SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

Oral Medicine and Oral Surgery

Gorlin-Goltz Syndrome: A Case Report

Ghodhbane Saida[1*], Garma Maroua[1], Walha Omar[1], Slim Afef[1], Khalifa Chaima[1], Bouguezzi Adel[1], Sioud Sameh[1], Hentati Hajer[1], Selmi Jamil[1], Hamdi Habib[1]

[1]Department of Oral Medicine and Oral Surgery, Dental Clinic of Monastir, Monastir, Tunisia

DOI: https://doi.org/10.36347/sasjs.2025.v11i04.001 | **Received:** 20.12.2024 | **Accepted:** 27.01.2025 | **Published:** 05.04.2025

***Corresponding author:** Ghodhbane Saida
Department of Oral Medicine and Oral Surgery, Dental Clinic of Monastir, Monastir, Tunisia

Abstract **Case Report**

Gorlin-Goltz syndrome (GGS) is a rare autosomal dominant inherited disorder; caused by mutations in the in the long arm of chromosome 9 (q22.3-q31) and loss or mutations in the hedgehog signaling pathway of human patched gene (PTCH1 gene), mainly in PTCH1. This pathway is involved in embryogenesis and tumorigenesis, and the loss of function of PTCH1 protein produces an aberrant increase in the hedgehog signaling pathway activity. It's characterized by a wide-range of developmental abnormalities (multiple odontogenic Keratocysts and basal cell carcinomas, skeletal, dental, ophthalmic, and neurological abnormalities, intracranial ectopic calcifications of the falx cerebri, and facial dysmorphism). This report highlights a case of GGS presenting in a young female patient with cranial, facial, dermatological, dental and skeletal involvement. The diagnosis of the syndrome was based on its clinical presentation, radiological features and histopathological findings. A literature review about this syndrome, it's clinical manifestations, diagnostic and therapeutic approach was conducted.

Keywords: Gorlin-Goltz syndrome, nevoid basal cell carcinoma, Odontogenic keratocysts, Features, diagnosis.

INTRODUCTION

Gorlin-Goltz syndrome (GGS) or nevoid basal cell carcinoma (BCC) syndrome is an unfrequent multisystemic disorder, which shows a high level of penetrance and variable expressiveness. The prevalence of the disease range from 1:57,000 to1:256,000 in the general population [1]. Shanley *et al.*, in Australia, and Lo Muzio *et al*., in Italy estimated the prevalence as 1 per 64,000 and 256,000, respectively [2, 3]. Evans *et al*., reported that the prevalence rate in the United Kingdom was 1 per 560,000 [4]. In India, only nine case series have been reported so far [5]. The Gorlin-Goltz syndrome has equal predilection for either sex [6]. The male-to-female ratio is 1:1.but predominate in white people. It's a condition that is inherited in a dominant autosomal way, which is caused by mutations in the patched tumor suppressor gene (PTCH), a human homologue of the Drosophila gene mapped to chromosome 9q21-23. Chromosomal mapping and genetic studies suggest that the underlying basis for this disease is an abnormality in the Hedgehog (Hh) signaling pathway. The role of this pathway in embryogenesis is well known. The PTCH gene product is part of a receptor for the protein called Sonic Hedgehog, which is involved in embryonic development [7].

The disease shows multiple organ (the skin, nervous system, eyes, endocrine system, and bones) involvement:: odontogenic keratocysts of the jaws, more than two sites of basal cell carcinomas or one site of basal cell carcinoma in persons younger than 20 years, three or more palmar or plantar pits, calcification of falx cerebri, bifid or fused ribs, macrocephaly, congenital malformations such as cleft lip or palate, frontal bossing, hypertelorism, skeletal abnormalities, vertebral anomalies, ovarian fibroma or medulloblastoma [8]. The establishment to the correct diagnosis of Gorlin-Goltz syndrome two major criteria or two minor and one major criteria must be present [9].

Among the clinical manifestations the oral-dental manifestations such as the jaw keratocysts which are a consistent feature of 'Gorlin-Goltz' and may be presented as the first sign of BCCS.

The aim of this work is to report a case of GGS, diagnosed in an 18-year-old girl, in order to highlight the characteristics of this syndrome, its treatment and therapeutic approach, and above all to emphasize the role of the dentist in performing an early diagnosis and to get a multidisciplinary approach in treating the condition.

