Pathology (June 2021) **53(4)**, pp. 478–486

ANATOMICAL PATHOLOGY

Should the solid variant of odontogenic keratocyst and keratoameloblastoma be classified as the same entity? A clinicopathological analysis of nine cases and a review of the literature

RAN ZHANG[1,2,3], JIE YANG[1], JIANYUN ZHANG[1,2,3], YINGYING HONG[1,2,4], XIAOYAN XIE[3,5], TIEJUN LI[1,2,3]

[1]*Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, China;* [2]*Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Chinese Academy of Medical Sciences, Beijing, China;* [3]*National Clinical Research Center for Oral Diseases, Peking University School and Hospital of Stomatology, Beijing, China;* [4]*The First Clinical Division, Peking University Hospital of Stomatology, Beijing, China;* [5]*Department of Oral and Maxillofacial Radiology, Peking University School and Hospital of Stomatology, Beijing, China*

Summary

The solid variant of odontogenic keratocyst (SOKC) is an extremely rare odontogenic lesion, which remains poorly defined even in the 2017 World Health Organization odontogenic tumour classification. It is difficult to distinguish between SOKC and so called keratoameloblastoma (KAB), both rare lesions that have similarities in clinical, histological and biological characteristics. Here, we report clinicopathological data and results of molecular analysis of nine cases with a literature review. First, they were compared to previously reported cases of SOKC and/or KAB, and many overlaps were found in clinical and pathological characteristics. Second, we performed PCR analysis for *BRAF* V600E mutation. Although ameloblastoma-like epithelia were often encountered, none exhibited *BRAF* V600E mutation, which has been reported to occur frequently in ameloblastomas but not in odontogenic keratocysts (OKCs). One of two cases of SOKC in the present series from which fresh frozen tissue specimens were available was found to harbour *PTCH1* mutations, indicating that these were more likely to be a subtype of OKC. Moreover, we also examined the differences between SOKC and primary intraosseous carcinoma (PIOC) with regard to the expression of cytokeratins (pan-CK, CK5/6, CK7, CK8/18, CK10, CK14 and CK19), p53 and Ki-67. The proportions of p53-and Ki-67-positive cells were significantly higher in PIOC than in SOKC. These findings suggest that immunostaining for p53 and Ki-67 would be useful to differentiate between SOKC and PIOC. We also conducted a review of SOKC and KAB cases reported in the English language literature.

Key words: Solid variant of odontogenic keratocyst; keratoameloblastoma; odontogenic tumour; primary intraosseous carcinoma.

Received 25 June, revised 31 August, accepted 8 September 2020
Available online 5 February 2021

INTRODUCTION

Odontogenic keratocyst (OKC) is a group of odontogenic cysts with characteristic histological features, high growth potential and a propensity to recur following surgical treatment.[1] OKC was once accepted as a neoplastic lesion in the 2005 World Health Organization (WHO) classification; however, it was moved back to the cyst category in the 2017 classification of odontogenic tumours.[1–3] Recently, the solid variant of OKC (SOKC) was described, but only nine cases have been reported in the English literature to date.[4–11] No criteria have been reported for the pathological diagnosis of SOKC due to the paucity of information regarding this type of lesion. Histologically, SOKC is similar to the so called keratoameloblastoma (KAB), a type of ameloblastoma that is also rarely encountered in the jaw and of which 26 cases have been reported in the English language literature to date.[4,9,10,12–35] The name KAB was proposed in 1970,[28] while the nomenclature SOKC was first introduced in 2003,[4] and several groups have suggested renaming KAB cases lacking ameloblastoma features as SOKC, due to the high degree of overlap between the two lesions.[6]

Here, we conducted a retrospective analysis of the clinicopathological features, treatments and outcomes of nine cases previously diagnosed as SOKC or KAB in our hospital.

Screening for *BRAF* V600E mutation was conducted in all cases, and fresh tissue specimens collected from two cases of SOKC were also screened for *PTCH1* mutation. To our knowledge, there have been no previous reports of molecular genetics of this group of lesions. Cytokeratins (pan-CK, CK5/6, CK7, CK8/18, CK10, CK14 and CK19), p53 and Ki-67 were analysed in the present cases and compared with primary intraosseous carcinomas (PIOC). An extensive review was also performed with regard to cases of both SOKC and KAB reported in the English language literature. Based on the findings of these cases and a clinicopathological review of the English language literature, we suggest that it is

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2020.09.028

not necessary to separate these lesions into two clinical entities.

MATERIALS AND METHODS

Patients

Patients diagnosed with SOKC or KAB between 2003 and 2020 in the Department of Oral Pathology, Peking University School of Stomatology, Beijing, China, were reviewed. Nine cases were selected and clinicopathological parameters were recorded, including patient age, sex distribution, location, radiology, treatment and prognosis. Of the nine cases, three had recurrent lesions, while the remaining six were new onset. Formalin fixed, paraffin embedded (FFPE) tissue samples of the nine cases were acquired and fresh tissues were collected from two patients (new onset). Fresh tissue specimens were collected and stored at −80°C for subsequent analysis. Considering the keratin production and intraosseous growth pattern, we selected two primary intraosseous carcinoma (PIOC) cases for comparison in immunohistochemical analysis. The selected PIOC cases had no OKC history. The experimental protocols used in this study were reviewed and approved by the Ethics Committee of the Peking University School of Stomatology.

Pathological information

We reviewed all haematoxylin eosin (H&E) and immunohistochemically (IHC) stained slides of these nine cases. Microscopic assessment was performed on H&E stained sections, and all diagnoses were re-confirmed by three specialised oral pathologists (TJL, JYZ, RZ). Paraffin section immunohistochemistry was performed on one representative block from each case (including recurrent lesions) using the avidin biotin peroxidase technique with antigen epitope enhancement by pressure cooker heating. The diaminobenzidine reaction was used as the final detection step. Characteristics of antibodies used and staining parameters were as follows: pan-CK (ZM-0069; clone name AE1/AE3; ZSGB-Bio, China); CK5/6 (ZM-0313; clone name OTI1C7; ZSGB-Bio), CK8/18 (ZM-0315; clone name B22.1 & B23.1; ZSGB-Bio), CK10 (ZM-0314; clone name DE-K13; ZSGB-Bio), CK14 (ZA-0540; clone name EP61; ZSGB-Bio), CK17 (ZA-0551; clone name EP98; ZSGB-Bio), CK19 (ZM-0074; clone name UMAB2; ZSGB-Bio), p53 (ZM-0408; clone name DO-7; ZSGB-Bio) and Ki-67 (ZM-0167; clone name MIB1; ZSGB-Bio). All the antibodies are designed for working solutions. The method for epitope retrieval was a heating water bath at 100°C with pH 6.0 citrate buffer for 35 min for all antibodies.

