

Gorlin-Goltz Syndrome: Conservative Treatment of Keratocystic Odontogenic Tumors, Frequent First Clinical Manifestation in Pediatric Age

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Abstract

Objective: Gorlin-Goltz Syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome, is a rare genetic condition resulting from mutations of the PTCH1 (9q22.3) gene. It involves multiple organs, such as the skin, skeleton and jaws. Aim of this study was to describe Keratocystic Odontogenic Tumors as frequent first clinical manifestation of NBCCS during pediatric age, and their conservative treatment, that is really important, especially among young patients.

Methods: We report on 20 pediatric patients affected by Gorlin-Goltz Syndrome, presenting totally 60 Keratocystic Odontogenic Tumors. Patients underwent conservative lesion enucleation with maximal permanent teeth preservation. The ostectomy and osteoplasty were made with both conventional rotative instruments and piezoelectric tools, in order to remove damaged bone, epithelial remnants and satellite cysts, and to possibly minimize the recurrence risk. All surgical samples were subjected to histopathological examination and the patients were followed-up for a minimum of 18 months.

Results: Overall, 60 Keratocystic Odontogenic Tumors were removed (8 patients with single and the remaining with multiple cysts) with healing of all the surgical wounds without complications. Nevertheless, recurrence of 5 lesions (8.3%) from 3 patients occurred: all of them were >5 cm in maximum diameter and associated with permanent teeth.

Conclusion: Keratocystic Odontogenic Tumors in pediatric patients require conservative approaches for permanent teeth preservation. While conventional enucleation leads up to 60% recurrence rates, cavity ostectomy with piezoelectric tools significantly reduced the recurrence risk and allowed preservation of permanent teeth.

Keywords: Nevoid basal cell carcinoma syndrome; Gorlin-Goltz syndrome; Keratocystic odontogenic tumors; Piezosurgery; Pediatric age

Abbreviations

NBCCS: Nevoid Basal Cell Carcinoma Syndrome; KCOT: Keratocystic Odontogenic Tumor; PUBS: Piezoelectric Ultrasonic Bone Surgery; BCC: Basal Cell Carcinoma; OKC: Odontogenic Keratocyst; WHO: World Health Organization; OPT: Ortho-Pan-Tomography; CLSM: Confocal Laser Scanning Microscope

Introduction

Gorlin-Goltz Syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome (NBCCS), is a rare autosomal dominant disorder showing a variable penetrance and resulting from mutations of the PTCH1 (9q22.3) gene [1]. Although its occurrence among family members is an important diagnostic criterion, 20-40% of cases

result from de novo PTCH1 gene mutation [2]. The assumed prevalence of the disease is 1:60,000, with no gender predilection. As symptoms gradually appear with child growth, NBCCS is very difficult to diagnose in early childhood, and in most cases it is detected in patients aged between 17 and 35 years and only exceptionally in very young patients [3].

A multidisciplinary colloquium (First International Colloquium on NBCCS Criteria) was organized to better define the physical findings associated with NBCCS [4]. To date, a suspected diagnosis of NBCCS should be considered based on the findings of: (1) one major criterion and molecular confirmation; (2) two major criteria or (3) one major and two minor criteria [5]. Both major and minor criteria according to this colloquium are shown in Table 1.

Basal Cell Carcinoma (BCC) and Keratocystic Odontogenic Tumors (KCOTs) are the most common manifestations of the syndrome in adult and pediatric age respectively [1].

Major criteria	Minor criteria
1. Multiple (>2) BCCs or one under 20 years	1. Macrocephaly determined after adjustment for height
2. Odontogenic keratocysts of the jaws proven by histopathology under 20 years	2. Congenital malformation: cleft lip or palate, frontal bossing, "coarse face", hypertelorism
3. Palmar or plantar pits (3 or more)	3. Other specific skeletal malformations and radiologic changes (i.e., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly).
4. Lamellar calcification of the falx cerebri	4. Lymphomesenteric cysts
5. Bifid, fused or markedly splayed ribs	5. Ovarian/Cardiac fibroma
6. First degree relatives with NBCCS	6. Medulloblastoma
	7. Ocular abnormalities (i.e., strabismus, hypertelorisms, congenital cataracts, glaucoma, coloboma)

Table 1: Major and Minor inclusion criteria of NBCCS [5].

