ORIGINAL PAPER

ODONTOGENIC KERATOCYST IN GERIATRIC POPULATION: A DEVELOPMENTAL CYST IN ELDERLY PATIENTS

Eman M. Abdulhady[1], Bacem Abdullah[2], Mohamed A. Tawfik[3]

[1]Department of Oral Medicine, Periodontology and Oral Diagnosis, Faculty of Dentistry, Horus University in Egypt, New Damietta, Egypt
[2]Department of Maxillofacial Pathology, Mansoura University, Mansoura, Egypt
[3]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mansoura University, Mansoura, Egypt

ABSTRACT

Introduction: Odontogenic keratocyst (OKC) was rarely reported in geriatric population. To the best of our knowledge, only 15 cystic cases, of which one radiograph was documented, and eight solid OKCs were reported in geriatric patients.

Objectives: This study investigated the difference between the histological and immuno-histochemical profile of juvenile and geriatric cases of sporadic OKC.

Material and methods: In this retrospective study, a control group of 15 sporadic juvenile OKCs (group 1), 15 juvenile syndromic OKCs (group 2), and 15 juvenile recurrent OKCs (group 3) patients were included and clinico-pathologically compared with newly reported cases. Group 4 was composed of three geriatric cases only. Paraffin wax blocks were sectioned to be stained with anti-NPM1/ALK (Abcam), anti-CK7, anti-CK14, anti-Ki-67, anti-SOX-10, and anti-Cyclin D1 in all groups. One-way ANOVA test was used to compare the studied groups.

Results: The difference between immuno-staining for anti-NPM1/ALK, anti-CK7, anti-CK14, anti-Ki-67, anti-SOX-10, and anti-Cyclin D1 was not statistically significant. Therefore, the nature of OKC in the geriatric population did not differ from that of the younger population, posing strong controversy about classifying OKCs as only developmental lesions.

Conclusions: True sporadic odontogenic keratocyst can affect geriatric populations, which defies the general theoretical consensus about the developmental origin of sporadic OKCs. This is complicated by the fact that the proliferation index is high in geriatric and juvenile populations.

Key words: cysts, geriatric OKC, immuno-histochemistry, odontogenic keratocyst.

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INTRODUCTION

In 2017, according to the World Health Organization (WHO) classification, odontogenic keratocyst (OKC) was re-classified as a cyst, except for para-keratinized OKC cases, which demonstrate *PTCH1* genetic mutations [1, 2]. The classification of OKC, either as a cyst or a tumor, was debated over 2 decades. In 2017, the WHO classified OKC referred keratocystic odontogenic tumor (KCOT) as sporadic and syndromic (when multiple OKCs, among other pathologies, are associated with nevoid basal cell carcinoma syndrome [3]), abandoning the previous designation of KCOT [4, 5]. The 'sporadic OKC' term was coined to describe OKCs that show no *PTCH1* mutation, and are not synchronized with other head and neck malignancies. The origin of OKC is be-

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Address for correspondence: Bacem Abdullah, Department of Maxillofacial Pathology, Mansoura University, Mansoura, Egypt, e-mail: bacemkhalele@std.mans.edu.eg

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lieved to be the remnant of dental lamina [6]. Most of the incidences of OKC are reported in the range group of 10 to 38 years old. These tumors are most encountered in the mandible, especially in the body and ramus regions [7, 8]. Clinically, patients may present with soft tissue swelling, pain in the jaw, and a discharge and paresthesia of lip/teeth; they may be also asymptomatic. OKC shows aggressive behavior, high growth potential, a higher expression rate of keratin than other odontogenic cysts, and liability to recur after being surgically excised, owing to the thin, fragile nature of the corrugated epithelial lining, which tears during surgical manipulation, populating tenable OKC residues [9]. If simple enucleation is combined with decompression therapy, the outcome is favorable. Adjuvant marginal ostectomy, cryotherapy, and Carnoy's solution application are also used. Resection provides the lowest recurrence rate, although it is the most aggressive [9, 10].

Molecular mechanisms underlying the initiation and progression of OKCs are still idiopathic. However, it is thought to be determined by complicated interactions among various molecular entities, which also have a definite role in physiological tooth formation. Mutations of human *PTCH1* genes was linked to the disruption of sonic hedgehog (SHH) signaling pathway [11].

