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Clinical and pathomorphological aspects of odontogenic tumors

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Abstract

Background: Odontogenic tumors (OTs) comprise a group of heterogeneous lesions ranging from hamartomatous or non-neoplastic tissue proliferation to benign or malignant neoplasms with metastatic potential. OTs are derived from epithelial, ectomesenchymal, and/or mesenchymal elements of tooth-forming ("odontogenic") tissues, which show variable clinical and histopathological features.

Objective: Herein, the authors summarize the World Health Organization (WHO) 2022 classification of OTs and further highlight diagnostic tips and differential clues for the most common OTs.

Conclusion: OTs may not be commonly encountered in the daily practice of many pathologists. This makes their diagnosis challenging as there is little practice in understanding the features required for their classification. However, diagnosing the vast majority of these lesions is not difficult provided the following aspects are considered: 1) the general knowledge of tooth development; 2) a few key histological observations; 3) very basic knowledge of the clinical and especially the radiographic features with which they are associated.

Keywords
Odontogenic tumors · Odontogenesis · Ameloblastoma · WHO classification

Odontogenic tumors (OTs) are a heterogeneous group of lesions with diverse clinical behavior and histopathologic types, ranging from hamartomatous lesions to malignancy [1]. The heterogeneity of OTs depends on the complex structure and interaction of dental tissues [1, 2]. Depending on the stage of differentiation during odontogenesis, tumors may demonstrate various histological characteristics, making classification and definitive diagnosis difficult [3]. Thus, we describe some of the most common OTs with a summary of the last World Health Organization (WHO) classification to outline the steps to take in establishing the correct diagnosis.

Alterations in the 2022 WHO classification of odontogenic tumors

The 2022 fifth edition of the WHO classification is not conceptually very different from the previous 2017 classification of odontogenic lesions (**Tables 1 and 2**). The OT classification, like earlier editions, is mainly divided into two categories based on biological behavior, as malignant and benign. Benign tumors are classified into three major categories according to their histogenetic origin: epithelial, mesenchymal, and mixed types (**Table 1**). The only new entity added to benign epithelial tumors is adenoid ameloblastoma, representing the most important change. It is defined as an epithelial odontogenic neoplasm composed of cribriform architecture and duct-like structures and frequently includes dentinoid. After being omitted in the 2017 edition as a descriptive term for ameloblastoma (AM), the term "conventional" was re-introduced in the new edition [4, 5]. Another change is seen in unicystic ameloblastomas (UAM). In the former classification, the possibility of moving the unicystic ameloblas-

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Table 1 WHO classification of benign odontogenic tumors

WHO 2022 classification	WHO 2017 classification
Epithelial	
Adenomatoid odontogenic tumor	Adenomatoid odontogenic tumor
Squamous odontogenic tumor	Squamous odontogenic tumor
Calcifying epithelial odontogenic tumor[a], clear cell, cystic/microcystic, non-calcified/ Langerhans cell rich	Calcifying epithelial odontogenic tumor
Ameloblastoma, extraosseous/peripheral	Ameloblastoma, extraosseous/peripheral type
Ameloblastoma, unicystic	Ameloblastoma, unicystic type
Ameloblastoma, conventional[a]	Ameloblastoma
Metastasizing ameloblastoma	Metastasizing ameloblastoma
Adenoid ameloblastoma[a]	–
Mixed epithelial and mesenchymal	
Primordial odontogenic tumor	Primordial odontogenic tumor
Odontoma[a]	Odontoma
	Odontoma, compound type
	Odontoma, complex type
Ameloblastic fibroma	Ameloblastic fibroma
Dentinogenic ghost tumor	Dentinogenic ghost tumor
Mesenchymal	
Odontogenic fibroma	Odontogenic fibroma
Odontogenic myxoma/fibromyxoma[a]	Odontogenic myxoma/myxofibroma
Cementoblastoma	Cementoblastoma
Cemento-ossifying fibroma[a]	Cemento-ossifying fibroma (discussed under the heading of Fibro-osseous and osteochondromatous lesions)
[a]Revised entities	

Table 2 WHO classification of malignant odontogenic tumors

2022 classification	2017 classification
–	*Odontogenic carcinomas*
Ameloblastic carcinoma	Ameloblastic carcinoma
Primary intraosseous carcinoma, NOS	Primary intraosseous carcinoma, NOS
Sclerosing odontogenic carcinoma	Sclerosing odontogenic carcinoma
Clear cell odontogenic carcinoma	Clear cell odontogenic carcinoma
Ghost cell odontogenic carcinoma	Ghost cell odontogenic carcinoma
Odontogenic carcinosarcoma	*Odontogenic carcinosarcoma*
Odontogenic sarcomas	*Odontogenic sarcomas*

toma (UAM) mural subtype to conventional AM was raised; however, in the 2022 classification, the UAM mural subtype has been retained within UAM. Calcifying epithelial odontogenic tumor (CEOT) has three histopathological subtypes: clear cell, cystic/microcystic, and non-calcified/ Langerhans cell rich. Cemento-ossifying fibroma (COsF), which was already defined as a benign mesenchymal OT in the 2017 classification but was then detained under the heading of fibro-osseous and osteochondromatous lesions, has become an integral part of the benign mesenchymal OTs in the 2022 classification. It is completely separated from the non-odontogenic juvenile trabecular and psammomatoid types. Odontogenic myxoma, with a greater amount of collagen, was termed myxofibroma in the 2017 classification, while in the 2022 edition it is termed fibromyxoma. There is no major alteration in the classification of malignant OTs. Some received minor revisions ([4, 5]; **Table 2**).