KCOT was first described by Mikulicz in 1876 as primordial cyst, a cyst formed from enamel organ before the production of calcified tissues at the expense of a deciduous, permanent or supernumerary tooth. Then the term odontogenic keratocyst (OKC) was introduced by Philipsen in 1956 [6], and was referred to a developmental benign but locally aggressive jaw cyst, that arise from the remnants of the dental lamina [7]. In 1963 Pindborg and Hansen suggested the histological criteria for diagnosing OKC [8].

Because of its aggressiveness and high recurrence rates after simple enucleation in comparison with other odontogenic cysts, OKC is now referred by the World Health Organization (WHO) as Keratocystic Odontogenic Tumor, "a benign uni- or multi-cystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior" [9].

Generally, KCOTs arise sporadically as a single lesion, but multiple cysts often occur in association with the NBCCS. KCOTs usually are diagnosed accidentally during routine X-ray examinations performed during regular dental treatment, and present as well circumscribed unilocular or multilocular lytic bone lesions, often involving an impacted tooth, with a well-defined osteosclerotic rim, which may become less visible while the lesion grows and transforms into a multilocular form [10]. Generally, KCOTs have few clinical manifestations such as the absence of deciduous or permanent teeth in the dental arches, which calls for radiological examination that usually highlights agenesis or dental inclusions in association with the cystic lesion. Subsequently, when they increase their size, KCOTs may cause bone expansion with swelling and facial asymmetry, dental dislocation or mobility, inflammatory symptoms and fistula when super-infection occurs; mild pain or paresthesia are rarely found. Despite cortical expansion, jaw fractures usually are undetectable [11].

At X-ray examination, KCOTs could mimic other cystic or neoplastic bone lesions occurring in pediatric patients, such as dentigerous cysts, ameloblastoma, ameloblastic fibroma or radicular cysts, which are the most frequent in pediatric age. Consequently,

histological examination is mandatory to obtain a correct diagnosis [12].

KCOTs therapy depends on the age of the patient, the size, extent and location of the lesion, possible perforation of the cortical bone or soft tissue infiltration. Both conservative treatments, such as simple enucleation or marsupialization, and more aggressive techniques, such as cryosurgery, chemical destruction or radical surgical treatments with bone resection have been proposed with variable results [13,14].

The aim of this study was to describe the clinical and histopathological features of KCOTs as first clinical sign of NBCCS in pediatric patients allowing an early diagnosis, and their treatment with conservative microinvasive piezosurgery.

Materials and Methods

Twenty-five pediatric patients (age range: 3,5-15 years) came to our attention at the Oral Surgery Unit of the "Aldo Moro" University of Bari from January 1996 to January 2014. The study inclusion criteria were: pediatric age (0-15 years) and the presence of cystic lesions of the jaws that could be clinico-radiographically classified as KCOTs; the exclusion criterion was a diagnosis different from KCOTs following histopathological examination. Accordingly, 5 of the 25 patients originally enrolled for the study were excluded in view of a histopathological diagnosis of odontogenic tumors other than KCOT.

After clinical examination and radiological analysis (OPT and Multislices Spiral Computed Tomography), all patients underwent conservative micro-invasive surgical treatment under general anesthesia, consisting in enucleation of KCOTs, followed by cavity ostectomy and osteoplasty with conventional rotative instruments and piezoelectric tools to remove damaged bone, the epithelial remnants and satellite cysts to possibly minimize the recurrence risk. Such surgical strategy was oriented to maximal permanent teeth preservation in consideration of the young age of the patients (Figures 1 and 2).