Several recent studies have focused on the increase in proliferative and anti-apoptotic features in the epithelial lining of juvenile OKCs. This assessment was based on an immuno-histochemical analysis or molecular detection of genetic abnormalities (Table 1). The expression of antibodies is checked with sporadic juvenile OKCs because they are most frequent. Some scholars contrasted the expression of the marker in *de novo* juvenile lesions against recurrent cases, while others assessed a sample of sporadic cases compared with syndromic OKCs [5, 6, 12-41]. However, OKC was rarely reported in geriatric populations. To the best of our knowledge, only 15 cystic cases [39, 42-52], of which one radiograph was documented [47], and 8 solid OKCs [39, 46-52], were reported in geriatric patients (Table 2). Here, we reported 3 cases and investigated the difference between the expression of 7 immunohistochemical markers in juvenile (age range, 10-22 years old) and geriatric (age range, 59-89 years old) cases of sporadic OKCs.

There are several surgical therapeutic modalities for treating OKCs, including enucleation, with or without applying Carnoy's solution. Enucleation may be implemented alone or associated with ostectomy or cryotherapy, marsupialization and decompression, and marginal or segmental resection [15]. This study investigated the difference between the histological and immunohistochemical profile of juvenile and geriatric cases of sporadic OKCs. We assumed that there could be some differences in the clinical behavior of OKCs in patients according to their age.

OBJECTIVES

This study investigated the difference between the histological and immuno-histochemical profile of juvenile and geriatric cases of sporadic OKC.

MATERIAL AND METHODS

In this retrospective analysis, a control group of 15 sporadic juvenile OKC cases (group 1), 15 juvenile syndromic OKCs (group 2), and 15 recurrent juvenile OKCs (group 3) were included to clinico-pathologically compare with newly reported cases. Group 4 was composed of three cases only. For the first three groups, inclusion criteria mandated the diversity of age groups of the studied cases. Sample size was calculated with G-power software. No cases were dropped off the study. The study included archive of three Egyptian institutes, using convenient sampling technique. Enrolled cases were selected between 2020 and 2022 to guarantee that the positivity of cells for markers would remain intact. Archival cases with medical history or paraffin wax blocks working were excluded.

After obtaining approval from Ethics Committee of Al-Azhar University (IRB Number: AUAREC202200006-09) and informed consents from patients, the paraffin wax blocks of the collated cases were sectioned to be stained with anti-NPM1/ALK (Abcam), anti-CK7 (Dako), anti-CK14 (Santa Cruz), anti-Ki-67 (Dako), anti-SOX-10 (Abcam), and anti-Cyclin D1 (Abcam) in all groups. One-way ANOVA test was applied to compare the studied groups.

Three µm-thick sections were taken onto poly-l-lysine adhesive-coated micro-slides, and incubated in hot air oven at 60°C overnight. After clearing and hydrating the cut sections, they were processed in three concentrations of xylene and alcohol before immersing in distilled water. Antigen retrieval was carried out in a pressure cooker, with tris EDTA for 0.7 hours. Tissue sections were in two buffers before being embedded in a 3% H_2O_2 and methanol for 10 minutes. Further, the sections were washed in distilled water for 3 minutes. For antigen retrieval, sections were mixed with EDTA-based heat-induced treatment for one hour. After treating the sections with protein block serum at room temperature, they were covered with primary antibodies and incubated overnight. The processed sections were stained for the following antibodies.

Two expert oral pathologists measured the immunostaining pattern and intensity, and compared the results with histomorphometric analysis generated from ImageJ software, as follows: 0 = no cells stained; 1 = 1-19%; 2 = 20-50%; 3 = 51-75%, and 4 = 76-100%. According to Khalele *et al.*, area fraction was also measured for the three experimental groups. Wilcoxon signed-rank test was applied to compare non-parametric data for the studied groups, utilizing IBM® SPSS® software (USA).

