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The Clinical and Histological Analysis of 140 Cases of Ameloblastoma: An Emphasis to Histological Variants

140 Ameloblastom Olgusunun Klinik ve Histolojik Analizi: Histolojik Varyantların Değerlendirilmesi

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ABSTRACT Objektive: The objective of this study is to evaluate the clinical and demographic features of ameloblastoma cases of a pathology center with a detailed examination of the histopathological properties of the subtypes and variants. **Material and Methods:** The clinical and radiological data and histologic slides of ameloblastoma cases diagnosed and treated between 2005 and 2017 were retrieved from the archives. Histopathological features of previously diagnosed cases were re-evaluated and re-classification of all cases was performed in accordance with the World Health Organization (WHO) classification of odontogenic tumors. The significance of the relationship between radiological appearance (multiocularity/unilocularity) and final histological diagnosis (solid/unicystic) was evaluated with statistical analysis. **Results:** There were a total of a hundred and forty cases of ameloblastoma. A hundred and twenty (85.7%) cases were diagnosed as solid type. Sixteen (11.4%) cases were diagnosed as unilocular ameloblastoma. Three cases showed admixed histopathological characteristics. There was a significant relationship between radiological appearance and histological diagnosis (p=0.005). All recurrent luminal unicystic ameloblastomas were re-diagnosed as mural subtype in the histopathological examination. **Conclusion:** The presence of rare variants should be diagnosed correctly with a thorough histopathological examination to contribute to the prognosis. The radiographic appearance of the tumor is correlated with the histological subtype. In the examination of recurrent unicystic cases, the surgical specimen should be entirely inspected to indicate mural ameloblastic invasions.

Keywords: Ameloblastoma; histopathology; diagnosis

ÖZET Amaç: Bu çalışmanın amacı, bir patoloji merkezindeki ameloblastoma olgularının alt tiplerinin ve varyantlarının histopatolojik özelliklerini detaylı şekilde inceleyip klinik ve demografik özelliklerini değerlendirmektir. **Gereç ve Yöntemler:** 2005-2017 yılları arasında tanı koyulan ve tedavi edilen ameloblastoma olgularının klinik ve radyolojik verileri ve histolojik kesitleri arşivlerden temin edildi. Önceden tanı alan olguların histopatolojik özellikleri yeniden değerlendirildi ve tüm olguların Dünya Sağlık Örgütü (DSÖ) odontojenik tümör sınıflamasına göre yeniden sınıflandırılması yapıldı. Radyolojik görünüm (multiloküler / uniloküler) ile nihai histolojik tanı (solid / unikistik) arasındaki ilişkinin istatistiksel analiz ile değerlendirilmesi yapıldı. **Bulgular:** Çalışmaya toplam 140 ameloblastoma olgusu dahil edildi. Yüz yirmi (%85,7) olgu solid tip olarak teşhis edildi. On altı (%11,4) olguya uniloküler ameloblastom tanısı kondu. Üç vakada rutin sınıflama içerisine girmeyen çeşitli histopatolojik özellikler gösterildi. Radyolojik görünüm ile histolojik tanı arasında anlamlı bir ilişki saptandı (p= 0.005). Tüm rekürrent lüminal unikistik ameloblastomlara histopatolojik incelemede mural alt tipi olarak tekrar tanı koyuldu. **Sonuç:** Ameloblastoma olgularında nadir varyantların varlığı prognoza katkıda bulunması için ayrıntılı bir histopatolojik inceleme ile doğru şekilde teşhis edilmelidir. Tümörün radyografik görünümü ile histolojik alt tipi arasında ilişki bulunmaktadır. Tekrarlayan unikistik olguların muayenesinde, cerrahi örnek, mural ameloblastik invazyonu göstermek için bir bütün olarak incelenmelidir.

