ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 01 | January - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

AN INHERITED WOE: A CURIOUS CASE OF GORLIN GOLTZ SYNDROME WITH BILATERALLY SYMMETRICAL FEATURES

Dentistry

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ABSTRACT

Gorlin-Goltz Syndrome (GGS) is a rare autosomal dominant disorder characterized by diverse clinical manifestations, encompassing cysts, neoplasms, and developmental anomalies. This report presents a case of GGS in an early adolescent female exhibiting bilateral symmetrical features, notably jaw swelling, polydactyly, and dental anomalies. Radiological imaging confirmed the diagnosis, revealing multiple bilateral jaw cysts, bifid ribs, and falx cerebri calcifications. A multidisciplinary team crafted a treatment strategy involving surgical intervention and histopathological examination. Despite the absence of basal cell carcinomas, the patient displayed typical GGS features, aligning with major and minor diagnostic criteria. This case underscores the criticality of early diagnosis, multidisciplinary care, and lifelong monitoring to effectively manage complications. While clinical and radiographic findings suffice for diagnosis, genetic testing targeting the PTCH1 gene may aid in ambiguous cases. Genetic counselling for patients and family members is imperative due to the syndrome's autosomal dominant inheritance pattern. This case underscores the prognostic implications and challenges associated with GGS, emphasizing the need for coordinated care and vigilant monitoring to optimize patient outcomes.

KEYWORDS

INTRODUCTION

Gorlin-Goltz Syndrome (GGS) is recognized as an autosomal dominant disorder characterized by a wide array of manifestations. This rare condition is known for its involvement across multiple systems, predisposing individuals to cysts, neoplasms, and various developmental abnormalities [1]. The foundational features of this syndrome were first outlined by Jarisch and White in 1894, who initially called it the nevoid basal cell carcinoma syndrome [2,3]. Several decades later, in 1960, American oral pathologist and human geneticist Robert Gorlin and American dermatologist Robert Goltz further detailed the clinical aspects of this syndrome in their study on "multiple naevoid basal cell epitheliomas, jaw cysts, and bifid rib syndrome." [4] and also coined the term Gorlin-Goltz Syndrome.

The pathogenesis is ascribed to mutations occurring in the patched tumour suppressor gene (PTCH), which is located on chromosome 9q21-23 [5]. Key characteristics of GGS typically include multiple keratocystic odontogenic tumours in the jaw, basal cell carcinoma, bifid ribs, palmar or plantar pits, and falx cerebri calcification. In addition to these, a variety of other signs have been documented, such as developmental anomalies like macrocephaly and cleft lip/palate, distinctive facial features like frontal bossing and hypertelorism, skeletal abnormalities, and tumours like ovarian fibroma and medulloblastoma.

Given the diverse presentation of symptoms, Evans et al. proposed a set of major and minor diagnostic criteria, which were later refined by Kimonis et al. in 1997. According to their criteria, a diagnosis of GGS requires the presence of at least two major and one minor criteria, or one major and three minor criteria [6] . This paper presents a case of GGS in a young female, diagnosed through clinical examination and radiological imaging.

CASE PRESENTATION

An early adolescent female patient was concerned about her appearance and reported to the outpatient clinic of the Department of Paediatric and Preventive Dentistry, Faculty of Dental Sciences, King George's Medical University, Lucknow with the chief complaint of swelling in the right upper jaw for one month. On examination, there was mild facial asymmetry with swelling on the right side of the face; however, the nasolabial folds on both sides were intact. She had a brachycephalic face with coarse features. Mild frontal bossing was present, along with a depressed nasal bridge and hypertelorism. Her lips were thick with an everted lower lip and a prominent lower jaw. The patient had tall stature and examination of her limbs revealed a striking feature of bilateral polydactyly in both her upper and lower limbs(Figure 1). The patient's father and her brother had accompanied her to the clinic, and they both appeared to have similar features as well which hinted the team towards a familial pattern of inheritance. Further questioning revealed that her brother had undergone surgery for odontogenic keratocyst (OKC) of the jawbone a few years back, suggesting a probable autosomal dominant inheritance pattern. The patient also had a delayed onset of puberty and was yet to achieve menarche.

