

ORIGINAL ARTICLE

Demographic and clinicopathological analysis of odontogenic keratocyst: A retrospective study

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Abstract

Introduction: Odontogenic keratocyst (OKC) is among the commonest odontogenic cysts known for its local invasiveness and high recurrence rate following treatment. The study on OKC among the Malaysian population is limited in recent years. The aim of this study is to evaluate the latest demographic and clinicopathological profile of OKC cases in the Faculty of Dentistry, Universiti Malaya (UM). **Materials and Methods:** The demographic and clinicopathological data of 147 OKC cases were extracted from the archive of the institution from 2003 to 2022. Descriptive statistics, Pearson Chi-square test and Fisher's Exact Test were employed for the statistical analysis. **Results:** OKC affected younger age groups with peak incidence in the third decade of life followed by the second decade of life. An almost equal distribution among males and females was observed. Predominance of OKC was seen within the Chinese ethnicity. The mandible was the commonest site of occurrence. Recurrence was observed in 11.1% of the cases where most of them were treated by enucleation only. Majority of the cysts were predominantly lined by parakeratinized stratified squamous epithelium (94.6%) with corrugated surface (89.8%). Presence of epithelial island (16.3%), satellite cyst (15.6%), dystrophic calcification (10%) and atypia (7.5%) were also observed. Significant association ($p < 0.05$) were seen in syndromic OKC involving both jaws, multilocular radiolucency in mandible and presence of satellite cysts in OKC involving both jaws. **Conclusion:** This study provides the latest demographic and clinicopathological profiles of OKC from this institution. This data could add value for current chairside assessment and treatment planning of OKC.

Keywords: Odontogenic keratocyst, keratocystic odontogenic tumour, nevoid basal cell carcinoma syndrome

INTRODUCTION

According to the latest World Health Organization (WHO) Classification of Head and Neck Tumours 2022, odontogenic keratocyst (OKC) is defined as an odontogenic cyst exhibiting thin parakeratinized stratified squamous epithelial lining with palisaded and hyperchromatic basal cells.¹ This lesion is the third most diagnosed odontogenic cyst in oral and maxillofacial region.² In 2005, WHO renamed OKC as keratocystic odontogenic tumour (KCOT), acknowledging the neoplastic behaviour with the justification of the high recurrence rate, locally aggressive clinical course, association with nevoid basal cell carcinoma syndrome and genetic mutation of PTCH tumour suppressor gene.³ It was then reverted to OKC in 2017

as few studies have shown that PTCH gene mutation can also be found in non-neoplastic lesion such as dentigerous cyst and the response towards marsupialization treatment did not engage with neoplastic characteristic.³ The commonest site of OKC found was on the mandibular, frequently on the posterior while OKC involving the maxilla was relatively low.^{4,5} The distinctive histopathological features and clinical presentation of OKC make it interesting to be further explored for a better understanding of the lesion's nature and subsequently deciding the best treatment for patients. Close resemblance in clinical presentation of OKC and other odontogenic cyst/tumour in some cases can be challenging for the pathologist and surgeon.

The study on OKC among the Malaysian population has been limited in recent years. The

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previous demographic and clinicopathological study of OKC in the Faculty of Dentistry, Universiti Malaya (UM) was conducted in 1995 and 2000.^{4,5} The present study specific objectives are to determine the latest demographic and clinicopathological distribution of OKC from UM's samples and to assess the association between odontogenic keratocyst of different sites with demographic and clinicopathological features. This will benefit the clinicians in their clinical chairside diagnosis making and subsequently facilitate the appropriate treatment planning for the patients.

MATERIALS AND METHODS

Study population

This is a retrospective study involving all OKC/KCOT cases diagnosed by Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya of 20 years duration from January 2003 to December 2022. Manual search of histopathology report and Haematoxylin and Eosin-stained (H&E) slides of OKC or KCOT was performed from the Diagnostic Oral Pathology Unit's archive. The demographic and clinicopathological features of the cases were extracted from the laboratory request form and histopathology report. Repeated biopsy will be considered as one case by considering histological features from the excisional biopsy if possible. Exclusion involved cases with inconclusive diagnosis from the histopathological report such as suggestive of OKC or odontogenic cyst/tumour suggesting OKC and cases that were reported as OKC but appeared to be orthokeratinized odontogenic cyst.