CASE REPORT

An 18-year-old female patient with no previous medical or surgical history was referred to the Oral Medicine and oral Surgery department at the academic dental clinic of Monastir, following the incidental discovery of radiolucent images on a panoramic radiograph taken during an initial consultation for restorative treatment of decayed teeth.

On endobuccal examination, gingival inflammation, dental plaque deposits and multiple caries were observed, particularly on 46, 36 and 26. There were also several missing teeth, as well as a small right maxillary canine. Palpation of the alveolar processes revealed no significant deformities.

The panoramic radiograph revealed several radiolucent lesions in the maxilla and mandible (Fig 1).

In the maxilla:

- A well-circumscribed unilocular radiolucent image, bounded by a border of osteocondensation, extending from the distal side of 11 to the mesial side of 14.
- Another unilocular radiolucent image, also well defined, encompassing the impacted 18.

At mandibular level:

- A unilocular radiolucent image related to 38, extending towards the mandibular ramus and angle, with the presence of a well-defined sclerotic borders.
- Two well-defined unilocular osteolytic images in the anterior region**.**

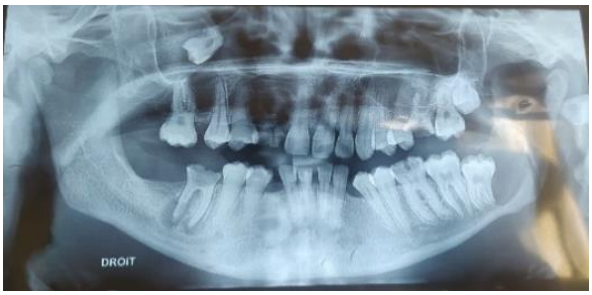


Fig 1: Orthopantomograph showing multiple radiolucent lesions, in maxilla and mandible

Computed tomography (CT) of facial bones and cranium was advised as a second-line procedure for detailed radiological assessment, to explore the extent of the lesions, their relationship with surrounding anatomical structures, and aspect of the cortical bone (Fig 2).

At mandibular level, the results revealed the following:

- A well-defined homogeneous zone of hypodensity at the mandibular angle, exerting harmonious pressure on the lingual cortical with localized interruptions, and pushing the mandibular canal down towards the basilar border. Moreover, lesions in the incisivo-canine sector showed well-limited, homogeneous areas of rounded hypodensity with ruptures of the buccal cortical.
- In the maxilla, the results showed:
- A homogeneous oval-shaped zone of well-marginated hypodensity in the anterior sector, with partial disruption of the vestibular cortex.
- A homogeneous zone of well-limited hypodensity encompassing the impacted 18.

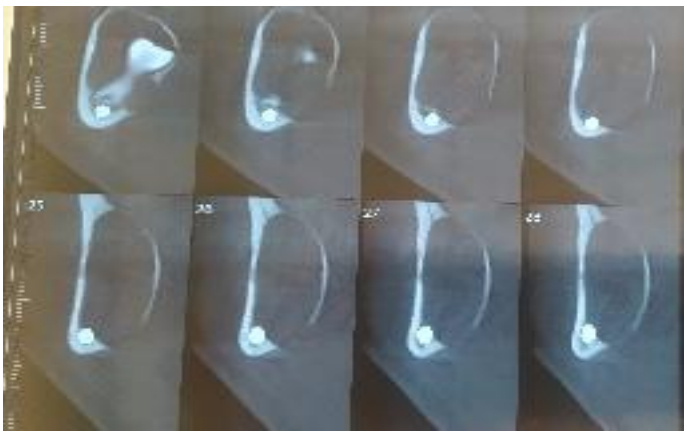


Figure 2.a: computed tomography in Coronal view showing a wide unilocular oval cystic lesion of the left hemimandible: The lesion pushing the mandibular canal towards the basilar border with a localized interruption of the lingual cortical