On Intraoral examination, it was noted that teeth numbers 17, 27, and 37 were missing clinically, while teeth numbers 13 and 23 were in the erupting stage. Further examination revealed a high-arched palate and a posterior palatal swelling on the right side which was bony hard and non-tender on palpation.

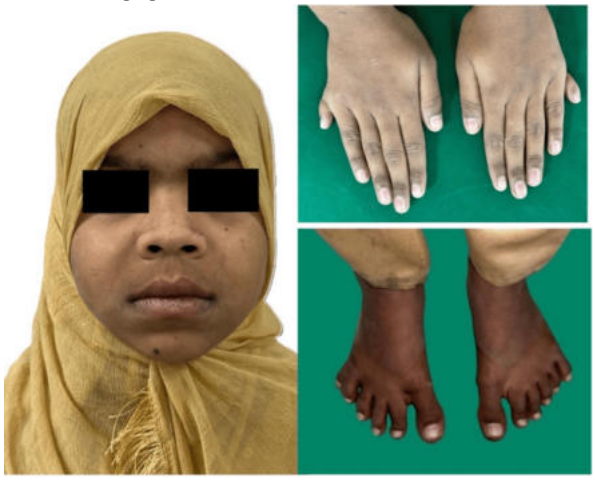

Figure 1: Clinical photographs of the patient depicting facial features and polydactyly of all four limbs

INVESTIGATIONS

The panoramic radiograph (Figure 2) of the patient exhibited multiple radiolucent lesions present bilaterally in both the maxilla and the mandible. These radiolucencies comprised a combination of unilocular and multilocular lesions characterized by well-defined corticated margins. The lesions were primarily associated with unerupted teeth, including the unerupted maxillary right and left second molars, the erupting maxillary right and left canines, and a multilocular radiolucency encircling the unerupted mandibular left second molar and ramus region. Additionally, radiolucencies were evident in the apical region of the maxillary premolars and the right mandibular ramus region. Within the mandible, the lesions on both sides appeared to have induced inferior displacement of the mandibular nerve canals.

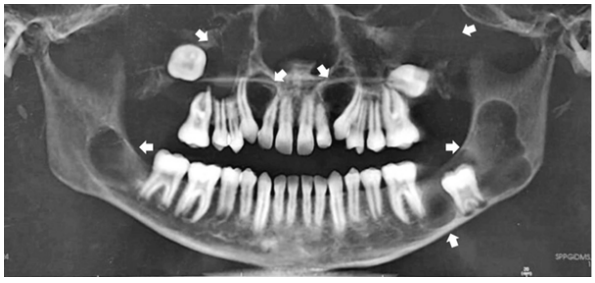

Figure 2: Panoramic radiograph of the patient showing locations multiple jaw cysts in both maxilla and mandible (arrows). Note the bilaterally symmetrical presentation of the lesions

The Cone Beam Computerised Tomography (CBCT) scan of the patient revealed numerous osteolytic lesions present in both jaws. Within the mandible, these lesions were noted to induce expansion and perforation of the buccal and lingual cortical plates. Similarly, within the maxilla, certain tumours appeared to have resulted in expansion and perforation of the hard palate, which was palpable during the patient's clinical examination(Figure 3). Bridging of the sella-turcica was also noticed (Figure 4). It is noteworthy that all the lesions observed thus far exhibited bilateral symmetry in their presentation.

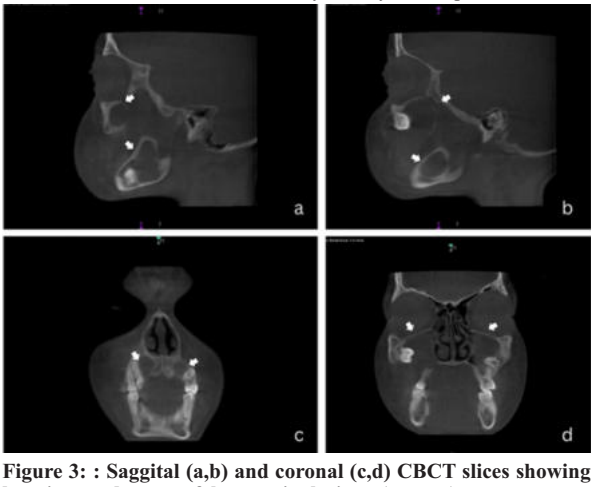

Figure 3: : Saggital (a,b) and coronal (c,d) CBCT slices showing locations and extent of the cysts in the jaws (arrows)

