Review

Morphological Variants of Ameloblastoma and Their Mimickers

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Ameloblastoma is the second most common intraosseous benign odontogenic tumor. This tumor exhibits a locally aggressive behavior. A number of morphological variants of ameloblastoma have been documented in the literature and at times, may pose a diagnostic challenge to the pathologist. The purpose of this paper is to discuss the spectrum of histopathological variants of ameloblastoma. Recognition of the subtypes of ameloblastoma is important, as it has been documented that some subtypes may exhibit a more aggressive biological behavior than the so-called "conventional" ameloblastoma.
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Key Words: *ameloblastoma, calcifying odontogenic cyst, squamous odontogenic tumor, ameloblastic fibroma, ameloblastic fibrosarcoma, odontogenic keratocyst*

INTRODUCTION

Ameloblastoma is a tumor that arises from odontogenic epithelium with an estimated incidence in the population of approximately 0.5 per million.[1] Ameloblastoma is a benign tumor that displays an insidious slow growth, and a locally invasive behavior with a high rate of recurrence. It is considered the most clinically significant odontogenic tumor.[2] The World Health Organization classifies ameloblastoma into four types: solid/multicystic; desmoplastic; unicystic, and extraosseous/peripheral types.[3]

A review of 3677 cases of ameloblastoma in 1995 summarized the clinical features of this tumor.[4] The average age of ameloblastoma is 36. However, younger populations, particularly females, are identified in developing countries. The most common location of ameloblastoma is the posterior region of the mandible with a mandibular to maxillary ratio of 5 to 1. Many cases of ameloblastoma are asymptomatic and are found by routine radiographic examination. The most common clinical sign is swelling and expansion of the jaws.[5] Other clinical findings may include pain and delayed tooth eruption.

Radiographically, amelobastoma is identified as a radiolucent lesion that presents either as a unilocular or multilocular lesion. In Reichart's study in 1995, a unilocular appearance was observed in 51% of the cases while a multilocular appearance was noted in 48.9%.[4] The unilocular pattern consists of a well-defined radiolucent lesion that may or may not be associated with a tooth and cannot be radiographically differentiated from other common cystic lesions in the jaws, such as dentigerous cyst or odontogenic keratocyst. The multilocular lesions are commonly described as radiolucent lesions displaying a "soap bubble" or "honeycomb" appearance.[6]

Ameloblastoma presents as a variety of histological types that may create diagnostic challenges. The purpose of this article is to present a comprehensive review of the histological types of ameloblastoma and to discuss its most common mimickers.

HISTOLOGICAL FEATURES OF AMELOBLASTOMA

Ameloblastoma consists of a proliferation of solid strands, cords and islands of odontogenic epithelium supported by connective tissue stroma. This proliferating epithelium can undergo cystic changes. Vickers and Gorlin in 1970 defined the histopathological features of ameloblastoma.[7] These features include hyperchromasia, palisading and reverse polarization of the basal nuclei of the epithelial cells with vacuolization of the cytoplasm. A variety of patterns are usually seen in ameloblastoma and they are described as follows:

1. Follicular ameloblastoma

In a large case study of ameloblastomas, the follicular pattern was found in 28.2 % of the cases. The follicular ameloblastoma is characterized by the presence of follicles that resemble the developing enamel organ. These islands of cells are surrounded by connective tissue. The periphery of these islands is comprised of tall columnar cells reminiscent

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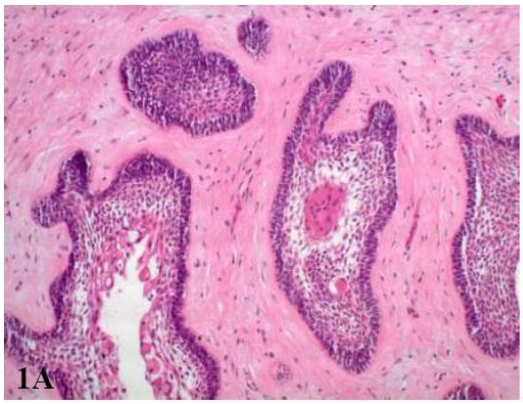
of ameloblasts. These cells show reverse polarization of the nuclei. The central areas of the islands consist of loosely arranged cells resembling stellate reticulum.[7] It is not infrequent to observe squamous differentiation or microcystic changes in the central areas (**Figures 1A** and **1B**).



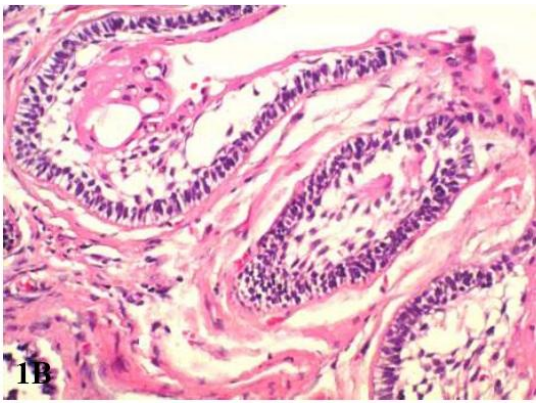
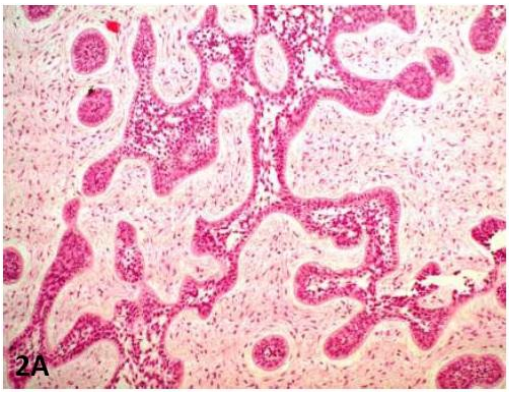


Figure 1. Follicular ameloblastoma.
1A. Follicles of ameloblastic epithelium displays squamous differentiation and microcystic formation (hematoxylin-eosin stain; original magnification x100).
1B. Higher magnification shows solid follicles with peripheral tall columnar basal cells displaying nuclear hyperchromatism, reverse polarization, palisading and a loose stellate-like reticulum in the center (hematoxylin-eosin stain; original magnification x200).



