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ORIGINAL ARTICLE

Ameloblastomas: clinical-histopathological evaluation of 85 cases with emphasis on squamous metaplasia and keratinization aspects

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Abstract

Objectives. Ameloblastoma is a benign odontogenic neoplasm with an origin reputed to reactivation of odontogenic structures. Histological classification is based on microscopic features and architectural distribution of neoplastic cells. The importance of squamous metaplasia and keratinization has been disputed in ameloblastomas. Clinical and histopathological aspects were evaluated of 85 ameloblastomas, with attention to keratinization and squamous metaplasia features. ***Study design.*** Clinical-demographical information of 85 ameloblastomas were gleaned from the medical records. Microscopic analysis of all cases was carried out with emphasis on keratinization aspects of each tumor. ***Results.*** Most ameloblastomas (54.12%) were diagnosed in males with a mean age of 37 years. Fifty-six patients were Caucasians (65.88%) and the mandible was affected in 68 (89.4%) cases. Most cases analyzed presented areas of squamous metaplasia/keratinization. Recurrence was detected in 16 cases; this was not related to keratinization aspects of the tumor. ***Conclusions.*** Keratinization is a common feature in ameloblastomas with no impact in tumor behavior.

Key Words: *ameloblastoma, squamous metaplasia, keratinization, odontogenesis*

Introduction

Ameloblastoma is a relatively rare entity that represents ~ 1% of all oral cavity tumors and cysts [1–4]. It is defined as a benign odontogenic neoplasm of epithelial origin without participation of the odontogenic ectomensenchyme.

Ameloblastoma origin is reputed to the induction and reactivation of odontogenic structures—remnants of dental lamina and reduced epithelium of the enamel organ [5,6]. The tumor frequently affects the jawbones, with ~ 80% of cases in the mandible and the other 20% in the maxilla [1,6–13].

Ameloblastomas are classified considering their clinical, histopathological and imaging aspects. This combined classification is important as it has an impact on the clinical management and prognosis of the illness [14].

Histological classification of ameloblastomas is based not only on their cellular features/phenotype, but also on the architectural distribution of neoplastic cells. The tumors are composed of epithelial odontogenic cells with various degrees of differentiation, similar to the epithelial structures of the enamel organ of the normal tooth germ. They are organized in irregular anatomizing strands, nests, islands and cords of odontogenic epithelium separated by variable amounts of connective tissue, with architectural patterns recognized as unicystic, follicular, plexiform, acanthomatous, desmoplastic, granular cell and basaloid [7].

Squamous metaplasia and keratinization have been described as one of the many features in ameloblastomas and, according to the WHO classification, the term acanthomatous should only be rendered when extensive keratinization is present [15,16]. In the past, some authors believed that keratinization in ameloblastomas was related to recurrence, invasion and malignancy [1,7]. More recently, this feature is reputed only as another aspect of ameloblastomas with no impact on their biological behavior [17].

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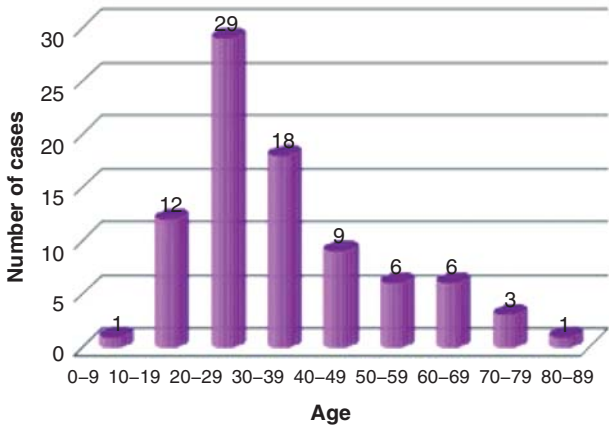

Figure 1. Distribution of age ranges in the cases of ameloblastomas included in the study.

The present study evaluated the clinical and histopathological aspects of 85 ameloblastomas, based on the WHO classification, with special attention to the presence of squamous metaplasia and keratinization and recurrences.

Cases and methods

The medical records of 85 cases of ameloblastomas were analyzed and information on age, gender, ethnic group, site of lesion, type of treatment and recurrence was collected.

Histopathological examination of the ameloblastomas included all slides representative of the surgical specimens of the tumors and followed the WHO classification criteria for ameloblastomas. Two pathologists reviewed all slides. In cases where there was disagreement, a third pathologist was consulted. All histological sections were stained with hematoxylin and eosin (H/E).