Sample size

A total of 269 cases of odontogenic keratocyst and keratocystic odontogenic tumour were obtained from the unit's archive. According to the exclusion criteria, 18 cases were removed. Patients with multiple biopsies will be reviewed and counted as 1 case. Recurrent OKC that was diagnosed for the first time in this institution, of which the original diagnosis was made in another centre, was included and considered as one case. The remaining 147 cases that met the inclusion criteria were included in this study. 21 cases were incisional biopsies, and 126 cases were excisional biopsies. All data was entered into Microsoft Excel.

Ethics approval

The ethics approval for this study was obtained

from the Medical Ethics Committee, Faculty of Dentistry, Universiti Malaya with reference code of DF OS2226/0066 (P).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 27.0. Descriptive statistics were employed for prevalence, demographic and clinicopathological features of odontogenic keratocyst. The categorical data was presented as frequencies and percentage while numerical data was presented as mean and standard deviation. The association between odontogenic keratocyst and parameters of interests were analysed using either Pearson Chi-Square test or Fisher's Exact test, where appropriate. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Prevalence

The total number of cases included in this study were 147 cases which comprises 21 incisional biopsies and 126 excisional biopsies. This accounts for 1.09% of the total biopsy cases reported by the Diagnostic Oral Pathology Unit from 2003 to 2022 (*n*=13536).

Demographic distribution

The demographic distribution is depicted in Table 1. There was a wide range of age seen in this study. The youngest was 5 years old and the eldest was 79 years old. The mean age with standard deviation was 30.85±15.32. The highest peak was seen in the third decade of life, followed by the second decade of life. No second peak is present at the later age. For syndromic OKC which comprised a small number from the total sample, the age of patient was younger, ranging from 8 to 28 years old. This study showed almost equal distribution among males and females, with male to female ratio of 1:1.01. For ethnicity distribution, the Chinese population outnumbered the cases followed by the Malay and Indian.

Clinical presentation

The clinical findings are summarised in Table 2. We found that more than half of patients experienced jaw swelling in this study. About one-third of the cases presented with pain which was usually associated with infection. Paraesthesia was seen in only a small number of cases (2.7%). The duration recorded from when the patient first noticed the lesion until presentation to the clinic varied between 3 days

Table 1: Distribution of demographic data

Demographic	n (total n= 147)	%
Age (year)		
0-10	4	2.7
11-20	35	23.8
21-30	47	32.0
31-40	22	15.0
41-50	17	11.6
51-60	10	6.8
61-70	6	4.1
71-80	3	2.0
Missing data	3	2.0
Mean age	30.85±15.32	
Median	27	
Gender		
Male	74	50.3
Female	73	49.7
Male: Female	1.01:1	
Ethnicity		
Malay	35	23.8
Chinese	77	52.4
Indian	28	19.0
Others	7	4.8

to 6 years. About one-third of patients noticed the lesion within less than 3 months. A minority of cases showed a duration of more than 5 years. Minority of patients were asymptomatic where the cyst was found as incidental finding by the clinician or surgeon reported at 12.2%.

In this study, the clinical presentation at posterior was defined from the mesial of first premolar to the distal of third molar tooth. Extended site presentation referred to area from distal of the third molar tooth until condyle/ coronoid or maxillary sinus. The majority of OKC cases were seen in mandible, predominately in mandible posterior and extended region. For maxilla, most of the cases were seen in the extended region (involving the maxillary sinus) and the least occurrence of OKC seen at the anterior maxilla (cross midline). Less than one-third of OKC cases involved both maxilla and mandible. The majority of OKC cases in this study were presented as solitary cyst. Cystic content was usually described as straw-coloured fluid or whitish cheesy content representing the keratin material. In this study, almost half of the cases described the presence of cystic content.