Anahtar Kelimeler: Ameloblastom; histopatoloji; teşhis

Ameloblastoma is a frequent odontogenic tumor that is characterized by progressive growth and a tendency for recurrrence.[1] It is usually seen in the fourth and fifth decades.[2,3] In the World Health Organization (WHO) classification in 2017, ameloblastoma is classified in four subtypes: solid, unicystic, peripheral and metastasizing.[4] Solid subtype includes several histological variants: follicular, plexiform, granular, des-

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moplastic, acanthomatous, basaloid and keratinizing, that mainly do not affect prognosis.[5,6] Unilocular ameloblastoma is also classified in three subtypes as luminal, intraluminal and mural. Luminal subtype lines the cystic cavity with peripheral palisading polarized tumoral cells with overlying stellate reticulum-like cells. Intraluminal subtype consists of intraluminal projections of plexiform ameloblastoma which is lining the cystic cavity as in luminal subtype. Mural subtype is an important subtype of unilocular ameloblastoma consisting of mural projections of ameloblast-like epithelium into the connective tissue wall and behaves aggressively similar to the solid subtype.[7] Therefore, the diagnosis of unilocular ameloblastoma subtypes is substantially important in the prognosis.

Ameloblastoma is an epithelial tumor and radiographic presentation varies even it is seen as well-defined radiolucency in most cases. Solid ameloblastoma is generally observed as a multilocular corticated lesion with a soap bubble or honeycomb appearance whereas unicystic ameloblastoma demonstrates a well-defined unilocular radiolucency around an unerupted tooth.[4] However, a unilocular appearance may be present in the radiological examination of solid subtype.[8] It is an important issue to diagnose the subtypes of ameloblastoma correctly because the treatment approach is usually different for solid and unicystic ameloblastoma.

Clinicopathological and radiological features with racial and geographic variations of the tumor were vastly studied so far.[5,9,10] However, there are no collective clinicopathological studies about ameloblastoma apart from individual case series in the Turkish population to our knowledge. Some of the subtypes and variants of ameloblastoma are identified with clinicopathological features. However, the exact diagnosis of several rare variants can be challenging due to the confusing histopathological characteristics and distinct clinical behaviours. A null hypothesis that there is no direct relationship between the histological subtype and radiological appearance (multilocularity/unilocularity) of the tumor is made and the aims of the study were established as;

1) to assess the relationship between the histological appearance and radiological presentation of the tumor.

2) to evaluate the clinical, histological and demographic features and available recurrence data of ameloblastoma cases of a pathology center with detailed examination of histopathological properties of the subtypes and variants.

MATERIAL AND METHODS

This study was approved by local ethics committee with approval number of 2019-128 and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The clinical and radiological data, histological slides and paraffin blocks of all cases of ameloblastoma diagnosed and treated between 2005 and 2017 were retrieved from the archives of a private pathology laboratory. A significant portion of the materials examined in this laboratory is oral pathology specimens. Histopathological features of previously diagnosed cases were re-evaluated and classification of all cases was performed under the WHO classification of odontogenic tumors in 2017. All slides had been stained with hematoxylin and eosin (HE). Additional cuts were taken from paraffin blocks and stained with HE if needed.

Maxilla was divided into 2 regions for the evaluation of the localization of maxillary tumors. The anterior part was between distal surfaces of the right and left canine teeth. The posterior part was between the mesial surface of the first premolar tooth and the third molar tooth. Mandible was divided into 3 regions as anterior, posterior and coronoid region. The anterior part was between distal surfaces of right and left canines. The posterior part was between the mesial surface of the first premolar tooth and condylar neck. Coronoid process was designated as the coronoid region. The data of localization and gender was demonstrated with case numbers and percentages.

The retrieved radiological data was transferred and evaluated on a computer program (Planmeca Romexis Viewer, Helsinki, Finland) for the evaluation of multi and unilocularity. Tumors with only one radiolucent locule on the radiograph were defined as unilocular. Tumors with more than one radioluscent locule on radiograph were diagnosed as multilocular.