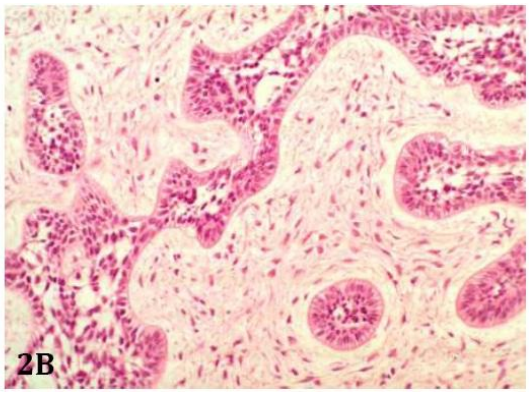
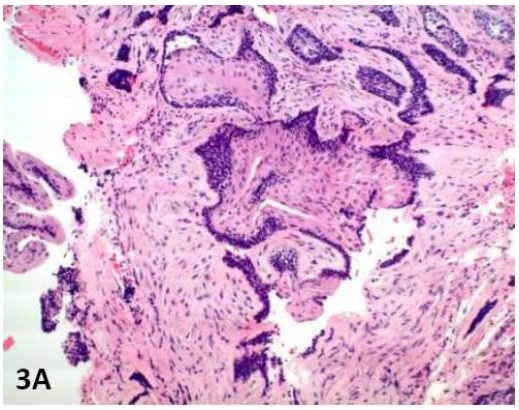


Figure 2. Plexiform amelobastoma.
2A. Anastamosing cords of ameloblastic epithelium supported by loose connective tissue stroma (hematoxylin-eosin stain; original magnification x100).
2B. The cords are thin and contain small number of centrally located cells. Nuclear palisading, and reversed nuclear polarization of the peripheral cells, and basal cells are evident (hematoxylin-eosin stain; original magnification x200).



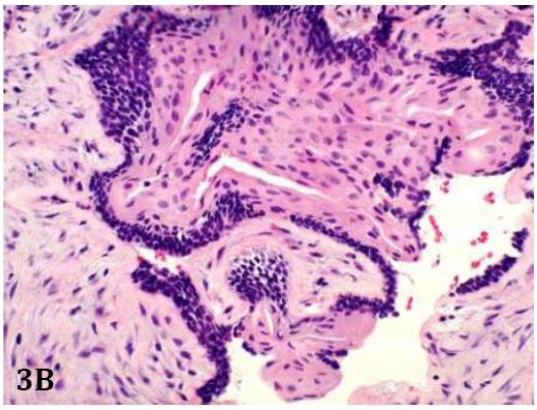
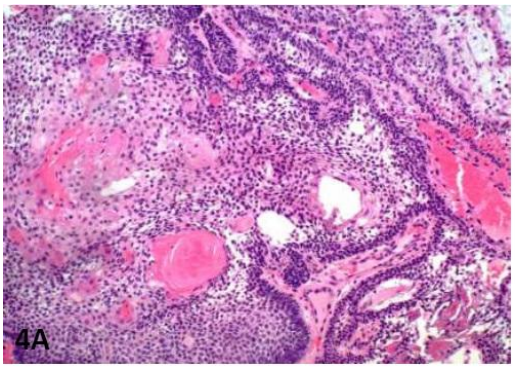


Figure 3. Acanthomatous ameloblastoma.
3A. Ameloblastic follicles with central squamous metaplasia. (hematoxylin-eosin stain; original magnification x100).
3B. A solid follicle demonstrates central squamous metaplasia with typical peripheral columnar to cuboidal basal cells with typical ameloblastic features. (hematoxylin-eosin stain; original magnification x200).



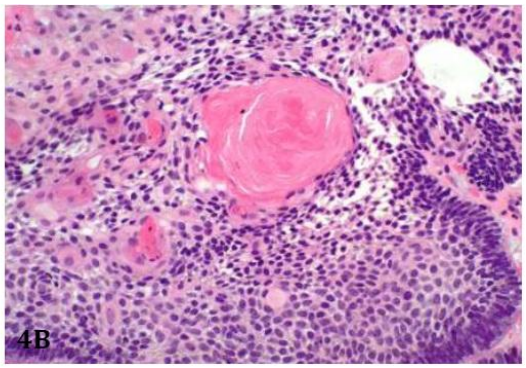


Figure 4. Keratoameloblastoma.
4A. This low magnification shows the presence of keratin masses in the ameloblastic tissue (hematoxylin-eosin stain; original magnification x100).
4B. Abrupt lamellar keratinization is seen within an ameloblastic follicle. (hematoxylin-eosin stain; original magnification x200).

2. Plexiform ameloblastoma

The plexiform ameloblastoma is another common pattern seen in approximately 32.5% of cases.[4] This pattern consists of anastomosing strands and cords of ameloblastic epithelium. Similar to follicular ameloblastoma, the plexiform subtype presents peripheral basal cells that are tall and columnar with reverse polarity of the nuclei and cytoplasmic vacuolization. The central parts of the cords and strands are thin and contain loosely arranged cells. The stroma varies from dense to loose collagenous tissue (**Figures 2A** and **2B**).