Subsequently, a sterile gel formulation of sodium hyaluronate and amino acids Gly-Pro-Leu-Lys was put into the bone defect, allowing for faster bone regeneration and healing at the surgical site.

All the surgical specimens were fixed in 10% buffered formalin, paraffin-embedded, cut and stained with hematoxylin- eosin and sent for histopathological examination. The patients underwent clinical and radiological (OPT) follow-up after 7, 15 and 30 days, 2, 3, 6 and 12 months, and, then, once a year. The follow-up time ranged from 18 months to 8 years (median 3 years).

This study fully comply with the principles stated in the Declaration of Helsinki and has been approved by the ethical committee related to our institution (Study n°4597 - Prot. 1526/C.E.); all patients preliminarily released informed consent on diagnostic and therapeutic procedures to be carried out and on possible use of biologic samples for research purposes.

Results

Overall, among the 20 enrolled patients affected by KCOTs in the context of NBCCS, there were 10 males and 10 females, with an average age of 10,6 years (range 3,5-15 years, median: 10 years). At the initial intra- and extra-oral evaluation, 13 patients showed swelling, facial asymmetry, dental inclusions or dislocations, teeth agenesis or discharging fistula as the first clinical manifestation of their disease; in

the remaining cases, KCOTs were asymptomatic and were diagnosed with X-ray examinations disclosing uni- or multi-locular radiolucent lesions. These data are summarized in Table 2.

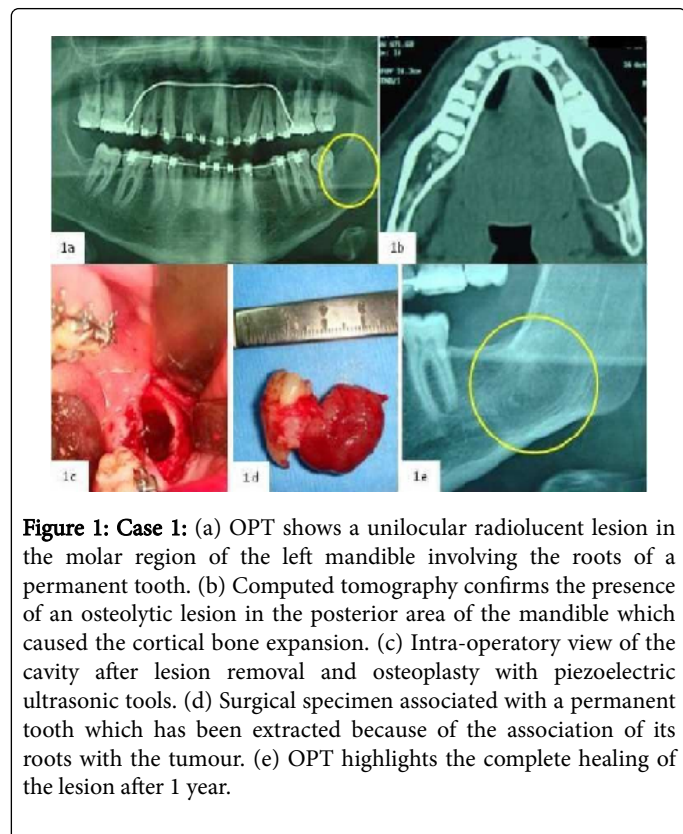


Figure 1: Case 1: (a) OPT shows a unilocular radiolucent lesion in the molar region of the left mandible involving the roots of a permanent tooth. (b) Computed tomography confirms the presence of an osteolytic lesion in the posterior area of the mandible which caused the cortical bone expansion. (c) Intra-operative view of the cavity after lesion removal and osteoplasty with piezoelectric ultrasonic tools. (d) Surgical specimen associated with a permanent tooth which has been extracted because of the association of its roots with the tumour. (e) OPT highlights the complete healing of the lesion after 1 year.