SPSS 20.0 software program (International Business Machines Corp., New York, USA) was used for statistical analysis. Descriptive statistics were performed to demonstrate the mean values and distribution of the data. A Shapiro-Wilk test ($p < 0.05$) and a visual inspection of their histograms, normal Q-Q plots, and box plots showed that the examination scores were not normally distributed for the data of age and recurrence period. Pearson Chi-square test was used for the evaluation of the relationship between radiological appearance (multiocularity/unilocularity) and final histological diagnosis. The confidence interval was set to 95% and $p < 0.05$ was considered statistically significant.

RESULTS

There were a total of 140 cases of ameloblastoma diagnosed and treated between 2005 and 2017. The mean age was 37.7±16.5 with a range between 11 and 82 years. Seventy-five (53.6%) cases were male and 64 (45.7%) were female. The gender data of 1 (0.7%) case and age data of 17 (12.1%) cases were not available. Clinical examination of the majority of cases revealed expansion and dull pain on the affected sites of the jaws. Generally, patients were asymptomatic and lesions were diagnosed incidentally on radiographic examination. The localization data is demonstrated in Table 1.

TABLE 1: Localization of all cases with percentage data.

	Localization n(%)			
	Mandible	Maxilla	Unavailable data	Total
Anterior Region	2 (1.4%)			2 (1.4%)
Left Posterior Region	50 (35.7%)	2 (1.4%)		52 (37.1%)
Right Posterior Region	44 (31.4%)	10 (7.1%)		54 (38.5%)
Right Posterior Region	2 (1.4%)			2 (1.4%)
Multi-segment	1 (0.7%)			1 (0.7%)
Incomplete Data*	21 (15%)	3 (2.1%)		24 (17.1%)
Unavailable Data			5 (3.5%)	5 (3.5%)
Total	120 (85.7%)	15 (10.7%)		140 (100%)

*Individual jaw localization without the regional localization data.

All radiological data was in the form of panoramic radiography and available in 109 cases. There were 71 multilocular lesions of which 66 cases showed a solid classical histological depiction of ameloblastoma and 5 of them were histologically diagnosed as unicystic ameloblastoma. Histological diagnosis of 28 cases showing radiological unilocularity was diagnosed as solid classical ameloblastoma and 10 of them were diagnosed as unicystic ameloblastoma. There was evidence of a relationship between radiological appearance and histological diagnosis (Table 2) ($p = 0.005$).

A hundred and twenty cases (85.7%) were diagnosed as solid type ameloblastoma. The number of cases of follicular, plexiform, granular, desmoplastic, acanthomatous, basaloid and keratinizing variants were 68 (48.5%), 38 (27.1%), 1(0.7%), 6 (4.2%), 3(2.1%), 3 (2.1%), 1(0.7%) and 3 (2.1%) , respectively.

The histopathological examination of granular ameloblastoma revealed peripheral reversed polarized ameloblast-like cell proliferation and centrally accumulated eosinophilic granular cells (Figure 1). Histopathological examination of 16 (11.4%) cases revealed palisaded reversed polarized ameloblastic

TABLE 2: The relationship between histological subtype and radiological appearance was determined with the aid of a contingency table.

			Histological Subtype of Ameloblastoma			
			Solid	Unicystic	n	p
Radiographic Appearance	Multilocular	Count	66	5	71	
		Expected Count	61.2	9.8	71.0	
	Unilocular	Count	28	10	38	
		Expected Count	32.8	5.2	38.0	
n		Count	94	15	109	
		Expected Count	94.0	15.0	109.0	
p						0.005

epithelium with overlying stellate reticulum-like cells that are lining a cystic cavity and they are diagnosed as unilocular ameloblastoma. Six (4.2%) of the unilocular ameloblastoma were of intraluminal type (Figure 2), 5 (3.5%) of them were of mural type (Figure 3), 5 (3.5%) of them were of luminal type. (Figure 4) Three cases (2.1%) were diagnosed as peripheral ameloblastoma. In 1 (0.7%) of the intraosseous, large and solid ameloblastoma cases, histopathological examination revealed numerous multinucleated giant cells and dentinoid-like material production in between ameloblastic epithelial nests and cords (Figure 5 A, B). This case recurred three times and last surgery was a wide en-bloc resection.