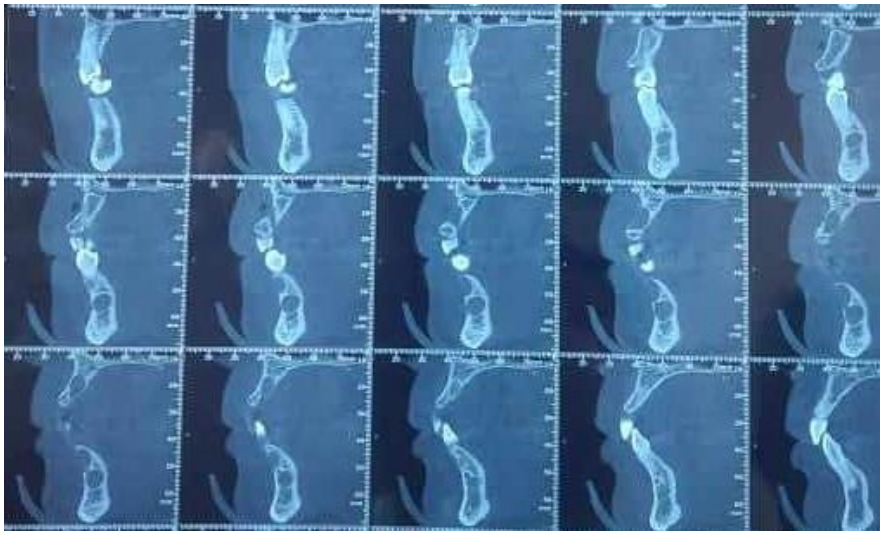


Figure 2.b: Oblique sagittal reconstructions showing mandibular and maxillary lesions in the anterior sector

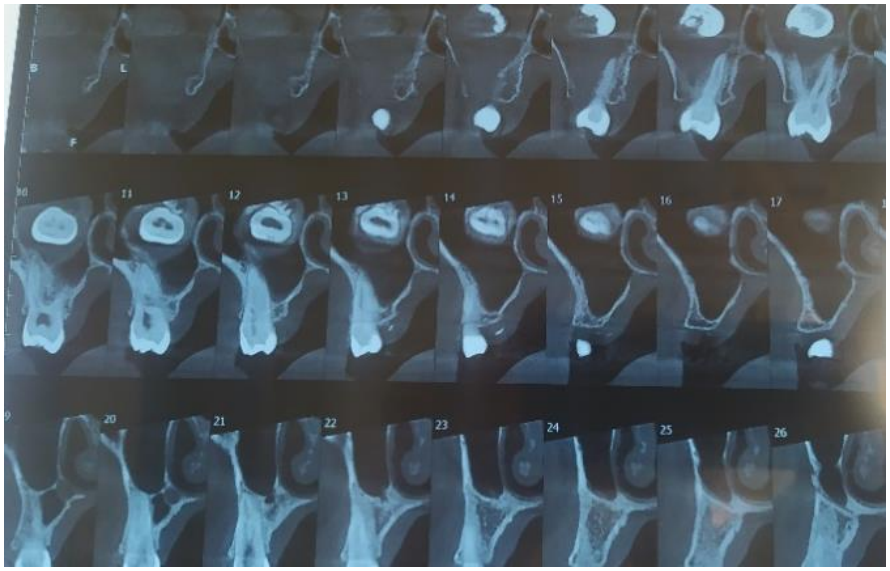


Figure 2.c: Oblique coronal reconstructions passing through the impacted 18

In addition to the panoramic radiograph and the CT-scan, a profile radiography was requested to research an eventual calcification of falx cerebri: it showed a normal appearance of the skull (Figure 3).

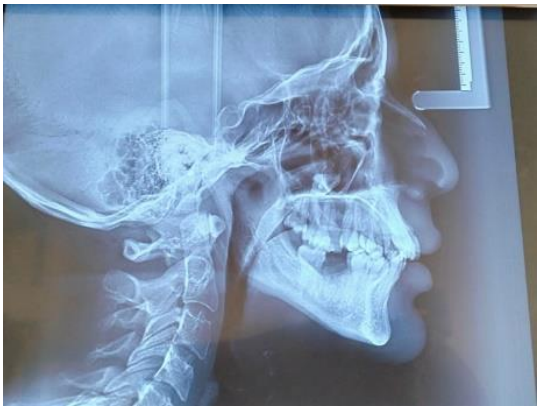


Figure 3: Profil radiography with normal appearance of the skull

In consideration of the clinical and radiological signs observed in this patient, notably the presence of multiple cystic-like images, a syndromic case was well suspected. From there, the general examination was cautiously underwent, revealing several significant symptoms. These included a widening of the nasal base,

telecanthus and hypertelorism, as well as prominent superciliary arches (Figure 4.a). In addition, multiple small nevi were noted on the abdomen (Figure 4.b), as well as the presence of palmar pits on the palms (Figure 4.c). All these clinical signs oriented to Gorlin-Goltz syndrome.