Types of treatment for OKC varied from conservative enucleation to radical surgery such as resection. Half of the cases underwent

enucleation (52.4%) followed by enucleation with curettage (22.4%). Only a small percentage of cases underwent enucleation with curettage and Carnoy solution application or peripheral osteotomy and resection. The majority of the cases reported no recurrence. There were two OKC variants observed in the study where sporadic OKC outnumbered the syndromic OKC by 140 to 7 cases. However, among the sporadic cases, 4 patients were suggested to rule out nevoid basal cell carcinoma syndrome. There were several provisional clinical diagnoses reported. Half of the cases were OKC followed by dentigerous cyst and ameloblastoma. A small proportion of cases were named radicular/ residual cyst, lateral periodontal cyst and odontogenic cyst/tumour as clinical diagnosis. Some of the provisional clinical diagnosis given by the surgeon were OKC, dentigerous cyst, ameloblastoma, radicular cyst, lateral periodontal cyst and odontogenic cyst/ tumour.

Radiographic finding

The radiographic finding distribution is illustrated in Table 3. Almost three-quarters of the cases were reported as unilocular (71.4%). The majority of the cases showed a well-defined margin of the radiolucency as compared to poorly defined margin. Bucco-lingual bone expansion without perforation was observed in almost half of the cases. Root resorption was reported rarely in this study. Association with impacted tooth either third molar tooth or any tooth were also observed. Only slight predominance towards OKC with association to impacted tooth were reported.

Histopathological features

Parakeratinization of cystic lining was predominantly seen in majority of OKC cases. Mixed types of keratinization consisting of parakeratinized and orthokeratinized were seen rarely. The corrugated surface of cystic lining was seen in most of the OKC cases. More than half cases displayed absence of rete ridge or as flattened epithelium connective tissue interface. Epithelial separation or epithelial detachment was reported in half of the cases. Most OKC cases in the study showed some degree of inflammation. Almost half of them displayed moderate to densely inflamed cystic walls. In contrast, less than a quarter of cases showed an uninfamed cystic wall. Only a small number of cases were reported to have dystrophic calcification. Satellite cyst or daughter cyst were observed in less than

Table 2: Distribution of clinical findings

Clinical presentation	n (total n=147)	%
1. Symptoms		
<u>Swelling</u>		
Yes	92	62.6
No	55	37.4
<u>Pain</u>		
Yes	45	30.6
No	102	69.4
<u>Paraesthesia</u>		
Yes	4	2.7
No	143	97.3
<u>Tooth mobility</u>		
Yes	9	6.1
No	138	93.9
2. Duration of cyst		
<1 month	26	17.7
1-3 months	18	12.2
3-6 months	10	6.8
6-12 months	11	7.5
1-3 years	11	7.5
3-5 years	2	1.4
>5 years	2	1.4
Incidental	18	12.2
Not specified	49	33.3
3. Site		
<u>Maxilla</u>	39	26.5
Maxilla anterior	12	8.2
Maxilla posterior	9	6.1
Maxilla extended	14	9.5
Maxilla cross midline	4	2.7
<u>Mandible</u>	98	66.7
Mandible anterior	5	3.4
Mandible posterior	39	26.5
Mandible extended	40	27.2
Mandible cross midline	14	9.5
Maxilla & mandible	10	6.8
4. Cystic content		
Present	63	42.9
Absent	13	8.8
Not stated	71	48.3
5. Number of cystic lesions		
Solitary	130	88.4
Multiple	17	11.6
6. Previous treatment		
Decompression	1	0.8
Enucleation	10	7.9
Marsupialization	18	14.3
No treatment stated	97	77.0

7. Type of submitted biopsy		
Incisional	21	14.3
Enucleation	77	52.4
Enucleation with curettage	33	22.4
Enucleation with curettage and Carnoy	6	4.1
Enucleation with peripheral osteotomy	4	2.7
Resection	6	4.1
8. Recurrence		
Yes	14	11.1
No	112	88.9
9. Variant		
Sporadic (4 cases to rule out NBCCS)	140	11.1
Syndromic	7	88.9

n= number of samples

a quarter of the cases. Less than 10% of the cases showed atypia features which were described in the histopathological reports as cellular and nuclear pleomorphism, dyskeratosis, basal cell hyperplasia and necrosis in epithelial lining. The distribution of histopathological features is summarised in Table 4.

Association between OKC of different sites with demographic and clinicopathological features.

The summary of the association between OKC of different sites with demographic and clinicopathological features is shown

in Table 5. For analytical purposes, certain clinicopathological features were combined into larger categories such as age (0-30 years, 31-60 years, 60-80 years), duration of lesion (≤ 12 months, between 13-60 months, >60 months), and inflammation (uninflamed, inflamed).

