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Basal Cell Nevus Syndrome with Unusual Associated Findings: A Case Report with 17 Years of Follow-Up

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 27-year-old
Final Diagnosis: Basal cell nevus syndrome
Symptoms: None
Medication: —
Clinical Procedure: —
Specialty: Dentistry • Pathology

Objective: Congenital defects/diseases

Background: Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome (GGS), is an inherited autosomal dominant disorder caused by mutations in the patched *(PTCH)* tumor-suppressor gene, which has high penetrance and variable phenotypic expressivity. In 1960, Gorlin and Goltz defined the condition by 3 main characteristics: multiple basal cell carcinomas, odontogenic keratocyst (OKC), and skeletal anomalies. Nowadays, many neurologic, ophthalmic, endocrine, and genital manifestations are known to be associated with this syndrome. Considering the complexity of the clinical manifestations, a multidisciplinary approach is necessary for the diagnosis and follow-up of patients with NBCCS.

Case Report: We report the case of a 27-year-old woman who presented with multiple maxillary and mandibular OKCs, as well as mandibular dentigerous cysts, all detected by X-ray. The medical records of the patient reported other findings such as falx cerebri calcification, osteolysis in femoral bones, and focal bone alteration suggestive of simple bone cysts. Based on the presented manifestations, it was concluded that the patient had characteristics of NBCCS. A multidisciplinary approach was necessary, and odontological intervention was used in managing treatment of the jaw cysts.

Conclusions: In view of this combination of findings, it is of primary importance for dental surgeons and physicians to be able to recognize the signs and symptoms of NBCCS in order to achieve an early diagnosis and avoid the progression of oral cysts, the metastasis of skin lesions, and progression of other less frequent manifestations.

Keywords: Basal Cell Nevus Syndrome • Bone Cysts • Odontogenic Cysts

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Background

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome (GGS), is a rare autosomal dominant disorder. It has a prevalence of 1 case in every 56 000 to 256 000 individuals, and it is predominantly (in 70-80% of cases) caused by hereditary mutations [1-3]. In 1960, Robert James Gorlin and Robert William Goltz established a classic triad which characterizes NBCCS: the presence of multiple nevoid basal cell carcinomas, jaw cysts, and congenital skeletal abnormalities. This classification was subsequently modified by Rayner et al, who added ectopic calcifications and plantar or palmar pits [4,5].

Numerous other manifestations are known to be present in NBCCS, such as labial or palatine cleft, frontal humps, hypertelorism, Sprengel deformity, thoracic deformity, vertebral alterations, syndactyly, bone cysts in the hands, macrocephaly, pontification of sella turcica, ovarian fibroma, and medulloblastoma [2,6-8]. Due to the huge variability in mutation sites and presentations of the syndrome, there is no clear manifestation in every patient [6]. Thus, the current criteria for diagnosis, established by Kimonis, consider some major and minor criteria, making it possible to establish an NBCCS diagnosis based on the number and type of manifestations [9]. More prevalent lesions, such as multiple basal cell carcinomas, OKCs, and skeletal anomalies at the ribs, are considered major criteria, while other less frequent manifestations (eg, vertebral alterations, syndactyly, bone cysts in the hands, macrocephaly, pontification of sella turcica, and ovarian fibroma) are classified as minor criteria. When there are 2 major criteria or 1 major and 2 minor criteria, the clinical diagnosis of NBCCS can be made [2,6-8,10]. Aside from these described manifestations, the existence of a first-degree relative with GGS is an additional major criterion [11].

Therefore, it is also very important to be able to recognize the variety of NBCCS manifestations and their long-term behavior to ensure safe treatment. Thus, we report the case of a woman presenting with NBCCS who was followed up over a period of 17 years.

Case Report

A female patient, now 27 years of age, attended the ambulatory clinic of the Dental School at the Universidade Federal do Pará (UFPA), Belém-PA Brazil, for the first time in 1999 when she was 10 years old, for a general dental appointment. Routine radiographic examination revealed the presence of a radiolucent, well-circumscribed area associated with tooth 43 (**Figure 1A**); thus, the diagnostic hypothesis were dentigerous cyst and odontogenic keratocyst. The lesion was assessed, and as the treatment of choice, enucleation of the cyst was performed and tooth 43 was maintained. The histopathological examination revealed a lesion compatible with a dentigerous cyst (the histopathological report is provided in supplementary material 1).

