cemento-osseous dysplasia; FLCD: florid cemento-osseous dysplasia; PSOF: psammomatoid ossifying fibroma; PCD: periapical cemento-ossifying dysplasia; SBC*: secondary simple bone cyst; SOD: segmental odontomaxillary dysplasia

Bone and Cartilage Tumours—Fibro-Osseous Tumours and Dysplasias (Fig. 4)

Cemento-osseous dysplasia, the most common benign fibro-osseous lesion of the jawbones, has three well established sub-types, defined according to anatomical location and extent of jawbone involvement: periapical, focal and florid; the familial florid cemento-osseous dysplasia (FFCOD) is the 4th sub-type introduced in the 2022 classification [1]. FFCOD onset is earlier than florid, often affects tooth eruption and is usually prone to cause considerable jawbone expansion. Genetic analysis revealed only one family with FFCOD mutations in the *ANO5* gene. FFCOD raises a challenging differential diagnosis with familial gigantiform cementoma and syndromes characterized by benign fibro-osseous lesions, such as hyperparathyroidism jaw tumour syndrome and gnathodiaphyseal dysplasia [40]. Currently, we still rely on clinical and radiological features to distinguish familial gigantiform cementoma, which presents with diffuse expansion in multiple quadrants early in the disease process resulting in marked facial disfigurement, from FFCOD, which presents with typical florid cemento-osseous dysplasia lesions that may exhibit localized areas of expansion [40].

The 2022 classification has added Segmental odontomaxillary dysplasia (SOD) within the group of fibro-osseous lesions [1]. This is defined as a non-hereditary, unilateral developmental disorder characterized by segmental maxillary and soft tissue enlargement with dento-osseous abnormalities and occasional homolateral, usually subtle, cutaneous manifestations [1]. This rare condition is slightly more frequent in males, with no precise etiologic factor and suspected mutations in *PIK3CA* or *ACTB* genes [41]. SOD is asymptomatic with onset in 1st-2nd decades that usually halts around puberty. Imaging highlights the coarse bony trabeculation and dentition-related changes. Surgical treatment is considered for esthetic or functional purposes.

Unlike the 2017 classification, juvenile trabecular ossifying fibroma (JTOF) and psammomatoid ossifying fibroma (PsOF), are currently separated from the odontogenic COsF and are individually discussed as benign fibro-osseous lesions [1]. Of interest, the term juvenile was included in the name of both variants in the 2017 edition [2]. Neither variant exclusively affects juveniles, but both do have a strong predilection for the 1st-2nd decades, although the trabecular variant more so than the psammomatoid variant. Accordingly, juvenile was dropped from the psammomatoid terminology in 2022 [1]. JTOF essential features consist of onset in childhood (mean age 11.3 years), rapid expansion, well-demarcation on imaging and hypercellular stroma with prominent anastomosing osteoid trabeculae [reviewed in 42]. The pathogenesis is assumed to be associated with *MDM2* and *RASAL1* gene amplifications [43]. JTOF consists of unique aggregates of curvilinear strands of edema, haemorrhage, osteoclasts and pseudocystic degeneration, which are also seen in macroscopic specimens [42]. A recurrence rate of ~ 20% was reported [42]; due to the young age of patients, disfiguring surgical procedures should be avoided. PsOF is defined as a benign fibro-osseous neoplasm of the craniofacial skeleton characterized by spherical ossicles histologically with a peak incidence in the 2nd – 4th decades [42]. Molecular studies are similar to JTOF [43]. Histopathologically, the tumours show hypercellular spindle cell stroma in which multiple, spherical, relatively uniform ossicles are generated. These are called "psammoma" bodies, better termed as ossicles, differ from classical psammoma bodies as they are considerable larger, not sharply defined and lack lamellar pattern. Recurrence rate is 30%-56% following surgical excision [44].