OKC of different sites were significantly associated with variants of OKC. The syndromic OKC tended to involve both jaws. Most of the cases were seen as unilocular radiolucency while multilocular radiolucency was more commonly seen in mandible OKC. Satellite cysts were significantly associated with OKC involving both jaws. No other significant associations were noted.

Table 3: Distribution of radiographic finding

Radiographic finding	n (total n=147)	%
1. Locularity		
Unilocular	105	71.4
Multilocular	34	23.1
Not stated	8	5.5
2. Margin		
Well-defined	136	92.5
Poorly defined	3	2.0
Not specified	8	5.5
3. Root resorption		
Yes	7	4.8
No	140	95.2
4. Association with impacted tooth		
Yes	76	51.7
No	71	48.3

n= number of samples

Table 4: Distribution of histopathological features

Histopathological features	n (total n=147)	%
1. Types of keratinization		
Parakeratinized	139	94.5
Parakeratinized (focal)	6	4.1
Mixed	2	1.4
2. Surface corrugation		
Yes	132	89.8
No	15	10.2
3. Rete ridge		
Present	51	34.7
Absent	96	65.3
4. Epithelial separation		
Yes	79	53.7
No	68	46.3
5. Inflammation		
Uninflamed	13	8.8
Mildly inflamed	34	23.1
Moderately inflamed	27	18.4
Densely inflamed	40	27.2
Densely inflamed (focal)	33	22.5
6. Dystrophic calcification		
Present	14	9.5
Absent	133	90.5
7. Satellite cyst		
Present	23	15.6
Absent	124	84.4
8. Epithelial island		
Present	24	16.3
Absent	123	83.7
9. Atypia		
Present	11	7.5
Absent	136	92.5

n= number of samples

DISCUSSION

The prevalence of OKC reported in the current study is slightly lower than in other studies with prevalence ranging from 1.4 to 1.7%.⁶⁻⁸ The lower frequency of cases seen in this centre is probably attributed to the distribution of cases to other dental healthcare institutions in Malaysia. To the best of our knowledge, there is a limited study specifically discussing OKC in recent years. There were also differences in describing the prevalence among the studies where some recorded the numbers of OKC in relation to all odontogenic cysts and others to the epithelial jaw cyst that resulted in varying frequencies reported.

OKC cases in our study demonstrated a wide range of age from 5 to 79 years old which is similar to most of the studies.^{5,9-11} The mean age of patients with standard deviation in this study was reported as 30.85±15.32, which is in line with a few studies but dissimilar with the previous study involving the Malaysian population that recorded a younger mean age of 26-28 years.^{4,5,7,9} The peak age of occurrence in the present study was the third decade of life followed by the second decade of life. There were few studies that showed two peaks of prevalence, first at around the second to third decades of life, followed by another peak at an older age, about the sixth to seventh decade of life.^{8,12} This suggested

Table 5: Association between odontogenic keratocyst (OKC) of different sites with demographic and clinicopathological features

Variables		OKC type, n (%)			P-value
		Maxilla OKC	Mandible OKC	Maxilla & Mandible OKC	
Variant of OKC	Sporadic	39 (100.0)	97 (99.0)	4 (40.0)	<0.001 ^b
	Syndromic	0 (0.0)	1 (1.0)	6 (60.0)	
Radiographic locularity	Unilocular	35 (89.8)	62 (63.3)	8 (80.0)	0.004 ^b
	Multilocular	2 (5.1)	31 (31.6)	1 (10.0)	
	Not specified	2 (5.1)	5 (5.1)	1 (10.0)	
Presence of satellite cyst	Present	8 (20.5)	10 (10.2)	5 (50.0)	0.003 ^a
	Absent	31 (79.5)	88 (89.8)	5 (50.0)	

n= number of sample, %=percentage

Significance level $p \leq 0.05$

^aPearson Chi-Square test

^bFisher's exact test

that there was a variation in age range among different populations. However, for syndromic OKC, most of the studies reported a younger age of presentation.^{13,14} The similarity was also observed in the present study. These findings are in contrast with a Turkish study that reported older syndromic OKC mean age which was 35 years.¹² The younger age in syndromic OKC may be due to the presence of other clinical features of NBCCS, leading to the early discovery of OKC. It may also be because of family screening after one of the family members is diagnosed with NBCCS.