DNA extraction, polymerase chain reaction (PCR) and direct sequencing

Tissue sections (10 mm thick) were prepared on glass slides from the FFPE blocks from the nine cases from which sufficient tissues were available for analysis. DNA extraction was performed with a QIAamp DNA FFPE tissue kit (Cat. 56304; Qiagen, USA) according to the manufacturer's instructions. *BRAF* mutation was detected by sequencing analysis using the following primers: forward 3′-TCATAATGCTTGCTCTGATAGGA-5′ and reverse 3′-CCAAAAATTTAATCAGTGGA-5′. For detection of *PTCH1*, we used a QIAamp DNA Micro kit (Cat. 163013346; Qiagen); 23 exons of the *PTCH1* gene were amplified using the primers described in our previous report.[36] Generally, PCR was performed in a total volume of 50 μL containing 200 μM dNTPs, 10 pmol of each primer, 1.25 U of Ex Tag DNA polymerase (Takara, Japan), 50 mM KCl, 10 mM Tris-HCl, 1.5 mM $MgCl_2$ and approximately 100 ng of template DNA. The thermocycling conditions were optimised for each primer pair. Reactions were performed with an initial denaturation step at 94°C for 5 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 60−65°C for 30 s and elongation at 72°C for 30 s, with a final extension at 72°C for 10 min. The amplified products were sequenced directly with the same primers as used for PCR on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, USA). All mutations detected were confirmed by reverse sequencing and at least two additional independent PCR experiments.

RESULTS

Clinical and radiological findings of the patients

The clinical data of the nine cases are presented in Table 1. The study population consisted of seven women and two men, aged 32−78 years (mean age 49.9 years). Overall, the most commonly affected location was the mandible, with lesions in the left posterior mandible in three cases and left anterior mandible in two cases. The lesions in the remaining

Table 1 Clinical data of the patients and results of *PTCH1* and *BRAF* V600E mutational analysis

Case no.	Age/sex	Site	PTCH1 mutation in SOKC				*BRAF* V600E mutation	Management	Follow-up
			Exon no.	Nucleotide change	Amino acid definition	Mutation type			
1	64/F	Anterior mandible (bilateral)	Exon22	c.3771A>T	p.Thr1044Ser	Missense mutation	N	Curettage 5 times; osteotomy	R, 5 times; NR, 1 y
2	42/F	Left mandible	N	N	N	N	N	1st enucleation; 2nd osteotomy	1st R, 10 y; 2nd NR, 5 y
3	42/F	Anterior mandible (bilateral)	NA	NA	NA	NA	N	1st marsupialisation; 2nd-3rd curettage; 4th osteotomy	1st R, 6 mo; 2nd R, 6 mo; 3rd R, 11 mo; 4th NR, 9 mo
4	51/M	Left mandible	NA	NA	NA	NA	N	1st curettage; 2nd osteotomy; 3rd osteotomy;	1st R, 4 mo; 2nd R, 10 mo 3rd NR, 15 mo
5	78/F	Right mandible	NA	NA	NA	NA	N	Osteotomy	R, 1 y
6	37/F	Left maxilla	NA	NA	NA	NA	N	Osteotomy	NR, 21 mo
7	57/F	Bilateral maxilla	NA	NA	NA	NA	N	Enucleation 5 times; resection 6 times; extended resection twice	R, 12 times; R, 17 mo
8	46/M	Left mandible	NA	NA	NA	NA	N	1st curettage; 2nd osteotomy; 3rd osteotomy; 4th osteotomy	1st R, 2 y; 2nd R, 9 mo; 3rd R, 28 mo; 4th NR, 15 mo
9	32/F	Left mandible	NA	NA	NA	NA	N	1st curettage; 2nd osteotomy	1st R, 2 y; 2nd R, 8 y

F, female; M, male; mo, months; N, none; NA, not available; R, recurrence; NR, no recurrence; RL, radiolucency; y, years.

four patients were located on the left anterior maxilla, left posterior maxilla, right anterior mandible and bilateral mandibles, respectively. All patients complained of swelling of the bone as the initial symptom. Four patients presented with pain and three patients suffered from numbness. None had specific systemic or syndromic diseases. Spiral computed tomography (CT) and panoramic radiography were performed in all patients. All lesions were multilocular (Fig. 1A), and other radiological features (i.e., borders and density) varied between cases. Either well defined margins with cortical borders (Fig. 1B), or ill defined with bone destruction (Fig. 1C,D) were revealed. Cases with ill defined margins were suggestive of malignant tumours, and should be differentiated from PIOC, which also showed radiolucency and erosion of the bone (Fig. 1E,F). The internal structure in some cases exhibited soft tissue density, which was significantly enhanced on contrast enhanced CT. Due to the ambiguous clinical and radiological characters as well as the limited information available regarding this group of lesions, only one received the initial biopsy in our hospital and was diagnosed as SOKC. The other eight patients underwent the initial operations at local hospitals; four were diagnosed as OKC, two as ameloblastoma, one as squamous cell carcinoma and one as inflammation. Seven patients received conservative operations (i.e., curettage, marsupialisation) as the initial treatment, but all exhibited recurrence. Two of the nine cases exhibited recurrence after receiving aggressive operations (i.e., osteotomy, extended resection). During clinical follow-up, Case 5 died of unrelated causes and Case 7 exhibited recurrence 13 times due to the special anatomical position of the lesion, which was located on the maxilla and close to the skull base. Case 1 was lost to follow-up, but the last radiological examination was performed one year post-surgery and revealed no recurrence. The other five patients were followed up for 10–60 months (average 21 months) without recurrence. To date, no lymph node or adjacent soft tissue involvement has been observed in any of the nine cases.