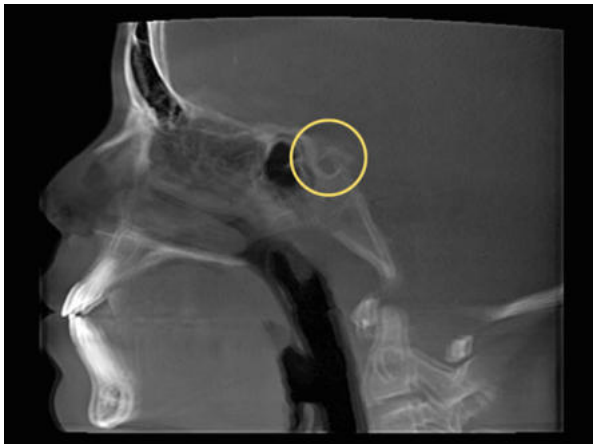

Figure 4: Saggital CBCT slice showing bridging of sella-turcica

Upon examination of the chest via a postero-anterior (PA) radiograph, the presence of numerous bifid ribs was noted(Figure 5).Furthermore, an assessment of the skull via radiography exhibited minor calcifications within the falx cerebri (Figure 6) These collective findings strongly suggest the likelihood of Gorlin-Goltz syndrome as the underlying diagnosis.

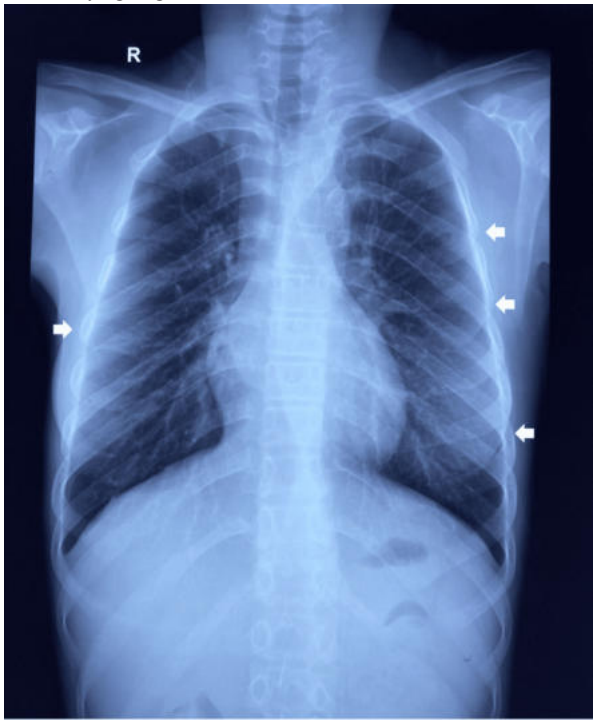

Figure 5: PA view chest x-ray showing multiple bifid ribs (arrows)

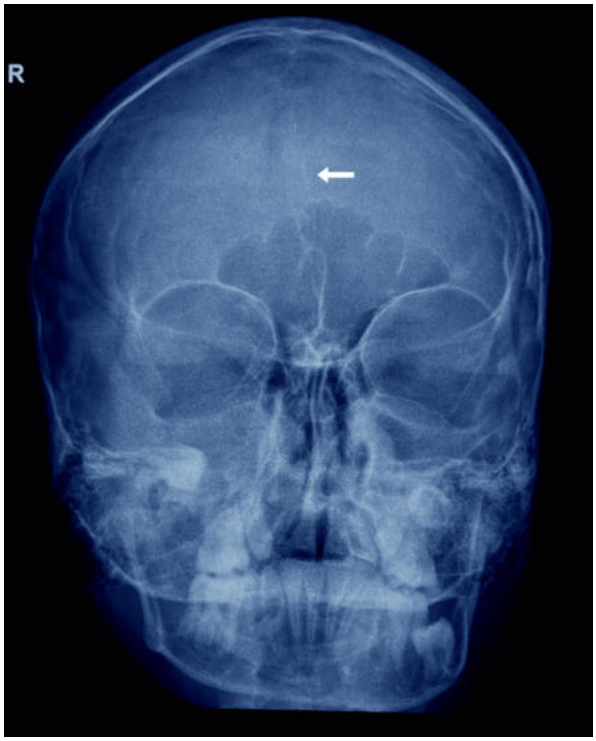

Figure 6: PA view of skull x-ray showing mild calcification of falx cerebri (arrow)