TABLE 1. Frequent immuno-histochemical markers commonly used in odontogenic keratocyst (OKC) cases

Marker	Sporadic juvenile OKC	Syndromic juvenile OKC	Recurrent juvenile OKC	Technique	Reference(s)
Epithelial expression					
BRAFV600E	–	+++	N.A.	IHC	12
Bcl-2	+++	+++	+++	IHC	13, 14, 36
Calretinin	–	+++	+++	IHC	15-17
CD44v6	+++	N.A.	N.A.	IHC	18
COX2	++	N.A.	N.A.	IHC	19
Cyclin-D1	++	+++	N.A.	IHC	20
EMMPRIN	+++	++++	N.A.	IHC	21
ErbB2	+++	+++	N.A.	IHC	22
Gli1	+++	N.A.	N.A.	IHC, PCR	23, 24
HER2	+++	N.A.	N.A.	IHC	22
Ki67	++	++	N.A.	IHC	1, 25
MCM3	++	++	N.A.	IHC	25
MMP-1	++	++	N.A.	IHC	26
MMP-2	++	++	N.A.	IHC	28
MMP-9	++	++	N.A.	IHC	29
MMP-13	++	++	N.A.	IHC	28
NF-κB	++	++	N.A.	IHC	19
p16, p21, p27, RB1	++	++	N.A.	IHC, PCR	31
p53	++	++	++	IHC	5
p-AKT	++	N.A.	N.A.	IHC	31
Podoplanin	++	N.A.	N.A.	IHC	18
PTCH	++	++	N.A.	IHC	32
PTCH2	++	++	N.A.	IHC, PCR	24, 36
RANK, RANKL, OPG	++	N.A.	N.A.	IHC	7
SHH	++	+++	+++	IHC	15
SMO	++	++	+++	IHC	24, 35
SOX2	++	++	+++	IHC	37
Stromal expression					
TrkB	+++	+++	+++	IHC	32
Interleukin-1α	+++	+++	+++	IHC	4, 28
Keratin layer					
p63/p40	–	N.A.	N.A.	IHC	38-40
Lumen					
PD-L1	Detected	N.A.	N.A.	PCR	41

IHC – immuno-histochemistry, N.A. – not applicable, PCR – polymerase chain reaction

RESULTS

For the group 4, the first case was a 72-year-old male, who presented with a large well-defined radiolucent area in the lower right mandible. The lesion crossed the midline, and was discovered incidentally on periapical X-ray film for an endodontic treatment of the mandibular right second premolar. The lesion was asymptomatic and caused neither tooth mobility nor root resorption. The buccal bone expansion was not observed either. Cone-beam computed tomography (CBCT) showed buccolingual bone loss, with a very thin buccal plate of the bone without a remarkable bone expansion. Panoramic view indicated a large lesion scalloping around the roots of the mandibular molars (Figure 1).

TABLE 2. Previously reported cases of odontogenic keratocyst (OKC) in elderly patients

Author(s) [Ref.]	Year	Age/sex	Site	Configuration	Radiographic depiction	Surgical management
Daley *et al*. [48]	2007	52/M	Left Md	Solid	Unilocular	Resection
Vered *et al*. [36]	2009	72/M	Right Mx	Solid	ML	Hemi-maxillectomy
Lezzi *et al*. [49]	2011	52/F	Left Md	Solid	Well-demarcated	Enucleation
Ide *et al*. [50]	2012	49/F	Left Md	Solid	Honeycomb	Enucleation/en bloc resection
Shuster *et al*. [51]	2012	47/M	Right Md	Solid	Scalloped, well-defined	Enucleation
Kawano *et al*. [52]	2013	57/F	Left Md	Solid	Moth-eaten	Hemimandibulectomy
Awni and Conn [42]	2017	61	Ramus condyle	Sporadic	N.G.	Decompression and enucleation
Awni and Conn [42]	2017	68	Md, ramus coronoid	Sporadic	N.G.	Incremental decompression and enucleation
Awni and Conn [42]	2017	61	Ramus and condyle	Sporadic	N.G.	N.G.
Alves *et al*. [43]	2018	52/F	Md, right ramus	Sporadic	N.G.	Decompression and enucleation
Alves *et al*. [43]	2018	80/M	Md, left body, angle and rami	Sporadic	N.G.	Decompression and enucleation
Resende *et al*. [44]	2018	62/F	Md, right ramus	Sporadic	N.G.	Decompression and enucleation
Resende *et al*. [44]	2018	72/M	Md, left body, angle and rami	Sporadic	N.G.	Decompression and enucleation
Zhong *et al.* [45]	2019	78/F	Md	N.G.	N.G.	Curettage
Zhong *et al*. [45]	2019	69/M	Md	N.G.	N.G.	Curettage
Zhong *et al*. [45]	2019	66/F	Md	N.G.	N.G.	Curettage
Zhong *et al*. [45]	2019	65/M	Md	N.G.	N.G.	Curettage
Zhong *et al*. [45]	2019	65/F	Md	N.G.	N.G.	Curettage
Zhong *et al*. [45]	2019	64/F	Md	NG	N.G.	Curettage
Zhang *et al.* [46]	2021	78/F	Right Md	Solid	MI	Osteotomy
Zhang *et al.* [46]	2021	64/F	Anterior Md (bilateral)	Solid	MI	Curettage 5 times, osteotomy
Milani *et al*. [47]	2021	67/M	Md, left ascending ramus	Sporadic	MI	Enucleation, followed by the application of Carnoy's solution