Bone and Cartilage Tumours—Benign Maxillofacial Bone and Cartilage Tumours (Fig. 4)

Osteoblastoma, either intra-osseous or periosteal, occurs most commonly in the 2nd-3rd decades and have a slight female preponderance [45]. Gene rearrangement in *FOS* or less frequent in *FOSB* genes, are encountered and are also shared by osteoid osteoma (deleted from the 2022 classification) and cementoblastoma, possibly inferring a common pathogenesis in these entities.

Chondroblastoma in the head and neck region is located around the temporomandibular joint and squamous part of the temporal bone [1]. Those tumours that harbor p.Lys36Met mutations occurring in either the *H3-3A* or *H3-3B* genes, are expected to be immunohistochemically positive for the histone mutant-specific antibody K36M [46].

Chondromyxoid fibroma (CMF), a rare benign chondroid neoplasm, with a zonal architecture composed of chondroid, myxoid and myofibroblastic areas, can develop either within bones or on bone surface [1]. In about 90% of tumours, the genetic driver event involves mutation in the glutamate receptor gene, *GRM1*, which seems to be unique for CMF, while it is rare-to-absent in other cartilaginous tumours [47].

Desmoplastic fibroma of bone (DFB) is a locally aggressive fibroblastic/myofibroblastic tumour composed of benign spindle cells embedded in a collagenous background, mimicking desmoid-type fibromatosis [1]. In the jaws, 82% affect the mandible, almost 70% are diagnosed before the age of 30 years [reviewed in 48]. Clinically, DFB is asymptomatic, however swelling, facial asymmetry, pain, trismus may be present. Radiologically, DFB manifests as a well-defined radiolucency, uni- or multi-locular. Phenotypically, spindle cells are primarily positive for vimentin and smooth muscle actin; Ki67 proliferative marker is low. Lack of nuclear beta-catenin expression is in conformity with the absence of *CTNNB1* mutations. This panel should be used

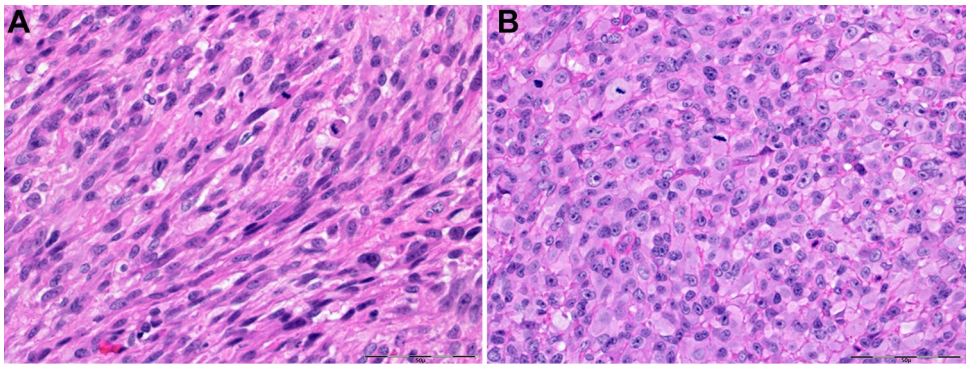

Fig. 5 A 48-year-old male with a lesion of the anterior maxilla. Microscopically, the tumour cells showed a bi-phasic morphology with both spindled (A) and epithelioid (B) cells (A, B—hematoxylin and eosin; scale bar 50μ). Cytogenetic study was positive for *TFCP2* gene aberration and confirmed the diagnosis of TFCP2-RMS. Photomics are courtesy of Robert D. Foss, DDS, MS, The Joint Pathology Center, Head & Neck Pathology, Silver Spring, MD., USA

to differentiate DFB from other intraosseous spindle cell lesions: desmoid tumour (nuclear expression of beta catenin, *CTNN1* or *APC* mutations), fibrous dysplasia (*GNAS* mutation), low-grade fibrosarcoma, low-grade central osteosarcoma (positive for SATB2; *MDM2, CDK4* gene aberrations), low-grade myofibroblastic sarcoma (positive for smooth muscle actin, desmin, nuclear beta catenin), synovial sarcoma (positive for TLE1; *SS18* gene rearrangement), spindle cell rhabdomyosarcoma of the jaw (*TFCP2* gene rearrangement) and myoepithelial tumours (positive for cytokeratin, S100; *EWSR1* gene rearrangement). Recurrence rate after curettage is ~ 31%, enucleation – 25%, and resection only 10%.