TREATMENT

A multidisciplinary team comprising specialists in pediatric dentistry, oral and maxillofacial surgery, paediatrics, and dermatology collaborated to devise a comprehensive treatment strategy for the

patient. Addressing the immediate concern posed by multiple odontogenic cysts, the team opted for marsupialization and enucleation procedures. Given the propensity of keratocystic odontogenic tumours (KCOTs) for recurrence, distinguishing between true recurrence and the development of new cysts presents a challenge, especially in patients with Gorlin-Goltz syndrome (GGS). Therefore, after enucleating the cystic cavities, the team utilized Carnoy's solution to treat the bony cystic lesions.

Subsequently, the excised cystic linings underwent histopathological examination, revealing a cystic lining containing a connective tissue stroma. The epithelium exhibited para keratinization and a thickness of 3-5 layers, with certain regions displaying para clefting and a corrugated pattern(Figure 7). Adjacent to the epithelium, the connective tissue stroma appeared condensed, featuring blood vessels lined with epithelial cells. Based on these findings, the definitive diagnosis of odontogenic keratocyst was established.

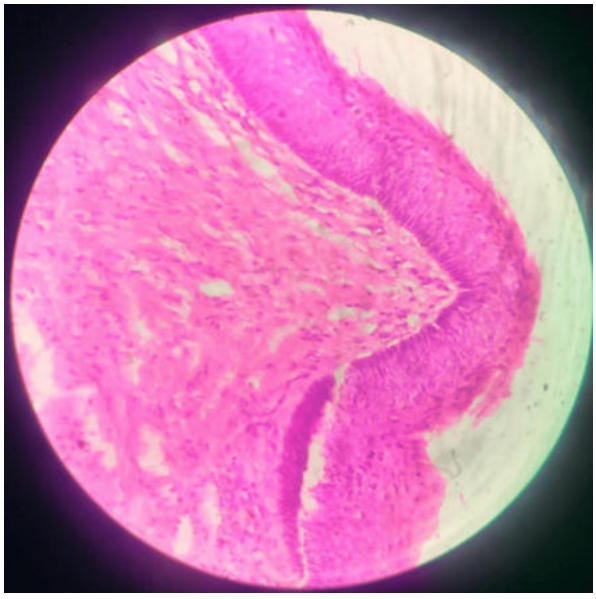

Figure 7: Histopathological section of the enucleted cystic lining showing parakeratinised epithelium which is 3-5 cell layers thick and dense connective tissue stroma suggestive of odontogenic keratocyst.

DISCUSSION

Gorlin-Goltz Syndrome (GGS) is a rare genetic condition characterized by highly variable manifestations, with its prevalence ranging from 1 in 57,000 to 1 in 256,000 in the general population [7]. The syndrome is caused by mutations in the PTCH1 gene located on the long arm of chromosome 9, and these mutations are inherited in an autosomal dominant pattern. Interestingly, 35 to 50% of GGS cases arise from spontaneous mutations, meaning they occur spontaneously without any known family history [8]. To date, researchers have identified over 225 mutations in the PTCH1 gene associated with Gorlin-Goltz Syndrome. The PTCH1 gene is crucial for producing the patched-1 protein, which has a significant role in regulating cell growth and differentiation. Mutations in this gene lead to either the absence or the creation of a defective protein that is unable to effectively control cell proliferation. Consequently, this unchecked cell growth results in the development of the cysts and tumours characteristic of GGS.