Benign odontogenic tumors

Benign OTs, which are shown in **Table 1**, are divided into three groups: epithelial, mixed, and mesenchymal. We included a few entities in each group for the review. Ameloblastoma and adenomatoid odontogenic tumor (AOT) are discussed among the most common epithelial OTs and need attention clinically and pathologically. Ameloblastic fibroma is chosen as an example in mixed OTs and myxoma is discussed as a mesenchymal OT.

Ameloblastoma

Ameloblastomas are the most common epithelial OT. They originate from the epithelium involved in tooth formation, the enamel organ, epithelial cell rests of Malassez, reduced enamel epithelium, and the epithelial lining of odontogenic cysts with special reference to dentigerous cysts. Approximately 80% of ameloblastomas arise in the mandible, foremost in the third molar region, and the remaining 20% in the maxilla [1, 2, 6]. According to the WHO 2022 classification, they are divided into five groups: conventional, unicystic, extraosseous/peripheral, metastasizing, and adenoid ameloblastoma ([4, 5]; **Table 1**).

Conventional ameloblastoma is the most common type of ameloblastoma, and is a benign but locally aggressive tumor. It can be seen in a wide age range with an average of 40.2 years. It usually presents as a slowly growing painless expansion of the molar region of the mandible (85% of cases). Large tumors can present with a significant facial deformity. Orthopantogram CT and MRI are used for radiodiagnostics. Radiologically, they are seen as multilocular radiolucencies in edentulous bone, or with impacted tooth or the apices of the teeth. The soap bubble appearance is its classical feature [1, 6]. Conventional ameloblastomas are neoplasms that are usually not difficult to recognize histologically. They are composed of mainly two types of cells: columnar cells resembling normal ameloblasts that palisade around epithelial islands with reverse nuclear polarity; and the more centrally located cells that resemble the stellate reticulum of enamel organ. There are six different histo-

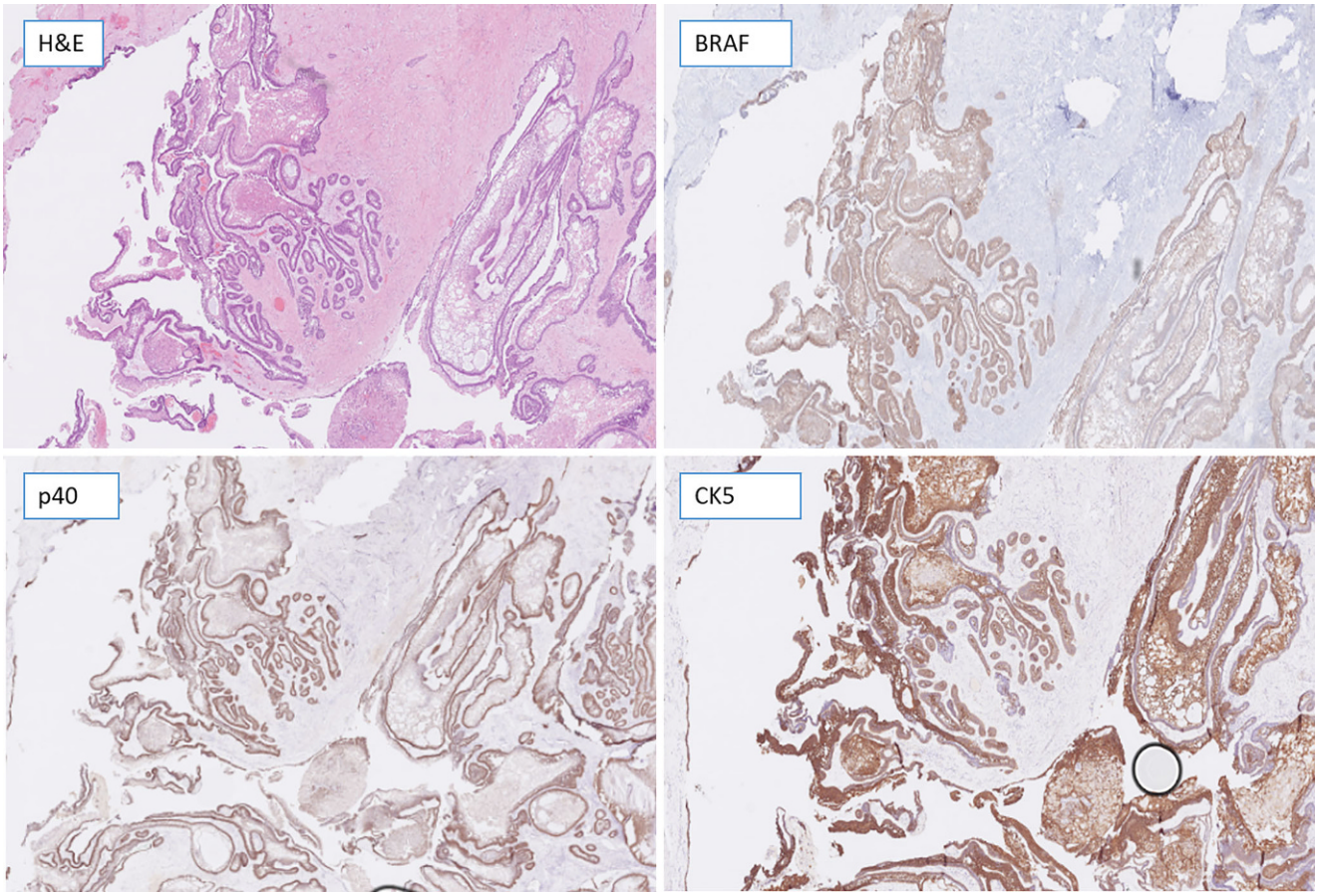

Fig. 1 ▲ Conventional ameloblastoma in a mandibular location with positive immunohistochemical (*IHC*) stainings. *H&E* Follicular pattern tumor islands with large and small cystic degeneration areas. (H.E original magnification ×100). *BRAF* Strong BRAF positivity of the tumor cells. (IHC BRAFV600E original magnification ×100). *IHC* positive staining with p40 and CK5 antibodies. (IHC original magnification ×100)