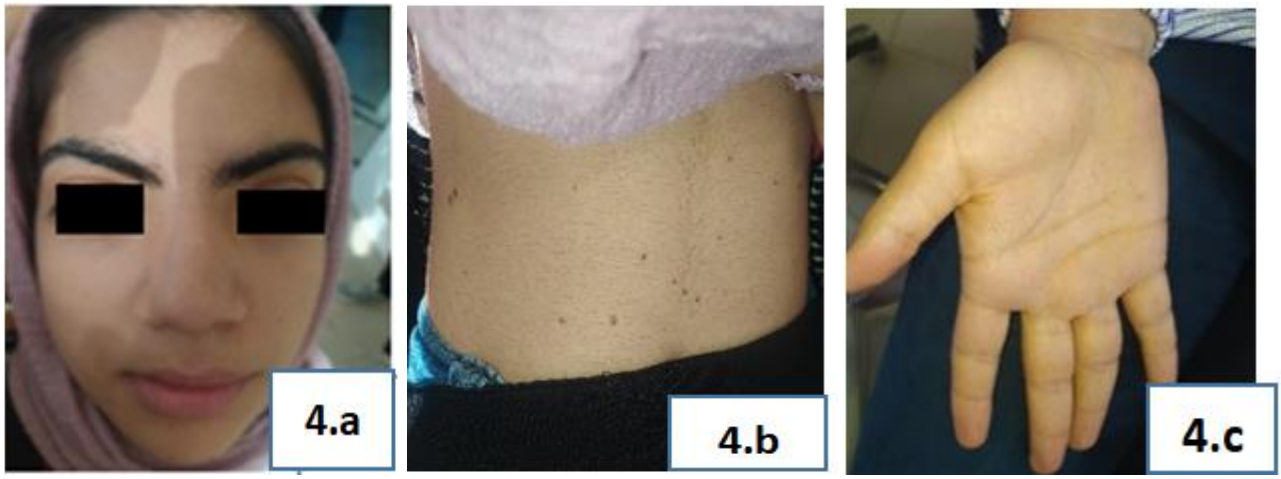


Figure 4: Clinical features seen in patient. (4.a) a widening of the nasal base, telecanthus and hypertelorism, as well as prominent superciliary arches; (4.b) The presence of multiple pigmented BCCs is noted at the belly that resemble melanocytic nevi;(4.c) palmer pits

Simple enucleation surgeries were planned in several sessions, beginning with excision of the lesion located in the posterior left region of the mandible, the entire lesion was removed, followed by vigorous curettage of the inside bone lodge, curettage was performed accompanied by extraction of the 38 under local anesthesia (Figure 5, 6 and 7).

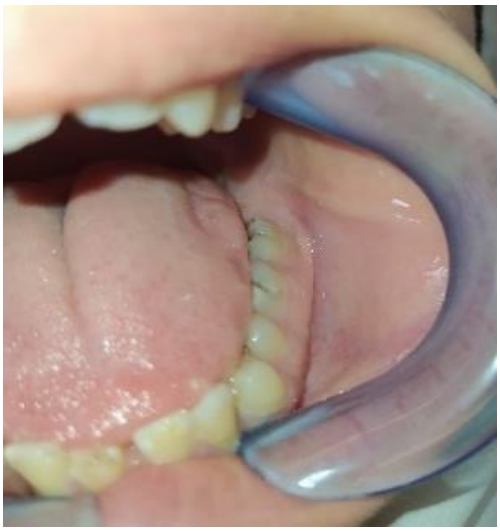


Figure 5: Preoperative endobuccal view of the mandibular angle lesion

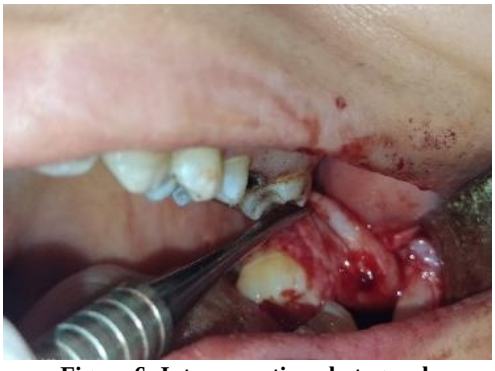


Figure 6: Intraoperative photograph

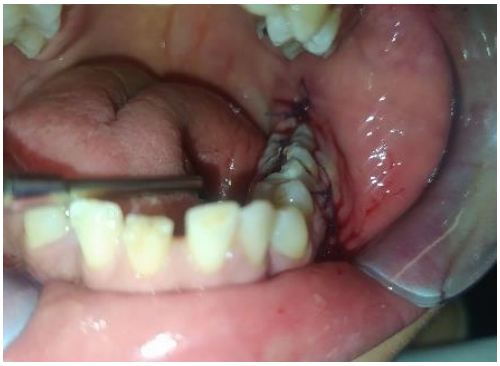


Figure 7: Flap repositioning and suturing

The specimen was sent for histopathologic examination (Figure 8).

