

Case Report

Gorlin-Goltz syndrome

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ABSTRACT

Gorlin-Goltz syndrome is an uncommon autosomal dominant inherited disorder, which is characterized by multiple odontogenic Keratocysts and basal cell carcinomas, skeletal, dental, ophthalmic, and neurological abnormalities, intracranial ectopic calcifications of the falx cerebri, and facial dysmorphism. Pathogenesis of the syndrome is attributed to abnormalities in the long arm of chromosome 9 (q22.3-q31) and loss or mutations of human patched gene (*PTCH1* gene). Diagnosis is based upon established major and minor clinical and radiological criteria and ideally confirmed by deoxyribo nucleic acid analysis. We report a case of a 9-year-old girl presenting with three major and one minor feature of Gorlin-Goltz syndrome. Radiologic findings of the syndrome are easily identifiable on Orthopantomogram, chest X-ray, and Computed tomography scans. These investigations prompt an early verification of the disease, which is very important to prevent recurrence and better survival rates from the coexistent diseases.

Key Words: Calcification of falx cerebri, fused ribs, Gorlin-Goltz syndrome, odontogenic keratocyst

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INTRODUCTION

Gorlin-Goltz syndrome which is also known as nevoid basal cell carcinoma (BCC) Syndrome is a rare autosomal dominant disorder with strong penetrance and extremely variable expressivity. It was reported by Jarish and White in 1894. Robert J. Gorlin and Robert W. Goltz described the distinct syndrome, consisting of multiple nevoid BCCs, jaw cysts, and bifid ribs.^[1] It is characterized by multiple odontogenic Keratocysts (OKC), multiple BCCs, skeletal, dental, ophthalmic, and neurological abnormalities, intracranial ectopic calcifications of the falx cerebri and facial dysmorphism.^[2-4] 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).^[5] Diagnosis is based upon established major and minor clinical and radiological criteria and ideally confirmed by deoxyribo nucleic acid (DNA) analysis. A case of Gorlin-Goltz syndrome is presented here in which the abovementioned findings are evident. This syndrome is also named as Gorlin Syndrome, Multiple Nevoid Basal Cell Epithelioma, Jaw Cyst Bifid Rib Syndrome, or Multiple Nevoid BCC syndrome.^[2] The frequency of the syndrome varies according to the country where the study has been carried out. On an average, the incidence of Gorlin-Goltz syndrome has been reported to be 1 in 50,000 to 150,000 in general population.^[3] The review of literature reveals that only seven cases of this syndrome are reported from India.^[3]

The syndrome manifests with some major and minor criteria like pigmented BCCs, OKC, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri. To establish diagnosis, two major and one minor or one major and three minor criteria are necessary.^[6,7] Treatment modalities may differ for small and large cysts. Small cysts can be enucleated, whereas large cysts can be marsupialized. Because of

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Figure 1: Clinical photographs (a, b and c) and Intraoral Photograph (d) of patient

aggressive nature and high rate of recurrence, there should be periodic follow-up at regular intervals of 6 months till 5 years, followed by once annually for the entire life.

CASE REPORT

A 9-year-old girl presented to the Department of Oral Medicine and Radiology in Vasantdada Patil Dental College and Hospital, Sangli, with complaint of swelling in the upper anterior region of right side of jaw since the last six months. Swelling had been increasing since the last 3 to 4 months and there was no pain associated with it. Lateral photograph shows the increased occipitofrontal circumference. Intraoral examination revealed that the buccal sulcus on both sides was obliterated and there was expansion of the buccal cortical plates [Figures 1a-d].

Orthopantomogram (OPG) was advised which revealed multiple round to oval radiolucencies which were suggestive of multiple cystic lesions [Figure 2].