3. Acanthomatous ameloblastoma

The acanthomatous ameloblastoma pattern is seen in approximately 12.1% of cases.[4] In this pattern, the stellar reticulum-like central area is replaced by squamous metaplasia with keratin pearl formation (**Figures 3A** and **3B**). Histologically, acanthomatous ameloblastoma may be confused with keratoameloblastoma. What separates keratoameloblastoma from acanthomatous ameloblastoma is the presence of an abrupt ortho- and parakeratinization (**Figures 4A** and **4B**) resulting in the accumnulation of keratin masses filling the center of the ameloblastic epithelial islands.[8]

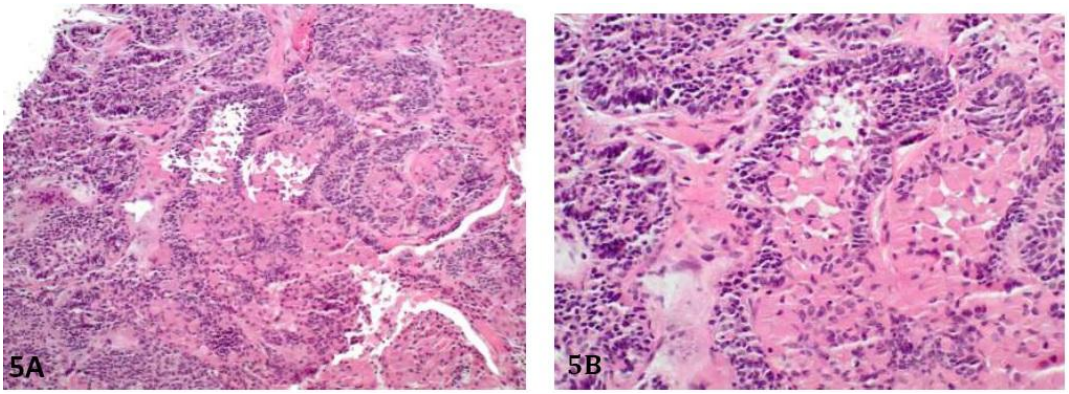


Figure 5. Granular cell ameloblastoma.
5A. Follicles of ameloblastic epithelium with central areas containing granular cells. (hematoxylin-eosin stain; original magnifycation x100).
5B. In this field, numerous granular cells are seeing in the center of the follicles. In addition, the granular cells replace some of the basal peripheral cells. (hematoxylin-eosin stain; original magnification x200).

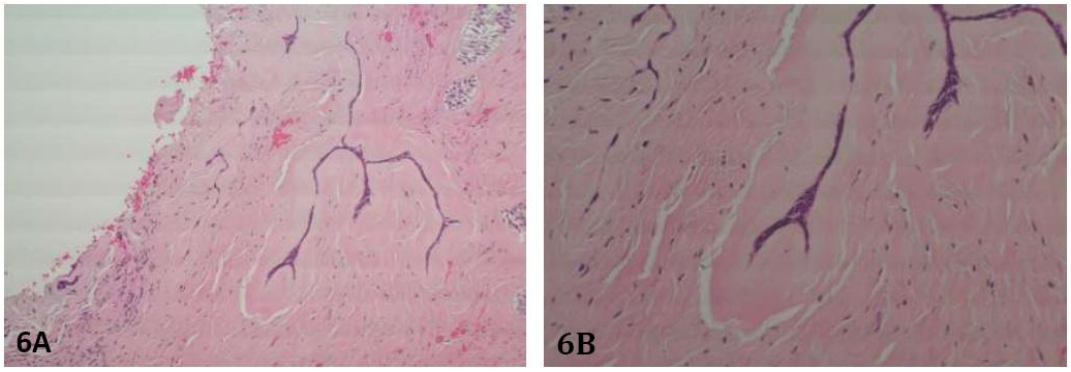


Figure 6. Desmoplastic ameloblastoma.
6A. Thin strands of epithelial cells compressed by desmoplastic connective tissue stroma. (hematoxylin-eosin stain; original magnification x100).
6B. Due to stromal compression, the nuclear palisading becomes less obvious. (hematoxylin-eosin stain; original magnification x200).

4. Granular cell ameloblastoma

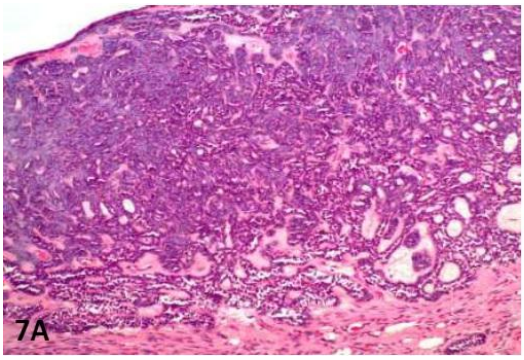
Approximately 4.28% of ameloblastomas show a granular cell pattern.[4] These granular cells display central vesicular nuclei with abundant cytoplasm containing eosinophilic granules that represent lysosomes under ultrastructural and histochemical examination. These granular cells may replace the central stellate reticulum-like areas and/or the basal peripheral cells (**Figures 5A** and **5B**).[9,10]

5. Desmoplastic ameloblastoma

The desmoplastic ameloblastoma represents 4-13% of all ameloblastomas.[11] Two distinctive characteristics allow the segregation of this subtype of ameloblastoma. One of these features is of the presence of desmoplastic fibrous connective tissue that contains thin strands and nests of odontogenic epithelium.[12] The second feature is the almost complete absence of discernable basal cells with the typical nuclear palisading, reverse polarization and vacuolization of the cytoplasm. Occasionally, few strands will display the cellular features of ameloblastoma, suggesting an odontogenic derivation (**Figures 6A** and **6B**), facilitating its identification as such. Otherwise, the identification of these strands as ameloblastic epithelium becomes a difficult task.