Three years after the first appointment (in 2002), a panoramic radiograph was taken to monitor the eruption process of tooth 43, which in addition revealed a radiolucent area distal of tooth 37 (**Figure 1B**). The patient did not keep the annual follow-up appointment as recommended, and returned after 3 years (in 2005). At that point, she presented a lesion (the second lesion) compromising the entire left ascending ramus of the mandible, and another less extensive lesion in the maxilla between the roots of teeth 14 and 15, without any clinical alteration or expansion of the mandible cortex bone (**Figure 2A**). The clinical and radiographic aspects of those findings suggested the hypothesis of OKC, central giant cell lesion, and ameloblastoma, which were then submitted to histopathological examination and confirmed the diagnosis of OKC (the histopathological report is provided in supplementary material 2).

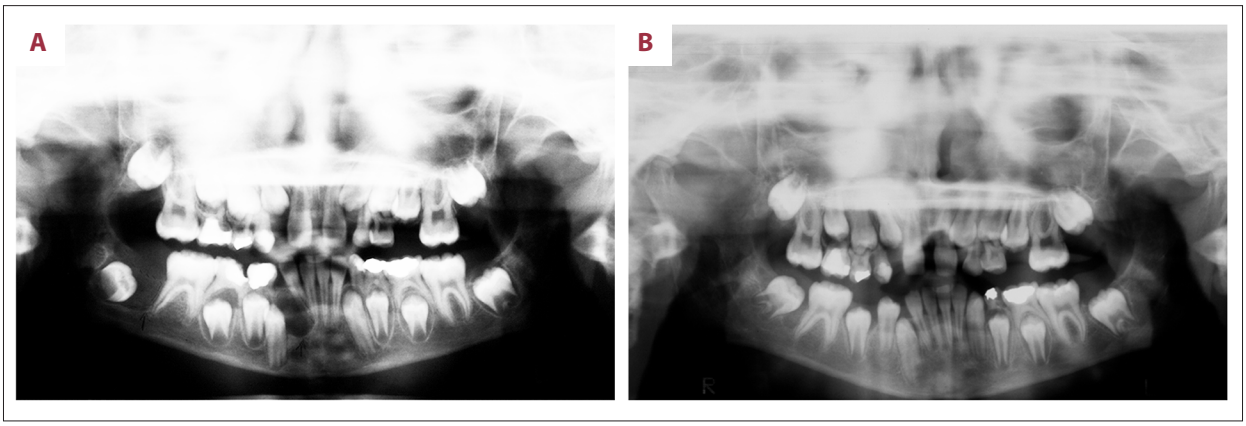

Figure 1. (**A**) Dentigerous cyst associated with tooth 43. (**B**) Radiolucent area at the distal surface of the tooth 37. After 3 years, it had expanded to the ascendant branch of the mandible, and it was diagnosed as an odontogenic keratocyst.

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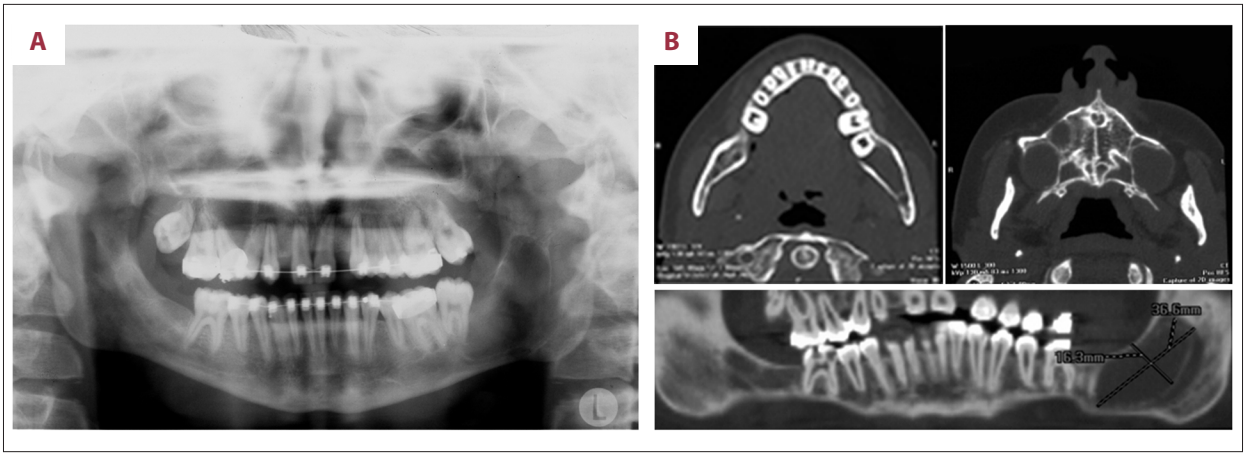