logical variants of ameloblastomas, including follicular, acanthomatous, plexiform, granular cell, basal cell, and desmoplastic subtypes. Follicular and plexiform subtypes are the most common [2, 3]. Cystic formation is mostly seen within the tumor islands in the "former" type, whereas it occurs in surrounding stroma in the plexiform variant. In the acanthomatous subtype, extensive squamous metaplasia of the central core is present. It is often associated with keratin formation. It may be confused with squamous cell carcinoma. The granular cell type is a clinically aggressive type in which tumor cells' cytoplasm shows abundant eosinophilic granules, and which is seen in younger persons. The desmoplastic type is characterized by densely collagenized stroma. It is clinically more aggressive with a higher rate of recurrence. It occurs in the anterior jaw and radiologically resembles a fibro-osseous lesion due to mixed opacity and lucency. Finally, the basal cell type is the least common type, with nests and sheets of hyperchromatic basaloid cells, which resemble basal cell carcinoma [1, 2].

Adenomatoid odontogenic tumors (AOT), UAM, ameloblastic fibroma (AF), odontogenic fibroma, clear cell odontogenic carcinoma, and dentinogenic ghost cell tumor should be considered in the differential diagnosis. Immunohistochemically, CK19 and CK14, CK5, CD56, calretinin, BRAF V600E (VE1), p63, and p40 show positive staining (◘ **Fig. 1**). In recent years, BRAF V600E positivity has been used for the differential diagnosis of mandibularly located ameloblastomas [1].

Unicystic ameloblastoma (UAM) is the second common type of ameloblastoma, which consists of a large single cyst. It is quite different from the conventional type in terms of clinical presentation and behavior. UAM occurs in young individuals (second and third decade) with a very low rate of recurrence. Its radiology shows a unilocular, well demarcated radiolucency, mostly with an unerrupted tooth resembling a dentigerous cyst ([1, 2, 6]; ◘ **Fig. 2a**). In the 2017 classification, the possibility of moving the unicystic ameloblastoma (UAM) mural subtype to conventional AM was raised, based on the need for an aggressive surgical treatment for both tumors. In the 2022 classification, the UAM mural subtype has been retained within UAMs [5]. UAM is again divided into three subtypes according to the pattern of proliferation of the ameloblastomatous epithelium: luminal, intraluminal, and mural. Histologically, the tumor is confined to the luminal surface of the cyst and fibrous cyst wall, with the lining comprised totally/partially of ameloblastic epithelium. The intraluminal variant shows the tumor from the cyst lining protruding into the lumen of the cyst in