6. Basal cell ameloblastoma

Basal cell ameloblastoma is the least common pattern comprising only 2.02% of all cases of ameloblastomas.[4] Basal cell ameloblastoma consists of nests of basaloid cells. The peripheral cells of the nests are cuboidal and may show reverse nuclear polarity. Usually, a net-like pattern of interconnecting nests is observed (**Figures 7A** and **7B**). The central area of the nests does not display a stellate reticulum.



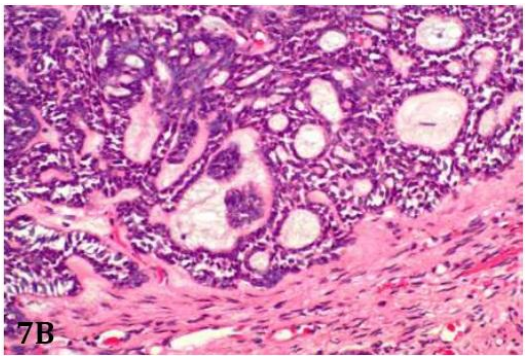


Figure 7. Basal cell ameloblastoma. **7A.** Nests of interconnecting ameloblastic epithelium form a net-like pattern. (hematoxylin-eosin stain; original magnification x100). **7B.** The peripheral cells of the interconnecting strands are cuboidal to columnar and show reverse nuclear polarization. (hematoxylin-eosin stain; original magnification x200).

7. Unicystic ameloblastoma

Unicystic ameloblastoma is a type of ameloblastoma seen in approximately 6% of all cases of ameloblastomas.[4] In contrast to the conventional ameloblastoma where the average age of presentation is the fourth decade of life, unicystic ameloblastoma is typically seen in young patients, around the second decade of life. Radiographically, the unilocular pattern is seen more often than the multilocular pattern, particularly when associated with an unerupted tooth.[13] Three subtypes of unicystic ameloblastoma are recognized. The first one is known as luminal unicystic ameloblastoma that consists of a cystic lesion lined by simple odontogenic epithelium demonstrating nuclear palisading and reverse polarization with cytoplasmic vacuolization of the basal cells. An overlying stellate reticulum-like area is present (**Figure 8**). The second subtype is called intraluminal unicystic ameloblastoma. This lesion consists of a cystic lesion showing an intraluminal plexiform proliferation of epithelium. In this pattern, the typical cytological features of ameloblastoma are not commonly observed, probably due to associated inflammatory changes. In areas where the inflammation is minimal, it is possible to note the typical ameloblastic changes. The third subtype is the mural unicystic ameloblastoma where the fibrous connective tissue cystic wall presents typical islands of plexiform or follicular ameloblastoma.

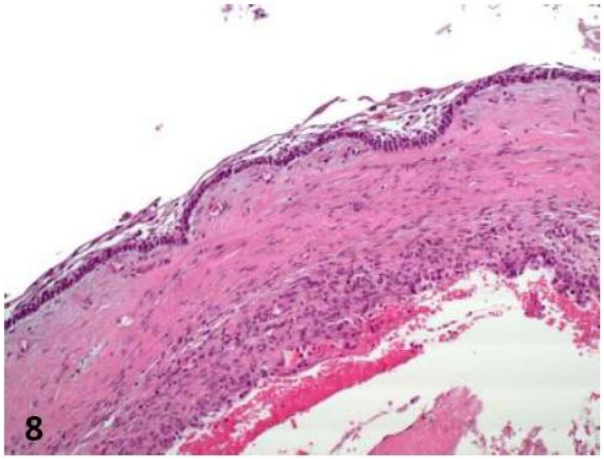
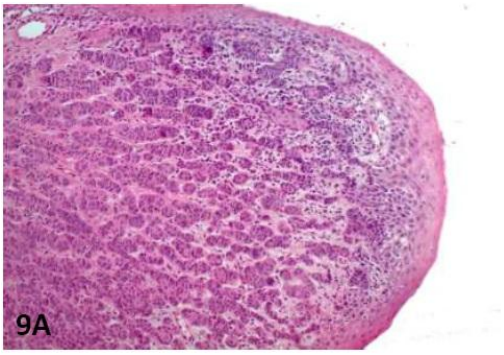


Figure 8. Unicystic ameloblastoma. Low magnification. The cyst is lined by odontogenic epithelium showing nuclear palisading, nuclear reverse polarization and cytoplasmic vacuolization of basal cells. The overlying epithelial cells resemble stellate reticulum. (hematoxylin-eosin stain; original magnification x100)

8. Peripheral ameloblastoma

This extraosseous subtype represents approximately 2-10% of all cases of ameloblastomas.[14] Clinically, peripheral ameloblastoma presents as a sessile or pedunculated gingival or alveolar mucosal lesion. In the majority of cases, there is no radiographically visible bone involvement. However, superficial alveolar bone erosion may be observed. Histologically, peripheral ameloblastoma shows islands of typical ameloblastic epithelium displaying follicular and/or plexiform patterns (**Figures 9A** and **9B**).[15] Only 50% of peripheral ameloblastomas show a connection between the overlying mucosal epithelium and the ameloblastic proliferation.[6]