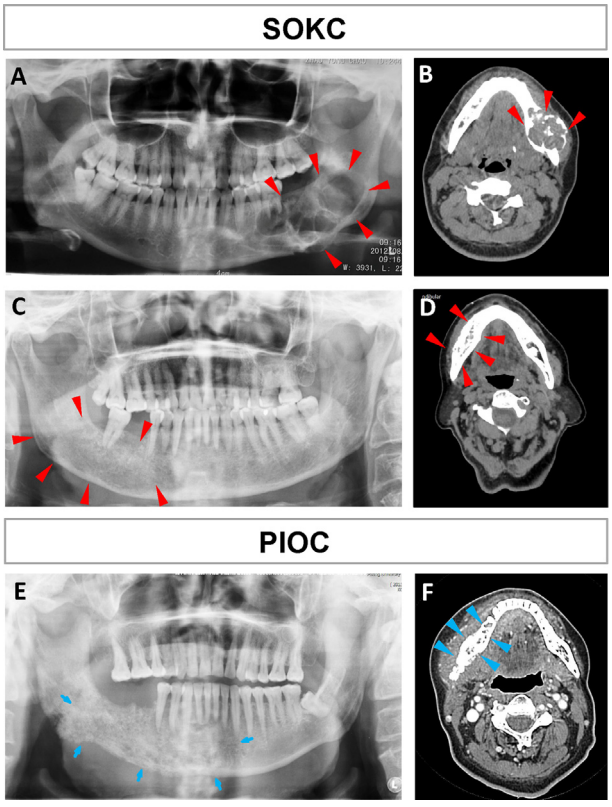

Fig. 1 Radiological features of the solid variant of odontogenic keratocyst (SOKC) compared with primary intraosseous carcinoma (PIOC). (A,B) Radiological appearance of Case 9 revealed multiloculated, well demarcated radiolucent lesion with corticated borders (red arrows). (C,D) Radiograph of the mandible of Case 5 showed an ill defined, motheaten radiolucent lesion (red arrows). (E,F) Radiological and computed tomography (CT) findings of the PIOC case showed an ill delineated radiolucent lesion and cortical bone osteolysis (blue arrows).

Histopathology

Histologically, all of the lesions were non-encapsulated and contained solid and cystic components of varying sizes infiltrating into the bone. The solid components were composed of multiple odontogenic epithelial islands (Fig. 2A); some were solid (Fig. 2B) and some had central spaces filled with layers of keratin and necrotic materials (Fig. 2C). The lining epithelium in one case had a papilliferous appearance, and two cases had clear cell components (Fig. 2D, red arrows). The cystic components were similar to typical OKC, lined by thin squamous epithelium of uniform thickness (the average thickness of our cases was 4–10 layers of cells) and with palisade nuclei in reverse polarity (Fig. 2E,F). Occasional mitoses were observed in all cases, but no dysplastic epithelium was found. Four of the nine cases had ameloblastoma-like epithelium, consisting of loosely arranged angular stellate reticulum epithelium similar to that in ameloblastoma (Fig. 2G,H). Microscopic examination of the PIOC cases revealed morphologically altered epithelial cells invading into the connective tissue, with islands or small nests of neoplastic squamous epithelium (Fig. 2I,J) and keratinisation (Fig. 2K), similar to the findings in our cases. Although some parts of the epithelium had a peripheral palisading pattern, cytological atypia was obvious in PIOC (Fig. 2L). To further compare this group of lesions with PIOC, IHC staining was performed. All lesions (in all cases, including the recurrent lesions and two PIOC cases) were positive for pan-CK, CK5/6, CK14 and CK19. Staining for p53 was negative in all of our nine cases, but strong staining was observed in both of the PIOC cases (Fig. 3A,F). Ki-67 proliferation index was much lower in the lesion cells from our nine cases (8%–10%) than in the PIOC cases (60%) (Fig. 3B,G). The greatest numbers of Ki-67 positive cells were observed in the parabasal and basal layers in our cases (Fig. 3B). Other IHC staining results in the present cases were as follows: CK7 (2/9 cases, 22.2%), CK8/18 (4/9 cases, 44.4%) and CK10 (6/9 cases, 66.7%) (Fig. 3C–E). In contrast, the PIOC lesion cells were negative for CK7 and CK8/18 but positive for CK10 (Fig. 3H–J).

Detection of *BRAF* V600E and *PTCH1* mutations in the nine cases

The results of our study and those of others reported previously indicated a rate of *PTCH1* mutation in OKC (sporadic and syndromic) of about 84% and a rate of *BRAF* V600E mutation in ameloblastoma of up to 90%.[36,37] Next, we performed molecular analysis of our two cases using DNA samples extracted from fresh tissue specimens for *PTCH1* mutation screening, and one missense mutation (c.3771A>T) that had not been reported previously was detected