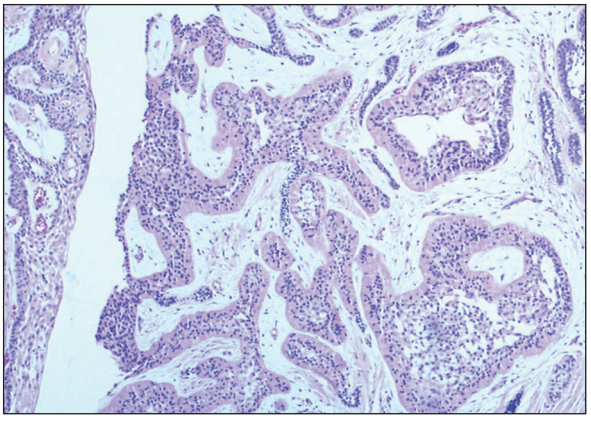

FIGURE 1: Granular ameloblastoma is composed of ameloblast-like cell nests with reverse polarity and centrally accumulated cells with eosinophilic granular cytoplasm dispersed in a loose connective tissue stroma (HEx40).

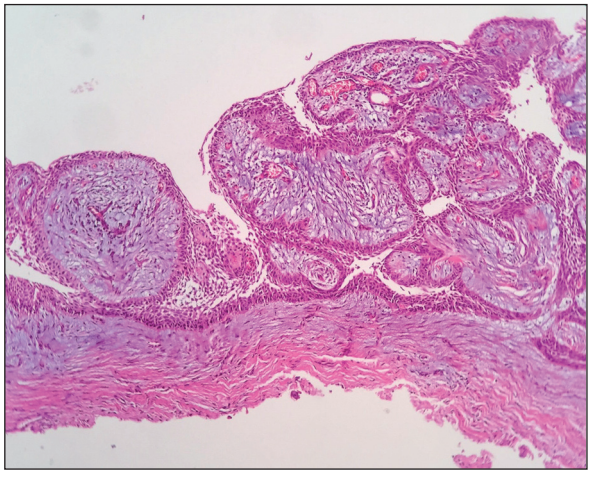

FIGURE 2: Ameloblastomatous cell nests proliferate into the lumen of the cystic lesion that is lined with palisaded and polarized ameloblastic epithelium in the intraluminal form of unicystic ameloblastoma (HEx40).

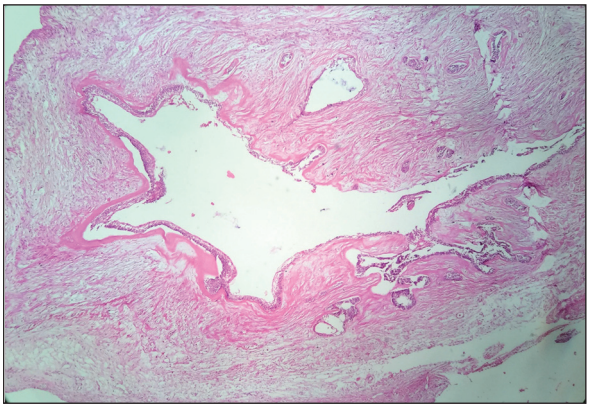

FIGURE 3: Ameloblastic satellite tumor nests invade the collagenous wall of the unicystic mural ameloblastoma (HEx40).