D&E – decompression and enucleation, F – female, M – male, Md – mandible, MI – multilocular, Mx – maxilla, N.G. – not given

The patient was a retired military officer, who underwent periodic medical checkups regularly. Previous radiographic records were free from any lesions. The second case was a 70-year-old female, who presented with painful swelling in the right mandible at the extraction site of right first molar. Panoramic X-ay showed large well-defined radiolucent lesion, which extended between the lower right second premolar and the roots of the lower right second molar. CBCT revealed a buccolingual bone expansion, with complete loss of the buccal plate of bone. The third case was a 68-year-old female, who presented with a large asymptomatic lesion in the left mandible. Similar to the first case, the lesion was discovered incidentally.

The mean age of the investigated cases in the first three groups was 22 years. The age ranged from 16 to 32 years. Majority of lesions were observed in the posterior mandible, and bone expansion was not remarkable. Surgical treatment modalities were enucleation for relatively small cysts, and decompression/marginal resection for large and recurrent cysts. Clinico-pathological behavior was assessed in terms of clinical aggressiveness of the cysts (e.g., bone destruction, pathologic fracture, and approaching vital structures) and high proliferative index (measured by Ki-67 expression). Automatic scoring of Ki-67 using ImageJ was recorded for each case. The four groups were compared using Wilcoxon signed-rank test.

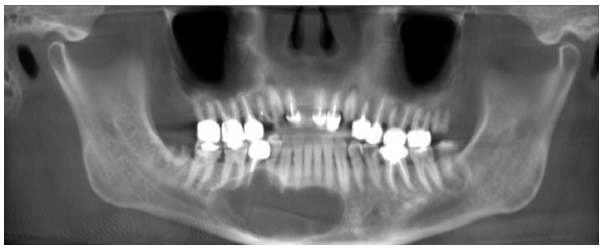

FIGURE 1. Panoramic view showing odontogenic keratocyst in a 72-year-old patient

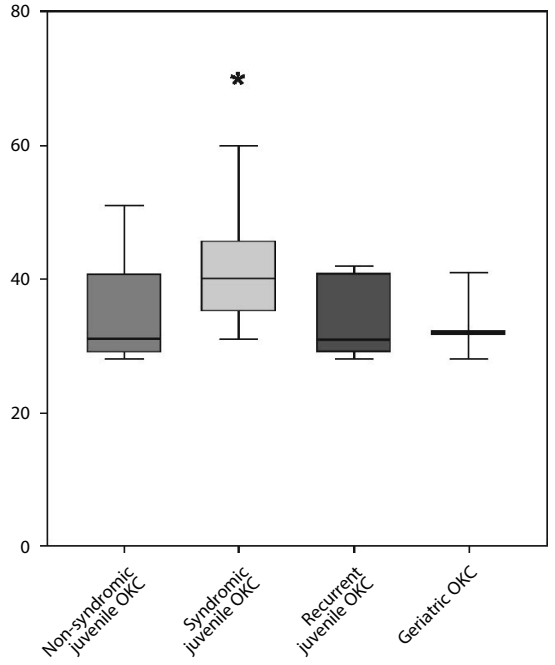

FIGURE 2. Box plot showing statistical difference among the four investigated groups based on Wilcoxon signed-rank test. Y-axis describes Ki-67 score. The difference in clinico-pathological behavior of syndromic and non-syndromic odontogenic keratocysts (OKCs) (G1 vs. G2) was statistically significant

The difference in the clinico-pathological behavior of syndromic and non-syndromic OKCs (G1 vs. G2) was statistically significant ($p < 0.0001$; CI: 96.48; Figure 2).