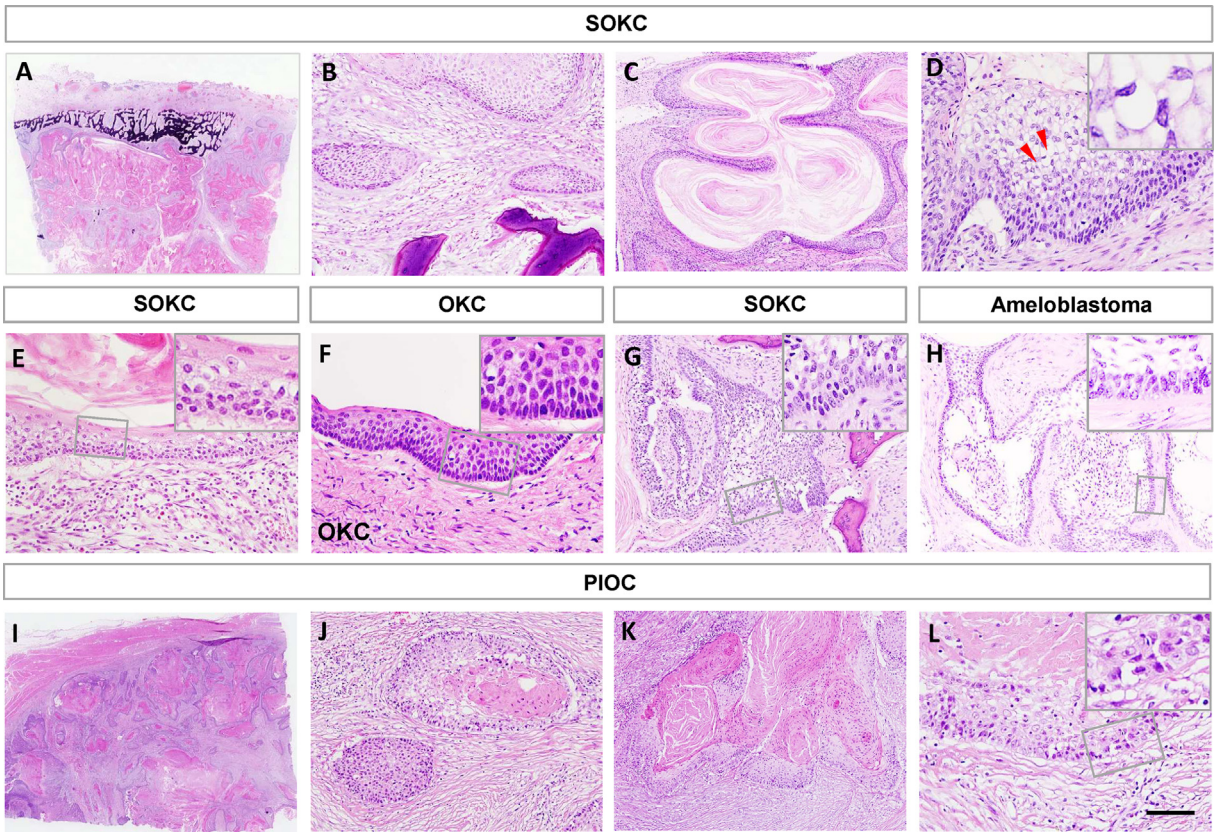

Fig. 2 Histological characteristics of the solid variant of odontogenic keratocyst (SOKC) and primary intraosseous carcinoma (PIOC). (A–C) Composite panoramic histology showed the SOKC cases were composed of squamoid epithelial islands and some cysts lined by parakeratinised stratified squamous epithelium in variable sizes, which infiltrated into the surrounding cancellous bone. (D) Clear cell component was observed in some cyst walls (grey frames, high magnification images of areas indicated by red arrows). (E,F) The basal layer of most individual tumour islands exhibited palisading, with cystic areas resembling cysts in classic OKC (grey frames, high magnification images of boxed areas). (G,H) Follicular epithelial structure lined by ameloblastoma-like cells presented in some part of the SOKC cases similar to the epithelium in ameloblastoma (grey frames, high magnification images of boxed areas). (I,J) PIOC case showed tumour infiltration into the adjacent bone. (K) The centre of the tumour epithelium was full of keratination. (L) High power magnification showed atypical tumour cells with mitoses. Scar bar: 500 μm (A,I), 100 μm (C), 50 μm (B,G,H,J,K), 25 μm (D–F,L).

(Fig. 4A,B). We also extracted DNA samples of nine cases from paraffin embedded tissue, however, none of these cases harboured *BRAF* V600E mutations (Fig. 4C,D).

Review of the literature

Table 2 summarises the clinical features of SOKC and KAB cases reported previously in the English language literature. In total, nine SOKC cases have been reported with an aggregate average patient age of 49 years (range 30–72 years), while the average age of patients with a diagnosis of KAB was 41.9 years (range 18–76 years). Both were close to the average age of our cases (49.9 years). There was no bias in terms of sex in the reviewed cases, with female to male ratios of 5:4 and 1:1 in SOKC and KAB, respectively, despite the slightly higher proportion of female patients in our series, in which SOKC occurred predominantly in the mandible (7/9 cases) rather than the maxilla (2/9 cases), and eight cases had lesions in the posterior portion. KAB had the same site distribution as SOKC, with 19 cases in the mandible, six in the maxilla and one case in the palate. Thirteen of these cases occurred in the posterior portion, while six cases were in the anterior portion of the jaw. The site distribution was consistent with the results in our nine cases. Both SOKC and KAB lesions were radiolucent. Four SOKC cases were described as exhibiting multilocular radiolucency. Three SOKC cases were described as having ill defined or moth eaten margins, two cases as honeycombed and two cases as scalloped radiolucent. The other ten KAB cases were described as exhibiting multilocular radiolucency, scalloped, ground glass-like with instinct borders, circumscribed lobulated, ill defined or having the appearance of a soft tissue mass. Radiological features of the reviewed cases were also non-specific in comparison with the reported nine cases. The average recurrence rates in the reviewed SOKC and KAB cases were 12.5% and 41.7%, respectively, depending on the therapeutic procedures. Conservative methods applied for both lesions included curettage and enucleation, while aggressive methods included resection and hemimaxillectomy/hemimandibulectomy. Of the SOKC cases for which information was available, three received conservative surgeries as the initial treatment. One case exhibited recurrence three times after receiving enucleation or curettage, but no recurrence was observed after *en bloc* resection over a follow-up period of 13 years. No recurrence was observed in the four cases treated with aggressive methods. The follow-up period of the described SOKC cases ranged from 6 months to 13 years. Among the KAB cases for which information was available, six cases received conservative surgery as the initial treatment, one case had no follow-up information and recurrence was observed in two cases. Of the 12 cases receiving aggressive surgeries, no information after surgery was available for six cases, and recurrence was