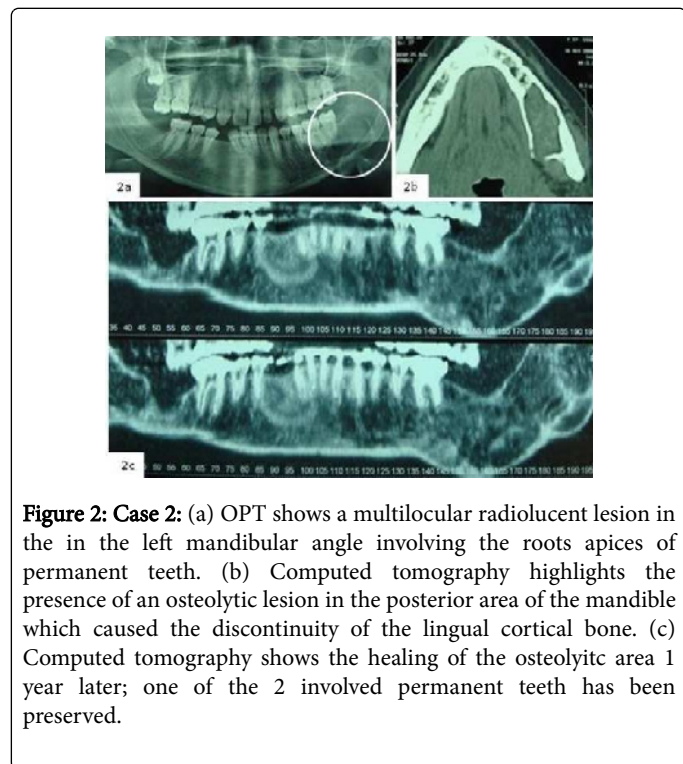


Figure 2: Case 2: (a) OPT shows a multilocular radiolucent lesion in the in the left mandibular angle involving the roots apices of permanent teeth. (b) Computed tomography highlights the presence of an osteolytic lesion in the posterior area of the mandible which caused the discontinuity of the lingual cortical bone. (c) Computed tomography shows the healing of the osteolytic area 1 year later; one of the 2 involved permanent teeth has been preserved.

Variable	Category	N	%
Gender	Males	10	50%
	Females	10	50%
	Male-to female ratio	1:01	
Age	Mean age	10,6	
	Median	10	
	Age range	3,5-15	
	0-5	1	5%
	10-Jun	11	55%
15-Nov	8	40%	
Extra-oral exam	Facial asymmetry/swelling	7	35%
	Fistula	-	
Intra-oral exam	Swelling	10	50%
	Dental inclusion/dislocation	13	65%
	Teeth agenesis	9	45%
	Fistula	2	10%
	Anesthesia/paresthesia	-	
Number of KCOTs	Single	8	40%
	Multiple	12	60%
Familial history	Positive	11	55%
	Negative	9	45%

Table 2: Patients' clinical data (N=20).

Of the 20 enrolled patients, 11 (7 females and 4 males) had been previously diagnosed with NBCCS (according to First International Colloquium on NBCCS Criteria) because of familiarity (parents, brothers or sisters affected), presence of characteristic multiple basal cell naevi, bifid or fused ribs (4 patients), and other skeletal anomalies such as scoliosis (3 patients) or sternal protrusion (1 patient); 7 patients showed palmar and plantar pits (Figure 3).

KCOTs were the first clinical sign of NBCCS for the remaining 9 patients (3 females and 6 males), who had not a familial history of the syndrome. Subsequently, they underwent genetic counseling and dermatological and radiological examinations, which highlighted basal cell naevi and PTCH1 mutations in all patients, bifid or fused ribs in 3, skeletal anomalies in 3, palmar pits in 5 and hypertelorism and frontal bossing in 2 patients (Figure 3).