Figure 2. (**A**) Radiographic examination showing a mandibular lesion compromising the distal area of tooth 37 and another less extensive area in the maxilla between the roots of teeth 14 and 15. (**B**) Tomography showing areas of uniform, well-circumscribed bone rarefaction in the maxillary posterior region and the left ascending branch of the mandible.

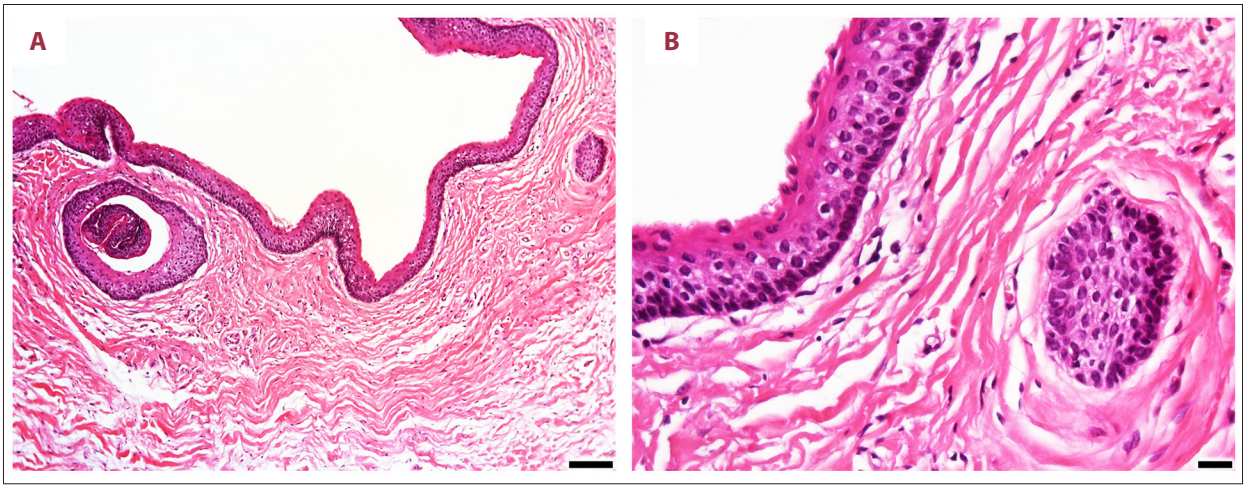

Figure 3. (**A, B**) Histopathological appearance of the maxillary lesion showing uniform epithelial lining characterized by palisaded hyperchromatic basal cell layer composed of cuboidal to columnar cells and the luminal surface has wavy ("corrugated") parakeratotic epithelial cells, suggesting the diagnosis of OKC.

A computed tomography (CT) examination was performed (in 2005), in which the extension of the left mandibular lesion was delimited in 16.3×36.6 mm, and the maxillary lesion was located between the roots of teeth 14 and 15 measured 11.5 mm. With the aid of CT, it was also possible to observe the presence of 2 other areas of uniform bone rarefaction, which were well-circumscribed and located in the maxillary posterior region, in both sides of the maxilla (**Figure 2B**). These maxillary findings were not clearly evident on panoramic radiography due to the overlapping of the maxillary sinus images. The diagnostic hypothesis was also OKC and the histopathological examination confirmed the diagnosis of OKC (**Figure 3**) (the histopathological report is provided in supplementary material 2).