An almost equal distribution of OKC was seen among male and female with the ratio of male to female being 1.01: 1 unlike most studies that reported marked male predominance and a higher male to female ratio in OKC.^{7,11,14,15} In contrast, the study conducted among the Malaysian population back in 1995 showed female predilection with female to male ratio of 1.2:1.⁴ A study among Singaporean-Malaysians in 2000 showed male predominance and male to female ratio of 1.35:1.⁵ These findings may be due to the dynamic changes of the awareness of different genders in seeking dental treatment and differences in the clinical attendance pattern of different populations.

There was a strong predominance observed within the Chinese ethnicity followed by Malay, Indian and others. Predilections towards Chinese were also observed in previous studies done among the Malaysian population in 1995 and 2000.^{4,5} However, our study differs slightly where the prevalence of Malay was seen to be higher than Indian, unlike the previous studies.

It seemed like the Malays developed a greater prevalence toward OKC within a 20-year period of time, probably due to the people becoming more well-informed to seek healthcare treatment. The predilection towards certain ethnicities is not uncommon in OKC in which few studies also reported predilection towards some races such as Caucasian showed higher incidence of OKC than blacks.^{16,17}

OKC can be an incidental finding during routine dental check-up which was reported at 12.2% in this study. This is in line with other studies that reported 13-15% of incidental cases.^{18,19} A possible explanation for this is due to the growth of OKC that occurs antero-posteriorly rather than bucco-lingually resulting in delay in noticing the jaw expansion. There was a wide range of duration of patients started noticing the lesion seen in this study with the earliest at 3 days and the longest was 6 years. About one-third of cases noticed the lesion in less than 3 months. This contrasts with other studies that reported much higher frequency ranging from 47% to 70% of patients noticing the lesion within less than 3 months.^{10,19} This could be attributed to the fact that these studies showed a much higher frequency of symptomatic patients such as swelling and pain that lead them to seek medical advice sooner.

As expected, the current study showed marked predilection to mandible, especially to the posterior region and extending to the ramus and condyle which was in agreement with other studies that reported more than half cases of this incidence.^{4,12,13,19} We found that OKC crossing midlines were more commonly seen in mandible.

This is in contrast with a study that showed comparable frequency of OKC crossing midline cases in maxilla and mandible.¹⁶ In 1997, Neville *et al.* reported that OKC at anterior midline of maxilla was uncommon, but they tended to be seen in older patients with mean age of nearly 70 years old.²⁰ Some researchers theorised that the cyst arises from the primordium of mesiodens while others believed that it developed from the anterior maxilla dental lamina remnant.^{20,21} The hypothesis was not observed in our study where there were 4 cases of OKC crossing the midline of maxilla. Only 1 case was seen in a 67-year-old patient, while the rest were below 50 years old. Studies involving larger sample sizes would enable the validation of this relationship.

Most of the clinical diagnosis given in this study was compatible with the definitive diagnosis of OKC. Other frequent clinical diagnoses were also reported, namely dentigerous cyst, ameloblastoma and radicular cyst. This result seems to be consistent with other similar studies.^{16,4,12} This is likely due to the association of OKC with the impacted tooth and the multilocular radiological appearance of OKC. Some OKC also presented in close relation to the non-vital tooth hence suggested the inflammatory odontogenic cyst as the provisional diagnosis. Dentigerous cyst was the second most common clinical diagnoses as OKC is commonly associated with impacted teeth. There are four different radiological types of OKC; replacement, envelopmental, extraneous and collateral type.²² The envelopmental type was described in OKC that embraces an adjacent unerupted tooth hence the clinical diagnosis of dentigerous was given. Besides that, OKC can also be confused with tumour lesion, especially with the large size and multilocular radiolucency that is similar to ameloblastoma.¹² Another study on the maxillary OKC and the common clinical misdiagnose stated that, OKC at the canine region was the most commonly mistaken for apical inflammatory or lateral periodontal cyst and only 31.5% of cases was given clinical diagnosis as OKC.²³ Hence, the study recommended to sample the whole specimen with thorough evaluation of the histopathological features.