In view of the presence of multiple cystic jaw lesions in 12 patients (average: 4 lesions, median: 4 lesions, range 2-6 lesions), 60 KCOTs were totally identified: these were mainly located in the mandible (39 cysts), 29 of which in the molar-ramus region (48%), and 10 in the incisor-canine region (17%), while 21 lesions were located on the upper jaw, 15 in the molar region (25%), and 6 in the incisor-canine region (10%). For practical purposes, the cysts were divided into 3 subgroups (≤ 3 cm, 3-5 cm, >5 cm), according their major diameter, as radiologically detected: 5 lesions (8,33%) were <3 cm in diameter, 16

(26,67%) were between 3 and 5 cm, and 39 (65%) were >5 cm. Also, KCOTs were associated with an impacted tooth in 23 cases or with erupted teeth roots in 31 cases. These data are synthetically illustrated in Table 3.

CLINICAL FEATURES			
	N	%	
MAJOR CRITERIA	Multiple basal cell naevi/ Basal Cell Carcinoma	20	100%
	KCOTs	20	100%
	Bifid or fused ribs	7	35%
	Palmar and plantar pits	12	60%
	First degree relatives with NBCCS	11	55%
MINOR CRITERIA	Other skeletal anomalies: scoliosis, sternal protrusion	7	35%
	Congenital malformation: frontal bossing, ocular hypertelorism	2	10%
	Ocular anomalies: strabismus	1	5%

Figure 3: Occurrence of NBCCS signs.

Variable	Category	N	%
Location	Mandible	39	65%
	Posterior region	29	48,3%
	Anterior region	10	16,7%
	Maxilla	21	35%
	Posterior region	15	25%
	Anterior region	6	10%
	Mandible-to-Maxilla ratio	1,9:1	
Size			8,33%
	Group 1: ≥ 3 cm	5	
	Group 2: 3-5 cm	16	26,67%
	Group 3: > 5 cm	39	65%
Tooth association	Present	54	90%
	Absent	6	10%
Recurrence	Yes	5	8,3%
	No	55	91,7%

Table 3: Clinical Features of KCOTs (N=60) in NBCCS patients.

The histopathological analyses highlighted thin connective tissue walls covered by para- and ortho-keratotic stratified squamous epithelium, usually about 5-8 cell layers thick, around cystic lumens filled with desquamated keratin. The epithelial lining included a well-defined, palisading basal layer of cuboidal to small columnar cells and a superficial layer with corrugated appearance (Figure 4). Satellite cysts

could also be seen due to tissue budding of the basal cell layers into the adjacent connective tissue. Numerous mitotic figures were highlighted in the suprabasal layer and different grades of epithelial dysplasia were also found.