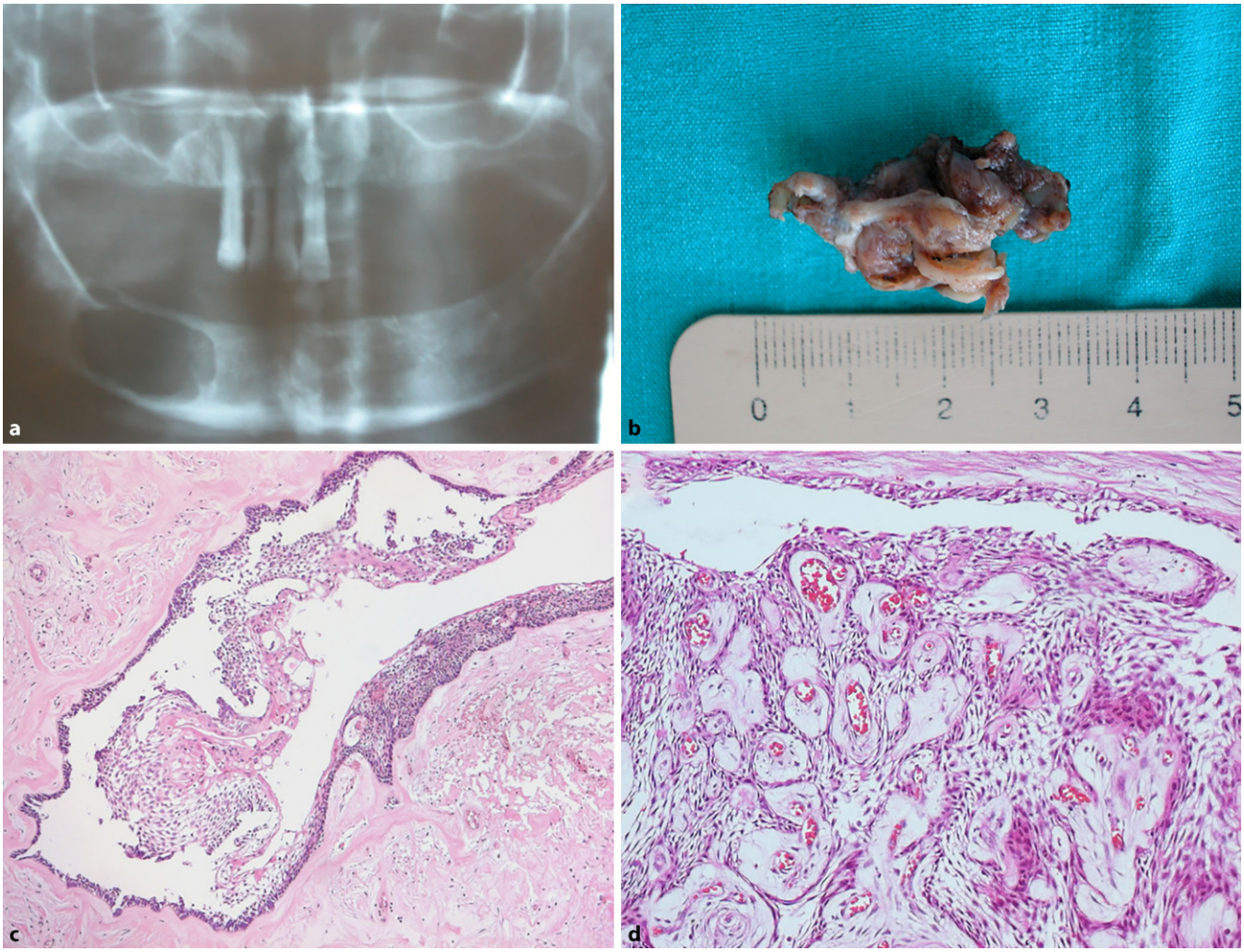

Fig. 2 ▲ Radiographic (**a**), macroscopic (**b**), and microscopic (**c**,**d**) features of unicystic ameloblastomas (UAM). **c** Intraluminal type UAM. **d** Mural type UAM. (H.E original magnification ×200)

which intraluminal projections resemble plexiform ameloblastoma in most cases, though not always. In the mural type, the lining ameloblastomatous epithelium invades into the connective tissue of the cyst wall ([1, 2]; ◘ **Fig. 2**). In some cases it may be hard to recognize the UA. Especially when the cystic lining is thin or the biopsy sampling is limited, dentigerous cyst or macrocystic degeneration components of conventional ameloblastoma cannot be distinguished from UAM. Therefore, conventional ameloblastoma, dentigerous cyst, odontogenic keratocyst (OK), and calcifying odontogenic cyst (COC) should be considered for the diagnosis [1, 4, 6, 7]. BRAF V600E positivity may be helpful for the differential diagnosis of this tumor from other cysts [1, 5].

Peripheral/extraosseous ameloblastoma is biologically a non-aggressive tumor arising from the cell rest of Serres, reduced enamel epithelium, and basal cells of the surface epithelium. It is seen in older adults (fourth to sixth decade) and located within the gingiva, mostly at the mandible premolar region. It does not invade underlying bone. Histologically, such ameloblastic tumor islands show communication with the overlying epithelium. Recurrence rate is very low (16–19%) [1, 2, 6].

Metastasizing ameloblastoma is a very rare variant, a benign but metastasizing OT. The diagnosis is made in retrospect and exhibits benign histological features. The tumor usually metastasizes to lymph nodes or lung, other sites are also possible with organ-associated symptoms [1, 4, 6].

Adenoid ameloblastoma

Adenoid ameloblastoma (AdAM) is a newly included entity separate from the AM group of tumors. It is a very rare tumor but characterized by an aggressive biological behavior with local infiltration and a high recurrence rate (>45.5%). It is mostly seen in the fourth decade (age range 25–52 year). The mandible is the most common anatomic site and AdAM usually manifests clinically as a painless swelling, occasionally with pain and paresthesia. Radiologically, most (~ 82%) tumors present as radiolucencies, with occasional radio-opaque foci with ill-defined margins and cortical perforation at the time of diagnosis. Histopathologically, AdAM is composed of ameloblastoma-like components, duct-like structures, whorled cellular condensations reminiscent of