Histologically, all cases of non-inflamed OKCs generally demonstrated 6 to 8 cell layer thick lining, overlying a flat basement membrane. The basal layer was composed of columnar or cuboidal cells, with intensely basophilic palisaded nuclei. When comparison was made between recurrent and non-recurrent cases, the suprabasal layers revealed higher mitotic activity and epithelial dysplasia beneath the corrugated thick epithelial lining in the recurrent cases than non-recurrent cases. However, this finding was not statistically significant ($p > 0.05$). The keratinized layers demonstrated areas of atrophic cells with vacuolated cytoplasm. Although all syndromic cases of OKCs were parakeratinized, including geriatric patients, only a few sporadic OKCs were ortho-keratinized. The ortho-keratinized OKCs did not meet histologic features needed to be re-classified as ortho-keratinized odontogenic cysts (the corrugated basement membrane showed palisaded nuclei). Chondroid metaplasia was not detected in any OKC cases. The epithelium–connective tissue interface was mostly intact. Within the same OKC lesions, sub-mucosal separation and sub-mucosal hyalinization were evident. However, these findings were consistently detected in all the studied groups, in which the number of daughter cysts, impregnated OKCs in the supporting stroma, varied. However, this variance was not statistically significant. The underlying stroma revealed abundant myofibroblasts, which are generally expected to support a rapid growth and aggressiveness of OKCs. Some OKCs demonstrate sub-epithelial hyalinization, corrugated thick keratin layers, and chronic inflammatory infiltrates. In the reported geriatric OKCs, the keratocystic wall, with variable thickness overlying a fibrous stroma, presented typical palisading basal cells of OKC and luminal keratin formation, mild suprabasal dysplasia, and splitting at the epithelial-connective tissue interface as well as a corrugated thickened keratin layer.

The selection of IHC markers was based on the emphasizing literature for markers that could distinguish between different variants of OKCs. We also conducted a genetic network analysis to characterize sporadic and syndromic OKCs. In the studied groups, the difference between immuno-staining for anti-NPM1/ALK and anti-Cyclin D1 was not statistically significant. Therefore, the nature of OKCs in the geriatric population did not differ from that of the younger population, posing fierce controversy about classifying OKCs as only developmental lesions. Figure 3 shows the immuno-expression of the studied antibodies in the group 4. The measures of area fractions in each group are showed in Figure 4 (Kappa index: 0.92). We sent formalin-fixed, paraffin-embedded tissues to three European molecular laboratories for FISH and next-generation sequencing, which is not fully available in our country. However, molecular pathologists and geneticists confirmed that the samples were not analyzable because of insufficient optical quality of the retrieved tissue. Processing the original samples in Egypt made extracting viable DNA/RNA impossible.

DISCUSSION

OKCs are rarely seen in geriatric populations, because they are developmental in origin, and developmental lesions tend to arise in young populations, except if they originate from vestigial remnants. Recently, a distinction between different types of OKCs has been made based on histological and genetic parameters of each lesion and one's possibility of developing malignancy [32, 33]. The current study aimed to assess changing of histological and immuno-histochemical findings in several syndromic and non-syndromic OKCs in different age groups. In the medical literature, some cases have been reported in older patients; however, they did not provide any radiograph or micrograph. For example, a Japanese study reported that 25 out of 183 cases in Japan were diagnosed with OKCs between the ages of 50 and 79 years or older. However, the provided data described only two cases within the defined age groups, with no reference to performing genetic investigations [53]. Moreover, some peripheral and solid keratocysts were described to be present in old age [50]. This incidence might correspond