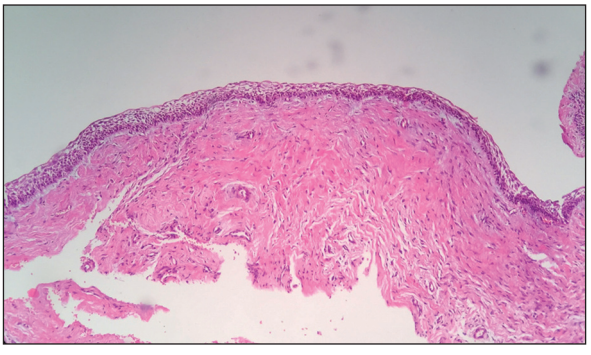

FIGURE 4: Cystic lesion lined with palisaded ameloblastic epithelium with overlying stellate-reticulum-like epithelial cells in the luminal form of unicystic ameloblastoma (HEx40).

Three cases showed admixed histopathological characteristics. One of them showed typical 3-5 layered parakeratinized epithelial lining of the odontogenic keratocyst on the upper parts of the cavity and transformation of squamous epithelium to ameloblast-like epithelium commenced gradually from the lateral parts of the cavity until the ameloblastic cells formed a mass at the lower part of the slide (Figure 6). This case did not show the characteristics of true keratoameloblastoma, therefore, it is diagnosed as ameloblastic transformation in odontogenic keratocyst. The other case showed the characteristics of true keratoameloblastoma with solid keratin accumulation that is integrated with the connective tissue stroma and scarce focal ameloblastic epithelium proliferation but without the foreign body reaction to keratin (Figure 7 A,B). A possible antigenic alteration is considered for the explanation of the massive keratin deposition without any foreign body reaction. The last case showed simultaneous occur-

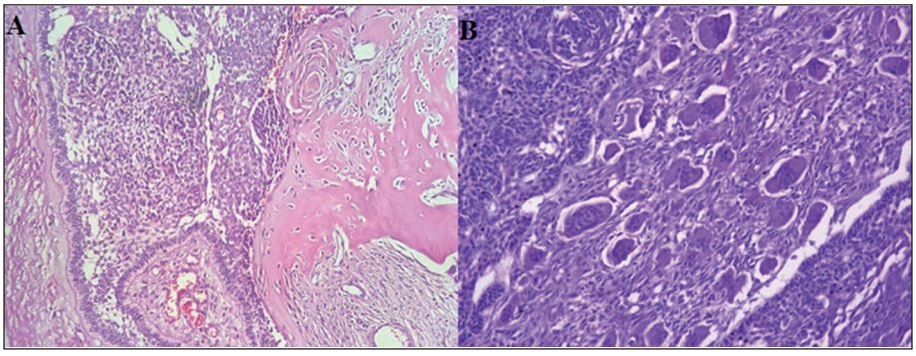

FIGURE 5: A) Histological examination reveals follicular nests of peripherally lined ameloblast-like palisading cells with nuclear polarity and dentinoid-like matrix deposition on the right side of the slide (HEx200). **B)** Abundant multi-nucleated giant cells dispersed in the tumoral stroma can be clearly seen (HEx200).

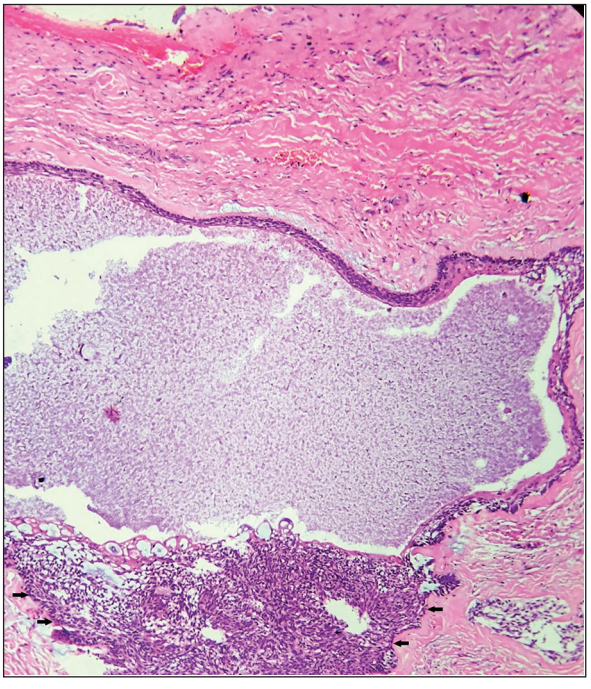

FIGURE 6: Histological examination revealed cystic lesion lined with parakeratotic odontogenic epithelium that shows ameloblastic differentiation on the inferior layers of the cystic lining (arrows). Keratinized debris can be seen in the lumen (HEx40).