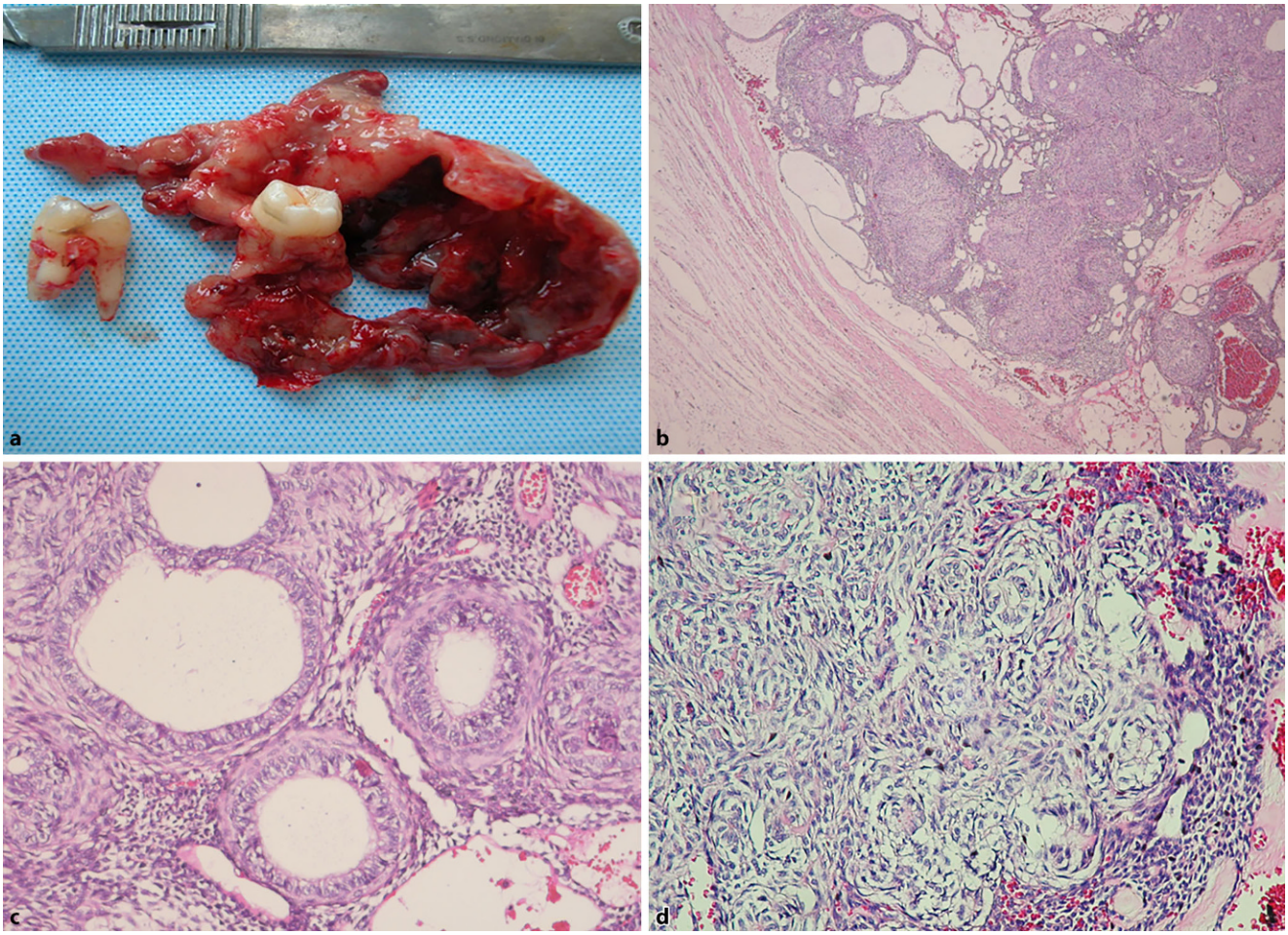

Fig. 3 ▲ Macroscopic and microscopic features of adenomatoid odontogenic tumor (AOT). **a** AOT presents with the crown of impacted maxillary molar tooth. **b** Tumor island with whorl-like, cystic, and duct-like pattern. Tumor encapsulated with the fibrous wall. (H.E original magnification ×100). **c**,**d** Higher magnification of tumor islands. (H.E original magnification ×200)

morules, and cribriform architecture with dentinoid. Differential diagnosis must be made with AOT, ameloblastoma, dentinogenic ghost cell tumor, and odontogenic carcinoma with dentinoid [3, 4].

Adenomatoid odontogenic tumor

AOT is a benign epithelial tumor that represents 3 to 7% of all OTs. It affects mostly young females (64%) in the first and second decades. AOT frequently occurs with an unerupted tooth in the anterior part of the maxilla (over 2/3 of cases). Clinically asymptomatic, small, and slow-growing lesions present with no risk of recurrence. Radiologically, the tumor appears as a circumscribed, unilocular radiolucency that involves the crown of an unerupted tooth, most often a canine. Three variants exist: peripheral, follicular, and extrafollicular. AOT is mostly a well-defined lesion with a thick fibrous capsule. They may be seen as solid or cystic lesions. Histopathologically, the tumor is composed of spindle- or columnar-shaped epithelial cells which are arranged in sheets, whorls, or ductal patterns. Columnar type cells with basal nuclei and clear cytoplasm may resemble pre-ameloblasts. Eosinophilic fibrillar material is present between tumor cells and within ductlike structures. Amyloid material and calcifications can be present ([1, 2]; ◘ **Fig. 3**). Microscopically, odontomas, adenoid ameloblastoma, adenomatoid odontogenic hamartoma, and adenomatoid dentinoma may have AOT-like areas and, conversely, AOT can include calcifying epithelial OT-like areas; therefore, these lesions should be taken into consideration for the differential diagnosis [1, 5].

Ameloblastic fibroma

Ameloblastic fibroma (AF) is rare benign mixed OT. It originates from dental papilla like ectomesenchyme and odontogenic epithelium. The tumor peaks in the first and second decades and is located in the mandibular posterior region (80%) [1, 2, 8]. The tumor is centrally located; however, a peripheral variant has also been reported. Small tumors are asymptomatic, while larger ones produce significant swelling of the jaws. Recurrence rate is around 18–19% for central lesions [8]. On radiographs, smaller lesions are well circumscribed and unilocular with a sclerotic border, while larger ones are multilocular (◘ **Fig. 4a**). Histopathologically, AF is a biphasic tumor, composed of both neoplastic mesenchymal and epithelial components. The epithelial component