Bone and Cartilage Tumours—Malignant Maxillofacial Bone and Cartilage Tumours

Osteosarcoma is a rare bone malignancy, with only 6% of all tumours involving the jawbones [1]. The pathogenesis and precise cell of origin are still unknown. Mutations in the *TP53* and *RB1* genes were found to be frequent, chromosomal instability was identified in *MDM2*, *CDK4 and RAS* genes, although the driver mutation remains unknown. Jaw osteosarcomas are staged using the 8th edition of the AJCC/UICC staging of bone and soft tissue sarcomas [49]. Histological grade of the tumour and stage of disease are the most important predictive factors. Surgical resection with clear margins is still the accepted standard of care, although more recent data showed a survival advantage for chemotherapy, especially in patients with positive margins, high-grade tumours and recurrent disease [50].

The chondrosarcoma family in the 2022 classification, [1] is replacing the chondrosarcoma in the 2017 classification [2]. This family of tumours is defined as malignant bone neoplasms arising in the medullary cavity that produces cartilaginous matrix. There is a periosteal variant. Dedifferentiated tumours show abrupt transition into a high-grade, non-cartilaginous sarcoma. Clear cell chondrosarcoma is a low-grade malignancy of lobules of cartilage with abundant clear cells. Pathogenesis shows that conventional, periosteal and dedifferentiated chondrosarcoma, but not clear cell chondrosarcoma, harbor somatic mutations in the *IDH1* and *IDH2* genes, however their rate of detection in the facial bone is quite low [51]. Staging is done according to the 8th edition of the AJCC/UICC staging of bone and soft tissue sarcomas [49].

Almost all mesenchymal chondrosarcomas harbor a specific *HEY1/NCOA2* fusion gene. Areas with small cells may also show loss of Tp53, Rb expression and homozygous loss of CDKN2A/p16 [52].

Rhabdomyosarcoma with *TFCP2* (TFCP2-RMS) rearrangement is a new tumour that has been introduced in the 2022 classification [1]. It is defined as a high-grade RMS characterized by fusion of *TFCP2* gene to *EWSR1* or *FUS* gene. This specific genetic aberration distinguishes TFCP2-RMS from other types of RMS and diagnosis can be confirmed by FISH study with break-apart probe for *TFCP2* or by sequencing. The tumour affects young adults, with about a third being less than 18-year-old [53, 54]. TFCP2-RMS has predilection for the craniofacial bones, especially the mandible and is characterized by frequent bone perforation and infiltration into the adjacent soft tissues. Histopathologically, TFCP2-RMS are usually bi-phasic with spindle and epithelioid areas in solid sheets or fascicles with scant stroma, brisk mitotic activity, conspicuous nucleoli and frequent necrosis. Immunohistochemical stains are positive for pan-cytokeratin and desmin/myogenin/MyoD1, reflecting the bi-phasic morphological appearance (Fig. 5). Additional positive immunostains include p63, CK7, SATB2, S100, CD30, CD4, caldesmon and others. Therefore, an array of malignancies can be listed in the differential diagnosis, such as metastatic carcinoma, triton tumour and anaplastic

lymphoma. TFCP2-RMS is associated with poor patient prognosis, with advanced clinical stage and distant metastases already present at time of diagnosis [53]. Despite aggressive multi-modal therapy, disease recurrence is frequent and there is only a 14-month median survival time. As less than 30 cases have been reported so far [54], data on prognosis is rather preliminary and more targeted treatment approaches likely to emerge.

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