Few cases in this study showed bone expansion with perforation at 19.0% which is lower than the study reported by a study in 1976.¹⁶ However, most of the expansion with perforation in the current study took place in the mandible which is in contrast to the previous. This was probably due to the less density of the maxilla

bone and the spaces within the maxillary sinus allowed it to expand in significant size before the perforation started unlike the mandible bone that showed mean bone density twice than the maxilla.²⁴ The longer duration time shown in most cases in the present study probably also plays role in this presentation as the OKC were growing in considerable size and resulting in perforation.

Our study showed 7.5% of cases with atypical features such as cellular and nuclear pleomorphism, dyskeratosis, basal cell hyperplasia and necrosis in epithelial lining. Three of the cases received marsupialization and one case underwent decompression prior to definitive treatment. 7 of the remaining did not receive any prior treatment. The atypical features were suggested due to reactive changes of the previous treatment. A study by Nakamura *et al.* showed that the most common findings post-marsupialization were hyperplastic, stratified, nonkeratinizing squamous epithelium with thick cystic walls.²⁵ Another study by August *et al.* found that there were changes seen in the OKC of epithelial lining after decompression, where they reported that the lining became hyperplastic as compared to the initial histology with mild to moderate inflammation and loss of CK10 expression observed at the suprabasilar region.²⁶ However, these studies did not highlight the atypical change that could arise from the previous treatment. According to the 5th Edition of WHO Classification of Head and Neck Tumours 2022, epithelial lining of OKC can give rise to odontogenic carcinoma in rare occasions and should be suspected in solid OKC. Further longitudinal follow up is recommended to assess the correlation of atypical features with long-term recurrence rate of OKC.

Even though OKC is one of the common odontogenic cysts being diagnosed, there is still limited data in the literature regarding the association of OKC of different sites and the demographic-clinicopathological parameters. In the current study, statistically significant association was found between different sites of OKC and the variant (sporadic or syndromic). It was noted that syndromic OKC tends to occur more frequently in both jaws which is similar to another study (Wang *et al.*, 2020).¹⁴ This is probably due to the part that syndromic OKC often presented with multiple OKCs that involved both jaws.

Another association that was found is between OKC and locularity. Most of the cases were

presented as unilocular which is similar to the latest WHO classification that stated three-quarter of OKC are presented as unilocular. It was observed that multilocular radiolucency tends to be present in mandible OKC which is in contrast to a study by Chirapathomsakul *et al.*, 2006 that found multilocular radiograph usually seen in maxilla OKC.¹⁶ The higher frequency of multilocular finding seen in the mandible was in line with study by Shear & Speight.¹⁷ In 1984, Voorsmit *et al.* (1981) suggested that this finding was probably a unilocular lesion with scalloped margin and was misinterpreted as multilocular OKC.²⁷ He also suggested that the scalloped margin was due to unequal growth activity occurring in different parts of the cystic lining.

The presence of satellite cyst was also associated with OKC where they tended to be found in OKC of both jaws. This is probably due to syndromic OKC that usually occurs in maxilla and mandible, presented with PTCH gene mutation that causes abnormality in cell proliferation resulting in higher number of satellite cysts present. In our study, recurrent cysts were frequently seen in mandible OKC which is similar to finding in few studies.^{9,19} The reasonable explanation is due to the challenge in surgical access and difficulty to completely remove the thin cystic lining in the area, especially the posterior region. However, all of these studies showed no statistically significant association.

CONCLUSION

This study presents the latest demographic and clinicopathological distributions of OKC for this institution from 2003 to 2022. Most of the demographic and clinicopathological features are in agreement with other studies. Although the current study is based on a small sample, the findings suggest significant association ($p < 0.05$) between OKC of different sites with variant of OKC, the radiographic locularity and presence of satellite cyst. A few limitations have been recognised in this study. Firstly, the sample size was relatively small as it is single institutional based and may not be representative of the national population. Hence, we recommend involvement of multicentre data collection for a better reflection of the population. Secondly, some of the data retrieved from the patient's record was incomplete leading to an increased number of missing or unspecified data. A protocol

or proforma for surgeons and pathologists will allow standardisation in reporting and subsequently a complete demographic and clinicopathological data collection. Overall, we believe this study will provide valuable insights for pathologists and clinicians in the management of OKC patients.

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