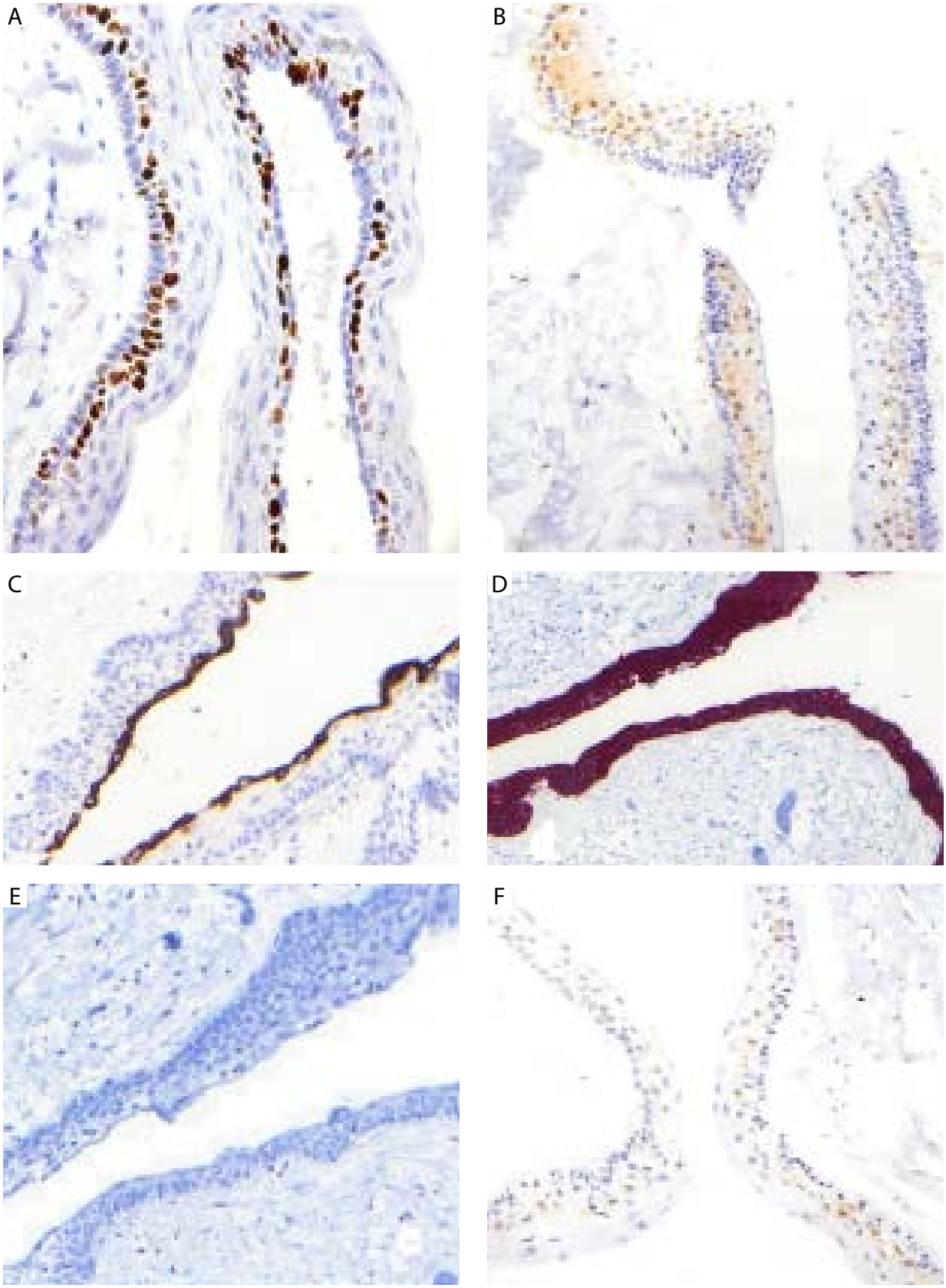

FIGURE 3. Immuno-histochemical expression in group 4: Geriatric odontogenic keratocyst (OKC). **A**) Immuno-positivity for Ki-67, ImageJ scoring: 33% (magnification ×40). **B**) Immuno-positivity for ALK, ImageJ scoring: 17% (magnification ×40). **C**) Immuno-positivity for CK14, ImageJ scoring: 28% (magnification ×40). **D**) Immuno-positivity for CK7, ImageJ scoring: 94% (magnification ×40). **E**) Immuno-positivity for SOX10, ImageJ scoring: 0% (magnification ×40). **F**) Immuno-positivity for Cyclin-D1, ImageJ scoring: 12% (magnification ×40)