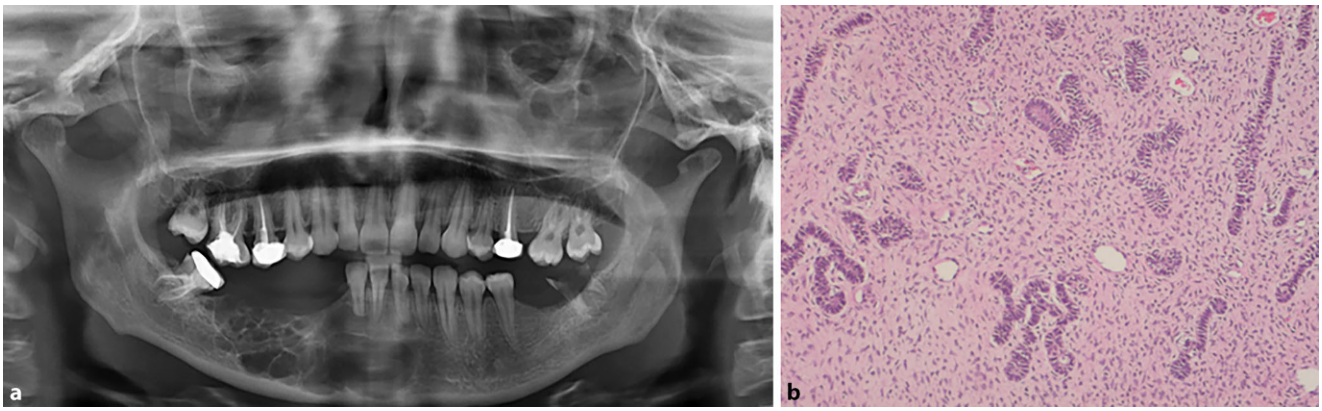

Fig. 4 ▲ Radiographic (**a**) and microscopic (**b**) features of ameloblastic fibroma (AF). **b** Ameloblastic epithelial islands/strands in the loose mesenchymal tissue. (H.E × original magnification ×200)

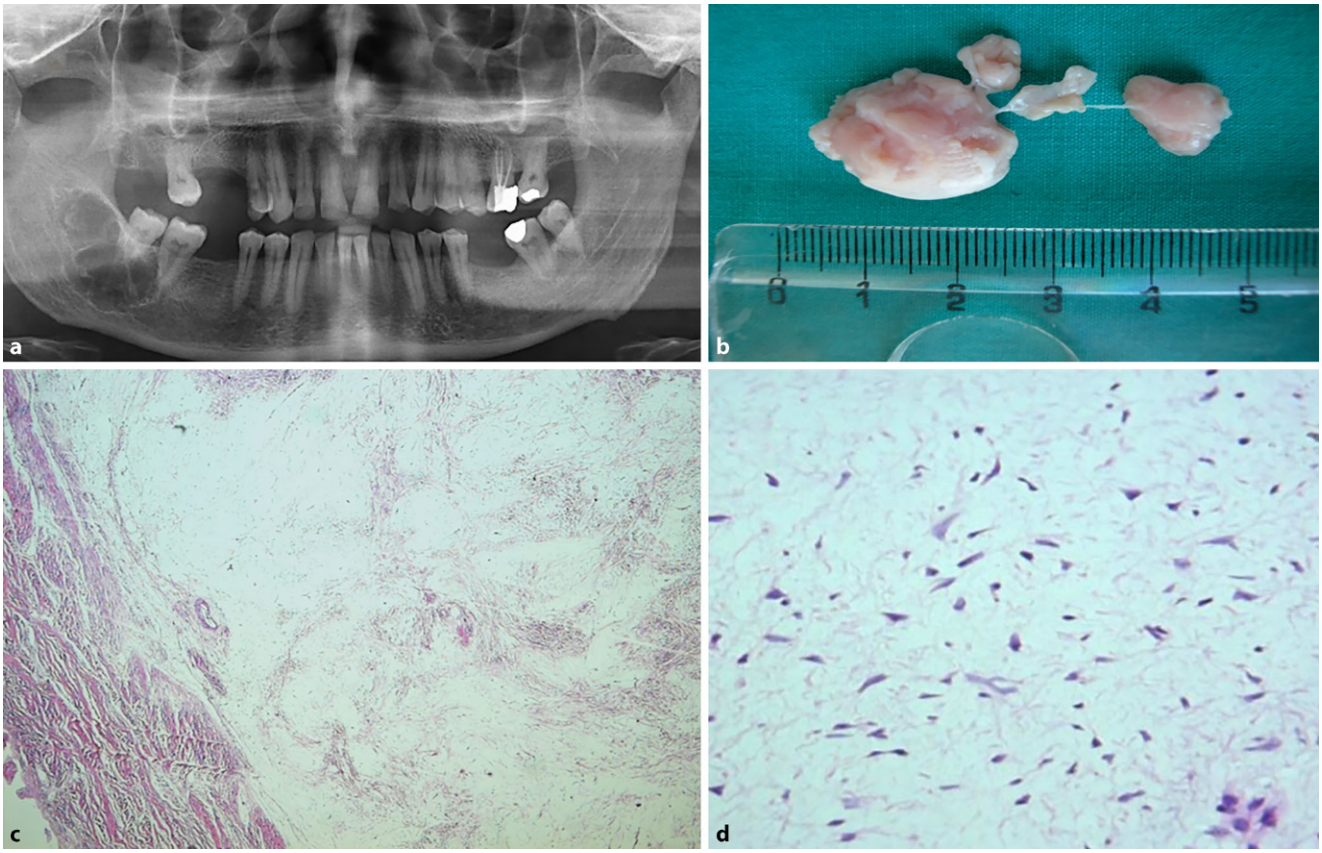

Fig. 5 ▲ Radiographic (**a**), macroscopic (**b**), and microscopic (**c**,**d**) features of odontogenic myxoma (OM). **c**,**d** OM consists of fine delicate stellate, fusiform, and round cells in a bland myxoid stroma. (H.E original magnification ×100 and 200)

consists of branching and anastomosing (◘ **Fig. 4a**), features often resembling dental papilla of the tooth bud ([1, 2, 8]; ◘ **Fig. 4b**). 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 [5, 7]. Hyperplastic dental follicles often show a myxoid stroma, which can be seen in some cases to be attached to a cuboidal epithelium that represents reduced enamel epithelium. The stroma may also contain small residual odontogenic rests. These small islands of epithelium in a fibromyxoid stroma can be confused with ameloblastic fibroma [3]. Differential diagnosis also includes ameloblastic fibrosarcoma and ameloblastoma. Long-term follow-up is recommended since transformation to ameloblastic fibrosarcoma is rarely observed [1, 2, 8].