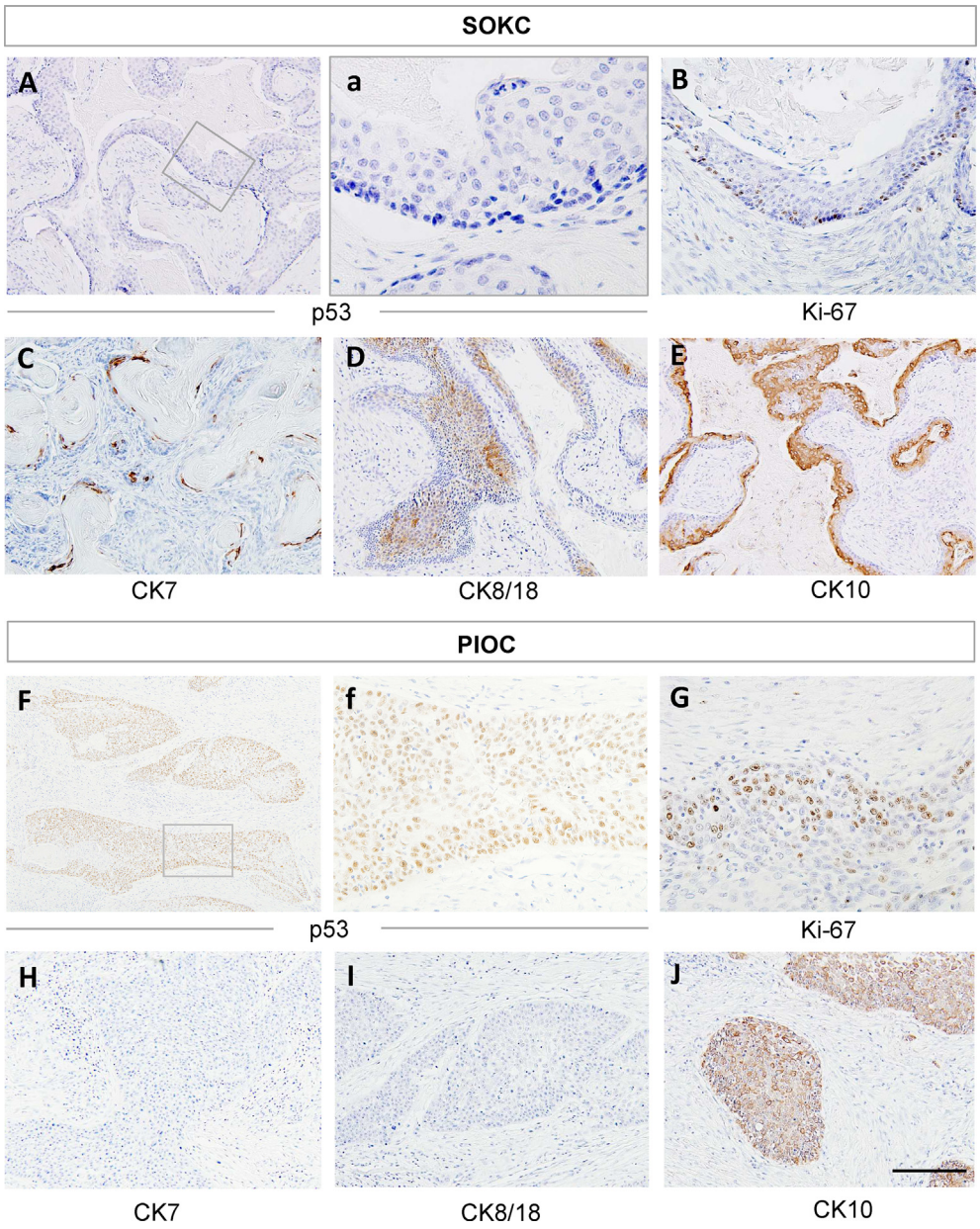

Fig. 3 Representative immunohistochemical results from the solid variant of odontogenic keratocyst (SOKC) and primary intraosseous carcinoma (PIOC). (A,F) Immunoactivity for p53 was absent in all the SOKC cases but was high in PIOC cases (A and F are higher magnification views of the boxed areas on the left). (B,G) Ki-67 activity was found in the basal and parabasal layers of the epithelium within SOKC and was much higher in PIOC. (C,D; H,I) CK7 and CK8/18 were positive in some of the SOKC cases, but were absent in PIOC. (E,J) CK10 was positive in PIOC and some of the SOKC cases. Scar bar: 120 μm (A,C–F,H–J), 40 μm (A,B,F,G).

observed in three cases. The follow-up periods of the KAB cases ranged from 10 months to 5 years.

DISCUSSION

In 2017, the WHO Working Group recategorised odontogenic keratocyst as a cystic lesion and described SOKC as a variant composed of multiple small cysts and epithelial islands in a dense collagenous stroma.[3] The latest mention of KAB in the WHO classification was in 1992, where it was loosely defined as ameloblastoma with extensive keratinisation.[38] The general consensus was that SOKC and KAB share similar histological architectures, raising questions regarding the differences between the two diseases and means of differentiating between them.

Analysis of both SOKC and KAB cases revealed no significant differences in clinical profiles related to age, sex, site preference or results of physical examination. Generally, most lesions occurred in the mandible and followed a more aggressive course than common OKC or ameloblastoma lesions, indicating its neoplastic nature. Radiologically, most cases of OKC were described as showing unilocular radiolucency with a well defined border, and most ameloblastoma cases appeared as multilocular lesions with honeycomb radiolucency and sometimes with an ill defined periphery.[39] The review of reported SOKC and KAB cases revealed that the majority of cases presented with multilocular radiolucency and well defined or ill defined margins.[8,21] Due to the small number of cases, it is not possible to reach definitive conclusions regarding the radiological features of both of

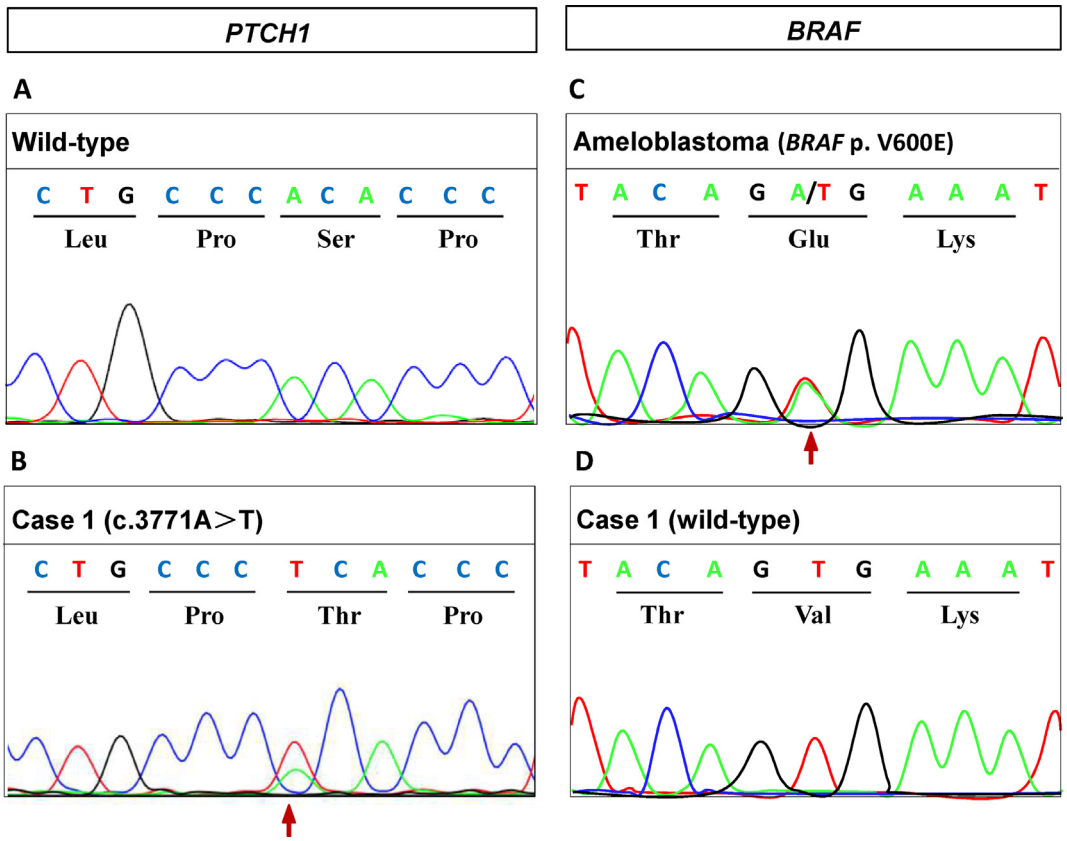

Fig. 4 Mutational analysis of the *PTCH1* gene and *BRAF* p.V600E. (A,B) *PTCH1* mutation identified in fresh tissues from Case 1 revealed a missense mutation (c.3771A>T), while it was absent in the wild type. (C,D) Example of DNA sequence analysis showing the presence of *BRAF* p.V600E mutation in an ameloblastoma but absence of the mutation in the reported cases.

these diseases. However, cases with ill defined margins should be carefully differentiated from malignant tumours, such as PIOC.