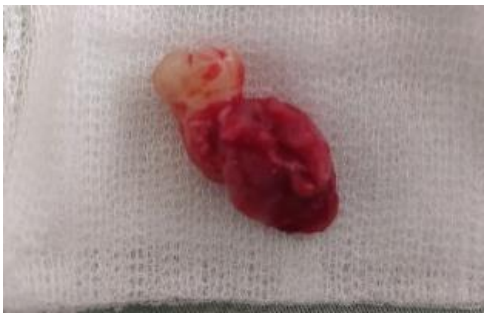


Figure 8: Photographs of excised tissue

Histological examination showed that the cyst wall is composed of dense and non inflammatory fibrous tissue. Lined by a rectilinear basal squamous epithelium, a palisade-like arrangement of basal cells and parakeratosis on the surface confirming the diagnosis of Keratocystic odontogenic cyst.

The diagnosis of Gorlin-Goltz syndrome will be confirmed in the presence of two minor criteria and one major criterion, or at least two major criteria, which is indeed the case for this patient: Major criteria include the presence of odontogenic keratocyst, multiple basal cell nevi and palmar pits, as well as minor criteria such as hypertelorism. No other family members were reported to be affected on interrogation.

In addition, a profile teleradiogram to look for possible intracranial calcifications was requested, the results of which were inconclusive. Consequently, a brain scan was requested for further clarification.

Overall clinical features, imaging characteristics and histological findings lead to a final diagnosis of Gorlin-Goltz syndrome.

The patient was referred to a dermatologic department for evaluation and continuous follow-up of basal cell nevi, and to a gynecologist to investigate other manifestations associated with the syndrome.

A follow-up panoramic radiograph was taken after 6 months, revealing partial bone healing of the surgical site (Figure 9). At 20 months, a cone-beam CT scan was performed, confirming complete bone healing (Figure 10).

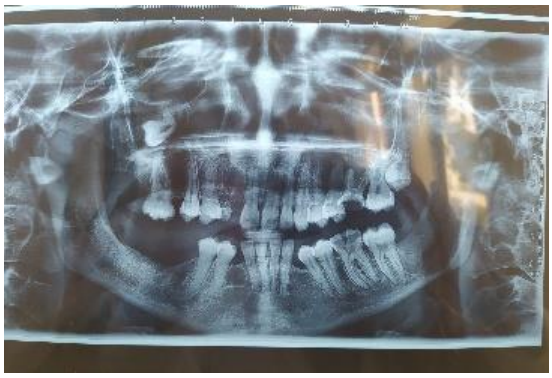


Figure 9: A 6-month follow-up panoramic radiograph showed signs of re-ossification of the mandibular angle lesion

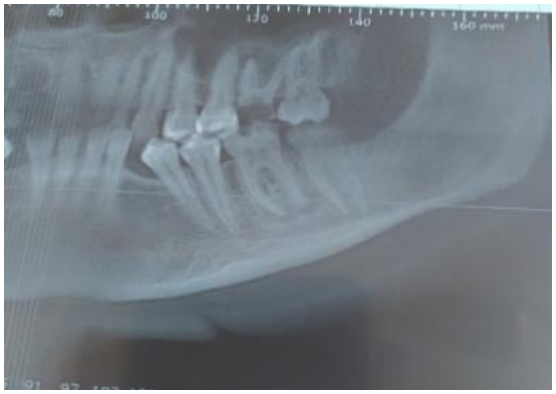


Figure 10: CT-SCAN at 20-month follow-up showing a complete recovery in mandibular left posterior area

Two further procedures, each performed in a separate session, were carried out to excise lesions located in the anterior region of the mandible (Fig 11, 12 and 13) and in the anterior region of the maxilla (Fig 14 and 15). Pathological examination confirmed the diagnosis of odontogenic keratocysts for these lesions too.