In a medical appointment in May 2010, computed tomography of the femoral bone was performed, which showed the presence of well-defined lytic images. Moreover, magnetic resonance imaging of the brain was also performed, in which could be seen a lamellar calcification of the falx cerebri in the interhemisphere region and the tentorial (**Figure 4**) (the medical report is provided in supplementary material 3).

One year later (in 2011), another magnetic resonance imaging of the left leg showed osteolytic areas measuring approximately 11.5 cm, suggestive of a simple bone cyst. In that same year, completing a total of 12 years of disease evolution, decompression of the maxillary left side cyst was performed. In June 2015, 16 years since the first diagnosis, a new magnetic resonance imaging of the legs showed osteolytic areas in the left and right legs (**Figure 5**) (the medical report is provided in supplementary material 4).

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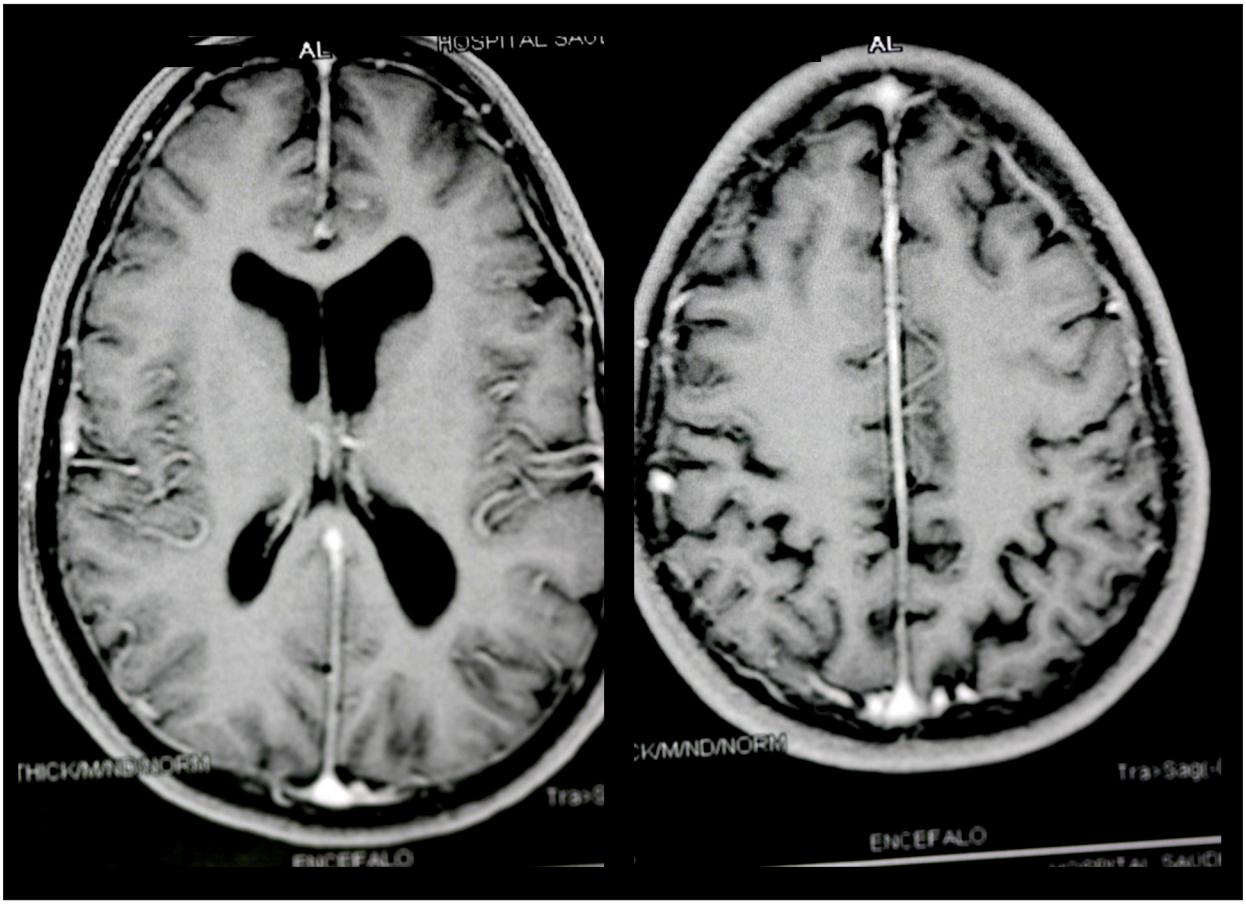

Figure 4. Magnetic resonance imaging of the encephaly, showing the calcification of the falx cereberi in the interhemispheric region and at the tentorium.