A semi-quantitative assessment of squamous metaplasia was established based on the percentage of total tumor islands showing keratinization/squamous metaplasia:

(1) 0–20%: mild keratinization/squamous metaplasia;
(2) 21–50%: moderate keratinization/squamous metaplasia; and
(3) 51%, intense keratinization/squamous metaplasia.

All histopathological data was compared with the clinical and follow-up data of each case.

Results

Out of the 85 cases examined, 46 (54.12%) were male and 39 (45.88%) female. Age of patients at time of histological diagnosis ranged from 9–82 years, with a mean of 37 years. Just over half (47 patients) were between the 2nd and 3rd decades of life; most (29 patients) were younger than 30 years of age, as shown in Figure 1. Fifty-six patients were Caucasians (65.88%), 26 Black patients (30.58%), two Asians (2.35%) and one Afro-Brazilian (1.17%).

The mandible was affected in most cases (89.4%): 68 cases occurred in the posterior region of the mandible and eight cases were recorded in the anterior mandible. Eight cases (9.41%) were diagnosed in the posterior maxilla and one (1.17%) case in the anterior maxilla. Only one (1.17%) case was restricted to soft tissues.

Histopathological aspects

Histopathological analysis of the ameloblastoma sections representative of the surgical specimens revealed a great architectural and morphological diversity within a single tumor. Therefore, a final classification for each case was established considering the predominant histopathological features at the end of the analysis of all slides of each ameloblastoma. Thirty-one cases (36.47%) were classified as follicular ameloblastomas, 34 (40%) were classified as plexiform ameloblastomas, two (2.35%) cases were classified as acanthomatous ameloblastomas, nine (10.58%) were granular cell ameloblastomas, one (1.17%) case was a basaloid ameloblastoma, three (3.53%) were desmoplastic ameloblastomas and five (5.88%) were unicystic ameloblastomas. Examples of the histopathological aspects of the ameloblastoma analyzed are depicted in Figure 2.

In most cases analyzed, variable areas of squamous differentiation (squamous metaplasia/keratinization) were observed (Table I) .

Recurrences

Recurrence was recorded in 16 cases: 13 (81.25%) cases were in the posterior mandible region, two (12.5%) in the anterior mandible region and one (6.25%) in the posterior maxilla region. In (Table II) the recurrences are shown according to the anatomical location, type of treatment and presence of squamous metaplasia/keratinization.

Discussion

Our study found that ameloblastomas have a wide morphological variety, especially when considering the analysis multiple sections. This variety, combined with the diversity of their clinical presentation, is reflected in the number of studies on ameloblastomas in the English literature.

The clinical and demographic data observed in our cases matched with previous studies on ameloblastomas: white male patients were the most affected, the mean age of diagnosis range at around the 3rd and 4th decades and there was no gender predilection [6,7,16], although others have reported a predominance of