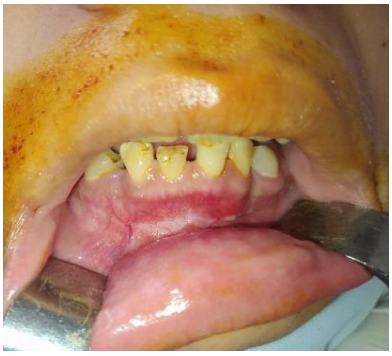


Figure 11: Preoperative photograph of the anterior mandibular region

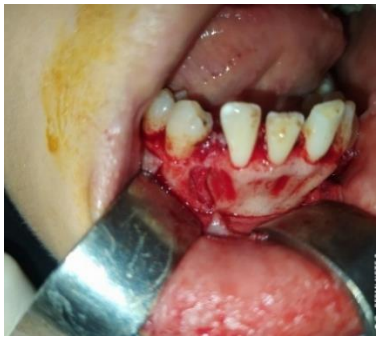


Figure 12: Peroperative photograph

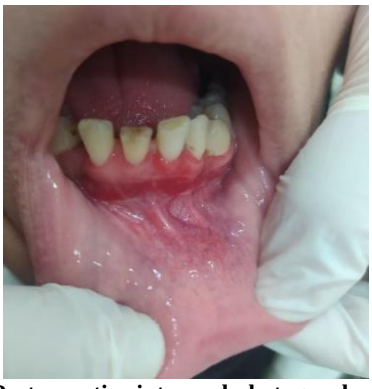
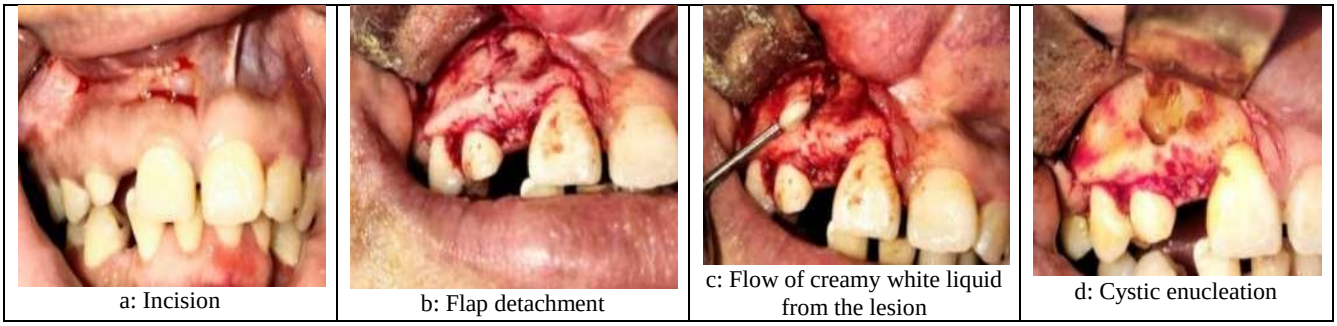


Figure 13: Postoperative intraoral photograph after 21 days



a: Incision | b: Flap detachment | c: Flow of creamy white liquid from the lesion | d: Cystic enucleation

Figure 14: Intraoperative appearance of the maxillary incivo-canine lesion

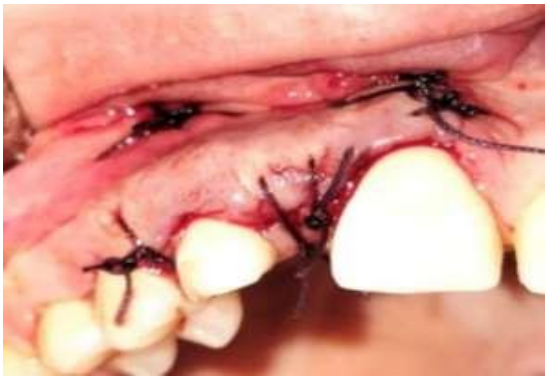


Figure 15: Postoperative appearance of the lesion (flap repositioning and sutures)

A clinical check-up and follow-up panoramic radiographs were considered after 4 months, showing good healing of the surgical site of the anterior mandibular lesion and almost complete bone healing. (Figures 16 and 17), and revealing partial bone healing of the maxillary surgical site (Figure 18).