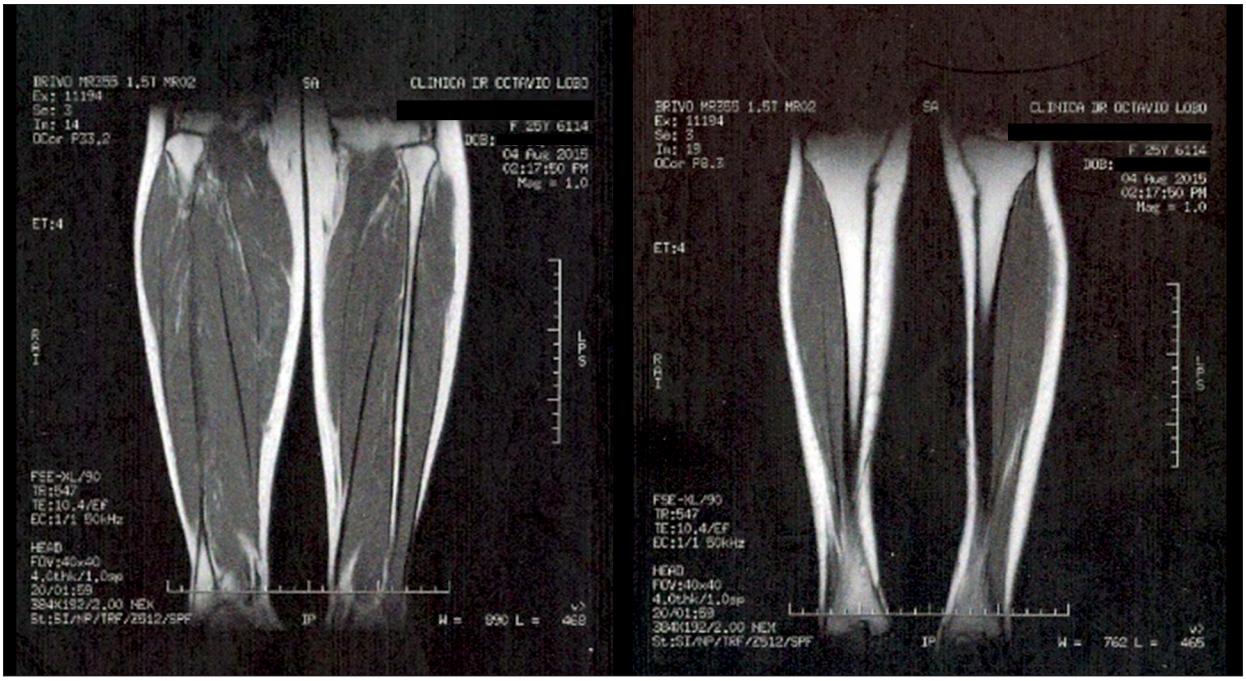

Figure 5. Magnetic resonance imaging of the legs showing osteolytic areas in both legs, with different sizes.