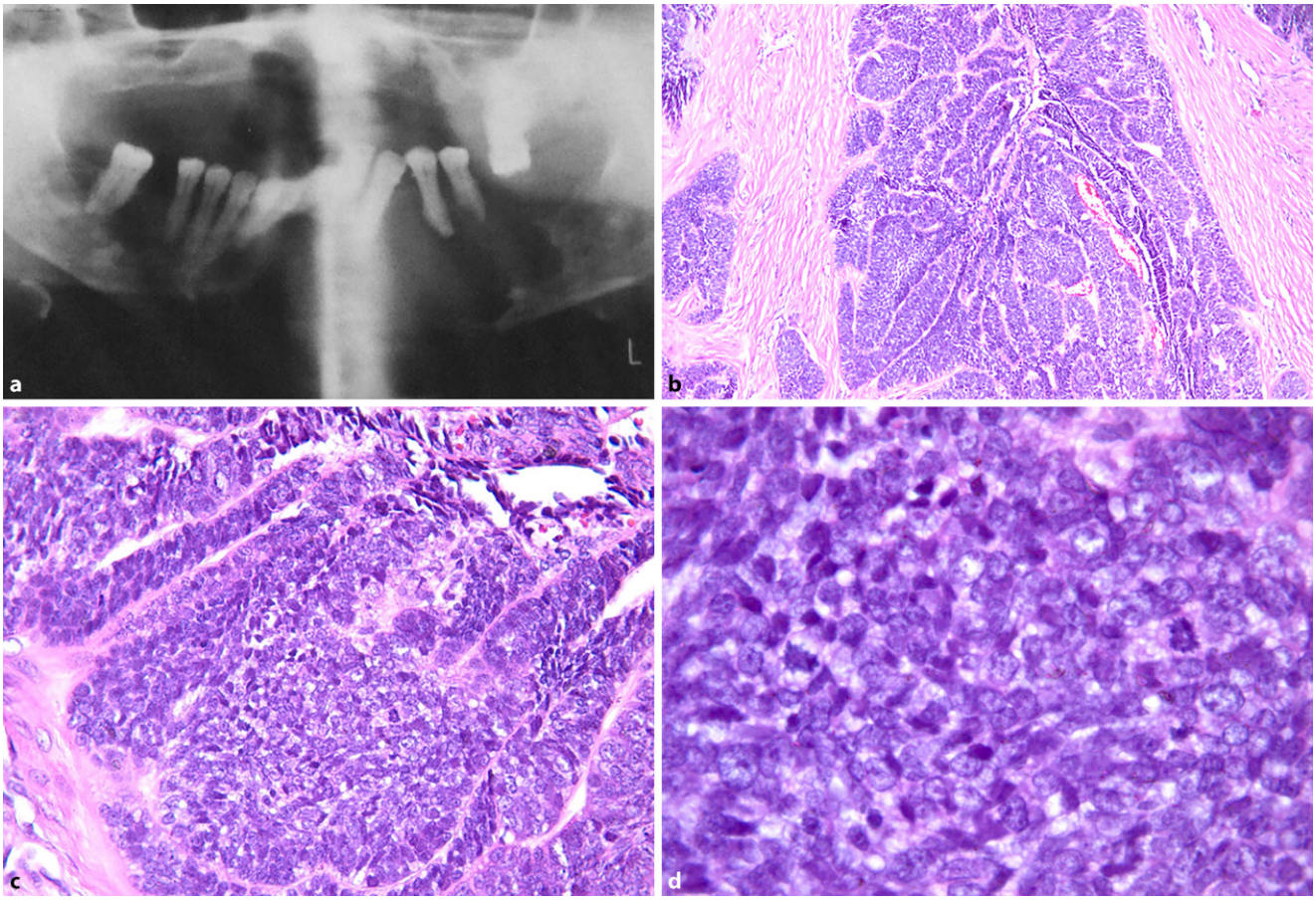

Fig. 6 ▲ Ameloblastic carcinoma (AMCa). **a** Radiographic features of the tumor in the mandible. **b**,**c**,**d** Microscopic features of AMCa, ameloblastic tumor islands with cellular atypia and prominent atypical mitosis. (H.E original magnification ×100, 200 and 400)