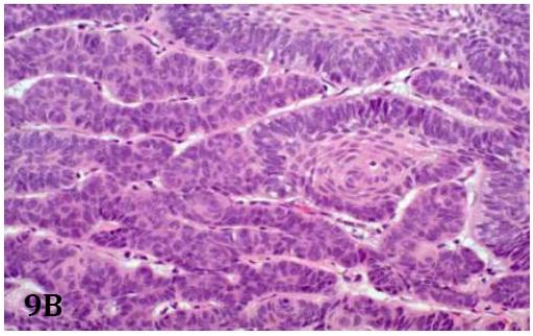
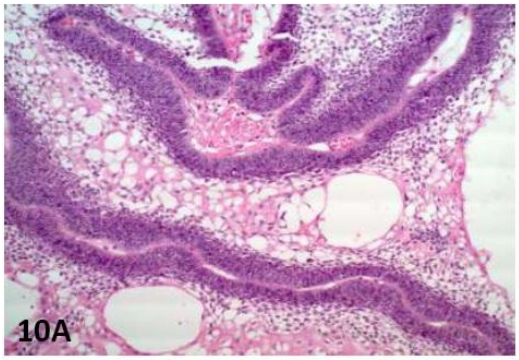


Figure 9. Peripheral ameloblastoma. **9A.** Low magnification shows islands of ameloblastic tissue connecting with the surface Epithetlium. The cellular phenotype resembles basal cell ameloblastoma (hematoxylin-eosin stain; original magnification x100). **9B.** Typical ameloblastic features (i.e., reverse nuclear polarization, nuclear palisading and cytoplasmic vacuolization of basal cells are evident. (hematoxylin-eosin stain; original magnification x200).



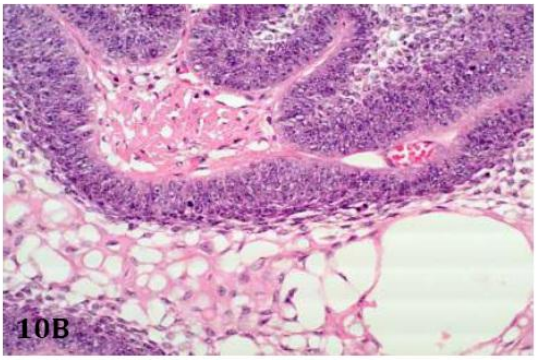
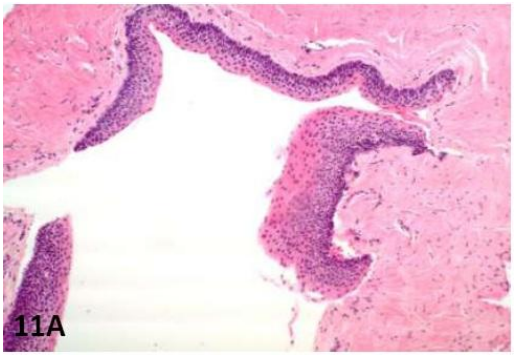


Figure 10. Ameloblastic carcinoma.
10A. Low magnification illustrates a tumor with central stellate reticulum and peripheral basal cells with malignant features. (hematoxylin-eosin stain; original magnification x100).
10B. Increased mitotic activity, cellular pleomorphism and disarray of the basal cells are observed. (hematoxylin-eosin stain; original magnification x200).



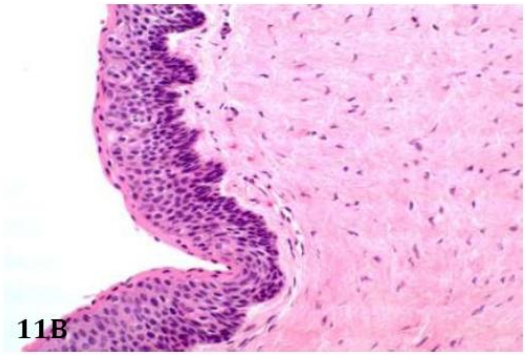
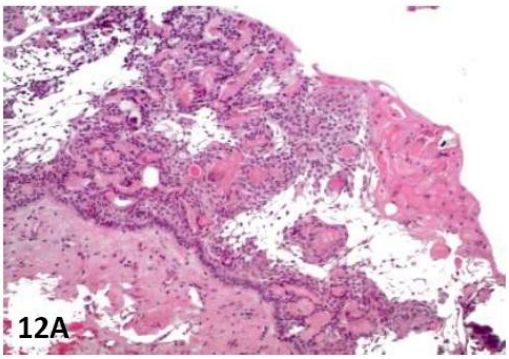


Figure 11. Odontogenic keratocyst.
11A. Corrugated surface of the cystic stratified squamous epithetlium shows parakeratosis.
(hematoxylin-eosin stain; original magnification x100).
11B. The cyst wall which is composed of squamous epithelium and fibrous connective tissue show palisading of the basal cells and parakeratinization epithelium without inflammation. (hematoxylineosin stain; original magnification x200).



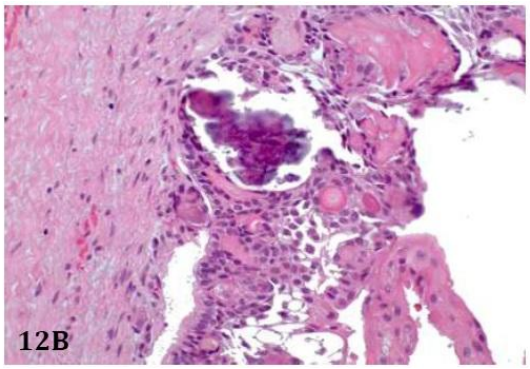


Figure 12. Calcifying odontogenic cyst.
12A. Superficial formation of ghost cells is noted. (hematoxylin-eosin stain; original magnification x100).
12B. Calcification of ghost cells and palisading of basal cells is observed in this microscopic field.
(hematoxylin-eosin stain; original magnification x200).