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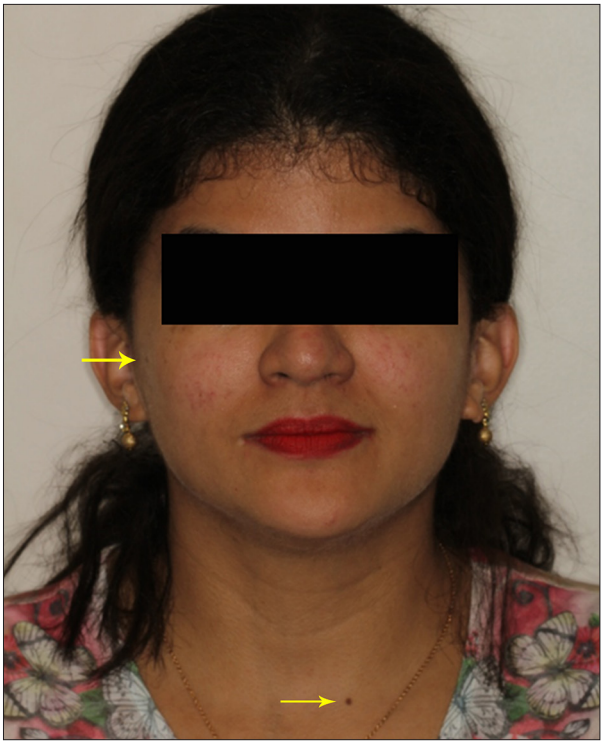

Figure 6. Head and neck skin maculae that were posteriorly removed by the dermatologist as a preventive intervention, avoiding the occurrence of basal cell carcinomas.

The combination of the first finding of a dentigerous cyst, multiple and periodic incidence of OKC, medical reports of bone alterations suggestive of simple bone cyst lesions, and lamellar calcification of the falx cerebri suggested the possibility of the patient being affected by NBCCS, even though she had not yet presented basocellular nevus carcinoma of the skin.

Routine laboratory tests were requested, which presented normal results, except for an alteration in alkaline phosphatase (118 u/L). Periodic maxillofacial radiographic monitoring was suspended because the patient became pregnant soon after starting the treatment. In January 2017, a new panoramic radiograph showed normal radiographic appearance of the mandible and reduction of the right posterior maxillary lesion.

Based on the presenting manifestations, it was concluded that the patient had characteristics of NBCCS, including multiple maxillary and mandibular OKCs (major criteria), dentigerous cyst (minor criteria) falx cerebri calcification (minor criteria), osteolysis in femoral bones (minor criteria), bone alteration suggestive simple bone cyst, and presence of head and neck skin maculae. Based on the dental history of the patient, the dermatologist then performed (between 2010 and 2015) removal of the skin lesions (**Figure 6**) as a preventive intervention, avoiding further manifestation of basocellular nevus carcinoma.

Areas of osteolysis were also observed on the left leg and right shoulder, without a conclusive diagnosis; however, these were suggestive of simple bone cysts, which can also be associated with NBCCS. Thus, chest, skeleton, skull, and abdomen radiographs are useful for detecting other manifestations of NBCCS. The patient in the present study signed a consent form. The full chronology of orofacial findings and interventions in the present case is displayed in **Table 1**.

Discussion

Although the clinical symptoms are well known, the current case presents a combination of manifestations that are less frequently reported in the literature, thus contributing to a better understanding of the phenotypical variability of NBCCS, and also reinforces the need for a multidisciplinary approach in the diagnosis and follow-up of NBCCS patients.

The NBCCS diagnosis is quite challenging because of the variety of manifestations, which requires the attention of a multidisciplinary team. These manifestations are frequently treated separately by different professionals according to the area affected, and diagnosis of the syndrome usually takes too long to be performed. Among the various findings, basal cell carcinomas are very common and generally appear during puberty or from the second to third decade of life; however, they can also be seen in infants. The number of tumors varies considerably among affected individuals, and are more common in White than in Black people [12]. They frequently appear in areas of skin that are not exposed to sunlight, although they commonly arise in the middle region of the face [11].

The presence of OKC is also common, appearing in at least 75% of cases. OKC generally occurs in the mandibular ascending branch and it is commonly associated with unerupted teeth; thus, it can mimic dentigerous cysts on radiographs. Accordingly, it is possible that the first lesion, initially diagnosed as a dentigerous cyst, could be the first OKC, since the presence of inflammatory infiltrate is able to modify the pattern of the cyst epithelium, making precise diagnosis at histopathological examination harder.

There are rare reports in the literature of OKCs in NBCCS patients that are not associated with dental elements [13]. In our case report, OKCs were seen in the mandible and maxillary posterior region, with the maxilla being the most common location for cysts in syndromic patients according to Kumar [14].