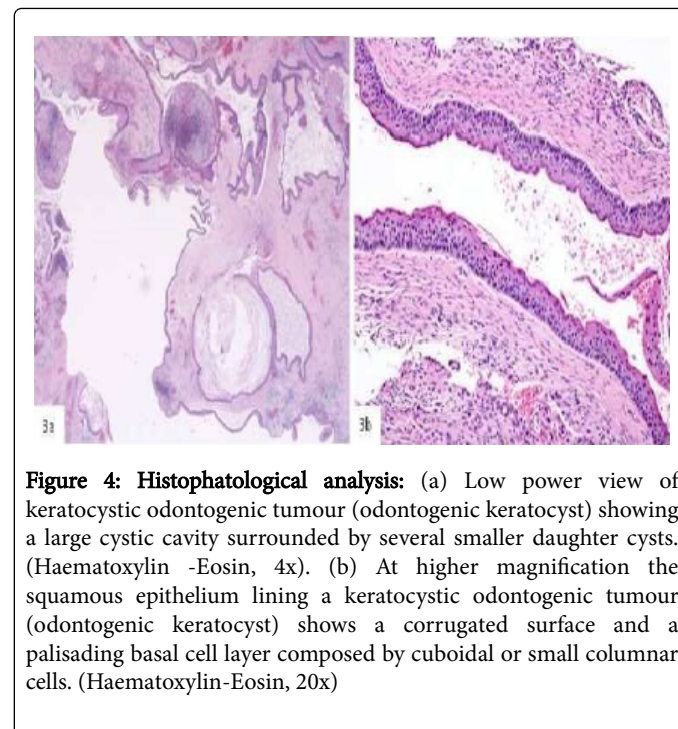


Figure 4: Histopathological analysis: (a) Low power view of keratocystic odontogenic tumour (odontogenic keratocyst) showing a large cystic cavity surrounded by several smaller daughter cysts. (Haematoxylin -Eosin, 4x). (b) At higher magnification the squamous epithelium lining a keratocystic odontogenic tumour (odontogenic keratocyst) shows a corrugated surface and a palisading basal cell layer composed by cuboidal or small columnar cells. (Haematoxylin-Eosin, 20x)

Following surgical treatments, the clinico-radiological follow-up of 51 lesions (85%) from 15 patients showed progressively decreased radiolucent areas up to complete healing within 12 months from the surgical treatment (Figures 1 and 2); 4 lesions (6,7%) from 3 patients healed within 12 months with the progressive decrease of the radiolucent area, and then appeared again in the following radiological control, but not less than 3 years after the first surgical excision thus suggesting that they could be considered as the occurrence of new lesions in the same place and not as the recurrence of the lesion already treated. Differently, follow-up radiological investigations (OPT) disclosed lack of decreasing radiolucency of 5 lesions from 3 patients (8,3%) after 12 months indicative of KCOT recurrence. Such recurrent lesions were always >5 cm in diameter and associated with permanent erupted teeth, which had not been not extracted with our semi-conservative approach. Nevertheless, post-operative discomfort such as pain, swelling or bleeding were minimal in all patients.

Discussion

NBCCS is a rare genetic disorder with a broad range of clinical symptoms involving multiple organ systems, such as the skin, skeleton and jaws.

During the first and the second decades of life, KCOTs are often the first sign of NBCCS [15]: they are detected in patients under 10 years of age [16] and 13% of patients develop a jaw tumor by the age of 10 years. These data suggest that KCOTs in syndromic patients arise earlier than those in non-syndromic subjects, which present a bimodal age distribution around the third and sixth decades [17,18].

In our study the average age was 10,6 years (range: 3,5-15 years, median: 10 years) and the presence of KCOTs was the first clinical

manifestation of NBCCS in 9 patients (45%) without familial history. As already reported in the literature, the most commonly involved site was the mandible, especially the molar-ramus region, the maxillary molar region being the second affected site. Woolgar et al. [19] noticed that maxillary KCOTs are more frequently detected in syndromic subjects in view of the presence of multiple cystic lesions in such patients.

One of the most problematic aspects of KCOT is its high recurrence rate after surgery, mainly due to incomplete removal with retention of odontogenic epithelial islands and/or presence of satellite micro-cysts [20]. Consequently, the therapeutic approach to KCOT remains controversial, both conservative (marsupialization and simple enucleation) or aggressive (enucleation and treatment of the bony defect with Carnoy's solution, enucleation and liquid nitrogen cryotherapy, block resection) having been proposed thus far [21,22].

Marsupialization converts the cystic lesion into a pouch, leading to cystic decompression [23], and it is often followed by enucleation, thus allowing partial KCOTs decrease in size and preservation of vital structures such as teeth or the inferior alveolar nerve. Some authors argued against the use of marsupialization because this technique does not guarantee complete removal of the cyst, thus potentially leading to recurrence of the lesion [24] and it does not provide adequate sampling for subsequent histopathological examination.