LESIONS MIMICKING AMELOBLASTOMA

There are a number of lesions that can be confused with ameloblastoma. Their proper identification is important because there are significant differences in the clinical biological behavior of these entities.

1. Ameloblastic carcinoma

Ameloblastic carcinoma is a rare malignant odontogenic tumor that shows clear cytological features of malignancy.[16] It occurs at a later age than ameloblastoma and it is locally much more aggressive.[17] It is more common in the mandible and shows a high propensity to recur. Histologic examination reveals malignant features that include cellular pleomorphism, nuclear hyperchromatism and high mitotic activity (**Figures 10A and 10B**). Some histologic features reminiscent of conventional ameloblastoma, such as a hint of nuclear palisading and reverse polarization, are also present (**Figure 10B**). About 22% of ameloblastic carcinomas produce metastases that show the same histopathological features as those of the malignant primary tumor.[17]

Metastatic ameloblastomas with histological features of conventional ameloblastoma (i.e., bland cytological features with nuclear palisading, reverse polarization if the nuclei and vacuolization of the cytoplasm) have also been described. In these cases, the term "malignant ameloblastoma" is used.[18]

2. Odontogenic keratocyst

Odontogenic keratocyst (OKC) is a controversial lesion that some pathologists classify as a cyst while others believe that it represents a benign tumor.[19,20] This lesion has a high recurrence rate and aggressive behavior.[21] Although OKC may occur at any age, but most cases are seen in the third decade of life.[21] It is seen most frequently in the mandible with clinical symptoms present in 50%-80% of the cases.[21,22] Multiple odontogenic keratocyst are associated with nevoid basal cell carcinoma syndrome.[21] The radiographs findings are not pathognomonic and may simulate other conditions, such as ameloblastoma, dentigerous cyst or other dental cysts.

The microscopic findings of OKC consist of a cystic wall lined by parakeratinized-stratified squamous epithelium with palisading of basal cell nuclei (**Figures 11A** and **11B**). A frequent finding is the detachment of the cystic lining from the connective tissue wall as well as the absence of rete pegs. In contrast to other dental cysts, there is an absence of inflammation in the connective tissue of cyst wall. In cases where inflammation is present in the cyst wall, the classic phenotype of odontogenic keratocyst is lost and conventional stratified squamous epithelium is found. The high rate of recurrence (up to 60%) is thought to be due to the presence of satellite cysts due to budding of the basal cell layer of the cystic epithelium.[21] Odontogenic keratocyst is usually confused with unicystic ameloblastoma on clinical, radiographic and histologic appearance. Treatment consists in enucleation of the lesion with vigorous curettage and close follow-up. In large cystic lesions, marsupialization of an odontogenic keratocyst can be performed, reducing the morbidity associated with this lesion. Repeated, periodic surgical interventions are not rare for this lesion.[23]

3. Calcifying odontogenic cyst

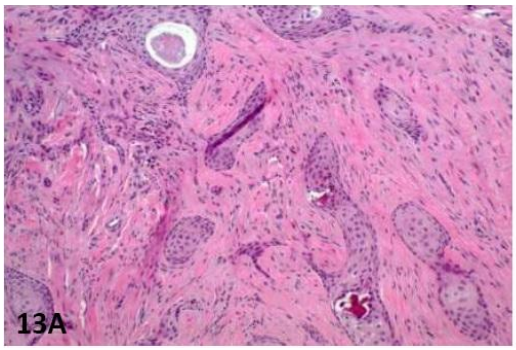
Calcifying odontogenic cyst (COC) was first described by Gorlin et al in 1962.[24] The mean age of this lesion is 33.[25] An extraosseous location for this typically intraosseous cyst has been documented in gingival tissues.[26] Radiographically, this lesion appears radiolucent. However, radiopaque structures may also be present. Microscopically, COC consists of cystic odontogenic epithelium displaying palisading of basal cell nuclei with adjacent spinous keratinocytes resembling stellate reticulum. In addition, ghost cells, some of them showing different levels of calcification are seen in the cystic epithelium (**Figures 12A** and **12B**). COC may be confused with unicystic ameloblastoma because of the nuclear palisading and the presence of tissue resembling stellate reticulum. COC has a good prognosis. Local curettage for intraosseous COC and conservative excision for peripheral COC are curative and only few recurrences have been reported.[27]

4. Squamous odontogenic tumor

Squamous odontogenic tumor (SOT) is a rare benign odontogenic neoplasm. It was first described as a separate entity in 1975.[28] This lesion is seen with similar incidence in the mandible and the maxilla at a mean age of 38. At the microscopic level, SOT closely resembles acanthomatous ameloblastoma with islands of benign appearing squamous epithelium. The main feature that allows the distinction between SOT and ameloblastoma is the fact that in SOT, reverse polarization and palisading of the nuclei of keratinocytes is absent. Some islands may show the development of microcysts and/or intraepithelial dystrophic calcifications (**Figures 13A** and **13B**). SOT has a good prognosis as its biological behavior is not linked to recurrences and conservative surgical intervention is curative.[29]

5. Ameloblastic fibroma

Ameloblastic fibroma is a rare odontogenic tumor that is usually diagnosed in the first decade of life.[30] The posterior mandible is the most common site where it presents as an asymptomatic slowly growing tumor.[31] Radiographically, this lesion shows either a unilocular or multilocular radiolucencies associated with an unerupted tooth.[32]