Odontogenic myxoma

Odontogenic myxoma (OM) is a benign mesenchymal odontogenic neoplasm. It has been listed as the third most frequent OT after odontoma and ameloblastoma [2]. The tumor often behaves in a locally aggressive and infiltrating fashion, with a 25% recurrence rate. It occurs in the second and third decades and is mostly located in the mandibular posterior and ramus area but can also be seen in the maxillary posterior site as well. Radiographic appearance is uni-/multilocular radiolucency with intrabony septa (soap bubble or honeycomb appearance; [9]; ◘ **Fig. 5a**). Histologically, OM consists of fine delicate stellate, fusiform, and round cells in a bland myxoid stroma, somewhat resembling dental papilla of the developing tooth germ. Variable amounts of collagen fibers may be observed, in which case the term of fibromyxoma is used. Bony invasion may be observed. Rarely, binucleated cells, mitoses and minimal atypia, and occasional epithelial rests can be seen (◘ **Fig. 5**). Immunohistochemically, orosomucoid 1 protein (ORM-1) and smooth muscle actin (SMA) stainings show positivity [2]. Dependent on the stage of development, either the dental papilla or the dental follicle can have similar histological features to an odontogenic myxoma. If the biopsy consists of fibromyxoid tissue, the presence of other structures suggestive of a developing tooth, e.g., fragments of reduced enamel epithelium, can be helpful [7]. Hyperplastic dental follicle, dental papilla, chondromyxoid fibroma, osteochondromyxoma, odontogenic fibroma, and low-grade fibromyxoid sarcoma, especially in the context of fibromyxoma, have to be considered for differential diagnosis. Follow-up is necessary [2, 5, 9].

Malignant odontogenic tumors

Malignant odontogenic tumors (MOTs) are very rare tumors which arise de novo or from the malignant transformation of benign OTs [1]. As shown in ◘ **Table 2**, there is a variety of tumors with different biological behaviors. Herein, we only discuss ameloblastic carcinoma (AMCa) as a representative MOT.

Ameloblastic carcinoma

Ameloblastic carcinoma (AMCa) is a highly aggressive malignant epithelial OT. It is defined in the 2022 WHO classification as a primary odontogenic carcinoma histologically resembling AM and not as the malignant counterpart of AM, as it was in the 2017 classification [4, 5]. AMCa, although rare, constitutes 30% of malignant odontogenic tissues [4]. Most of them occur de novo, but some might arise in pre-exist-

ing longstanding, untreated, or recurrent AM. AMCa usually presents as rapid painful growth in the posterior mandible and the mean age of the patients is 45 years. The local recurrence rate is 40%, lung metastasis occurs in around 33%, and 5-year survival is 70%. Radiographic appearance is initially a well-defined unilocular and multilocular radiolucency with sclerotic borders. As the tumors increase in size, patients may experience tooth displacement, root resorption, and osteolytic destruction [2]. Histologically, the tumor shows some of the typical histologic features of benign ameloblastoma, but it mainly presents with malignant features, such as atypia, local necrosis, atypical mitosis, and perineural infiltration. AMCa exhibits islands and cords of odontogenic epithelium, sometimes with fibrous septa. The classical features of ameloblastoma, like reverse polarization and peripheral palisading, are usually lost. Crowding of basal cells with expansion into the other epithelial layers can be seen. Loss of cohesion between tumoral cells can be significant. Squamous metaplasia can be observed ([5, 10]; ◘ **Fig. 6**). Immunohistochemical stainings with BRAF V600E, CK 19, Ki 67, and p63 antibodies are helpful [11]. Differential diagnosis includes basaloid squamous cell carcinoma, basal cell type ameloblastoma, sarcomatoid squamous cell carcinoma, and clear cell odontogenic carcinoma [5, 10]. AMCa diagnosis should be combined with clinical, imaging, and pathological manifestations to improve diagnostic accuracy.

Practical conclusion

- **From the diagnostic point of view, the presence of ameloblast-like cells and the formation of dental hard tissues, especially dentine, are useful indicators of the odontogenic origin of epithelial lesions encountered within the jaws.**
- **Radiographic consideration and clinical information are generally essential for the definitive diagnosis of odontogenic tumors.**
- **Diagnosis of cystic lesions is critical in incisional biopsies.**
- **Diagnosis of myxoid lesions requires a careful approach.**
- **Ameloblastic cells, clear cells, ghost cells, and amyloids can be seen in various odontogenic lesions.**
- **The specimen should be widely sampled for assessment of malignancy.**

Zusammenfassung

Klinische und pathomorphologische Aspekte odontogener Tumoren

Hintergrund: Odontogene Tumoren (OT) umfassen eine Gruppe heterogener Läsionen, die von hamartomatösen oder nichtneoplastischen Gewebeproliferationen bis hin zu benignen oder malignen Neoplasmen mit Metastasierungspotenzial reichen. OT entstehen aus epithelialen, ektomesenchymalen und/oder mesenchymalen Elementen zahnbildender („odontogener") Gewebe und weisen unterschiedliche klinische und histopathologische Merkmale auf.
Ziel der Arbeit: Die Autoren haben hier die Klassifikation der Weltgesundheitsorganisation (WHO) aus dem Jahr 2022 für OT zusammengefasst wie auch diagnostische Hinweise und Differenzialdiagnosen für OT aufgezeigt.
Schlussfolgerung: In der täglichen Praxis vieler Pathologen sind OT nicht unbedingt häufig anzutreffen. Dies macht ihre Diagnose schwierig, da es wenig Erfahrungen im Verständnis der für ihre Klassifizierung erforderlichen Merkmale gibt. Die Diagnose der überwiegenden Mehrheit dieser Läsionen ist jedoch nicht schwierig, wenn man Folgendes berücksichtigt: 1) das allgemeine Wissen über die Zahnentwicklung, 2) einige wichtige histologische Beobachtungen, 3) sehr grundlegende Kenntnisse der klinischen und insbesondere der röntgenologischen Merkmale, mit denen sie einhergehen.

Schlüsselwörter
Odontogene Tumoren · Odontogenese · Ameloblastom · WHO-Klassifizierung

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Declarations

Conflict of interest. S. E. Gültekin and R. Büttner declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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