Simple enucleation of KCOTs has been widely adopted and is considered effective for complete morphological analyses; nevertheless, such procedure shows recurrence rates as high as 62.5%, possibly because fragments of the friable wall of KCOT may be left behind within the bone. Consequently, simple enucleation "per se" is no longer considered an effective treatment for KCOT [25] and some authors proposed to supplement such treatment with washing of the bony defect with Carnoy's solution. This cauterizing agent [22] would be able to kill epithelial remnants of the cyst wall, thus reducing the recurrence risk. Nevertheless, alterations in neural conductivity 2 minutes after direct application of Carnoy's solution were noticed [26], with slow recovery even after two weeks from treatment.

Liquid nitrogen cryotherapy was proposed as an alternative to Carnoy's solution to possibly induce cell death of odontogenic epithelial remnants by ice crystals, while leaving the almost unaltered bone matrix able to act as a clean scaffold for new bone formation [27]. Such treatment allowed for reduced recurrence rates (3–9%) [23,28] but, due to difficult control of the amount of liquid nitrogen to be injected into the cavity, bone necrosis and paraesthesia or anaesthesia of the inferior alveolar nerve unpredictably occurred in several patients [29].

As to more aggressive surgical treatments, either segmental (surgical removal of a segment of the mandible or maxilla, without maintaining the continuity of the bone) or marginal resection (surgical removal of the intact lesion with a rim of uninvolved bone, maintaining the continuity of the bone) have been proposed [30]. These are invasive techniques that may result in considerable morbidity and may require reconstructive measures to restore jaw function and aesthetics. In a systematic review, Blanas et al. [30] reported the lowest recurrence rates (0%) but the highest morbidity rates in patients with KCOT undergoing surgical resection.

In the current study we opted for cyst enucleation followed osteotomy and osteoplasty with both conventional rotative and piezoelectric ultrasonic tools to possibly remove both epithelial remnants and satellite cysts, thus limiting the risk of recurrence.

Piezoelectric ultrasonic bone surgery is a minimally invasive technique, which selectively acts on bone structures preserving soft tissues and adjacent structures, such as nerves, vessels, and mucosal layers. Also, it minimizes osteocytes damage, allowing for faster healing of the lesion [31,32]. The use of such surgical approach in the current study resulted in a 8,3% recurrence rate after prolonged follow-up, without relevant postoperative side effects such as swelling, paresthesia or pain. These results testify the superiority of enucleation followed by osteotomy and osteoplasty with both conventional rotative and piezoelectric ultrasonic tools over simple enucleation but apparently remain less effective than surgical (segmental or marginal) resection in terms of risk for recurrence. Nevertheless, it should be taken into account that all the patients enclosed in this study were affected by the NBCCS, that 12/20 patients showed multiple KCOTs and that, in view of the pediatric age of the patients, maximal preservation of permanent teeth and alveolar nerves was required. Consequently, while it seems very difficult to compare the post-treatment recurrence rates for KCOT in syndromic patients, as these most frequently are not independently evaluated in the published studies [33], we consider the minimally aggressive surgical procedures employed for this study an adequate answer to the need for limiting the risk of recurrence while allowing maximal preservation of permanent teeth and minimal neural damage.

Conclusions

KCOT is a locally aggressive lesion with high recurrence rates, which may present during pediatric age, especially in a syndromic context. KCOTs arising in NBCCS patients often are the first clinical sign of the syndrome, thus prompting for early diagnosis and less invasive surgical approach. Based on the results of the current study, cyst enucleation followed by cavity osteotomy and osteoplasty with piezoelectric ultrasonic tools can be considered an effective treatment that allows for rapid healing of the lesions, minimal recurrence rates, maximal preservation of permanent teeth and absence of relevant postoperative morbidity.

Submission Declaration

This work has not been published previously and is not under consideration for publication elsewhere; its publication is approved by all authors and, if accepted, it will not be published elsewhere.

This study was performed in accordance to the principles of the Declaration of Helsinki and has been approved by our institution ethical committee (Study n°4597 – Prot. 1526/C.E.).

Data from the patients included in this study were treated anonymously; the patients released informed consent on diagnostic and therapeutic procedures, and for the use of such data and possible use of biological samples for research purposes and scientific publication.

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