Histologically, SOKC is characterised by multiple cysts of various sizes forming a solid neoplasm and the lining epithelium exhibiting characteristics of OKC.[3,8] The distinction of KAB from SOKC is not clear, and the only diagnostic difference is the appearance of ameloblastic follicles with stellate reticulum-like cells.[9,24] Occasionally, OKC may provide the source of epithelium from which ameloblastoma can arise.[26,40] Shuster also suggested reclassifying previous KAB cases that lacked clear features of ameloblastoma into SOKC, as there are many overlaps between the two lesions.[6] Ameloblastic differentiation was seen in four of our cases. However, as they exhibited architectural characteristics of SOKC with no typical follicular or plexiform ameloblastoma components and lacked keratinisation at the centre of ameloblastomatous lining epithelia, we tended to call them SOKC with ameloblastomatous transformation. Clear cell components were identified in two of the reported cases, which were likely to have been transformed from the typical components of OKC.[7] Differential diagnosis of this group of lesions with PIOC is important and challenging. Some pathologists have suggested that the superficial layer of the epithelium is thinner in SOKC.[41] Additionally, prominent cytological atypia and aggressive infiltration into the surrounding tissues and bone could be considered for differentiation under the microscope.

Previous reports have indicated that cytokeratin expression in the epithelial lining of the odontogenic cysts is correlated with the degree of differentiation.[42] CK7 and CK8/18 are expressed in less well differentiated epithelium. Some of our cases expressed CK7 and CK8/18, while PIOC exhibited no discernible expression of either CK7 or CK8/18. CK10 is a marker of cornification, which was expressed in PIOC but was absent in three of our reported cases. Thus, cytokeratin expression may be useful to differentiate this group of lesions from PIOC. Notably, p53 and Ki-67 staining demonstrated marked differences between the present cases and PIOC. Disturbance of p53, which is one of the most common tumour suppressor genes, can result in uncontrolled cell proliferation.[43] The immunoreactivity for p53 was strong throughout the epithelium in PIOC, but weak or undetectable in our reported lesions, indicating their benign status. Additionally, all of the reported cases exhibited much lower proportions of cells (8%–10%) positive for Ki-67 (which is strictly associated with cell proliferation) than PIOC cases (60%), but these were slightly higher than in OKC cases (5%). Thus, both p53 and Ki-67 could be useful as markers for differentiation between SOKC and PIOC.

Detection of specific DNA mutations has been suggested as a useful way to define this group of lesions.[17,26] Our data and the findings of previous studies indicate that *PTCH1* mutations are found frequently in sporadic and syndromic OKC but are not frequent in ameloblastoma.[36] Up to 90% of ameloblastomas were recently reported to have *BRAF* V600E mutation, but the rate is almost 0% in OKC.[37,44] None of the nine cases in the present study harboured *BRAF* V600E mutation, while one of two cases was positive for *PTCH1* mutation, suggesting that this group of lesions should be

Table 2 Solid variant of odontogenic keratocyst (SOKC) and keratoameloblastoma cases in the English language literature

Authors	Age, sex	Site	Radiogram	Management	Follow-up
SOKC cases					
Ide *et al.*	49/F	Left mandible	Honeycombed RL	1st enucleation; 2nd en bloc	1st R, 3 times; 2nd NR, 4 y
Vered *et al.*	72/M	Right maxilla, from premolar region to tuberosity	Multilocular, ill-defined RL (honeycombed appearance)	Hemi-maxillectomy	NR, 4 y
Daley *et al.*	52/M	Left mandible, between cuspid and first bicuspid	Unilocular RL	Resection	ND
Iezzi *et al.*	52/F	Left mandible, premolar region of left hemimandible	Well-demarcated RL	Enucleation	NR, 6 y
Shuster *et al.*	47/M	Right mandible, first molar to canine	Scalloped, well-defined RL	Enucleation	NR, 6 mo
Geng *et al.*	38/F	Left maxilla, premolar region to tuberosity	Multilocular ill-defined RL	Segmental resection	NR, 3 y
Kawano *et al.*	57/F	Left mandible, canine to the retromolar area	Ill-defined, moth-eaten RL	Hemi-mandibulectomy	NR, 20 y
Kahraman *et al.*	42/M	Mandiblular posterior area	Mutiloculated RL with scalloped and corticated border	ND	NR, 3 y
	30/F	Mandiblular posterior area	Mutiloculated, well demarcated RL with corticated border	ND	ND
Keratoameloblastoma cases					
Pindborg	57/F	Right mandible	Multilocular RL	ND	ND
Altini *et al.*	28/M	Anterior maxilla	Multilocular RL	ND	ND
Altini *et al.*	76/F	Right mandible, from bicuspid area to sigmoid notch	Multilocular RL with scalloped margin	Hemi-mandibulectomy	NR, 1 y
Siar *et al.*	30/M	Anterior mandible	Multilocular RL	Resection	ND
	35/M	Left mandible	ND	Hemi-mandibulectomy	ND
	35/F	Right maxilla	Ground glass with instinct borders	ND	ND
	39/F	Left anterior mandible	Unilocular RL	Enucleation	ND
Norval *et al.*	26/F	Right mandible, from 1st premolar and 3rd molar	Circumscribed obulated RL	Segmental resection	ND
Raubenheimer *et al.*	57/F	Mandible	ND	ND	ND
Said-al-Naief *et al.*	26/M	Right posterior maxilla	Unilocular RL	1st curettage; 2nd resection	1st R, 6 mo; 2nd ND
Zhao	62/M	Right posterior maxilla	Unilocular RL with well-defined borders	Wide surgical excision	NR, 4 y
Takeda *et al.*	76/M	Left mandible body	Multilocular RL	Resection	RD
Collini *et al.*	62/M	Right mandible, involving ramus and condyle	Irregular RL	Hemi-mandibulectomy	R, 38 mo
Whitt *et al.*	45/M	Left anterior maxilla	Ill-defined RL	Curettage	NR, 10 mo
Adeyemi *et al.*	38/M	Right mandible, canine to first molar	Multilocular RL	Mandibular resection	NR, 24 mo
Sisto *et al.*	35/F	Right posterior mandible	Multilocular mixed RL	Transoral resection	ND
Ketabi *et al.*	21/F	Right mandible, roots of the central and lateral incisors	Unilocular RL with well-defined borders	Enucleation	NR, 12 mo
Mohanty *et al.*	46/M	Right mandible, 44 to 48	Multilocular RL	ND	ND
Raj *et al.*	22/F	Right posterior mandible	Unilocular RL with well-defined sclerotic margins	Segmental mandibulectomy	NR, 24 mo
Lee *et al.*	56/M	Right maxilla, maxillary molars	Well-defined RL	Enucleation three times; resection	1st R, 3 mo; 2nd R, 11 mo; 3rd R, 10 mo; 4th R, 4 mo; 5th R, 19 mo; 6th NR, 10 mo
Palaskar *et al.*	65/F	Anterior mandible, left to right canine region	Unilocular RL causing erosion of bone	1st excision; 2nd block resection	1st R, 4 mo; 2nd ND
Bedi *et al.*	27/F	Right posterior mandible	Soft tissue mass	Wide surgical excision with distinct borders	Under follow-up
Anajar *et al.*	32/F	Right posterior mandible	Multilocular RL	Wide resection	ND
Konda *et al.*	44/M	Right posterior mandible	Well-defined unilocular RL	Excision	NR, 1 y
Rathore *et al.*	18/M	Right posterior mandible	Multilocular RL	Wide local excision	NR, 2 y
Parikah *et al.*	32/F	Left posterior palate	ND	ND	ND