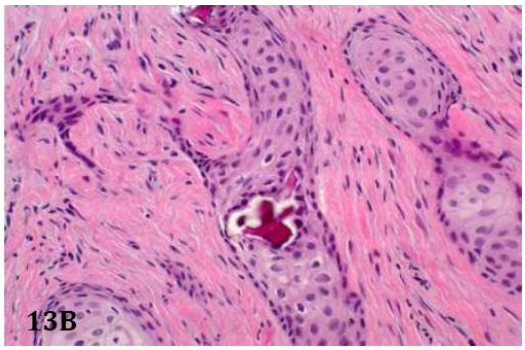
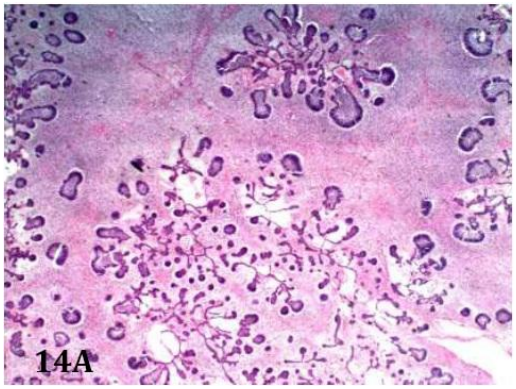


Figure 13. Squamous odontogenic tumor.
13A. Islands of bland-appearing epithelial cells arranged in ovoid to elongated strands. (hematoxylin-eosin stain; original magnification x100).
13B. Absence of reverse polarization of basal cells and conspicuous intraepithelial calcifycations are typically noted. (hematoxylin-eosin stain; original magnification x200).



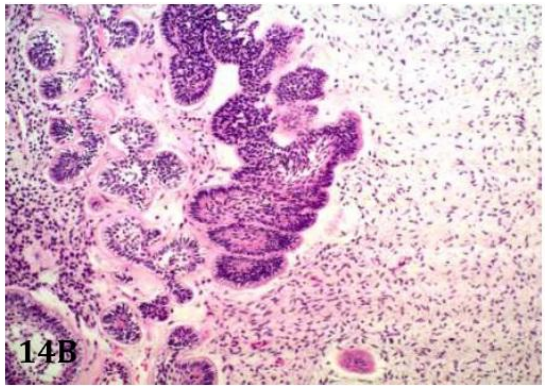


Figure 14. Ameloblastic fibroma.
14A. Cords, strands and buds of odontogenic epithelium amidst an hypercellular connective tissue stroma. (hematoxylin-eosin stain; original magnification x10).
14B. Zones of hyalinization around the epithelial buds are observed. (hematoxylin-eosin stain; original magnification x100).

Histologically, the tumor is composed of islands, cords, and strands of odontogenic epithelium amidst a hypercellular connective tissue stroma that resembles primitive dental papillae (**Figures 14A** and **14B**). At times, areas of hyalinization may be found at epithelial-mesenchymal interfaces.[31] This lesion may be confused with follicular ameloblastoma. However, follicular ameloblastoma lacks the stromal hypercellularity of spindle cells that are characteristic of ameloblastic fibroma. Conservative surgical excision and regular follow-ups are indicated for primary lesions. Wider and more aggressive surgical excision is indicated for recurrences because one third of ameloblastic fibrosarcoma cases arise from recurrent ameloblastic fibromas.[6,33]

6. Ameloblastic fibro-odontoma

Ameloblastic fibro-odontoma is often diagnosed during the first and second decades of life. Ameloblastic fibro-odontoma is usually asymptomatic and may prevent a tooth from erupting or may displace adjacent teeth. Ameloblastic fibro-odontoma represents an ameloblastic fibroma with varying amounts of soft and calcified dental tissues.[34] If there is sufficient calcification of the enamel and dental matrix, the lesion shows radiopaque areas on radiographic films. The hard tissues may be minimal or extensive (**Figures 15A** and **15B**). Confusion with ameloblastic fibroma may occur if the amount of dental tissues is minimal.

7. Ameloblastic fibrosarcoma

Ameloblastic fibrosarcoma is a very rare odontogenic malignancy (**Figures 16A** and **16B**), in which the connective tissue shows microscopic features reminiscent of fibrosarcoma.[35,36] Some of these cases arise *de novo*, but about half of them may arise from a preexisting ameloblastic fibroma.[35] Ameloblastic fibrosarcoma is a locally aggressive tumor and radical resection is indicated. Metastases are not unusual. This tumor can be confused with ameloblastic fibroma and/or ameloblastoma. However, the distinction is easily done by paying attention to the cytological characteristics of the malignant mesenchymal spindle cells of ameloblastic fibrosarcoma that show frequent mitotic figures. Some of them also show aberrant, variation in nuclear chromatism and anisonucleosis.

8. Craniopharyngioma

Craniopharyngioma is a rare epithelial tumor that is identical to ameloblastoma with basal cells showing nuclear palisading, areas of stellate reticulum, keratinization and calcifications. Clinical information is crucial to render the proper diagnosis since craniopharyngioma is located in sellar and suprasellar regions of the sphenoid bone, sites that preclude a diagnosis of ameloblastoma.[37]

9. Adamantinoma

Another lesion that may mimic ameloblastoma histologically is the adamantinoma of long bones. While these two lesions have similar histological appearance, there is no evidence that supports the notion of a common histogenesis.[38] Adamantinoma is considered a low-grade malignant tumor of long bones (tibia or fibula) and the information on the location allows an easy separation of this tumor from ameloblastoma.