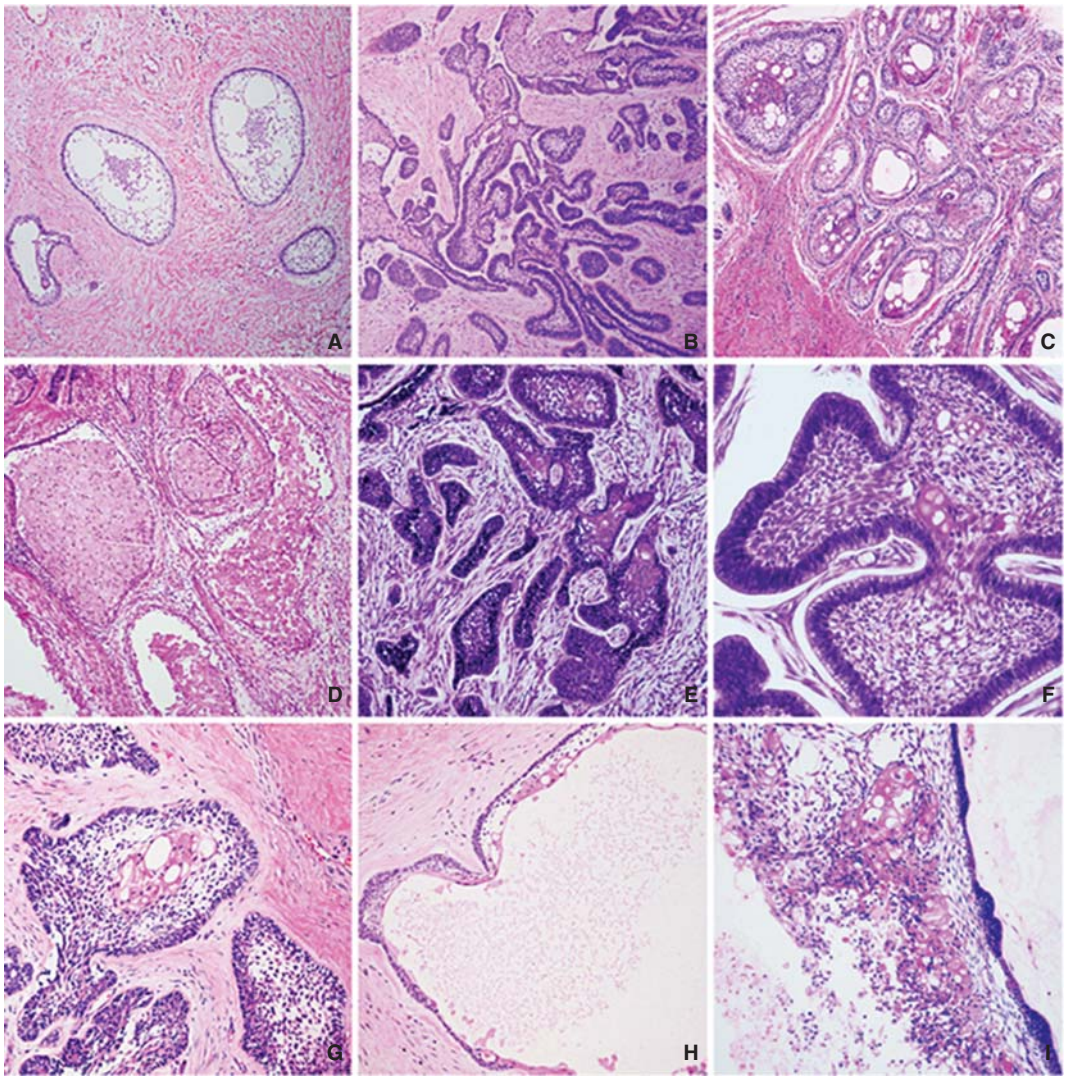

Figure 2. Examples of histopathological aspects of the ameloblastomas included in the study. (A) Follicular aspect of a multilocular ameloblastoma (H&E, original magnification ×100). (B) Anastomosing islands of neoplastic epithelium forming a plexiform aspect of ameloblastoma (H&E, original magnification ×100). (C) Ancanthomatous ameloblastoma with widespread keratinization in the neoplastic islands (H&E, original magnification ×200). (D) Granular-cell ameloblastoma—epithelial cells with eosinophilic granules in the cytoplasm (H&E, original magnification ×200). (E and F) Basaloid ameloblastoma: epithelial cells with basophilic hiperchromatic large nuclei, organised in anastomosing islands intermingled with a cellular fibrous connective tissue (H&E, original magnification ×100 and ×400, respectively). (G) Desmopastic ameloblastoma: note the highly collagenized stroma surrounding the ameloblastoma island (H&E, original magnification ×200). (H and I) Unicystic ameloblastoma: note the ameloblastic epithelium surrounding the cystic cavity in (H) and the mural growth in (I) (H&E, original magnification ×100 and ×400, respectively).

males [12,18,19]. Regarding race, most authors report that there is no predilection and a higher frequency among black patients is debated [16,20].

The posterior mandible was the most affected site in our cohort, with 80% of cases diagnosed in this location. This is similar to other studies, which report that 80% of cases of ameloblastomas occur in the mandible and the other 20% in the maxilla [1,6–13].

In the histopathological evaluation, our study found a large morphological diversity within a single tumor, with areas representative of more than one histological and architectural aspect. It is important to emphasize that our classification was based on a rigorous review of slides of surgical specimens and they were not only classified according to slides of incisional biopsies. This analysis revealed a slight predominance of the plexiform sub-type of ameloblastomas.

Many authors discuss the importance of identifying histological variants of ameloblastomas in order to reach a consensus in classification of the tumor and also to provide a better type of treatment and prognosis. However, Mehlisch et al. [8] believe that the histological variations have no effect on the prognosis of ameloblastomas and Ferretti et al. [14] found that the histological variant does not alter the type of treatment. Additionally, Gardner and Pecak [2] and Gardner [21] believe that these histological variations are only relevant to recognize the morphological differences of ameloblastomas, but have no value in determining the clinical or biological behavior, the

Table I. Semi-quantitative analysis (percentage) of squamous metaplasia and keratinization for each type of ameloblastoma.