rence with the glandular odontogenic cyst. There was no diagnosis of metastasizing ameloblastoma in these series.

There were 17 (12.1%) cases with documented recurrence. The mean recurrence period was 3.3±4.2 years. Three of the recurrent cases were unicystic ameloblastoma with luminal subtype and 13 of them showed classical histology of solid subtype with 2 acanthomatous, 1 desmoplastic, 6 follicular and 4 plexiform subtypes. All recurrent luminal unicystic ameloblastomas were re-diagnosed as mural subtype in the histopathological examination.

DISCUSSION

The gender distribution found in this study showed a slight male preponderance with a ratio of 1.1 and this is consistent with the literature findings.[11-13] In several studies, it is reported that equal distribution may also be observed.[10] The reported mean age of the patients with ameloblastoma at the diagnosis stage is about 34 years.[4] In this study, the mean age was 37.7 ±16.5 years and it is similar to the literature data. However, in developed countries, it is reported that mean age at diagnosis may be higher compared to overall mean age.[1,12]

The radiological presentation of ameloblastoma becomes the first line of diagnosis and aids the clinician to contemplate a surgical approach for the treatment of the tumor. It is suggested that the solid subtype generally presents a multilocular appearance whereas unicystic subtype presents a unilocular appearance in the radiography.[4] Unicystic ameloblastoma is mostly represented as a well-defined radiolucency usually associated with an unerupted tooth, however, radiological presentation of solid ameloblastoma may be identical to the unicystic subtype showing unilocular radiolucencies in radiography as well.[11] Similarly, tumors showing multilocular radiolucency may show histological characteristics of unicystic subtype. In the study of Bansal et al., it is reported that 10 cases of solid ame-

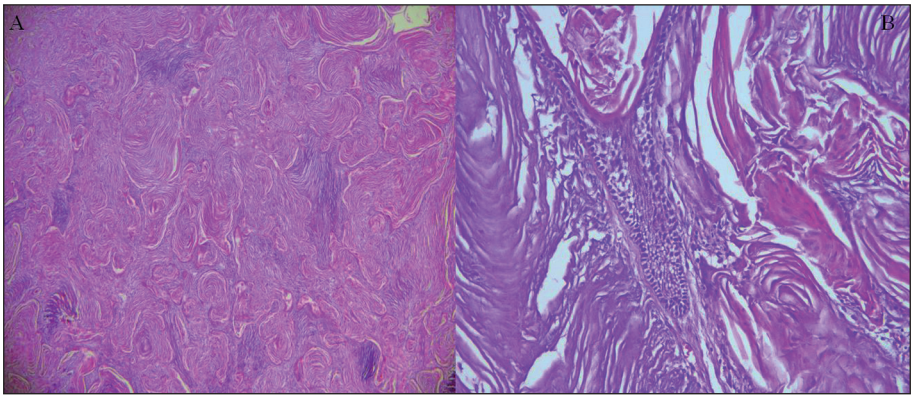

FIGURE 7: A) There are abundant keratin corpuscules dispersed throughout the slide with regional ameloblast-like cell proliferation (HEx40). **B)** Ameloblast-like cell layers within the wave-like keratin production can be clearly seen (HEx200).

loblastoma demonstrated well-defined unilocular radiolucency and 5 cases of unicystic ameloblastoma exhibited multilocular radiolucency.[8] In the present study, the majority of tumors presenting as multilocular radiolucency showed histological characteristics of solid ameloblastoma and there was a significant relationship between radiological appearance and histological pattern.