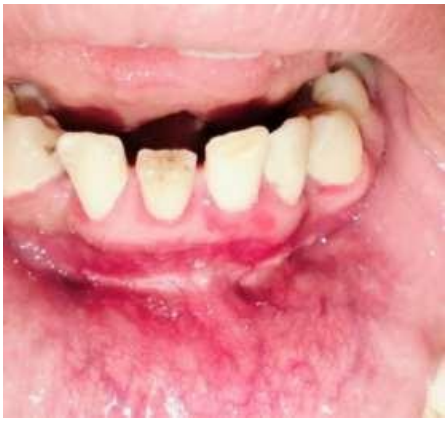


Figure 16: Clinical inspection of the anterior mandibular lesion after 4 months (well-healed surgical site)

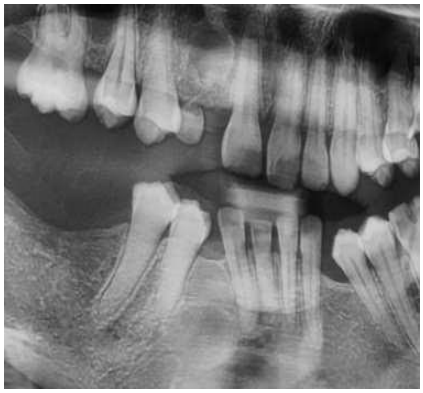


Figure 17: A 4-month follow-up panoramic radiograph shows signs of re-ossification of anterior region of the mandible

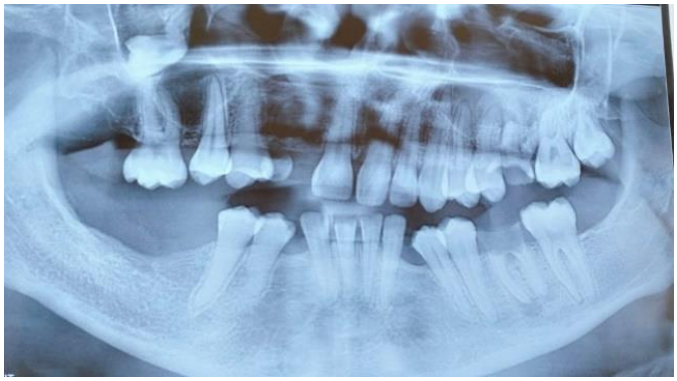


Figure 18: A 4-month follow-up panoramic radiograph shows signs of partial bone healing of anterior region of the maxilla

The patient is still undergoing follow-up for the remaining cystic lesions and ongoing monitoring of her condition.

DISCUSSION

Gorlin-Goltz syndrome is an autosomal dominant disorder which is characterized by a high penetrance and variable manifestations. This syndrome has received several names throughout the time such as nevoid basal cell carcinoma syndrome, Gorlin syndrome, basal cell nevus syndrome, fifth phacomatosis, multiple basilioma syndrome, hereditary cutaneo mandibular polyoncosis and the most complex one 'Jaw-cyst-basal-cell-nevus, bifid rib syndrome [1].

The incidence reported ranges from 1 in 50,000 to 1 in 150,000 in the general population [2]. The male-to-female ratio is 1:1 [3].

Pathogenesis of the syndrome is attributed to abnormalities in the long arm of chromosome 9 (q22.3-q31) and loss of, or mutations of human patched gene (PTCH1 gene) [4].

Clinical manifestations of the syndrome are grouped into the following five categories [5]:

1. Cutaneous anomalies: Basal cell nevus, other benign dermal cysts and tumors, palmar pitting, palmar and plantar keratosis and dermal calcinosis.
2. Dental and osseous anomalies: Multiple OKC, mild mandibular prognathism, frontal and temporoparietal bossing, kyphoscoliosis or other vertebral defects, bifurcated ribs, spina bifida and brachymetacarpalism.
3. Ophthalmic anomalies: Hypertelorism, wide nasal bridge, dystopia canthorum, congenital blindness and internal strabismus.
4. Neurological anomalies: Mental retardation, dural calcification, bridging of sella, agenesis of the corpus callosum, congenital hydrocephalus, occurrence of medulloblastoma.
5. Sexual anomalies: Hypogonadism, ovarian tumor-like fibrosarcoma.

Kimonis and Evans divided the features into major and minor criteria in 1993 [6]. The major criteria are histologically proven OKCs of the jaws, palmar or plantar pits (three or more), multiple basal cell carcinomas or one occurring under the age of 20 years, bilamellar calcification of the falx cerebri, bifid, fused, or markedly splayed ribs, and first-degree relatives with naevoid basal cell carcinoma syndrome. The minor criteria are more than 100 (Table 1) [7, 8].