Skeletal anomalies are present in 60% to 75% of patients with this syndrome [6]. A characteristic lamellar calcification of the falx cerebri, evidenced in skull radiographs or in CT images with anteroposterior incidence, is a common finding seen in the majority of affected patients [15,16].

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Table 1. Chronology of the orofacial findings and their respective interventions in the present case.

	1999	2002	2005	2006	2007
Lesion	Dentigerous cyst	Radiolucent image	OKC	OKC	OKC
Location	Associated with tooth 43	Distal of tooth 37	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side
Conduct and follow-up	Enucleation	------	1. Decompression 2. Enucleation 3. Decompression	1. Enucleation 2. Bone neoformation 3. Decompression	1. Bone neoformation 2. Bone neoformation 3. Decompression
	2009	**2011**	**2015**	**2018**	
Lesion	OKC	OKC	OKC	OKC	
Location	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	1. Ascending mandible branch associated with tooth 37 2. Maxilla between the roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	1. Ascending mandible branch associated with tooth 37 2. Maxilla the between roots of teeth 14 and 15 3. Maxilla posterior region on the right and left side	
Conduct and follow-up	1. Bone neoformation 2. Bone neoformation 3. Right side enucleation and left side decompression	1. Bone neoformation 2. Bone neoformation 3. Right osteolytic lesion; left side decompression	1. No recurrence 2. No recurrence 3. Left osteolytic lesion; right side decompression	1. No recurrence 2. No recurrence 3. Left osteolytic lesion; reduction in right side injury	

OKC – odontogenic keratocyst.

The simple bone cyst is an intraosseous non-epithelium-lined cyst formation that can be empty or filled with serous or bloody fluid. In the present case, magnetic resonance imaging of the left leg suggested the presence of cystic lesions on the extremities, which are not commonly reported in the literature in association with NBCCS.

Tarnoki et al (2014) reported the case of a patient diagnosed with NBCCS who presented cystic lesions in cortical and subcortical bone of the tibia and fibula on radiographs and CT scans, without a well-defined cyst aspect, being described by the authors as looking "mouse-eaten", and they attributed these injuries to the long-term use of isotretinoin (a retinoid derived from vitamin A) by the patient [17]. However, McMullen et al (2003) reported that the long-term use of acitretin (as the dose administered daily, the total dose, or the dose administered throughout the duration of treatment), which is composed of vitamin A, was not associated with osteopenia or osteoporosis compared to the control group [18]. In addition, Vestergaard et al (2010) concluded that the risk of bone fractures was not associated with treatment with increasing doses or durations of vitamin A analogs, isotretinoin and acitretin, when comparing to the control group [19].

In our particular case, the patient only used Aderogil D3 (which is a vitamin D compound associated with vitamin A) for 1 year during childhood. However, the intake of vitamin A does not appear to be associated with the outcomes reported in the present case in the long bones, since they differ from the case reported by Tarnoki et al (2014) due the well-defined and circumscribed appearance in our patient.

Over 100 minor criteria for diagnosing NBCCS have been reported in the literature [20]. If the main criteria, such as basal

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cell carcinomas, mandibular cysts, or calcification of the cerebral sickle, are absent until adolescence, other radiologic manifestations of the disease may allow early diagnosis in childhood [15]. It is recommended that patients be followed clinically and radiographically for a long period for early diagnosis of the manifestations and to allow use of less invasive interventions.

Long-term follow-up is very challenging and it depends in part on patient collaboration. The complexity of the case and the various professionals involved in the management of the patient may have limited the compilation and acquisition of the complete medical history of all outcomes presented by the patient, which might be a limitation of this study.

Conclusions

Considering the complexity and recurrence of the clinical manifestations, a multidisciplinary approach is necessary for the diagnosis and follow-up of patients with NBCCS. Therefore, it is of primary importance for dental surgeons and physicians to be able to recognize the signs and symptoms of NBCSS in order to achieve an early diagnosis and avoid the progression of oral cysts and the metastasis of skin tumors and other less frequent manifestations, thereby improving the quality of life of NBCCS patients.

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Conflict of Interest

None.

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