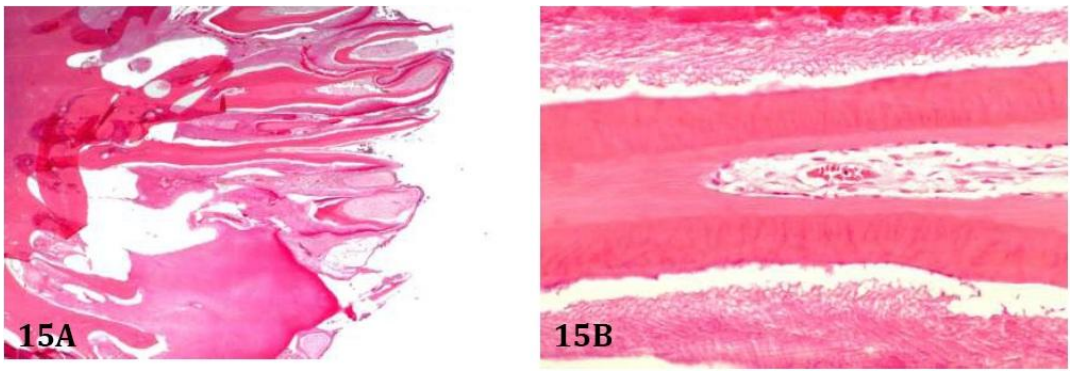


Figure 15. Ameloblastic fibro-odontoma.
15A. Dental structures with a haphazards configuration are present (hematoxylin-eosin stain; original magnification x100).
15B. Enamel matrix (honeycomb appearance) is seen surrounding dentin, predentin and pulp tissues in the odontoma portion of an ameloblastic fibro-odontoma. (hematoxylin-eosin stain; original magnification x200).

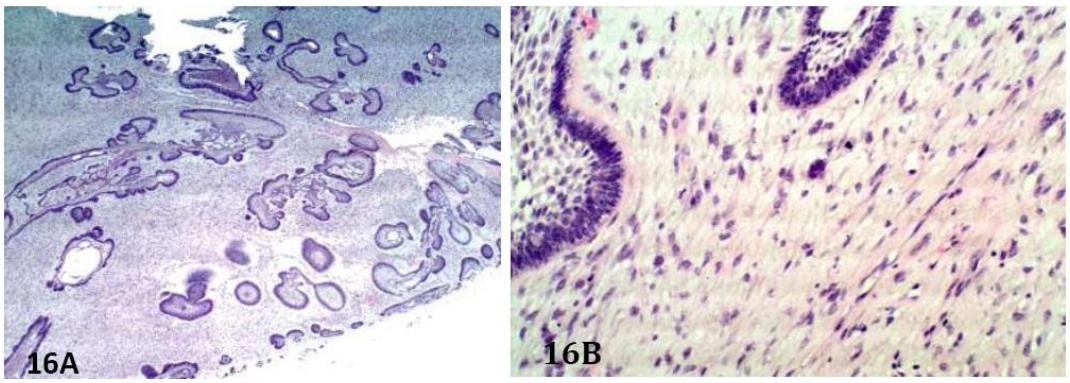


Figure 16. Ameloblastic fibrosar-coma.
16A. Low power view of this tumor suggests a diagnosis of ameloblastic fibroma. (hematoxylin-eosin stain; original magnification x10).
16B. High power view reveals the presence of nuclear pleomorphism and abundant mitotic figures of the malignant stromal cells. (hematoxylin-eosin stain; original magnification x200).

Table 1. Subtypes of Ameloblastoma and Its Mimickers.

Variant	Morphological Features	Mimickers
Follicular ameloblastoma	Multiple islands of odontogenic epithelium exhibiting peripheral nuclear palisading with reverse polarization. Central areas resemble stellate reticulum	• Ameloblastic fibroma • Ameloblastic fibro-odontoma • Ameloblastic fibrosarcoma • Ameloblastic carcinoma • Craniopharyngioma • Adamantinoma
Plexiform ameloblastoma	Anastomosing cords of odontogenic epithelium exhibiting peripheral nuclear palisading with reverse polarization. Areas resembling stellate reticulum mostly absent	• Craniopharyngioma
Acanthomatous ameloblastoma	Islands of odontogenic epithelium exhibiting peripheral nuclear palisading with reverse polarization and conspicuous central squamous differentiation	• Squamous odontogenic tumor (SOT)
Granular cell ameloblastoma	Island of odontogenic epithelium demonstrating basal and /or central cells with prominent granular cytoplasm	
Desmoplastic ameloblastoma	Thin cords of ameloblastic epithelium within a dense fibrous connective tissue stroma. Nuclear palisading of basal cells is tenuous to absent	• Adamantinoma
Basal cell ameloblastoma	Islands of hyperchromatic basaloid cells with peripheral nuclear palisading	• Adamantinoma
Unicystic ameloblastoma	The cyst is lined by ameloblastic basal cells. The overlying epithelial cells are loosely cohesive and resemble stellate reticulum	• Odontogenic keratocyst (OKC) • Calcifying odontogenic cyst (COC)
Peripheral ameloblastoma	Interconnecting cords and islands of ameloblastic epithelium. Only 50% of cases show origin from overlying mucosal epithelium	• Ameloblastoma

SUMMARY

Ameloblastoma is a benign neoplasm that arises from odontogenic epithelium residing in the mandible and to a lesser extent, in the maxilla. This neoplasm shows a wide variety of histological patterns. The main distinctive features of these variants are summarized in **Table 1**. Follicular and plexiform ameloblastomas are the most common variants.

A number of benign and malignant neoplasms as well as cystic lesions may mimic the histological appearance of ameloblastoma. It is important to establish the precise diagnosis of these lesions since the biological behavior and treatment varies according to the diagnosis.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

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