Gorlin-Goltz Syndrome is identified by a set of recognizable features that tend to occur together due to the common cause of a PTCH1 gene mutation. The syndrome's clinical presentations can vary widely, affecting different organ systems. The number of symptoms that might manifest in a patient remains elusive. In the case discussed in this report, the patient's father's family history was seemingly non-contributory, as he didn't give any history of basal cell carcinoma or jaw cysts. But his facial features and presence of polydactyly indicated the presence of the mutation in him as well. That was as far in the family tree as these symptoms went, which indicates that the mutation probably originated in the father, and the presenting symptoms are getting progressively severe with each generation, with a particularly severe presentation in the present case.

The diagnostic criteria for GGS, initially proposed by Evans et al. and later refined by Kimonis et al. in 1997, include both major and minor criteria to guide diagnosis [6]. According to Spiker and colleagues [9], the diagnosis of Gorlin-Goltz syndrome necessitates the identification of two major criteria or one major criterion along with two minor criteria as under:

- Major criteria encompass the presence of multiple (>2) basal cell carcinomas (BCCs) or the occurrence of a single BCC before the age of 20, histologically confirmed odontogenic keratocysts of the jaw, palmar or plantar pitting, calcification of the falx cerebri, and anomalies in rib structure such as bifid, fused, or splayed ribs. Additionally, a familial history of BCNS in a first-degree relative is considered a major criterion.
- Minor criteria encompass a broader spectrum of manifestations, including the presence of medulloblastoma, macrocephaly, congenital anomalies such as frontal bossing, coarse facies, or cleft lip/palate, various skeletal abnormalities like Sprengel deformity or syndactyly, radiological findings such as sella turcica bridging or vertebral abnormalities, and the occurrence of ovarian and cardiac fibromas.

In the case presented, four major features were identified: multiple odontogenic keratocysts, bilamellar calcification of the falx cerebri, rib anomalies, and family history of father and brother. Along with this, three minor criteria were also fulfilled: frontal bossing with hypertelorism, coarse facial features, and bridging of the sella-turcica. The most common and significant features of Gorlin-Goltz syndrome are summarized in Table 1. All these findings helped us to arrive at a diagnosis of Gorlin-Goltz syndrome with an appreciable level of certainty.

Spiker et al. [9] suggested genetic testing for the PTCH1 gene to be performed in case one of the following clinical scenarios arises: firstly, it serves to confirm the diagnosis in individuals who lack adequate clinical diagnostic criteria; secondly, it offers predictive testing for individuals at risk due to a family history of the condition, even if they do not fulfil the clinical criteria; thirdly, it facilitates prenatal testing in cases where a familial mutation is already identified. In this instance, we observed a satisfactory fulfilment of the clinical criteria, which provided a reliable basis for diagnosis. Consequently, genetic testing was deemed unnecessary in this scenario.

One prominent characteristic frequently highlighted in the literature concerning this syndrome is the emergence of multiple basal cell carcinomas, particularly in the head and neck area [10]. Cutaneous basal cell carcinoma (BCC) represents the most frequent skin manifestation of Gorlin-Goltz Syndrome (GGS), showing a higher prevalence in white populations (80%) compared to populations with higher melanin pigmentation (38%) [11]. Epidemiological studies have highlighted sunlight, particularly UV radiation, as a significant risk factor for BCC development. Recent research has confirmed that UV irradiation accelerates BCC formation in mice with PTCH gene mutations, reinforcing the notion that UV exposure exacerbates BCC risk in GGS patients. BCC presentation in GGS can range from light to dark brown papules with a smooth surface and firm consistency, to ulceroproliferative lesions. The number of BCCs may vary widely, from a single lesion to hundreds, typically arising between puberty and 35 years of age. Commonly affected sites include the thoracic and cervicofacial skin, periorbital areas, eyelids, nose, malar region, and upper lip. Patients with GGS are extremely sensitive to ionizing radiation and should be counselled to avoid sun exposure [8]. However, in this instance, the presence of basal cell carcinomas could not be identified. This circumstance may be attributed to the patient's age as she is only in her early adolescence. It is plausible that these carcinomas may manifest in the future, possibly during the late second and third decades of life.

Another defining feature of GGS is the presence of multiple keratocystic odontogenic tumours (KCOT) of the jaw [12] These are among the most consistent and early signs of GGS, often discovered incidentally during dental treatments through radiographic examination. KCOTs may present clinically with pain if infected, or manifest as swelling. The presence of multiple jaw cysts in a patient is a strong indication for a thorough investigation to rule out Gorlin-Goltz syndrome. Oral surgeons and radiologists are particularly well-positioned to make an early diagnosis of this condition.