Ameloblastoma type	Total cases	% Squamous metaplasia/ keratinization		
		0–20%	21–50%	> 51%
Folicular	31	16	8	7
Plexiform	34	30	3	1
Acanthomatous	2	0	1	1
Granular cells	9	9	0	0
Basaloid	1	1	0	0
Desmoplasic	3	3	0	0
Unicystic	5	3	2	0

degree of invasion or even to predict rare cases of malignancy or metastasis.

In addition to classifying ameloblastomas subtypes, we used a semi-quantitative analysis for the presence of squamous metaplasia and keratinization in the tumors included in our study. This analysis revealed that most ameloblastomas presented some degree of squamous metaplasia/keratinization.

The assessment of squamous metaplasia/ keratinization in ameloblastomas has been a controversial issue for several decades. For many authors, this histological presentation of ameloblastomas does not indicate an aggressive course of the lesion; and that this aspect can sometimes be confused with a squamous odontogenic tumor, squamous cell carcinoma or basal cell carcinoma [8,17].

Small and Waldron [1] believed that squamous differentiation was not an indicative point for recurrence or malignancy. However, Aisenberg [15] related this characteristic to a greater predisposition to extensive invasions and recurrence. According to Anneroth and Hansen [17] it is important to emphasize that there is no evidence that the presence of squamous metaplasia and keratinization in acanthomatous ameloblastoma is indicative of increased rates of malignancy or recurrence. Additionally, biological evidence shows that keratinization is a complex process involving tonofilaments and keratohyaline granules. Epithelial cells of odontogenic tumors contain tonofinalments and can, theoretically, become keratinized, according to Regezi et al. [22]. Our results agree with these authors, as we have found no relation between keratinization and recurrences in the cases studied.

Several factors may result in increased rates of recurrence: clinical and image size/aspects of the tumor, anatomical location, histological features and inappropriate surgical procedure [12,14]. Kim and Jang [23] found that when the follow-up period after surgery is too short, this hinders the presentation of specific data on rates of relapse and that there should be a minimum of 5 years of revaluations since 50% of all recurrences occur in this period.

The squamous metaplasia/keratinization aspects of the ameloblastomas analyzed in our study presented similar features to those described in phases of odontogenesis. Recently, it has been postulated that ameloblastoma origin is associated to the remnants of dental lamina [5,6,12]. For Joseph and Savage [24], the aggressive nature of the ameloblastomas may be closely linked to the similarity between their behavioral characteristics and those of the dental lamina. Both the dental lamina and the ameloblastoma have the ability to invade adjacent tissue, and the finger-like projections of proliferating cells of dental lamina resemble peripheral invasive growth observed in association with the growth of the ameloblastoma [25]. We agree with this hypothesis as the degree of differentiation of cells or ameloblastic islands seen in our study recalls early stages of the odontogenesis and, especially, areas of keratinization can be observed in the ameloblastomas similar to keratinized areas of the dental lamina.

Confirming this hypothesis based on our morphological analysis, some immunohistochemical studies revealed that the ameloblastoma cells express various cytokeratins, which are also expressed in cells of the stellate reticulum, the dental lamina, reduced enamel epithelium of the enamel organ and metaplastic keratinizing cells and squamous cells, respectively [26].

Thus, the most probable theory for the origin of ameloblastomas is reinforced, as seen in our histopathological study. Some ameloblastoma also

Table II. Ameloblastomas: Comparison of recurrences according to site, type of treatment and presence of squamous metaplasia/ keratinization.

	Curetage				Curetage and cryotherapy				Surgical resection			
		% squamous metaplasia/ keratinization				% squamous metaplasia/ keratinization				% squamous metaplasia/ keratinization		
	Total	0–20%	21–50%	> 51%	Total	0–20%	21–50%	> 51%	Total	0–20%	21–50%	> 51%
Posterior Mandible	2	2	—	—	8	4	3	1	3	3	—	—
Anterior Mandible	1	—	1	—	1	—	1	—	—	—	—	—
Posterior Maxilla	1	1	—	—	—	—	—	—	—	—	—	—

resemble other more developed phases of odontogenesis—bud, hood and Bell phases in which epithelial cells begin to differentiate into with high proliferative activity due to the intense activity of mitosis.

Therefore, we believe that the origin of the ameloblastoma from remnants of dental lamina and the reduced epithelium of the enamel organ explains the variety of histopathological aspects of the tumors. The histopathological aspects of keratinization in ameloblastomas are similar to the aspects of the dental lamina and occur, in most tumors, without association with recurrence. Therefore, keratinization in ameloblastomas may be only another histopathological feature with no impact in the tumor behavior.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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