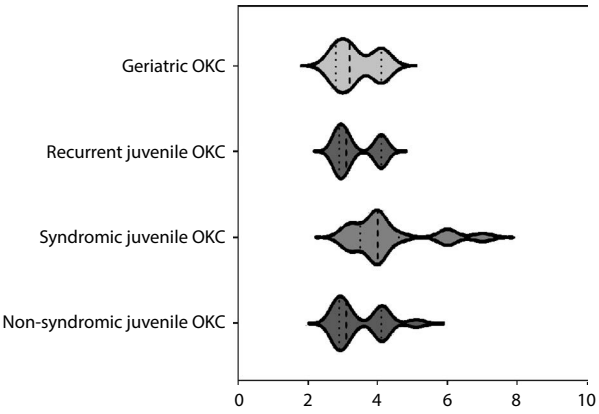

FIGURE 4. The recorded measures of area fractions in each group

to neoplastic rather than cystic OKCs. Given the premise that a non-syndromic OKC is a developmental cyst with no neoplastic potential, the development of odontogenic cysts is rarely encountered in the geriatric population. Indeed, the reported OKCs in middle-aged and geriatric populations in the medical literature were not tested for genetic mutation, and could have demonstrated a neoplastic potential. What distinguishes OKCs from other developmental odontogenic cysts is their aggressive nature that might cause a gnathic pathological fracture. Late development of OKCs, other than juvenile OKCs, indicates a change in the mechanism of their development, although there is no rigid definition of what a development lesion constitutes depending on the age of an individual.

Classic intra-osseous OKCs are rarely seen in patients older than 42 years. Only a few cases were reported in very elderly persons (Table 2). Of these cases, a single case is well-documented by radiographs and clinical picture [47]. The majority of the other reported geriatric cases lack precision and clinical/ radiological documentation because they are either epidemiological studies, retrieving data from a registry, where no patients are examined, or the main focus was some experimental workup. In the latter case, the filling out of clinical data is not prioritized. The reviewers and journal editors could have missed the data, focusing on the molecular or immuno-histochemical findings [43, 45]. The age-related data can be inferred from a panoramic view, in which maxillary sinuses might show age-based pneumatization, the occlusal surface of molars and premolars may demonstrate signs of attrition and history of chronic dental caries, or old sites of extracted sites could be found. However, long-standing histological features are not determinant of the patient's age. Although the onset of some developmental cysts tends to affect middle-aged population (e.g., nasopalatine duct cyst), this finding should neither imply that developmental cysts can appear at any age, nor that these cysts are prone to affect geriatric population. Moreover, vestigial cysts are usually soft tissue cysts that show a very slow rate of growth, unless they are infected. This scenario does not apply to OKCs.

Previous studies have compared the prolific activity of sporadic and syndromic OKCs; however, the reported results were conflicting. Even the long list of immunohistochemical markers commonly expressed in OKCs (Table 1) did not specify a biomarker that could differentiate between sporadic, syndromic, or recurrent juvenile OKCs.

In our reported cases, the surgical intervention was removing OKC from the bone cavity without leaving any macroscopic remnants of the lesion (enucleation), with meticulous follow-up. There is no history of recurrence 9 months after the surgical maneuver. The lesions that were in close proximity to vital structures were marsupializes, and were not associated with the permanence of the impacted teeth either, excluding the need for a radical resection [54]. Carnoy's solution was not used, given its' inevitable irreversible neuro-toxicity and devitalized osseous margin [3, 54]. Pogrel and Jordan observed that the epithelial lining of OKC after marsupialization/ decompression displayed similar characteristics of the normal oral epithelium [9].

Radiographically, OKCs appear as a well-defined unilocular or multilocular radiolucency bounded by corticated margins. In this study, the group 4 showed one multilocular case and two unilocular cases. CBCT images revealed a well-defined mandibular OKC with lobulated margins. The classic appearance of OKC may include root resorption and perforation of the cortices [43, 55]. Notwithstanding, cortical bone perforation was observed in one patient, with no root resorption noted. Although the clinical picture (showing asymptomatic non-expansile OKCs without resorbing roots) may suggest a less aggressive clinical course, the Ki-67 immuno-expression was relatively higher compared with previously reported findings from syndromic and recurrent OKCs.

Therefore, OKCs were rarely reported in elderly patients, excluding the alleged number of non-documented cases. We postulated that the behavior of OKCs could differ according to the age of the patient, if it could be observed in all age groups. The histologic and immuno-histochemical findings did not change among the different age groups. Nevertheless, we documented the incidence of OKCs in geriatric cases. The limitation of this study includes the small number of cases in the group 4. However, OKC occurrence in elderly patients is rare worldwide. This study could be supported by similar findings in future studies.

CONCLUSIONS

We reported three rare sporadic OKCs in geriatric population, whose clinico-pathological profiles did not differ from that of sporadic and syndromic juve-

nile OKCs. This finding defies the theoretical consensus about the developmental origin of sporadic OKCs, especially since the proliferation index is very high. Therefore, the same surgical treatment modalities commonly used with juvenile OKCs apply to geriatric cases. Future studies may investigate the molecular findings in geriatric OKCs, especially solid and peripheral OKCs.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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