Thoracic cage anomalies are common (43%), particularly bifid and

fused ribs. These anomalies may include bifid, fused, or splayed ribs [13]. Toe syndactyly and polydactyly are less common, occurring in approximately 3% of cases. Acharya S [11] reported an instance of Gorlin-Goltz syndrome with the patient exhibiting polydactyly on both feet.

Various skeletal anomalies have also been associated with GGS, including a high and broad forehead, frontal and parietal bossing, and a broad nasal root often accompanying ocular hypertelorism. The maxilla may be underdeveloped, and mandibular hyperplasia with variable prognathism may occur. Less common skeletal anomalies include a high-arched palate, cleft palate and lip, and multiple impactions of teeth.

One notable skeletal anomaly associated with this syndrome is the bridging of the sella turcica. The sella turcica is a saddle-shaped depression in the sphenoid bone of the skull where the pituitary gland is situated. This bridging, which refers to the complete or partial fusion of the anterior and posterior clinoid processes across the sella turcica, can be visualized through radiographic imaging. This anomaly has been extensively studied in the context of GGS, with several scientific articles reporting its prevalence and clinical significance. For instance, in a study by Kimonis et al. [6], they observed bridging of the sella turcica in 70% of GGS patients, highlighting its high prevalence in this syndrome. Additionally, a more recent study by Karaman et al. [14] investigated the relationship between sella turcica bridging and other skeletal anomalies in GGS patients, providing valuable insights into the clinical implications of this radiographic finding. Moreover, the study by Lo Muzio et al. [15] explored the potential association between sella turcica bridging and the severity of GGS phenotypes, shedding light on its role as a diagnostic marker and prognostic indicator in affected individuals.

This case highlights the unique position of pediatric dentists in the early diagnosis of such syndromes and the important responsibility of referring the patient to other specialties for effective care and counselling. Once a definitive diagnosis of GGS has been arrived at, a multidisciplinary team approach should be adopted in addressing the multitude of symptoms that manifest from the syndrome. GGS doesn't alter the life expectancy of the patient to any appreciable degree, however, resulting complications may cause substantial morbidity [7]. Additionally, an early diagnosis facilitates patient counselling regarding the prevention of detrimental exposure to ultraviolet radiation. It also underscores the importance of regular screenings to detect various cysts and tumours, such as intestinal polyps, uterine and ovarian fibromas in females, and cardiac fibromas, which have a heightened incidence rate in such individuals [11].

The patient exhibited polydactyly in all four limbs, which, along with the remarkable bilateral symmetry of the jaw lesions, constitutes the most intriguing and distinctive aspects of this case. As far as the authors are aware, no similar case has been documented to date.

The significance of this syndrome Is underscored by its serious prognostic implications. Notably, ameloblastomatous [16] and carcinomatous [17] transformations have been reported in jaw cysts. This underscores the importance of complete surgical excision of the cyst linings, followed by a thorough histological examination. Patients must be referred to the genetics department for counselling. Each child of an affected individual has a 50% chance of inheriting the faulty gene and exhibiting symptoms of the syndrome. Gene tracking and mutation analysis can be instrumental for early, presymptomatic diagnosis.

CONCLUSION

Gorlin-Goltz syndrome is a rare genetic disorder characterized by a wide spectrum of clinical manifestations, including developmental anomalies and an elevated risk for various neoplasms. Early diagnosis and a multidisciplinary approach to treatment are crucial for optimizing patient outcomes and reducing associated morbidity. Continuous lifelong monitoring is essential for the early detection and management of recurrent or newly emerging cysts, tumors, and other complications.

Although diagnosis is often based on clinical and radiographic findings, genetic testing targeting the PTCH1 gene may be indicated in cases where clinical criteria are inconclusive. Due to its autosomal dominant inheritance, genetic counseling is strongly recommended for both affected individuals and their families to provide insight into potential risks and hereditary implications. Timely intervention and long-term surveillance can significantly enhance the prognosis and quality of life for patients with this condition.

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