Diagnosis confirmation required one major and two minor criteria [9].

When multiple basal cell carcinomas (BCCs) are the initial clinical signs, a thorough clinical examination and radiographs should be used to diagnose Nevoid Basal Cell Carcinoma Syndrome (NBCCS). However, it is crucial to also consider other inherited conditions that can present with similar skin features, such as Bazex-Dupré-Christol syndrome (BDCS), Rombo syndrome, and Xeroderma pigmentosum (XP).

Another hallmark of GGS is occurrence of multiple KCOT of jaw [10]. Multiple KCOTs are the most consistent and representative signs of GGS in the first and second decades of life. About 90% of BCNS patients present multiple jaw keratocysts [11]. Like in the present case, jaw cysts may be found as an incidental radiographic finding, during dental treatment. However it may clinically manifest as pain if the cyst is infected or cause symptoms such as swelling. KCOTs associated with GGS usually occur at an early age, usually in the first decade of life. Number of jaw cyst may range from a single lesion to as high as 30. In present case four cysts were discovered on orthopantomogram, occupying all the quadrants of jaw. Both of our patients had multiple jaw keratocysts. Furthermore, both of the present patients had keratocysts of the jaw, and the present cases suggest that keratocysts of the jaw might be an important clue for diagnosing BCNS.

OKCs associated with NBCCS have greater predilections for the mandible (69%) than the maxilla (31%) [12, 13]. In the mandible 43% occurs in the

molar ramus region followed by 18% in the incisor–canine area, and 7% in the premolar area [14]. In the maxilla, 14% occurs in the incisor and canine region followed by 12% in the molar tuberosities, and 3% in the premolar region [14]. In the reported case both the OKCs were in the mandible and the maxilla: molar ramus area of the mandible, posterior region of upper jaw and the anterior regions as well. The teeth 38 and 18 were impacted.

The diagnosis of the GGS was confirmed by the presence of four major criteria (multiple OKC histologically proven, basocell naveus and Palmar pits and two minor criteria (hypertelorism and wide nasal bridge) as it was the case in the reported patient.

Currently, there is no specific treatment for this syndrome, the management is symptomatic and involves specialized cancer surveillance [15].

Treatment therefore requires a multidisciplinary approach between different health areas to ensure an adequate quality of life and effective treatment of the symptoms. It may require a maxillofacial unit, a pediatric unit, a cardiac unit, a gynecological unit, and a genetic counselor to assess different organs.

The treatment decision depends on various factors, such as the size, location and extension of the lesion, as well as damage to surrounding tissue and the patient's age. It is important to take into account the particularities of keratocysts associated with Gorlin syndrome, which present a higher risk of recurrence and malignant transformation [16, 17].

Given that odontological manifestations often occur at an early age usually in the first two decades of life, the role of the dentist is crucial, as he or she must be particularly attentive to any clues suggesting one or more odontogenic keratocysts in a young patient, or the recurrent appearance of such cysts. He must also investigate other clinical manifestations of the disease, referring the patient to the other specialists.

Treatment modalities of keratoysts can be grouped into three categories: conservative, aggressive and radical [18]. They range from conservative methods such as marsupialization and simple enucleation to more aggressive approaches such as enucleation with peripheral osteotomy and chemical curettage with application of products such as carnoy's solution. Block resection with or without preservation of jaw. It should be reserved only for tumors that have perforated the cortical layer. This demolition technique is the only approach that does not show recurrence of keratocysts in surgical follow-ups and improve prognosis.

The cysts are generally parakeratinized and occasionally may have a neoplastic degeneration, for this reason, surgical treatment and careful follow-up are indicated.

CONCLUSION

Gorlin syndrome, an autosomal dominant inherited disease resulting from mutations in the PTCH1 gene. This pathology is manifested by a predisposition to tumours, congenital anomalies abnormalities, and a variety of symptoms.

Due to the complexity and variability of the clinical manifestations, a multidisciplinary approach is essential to diagnose and manage patients with this syndrome. The role of the dentist is crucial, a particularly attention to any signs suggesting one or more odontogenic keratocysts in a young patient, or the recurrent appearance of these cysts. Once the diagnosis has been established, regular monitoring by a multidisciplinary team is desirable to avoid complications. This approach improves the prognosis and the quality of life of patients suffering from this syndrome.

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