The solid subtype is the predominant form of ameloblastoma. Follicular and plexiform variants are the most common histopathological patterns of solid subtype.[9,10] These variants occasionally coexist in an individual tumor and classified using the predominant variant in the identification of the lesion.[13,14] In the current study, follicular and plexiform variants also dominated the histological appearance and denomination of each case was made with the predominant histological pattern. All histological variants of solid form such as granular, basaloid, desmoplastic and acanthomatous ameloblastomas defined in the original classification are also identified in our case series.

Unicystic ameloblastoma constitutes 5-22% of all ameloblastomas and mostly located on the third molar area and ascending ramus.[15,16] Radiographically, it is almost always observed as a well-defined unilocular radiolucency and may be misdiagnosed as an odontogenic cyst. The clinical behaviour of luminal and intraluminal types are deemed to be non-aggressive due to the tumor growth towards lumen and mostly treated with conservative methods. The prognosis of the mural type is questionable due to the ameloblast-like cell islands or daughter tumor formations towards the collagenous tumoral wall. Filizzola et al. reported that the majority of unilocular forms in their case series are mural type.[13] In the present study, a diagnosis of mural ameloblastoma was made in the histopathological examination of three recurrent cases of unilocular ameloblastomas with luminal subtype indicating that the previous first-line treatments of these recurrent cases may have been insufficient to eradicate the mural counterpart of the lesion or luminal form may have been transformed into an aggressive stage and invaded the bony wall of the cystic cavity as mural form. Unfortunately, the treatment modalities applied to each patient could not be achieved due to the limited data about the clinical presentation of the cases and reliable comparison between treatment modalities and recurrence patterns could not be made.

Granular and desmoplastic forms of ameloblastoma show distinct histopathological features and they are included as histological variants rather than separate subtypes in the current classification of the tumor. The granular form consists of granular cells with eosinophilic cytoplasm replacing the stellate reticulum in the central areas of the epithelial ameloblastic nests. Although it is suggested that the behaviour of granular variant does not differ from other histological variants of solid form and granular degeneration do not have any effect on prognosis as any other histological variant.[17] However, the tumor demonstrates a higher recurrence rate when compared with follicular, plexiform and acanthomatous

subtypes.[1] Therefore, the morphological features of the variant should be identified properly in the diagnosis. Desmoplastic ameloblastoma is a rare histological variant of ameloblastoma and it is not included in the current classification as a subtype similar to granular form. Histological examination of this form reveals scattered ameloblastic epithelial nests with significant stromal collagen production. Desmoplastic form may be misdiagnosed as squamous odontogenic tumor or squamous cell carcinoma due to the absence of typical palisading ameloblastic columnar cells. Myxoid changes may also be present around the tumoral nests. The desmoplastic feature of this variant does not determine prognosis similar to other histological variants.[5] However, higher recurrence rates compared to other histological subtypes of the solid form were reported.[18,19] Further case series may illuminate the true nature of this variant.

Keratoameloblastoma is a variant of solid ameloblastoma consisting of intense keratinization with ameloblastic cell proliferation.[20] Although this variant is not included in the fourth WHO classification of Head and Neck Tumours in 2017, recently published reports agree upon the authenticity of this entity. There are conflicting opinions about the classification and characterization of keratoameloblastoma because of the multifarious histopathological features of the lesion. The histopathological examination of keratoameloblastoma usually reveals cystic cavities lined with parakeratinized squamous epithelium resembling odontogenic keratocyst with the ameloblastic epithelial component in the follicular form.[21] A combined lesion of ameloblastoma and odontogenic keratocyst was also reported in the literature.[22] Keratinization is considered to be a part of acanthomatous ameloblastomas and Sisto and Olsen suggested that keratoameloblastomas should be included in the acanthomatous ameloblastoma subgroup.[21] Keratoameloblastoma is classified in four main forms as papilliferous, simple, simple with odontogenic keratocyst and complex form to diminish the debate and establish a standard for the differential diagnosis.[23] However, there still seems to be ongoing confusion because there is no exact histopathological data to differentiate ameloblastoma arising in an odontogenic keratocyst and a separate entity of keratoameloblastoma. In the present study, there were 3 cases of keratoameloblastoma with distinct keratinization dispersed throughout the lesion. In one case, there was ameloblast-like differentiation on the parakeratinized epithelial lining of an odontogenic keratocyst. We felt that this entity demonstrated histological features of a combined lesion of ameloblastoma and odontogenic keratocyst rather than a keratoameloblastoma.