F, female; M, male; mo, months; N, none; NA, not available; R, recurrence; NR, no recurrence; RL, radiolucency; y, years.

classified as SOKC rather than KAB. However, further studies involving additional fresh tissue samples will be required for confirmation.

From the viewpoint of treatment, there is no difference between SOKC and KAB, as osteotomy is the method with the lowest recurrence rate.[9] It has been suggested that SOKC is more aggressive than purely cystic cases due to its infiltrative growth pattern and strong tendency to recur after removal, and it should be classified as a neoplastic lesion.[8] A smooth radiographic profile with appropriate surgical resection of the lesion are indicators of non-aggressive behaviour.[10] Seven of the cases receiving conservative surgery in the present study exhibited recurrence in the present study. Cases 5 and 7 were the only cases with recurrence after osteotomy/wide resection: in Case 5 the radiological borders were ill defined, and in Case 7 complete removal of the lesion was difficult due to the complex tumour location.

Based on our experience and the review of the relevant literature, SOKC and KAB overlap significantly in terms of clinical appearance, histology and biological behaviour, and it is not necessary to separate them into two distinct entities. Genetic analysis suggested the lesions should be classified as SOKC. Immunohistochemical analysis of p53 and Ki-67 may be useful to differentiate between these lesions and PIOC. Additional studies involving larger numbers of cases will be required to improve understanding of these lesions.

Acknowledgements: The English in this document has been checked and corrected by Textcheck (http://www.textcheck.com/certificate/dT6FnY).

Conflicts of interest and sources of funding: This study was supported by the National Natural Science Foundation of China (81671006, 81702689, 81700945), the Beijing Nature Science Foundation (7172238) and CAMS Innovation Fund for Medical Sciences (2019-12M-5-038). The authors state that there are no conflicts of interest to disclose.

Address for correspondence: Dr Tiejun Li, Department of Oral Pathology, Peking University School and Hospital of Stomatology, 22 South Zhongguancun Avenue, Haidian District, Beijing 100081, China. E-mail: litiejun22@vip.sina.com