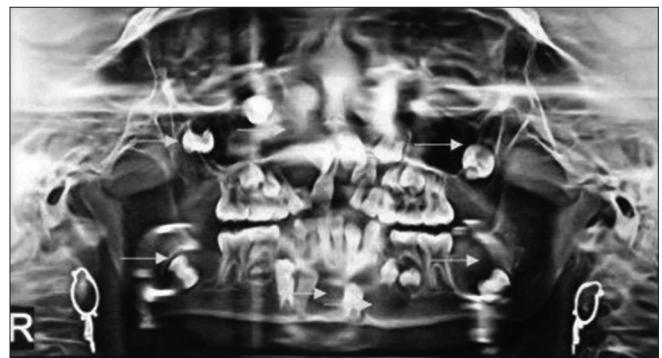


Figure 2: OPG showing multiple cystic lesions, three in maxilla and four in mandible

The erupting left and right second molar tooth also had a cyst-like radiolucency over the crown. Thus, seven cystic lesions (three in maxilla and four in mandible) were seen on OPG. Due to the presence of multiple cyst-like lesions in the jaws, Gorlin-Goltz syndrome was suspected and further investigations were carried out.

An X-ray of the skull revealed calcification of falx

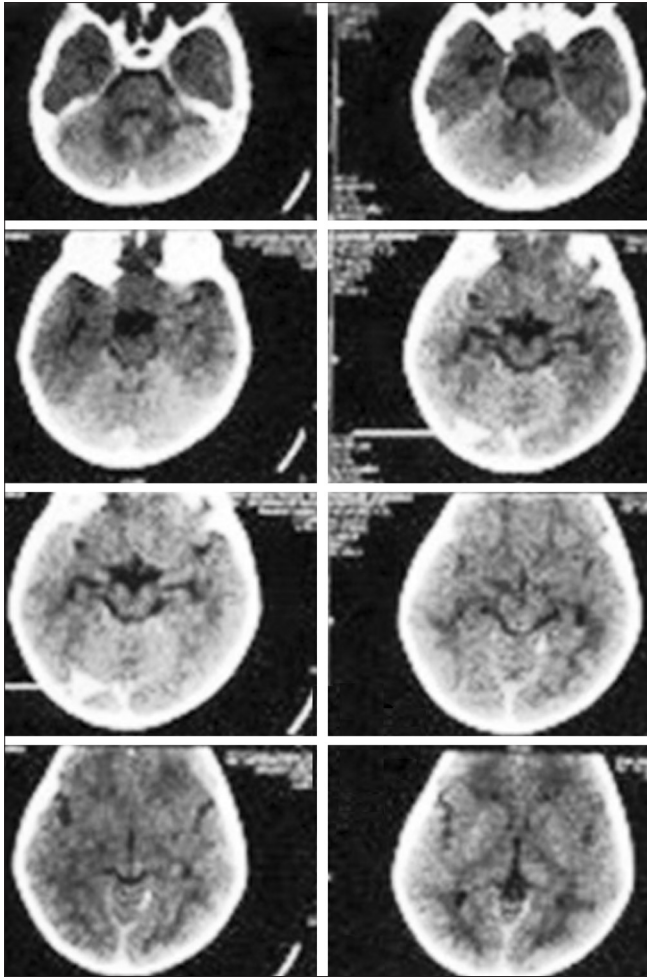


Figure 3: CT scan brain showing calcification in falx cerebri



Figure 4: Chest X-ray showing fusion of 3rd and 4th ribs on left side

cerebri [Figure 3] and a chest X-ray showed fused ribs [Figure 4]. Other findings included frontal bossing. No skin lesion in the form of basal cell nevus, palmar or plantar pits, or keratosis were present.

All the cystic lesions of the jaw were enucleated surgically. Intraoperative photographs and photographs of excised tissue are shown in Figures 5 and 6, respectively. The histopathologic examination of enucleated tissue was done. The cystic lining was made up of uniformly thick, stratified squamous epithelium of 5 to 6 layers thick, flat with corrugated parakeratin surface. The basal cell layer was cuboidal to columnar with well-polarized nuclei. Underlying connective tissue capsule was loose fibrocellular, with supporting vasculature, extravasated blood elements, strands, and nests of odontogenic epithelium [Figures 7 a-c]. In all seven cysts, histopathologic features were suggestive of OKC [Figure 7]. Ki 67 immunohistochemical staining was done which was positive (25%) [Figure 8].

In our patient, the diagnosis of Gorlin-Goltz syndrome was established by the presence of three major criteria (multiple OKC, bifid ribs, and calcifications of falx cerebri) and one minor criterion (Figure 1c showing increased occipitofrontal circumference).