Giant cell accumulation is not a frequent histological feature of the ameloblastoma, however, it can be observed in the septal connective tissue of the tumor.[24,25] Several studies reported that multinucleated giant cells in ameloblastoma are from macrophage lineage rather than bone-resorbing osteoclast lineage.[25,26] Bone or hard tissue formation in ameloblastoma is very rare, though reported previously.[24,25,27] Calcified material producing ameloblastoma may present histological features of both ameloblastoma and adenomatoid odontogenic tumor which comprises duct-like structures that form from the odontogenic epithelium component of the tumor.[28] This entity was named as adenoid ameloblastoma with dentinoid due to the adenomatoid features of the lesion. The case with dentinoid induction in our series was an interesting one with histological features showing coexistence of both multinucleated giant cell formation in the connective tissue stroma and dentinoid-like material formation. The case was quite aggressive with three recurrences. Although WHO classification in 2017 did not include them, rare cases of ameloblastomas showing giant cell accumulation were reported with explanatory histological features previously.[25,29]

Ameloblastoma has a high tendency for recurrence after treatment. Conservative treatments with enucleation, marsupialization or curettage show high recurrence rates when compared with radical surgical treatments.[2,8] It is reported that more than 50% of the recurrences occur after first-line treatment.[4] Milman et al. reported a recurrence rate of 24% with an average time to first recurrence as 4.6 years and it is also suggested that there was no significant association between tumor location, age or histological pattern and recurrence.[12] In the present study, the recurrence data was extracted from the data of the

previous referrals of the patient to our institution. There was a recurrence rate of 12.1% which is consistent with the study of Krishnapillai et al., however, fairly lower than the other previously reported data.[1,21,30]

CONCLUSION

The demographic data in our series were generally consistent with the literature. Our results showed that the unilocularity or multilocularity of the tumor is evidently related to the histological subtype. However, the surgical treatment of ameloblastomas showing unicystic radiolucency should not be underestimated because the tumor may demonstrate solid features histologically and behave more aggressive than the unicystic form. Granular and desmoplastic variants are classified as histological subtypes of solid form and show recurrent nature and distinct histopathological features. Increasing number of future case series and clinicopathological studies of these variants may result in alternation in the classification. Ameloblastoma arising from odontogenic keratocyst reported in this study seems to occur by the process of transformation of cystic epithelium to the ameloblastic epithelium and the presence of this form should be studied carefully in the future case series to define the entity in detail. Luminal subtype of unicystic ameloblastoma is seen to recur in mural form. This situation may be related to the misdiagnosis of the mural form as luminal form due to the inadequate surgical technique in the first-line surgery. In the examination of unicystic cases, the surgical specimen should be entirely inspected to indicate mural ameloblastic invasions.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ömer Günhan;* ***Design:*** *Ömer Günhan;* ***Control/Supervision:*** *Ömür Dereci;* ***Data Collection and/or Processing:*** *Devrim Kahraman;* ***Analysis and/or Interpretation:*** *Ülker Yalçın Karagece;* ***Literature Review:*** *Yasin Çağlar Koşar;* ***Writing the Article:*** *Ömür Dereci;* ***Critical Review:*** *Devrim kahraman;* ***References and Fundings:*** *Yasin Çağlar Koşar.*

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