References

1. Wright JM, Vered M. Update from the 4th edition of the World Health Organization Classification of Head and Neck Tumours: Odontogenic and Maxillofacial Bone Tumors. *Head Neck Pathol* 2017; 11: 68–77.
2. Barnes L, Eveson EJ, Reichart PA, Sidransky D, editors. *World Health Organization Classification of Tumors: Pathology and Genetics of Head and Neck Tumors*. Lyon: IARC Press, 2005.
3. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg P, editors. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon: IARC Press, 2017; 205–60.
4. Ide F, Mishima K, Saito I. Solid-cystic tumor variant of odontogenic keratocyst: an aggressive but benign lesion simulating keratoameloblastoma. *Virchows Arch* 2003; 442: 501–3.
5. Vered M, Buchner A, Dayan D, Shteif M, Laurian A. Solid variant of odontogenic keratocyst. *J Oral Pathol Med* 2004; 33: 125–8.
6. Shuster A, Shlomi B, Reiser V, Kaplan I. Solid keratocystic odontogenic tumor-report of a nonaggressive case. *J Oral Maxillofac Surg* 2012; 70: 865–70.
7. Kawano K, Okamura K, Kashima K, *et al*. Solid variant of keratocystic odontogenic tumor of the mandible: report of a case with a clear cell component and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; 116: e393–8.
8. Kahraman D, Gunhan O, Celasun B. A series of 240 odontogenic keratocysts: should we continue to use the terminology of 'keratocystic odontogenic tumour' for the solid variant of odontogenic keratocyst? *J Craniomaxillofac Surg* 2018; 46: 942–6.
9. Geng N, Lv D, Chen Q, *et al*. Solid variant of keratocystic odontogenic tumor with ameloblastomatous transformation: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 114: 223–9.
10. Daley TD, Multari J, Darling MR. A case report of a solid keratocystic odontogenic tumor: is it the missing link? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 103: 512–5.
11. Iezzi G, Rubini C, Zizzi A, Aspriello SD, Fioroni M, Piattelli A. Solid variant of keratocystic odontogenic tumour: report of a case. *Minerva Stomatol* 2011; 60: 133–8.
12. Altini M, Slabbert HD, Johnston T. Papilliferous keratoameloblastoma. *J Oral Pathol Med* 1991; 20: 46–8.
13. Norval EJ, Thompson IO, van Wyk CW. An unusual variant of keratoameloblastoma. *J Oral Pathol Med* 1994; 23: 465–7.
14. Said-al-Naief NA, Lumerman H, Ramer M, *et al*. Keratoameloblastoma of the maxilla. A case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84: 535–9.
15. Takeda Y, Satoh M, Nakamura S, Ohya T. Keratoameloblastoma with unique histological architecture: an undescribed variation of ameloblastoma. *Virchows Arch* 2001; 439: 593–6.
16. Collini P, Zucchini N, Vessecchia G, Guzzo M. Papilliferous keratoameloblastoma of mandible: a papillary ameloblastic carcinoma: report of a case with a 6-year follow-up and review of the literature. *Int J Surg Pathol* 2002; 10: 149–55.
17. Whitt JC, Dunlap CL, Sheets JL, Thompson ML. Keratoameloblastoma: a tumor sui generis or a chimera? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104: 368–76.
18. Ketabi MA, Dehghani N, Sadeghi HM, *et al*. Keratoameloblastoma, a very rare variant of ameloblastoma. *J Craniofac Surg* 2013; 24: 2182–6.
19. Mohanty N, Rastogi V, Misra SR, Mohanty S. Papilliferous keratoameloblastoma: an extremely rare case report. *Case Rep Dent* 2013; 2013: 706128.
20. Bedi RS, Sah K, Singh A, Chandra S, Raj V. Keratoameloblastoma or Kerato-odontoameloblastoma: report of its soft tissue recurrence with literature review. *Quant Imag Med Surg* 2015; 5: 898–908.
21. Lee C, Park BJ, Yi WJ, Heo MS, Lee SS, Huh KH. Keratoameloblastoma: a case report and a review of the literature on its radiologic features. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; 120: e219–25.
22. Palaskar SJ, Pawar RB, Nagpal DD, Patil SS, Kathuriya PT. Keratoameloblastoma a rare entity: a case report. *J Clin Diagn Res* 2015; 9: ZD05–7.
23. Konda P, Bavle RM, Muniswamappa S, Makarla S, Venugopal R. Papilliferous keratoameloblastoma of the mandible - a rare case report. *J Clin Diagn Res* 2016; 10: ZD08–11.
24. Anajar S, Lakhbal A, Abada R, Mahtar M. Keratoameloblastoma of the mandible. *Eur Ann Otorhinolaryngol Head Neck Dis* 2017; 134: 205–6.
25. Rathore AS, Juneja S, Khurana N, Shetty DC. Papilliferous keratoameloblastoma: a rare case report. *Int J Appl Basic Med Res* 2017; 7: 139–42.
26. Ide F, Ito Y, Muramatsu T, Saito I, Abiko Y. Histogenetic relations between keratoameloblastoma and solid variant of odontogenic keratocyst. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 114: 812–3. author reply 813–4.
27. Altini M, Lurie R, Shear MA. Case report of keratoameloblastoma. *Int J Oral Surg* 1976; 5: 245–9.
28. Pindborg JJ. *Pathology of the Dental Hard Tissues*. Philadelphia: Saunders, 1970; 371–6.
29. Siar CH, Ng KH. Combined ameloblastoma and odontogenic keratocyst' or 'keratinising ameloblastoma. *Br J Oral Maxillofac Surg* 1993; 31: 183–6.
30. Raubenheimer EJ, van Heerden WF, Noffke CE. Infrequent clinicopathological findings in 108 ameloblastomas. *J Oral Pathol Med* 1995; 24: 227–32.
31. Zhao Y, Zheng YG, Wu LY. Papilliferous keratoameloblastoma: report of a case. (Chinese.). *Zhonghua Bing Li Xue Za Zhi* 2008; 37: 357–8.
32. Adeyemi B, Adisa A, Fasola A, Akang E. Keratoameloblastoma of the mandible. *J Oral Maxillofac Pathol* 2010; 14: 77–9.
33. Sisto JM, Olsen GG. Keratoameloblastoma: complex histologic variant of ameloblastoma. *J Oral Maxillofac Surg* 2012; 70: 860–4.
34. Raj V, Chandra S, Bedi RS, Dwivedi R. Keratoameloblastoma: report of a rare variant with review of literature. *Dent Res J (Isfahan)* 2014; 11: 610–4.
35. Parikh N, Nandini C, Jain S, Mansata AV. Peripheral keratoameloblastoma: a novel case report. *J Oral Maxillofac Pathol* 2018; 22: 249–53.
36. Qu J, Yu F, Hong Y, *et al*. Underestimated PTCH1 mutation rate in sporadic keratocystic odontogenic tumors. *Oral Oncol* 2015; 51: 40–5.
37. Oh KY, Cho SD, Yoon HJ, *et al*. High prevalence of BRAF V600E mutations in Korean patients with ameloblastoma: clinicopathological

significance and correlation with epithelial-mesenchymal transition. *J Oral Pathol Med* 2019; 48: 413–20.
38. Kramer IRH, Pindborg JJ, Shear M. *World Health Organization International Histological Classification of Tumors*. 2nd ed. Heidelberg: Springer-Verlag, 1992.
39. Kitisubkanchana J, Reduwan NH, Poomsawat S, Pornprasertsuk-Damrongsri S, Wongchuensoontorn C. Odontogenic keratocyst and ameloblastoma: radiographic evaluation. *Oral Radiol* 2020; Feb 6: https://doi.org/10.1007/s11282-020-00425-2.
40. Ren C, Amm HM, DeVilliers P, *et al*. Targeting the sonic hedgehog pathway in keratocystic odontogenic tumor. *J Biol Chem* 2012; 287: 27117–25.
41. Soluk-Tekkesin M, Wright JM. The World Health Organization Classification of Odontogenic Lesions: a summary of the changes of the 2017 (4th) edition. *Turk Patoloji Derg* 2018; 34: https://doi.org/10.5146/tjpath.2017.01410.
42. Bhakhar VP, Shah VS, Ghanchi MJ, *et al*. A comparative analysis of cytokeratin 18 and 19 expressions in odontogenic keratocyst, dentigerous cyst and radicular cyst with a review of literature. *J Clin Diagn Res* 2016; 10: ZC85–9.
43. Moon SH, Huang CH, Houlihan SL, *et al*. p53 represses the mevalonate pathway to mediate tumor suppression. *Cell* 2019; 176: 564–80.
44. Franca JA, de Sousa SF, Diniz MG, *et al*. Absence of BRAFV600E mutation in odontogenic keratocysts. *J Oral Pathol Med* 2018; 47: 186–91.