DISCUSSION

In order to make a diagnosis of the Gorlin-Goltz syndrome, some diagnostic criteria have to be taken into account. The most important criteria to make a diagnosis for this syndrome are the presence of pigmented basocellular carcinomas, OKC, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri.^[8-11] Together with these major features, more than 100 minor features have been described. The more relevant are the following: cardiac or ovarian fibroma, macroencephaly, bifid ribs, kyphoscoliosis, cleft palate, medulloblastoma, alterations in the sella turcica, mandibular prognathia, lateral displacement of the inner canthus, frontal and biparietal bossing, imperfect segmentation of the cervical vertebrae, lymphoenteric cysts that tend to calcify, meningiomas, fibrosarcoma, rhabdomyosarcoma, short fourth metacarpal, ocular hypertelorism, congenital blindness, high arched eyebrows and palate, narrow sloping shoulders, immobile thumbs, low pitch voice in women, renal anomalies, and hypogonadism in men. In certain occasions, a tall height and even similar characteristics to acromegaly have been associated with the syndrome.^[4,8,12,13]

Evans *et al.*^[6] first established major and minor criteria for the diagnosis of the syndrome and later were modified by Kimonis^[7] *et al.* in 2004. The presence

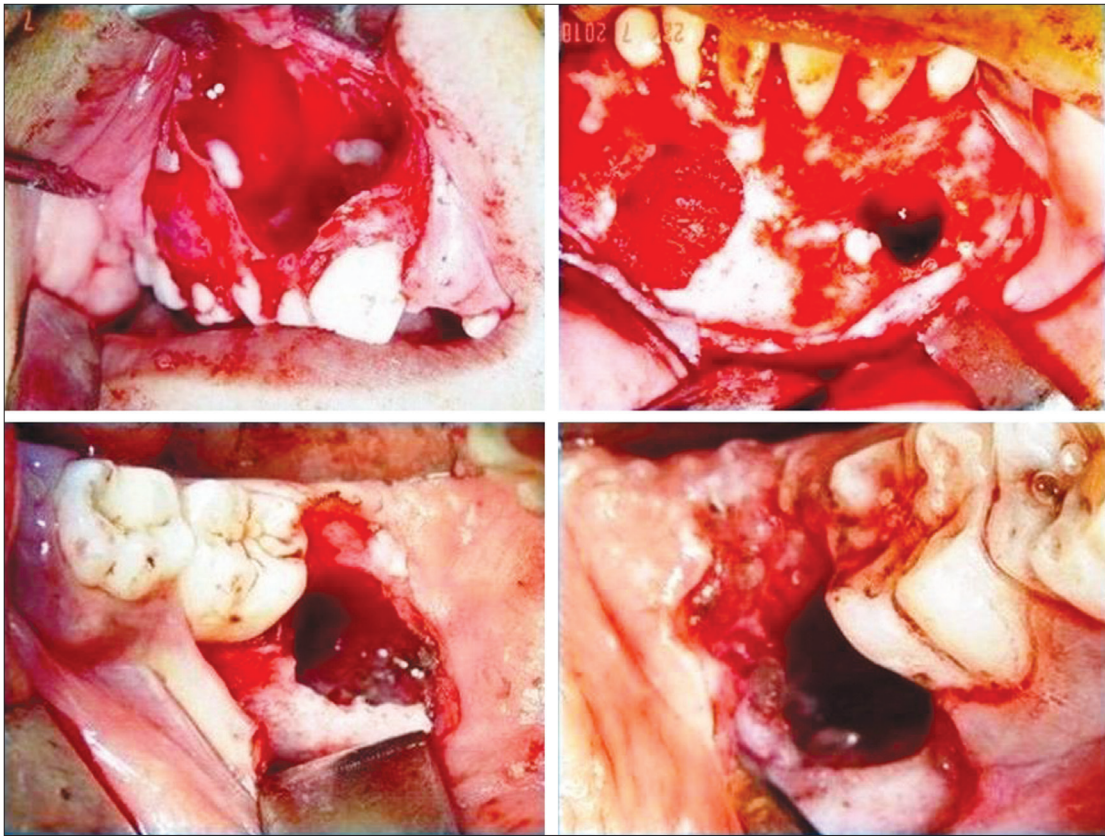


Figure 5: Intraoperative photographs

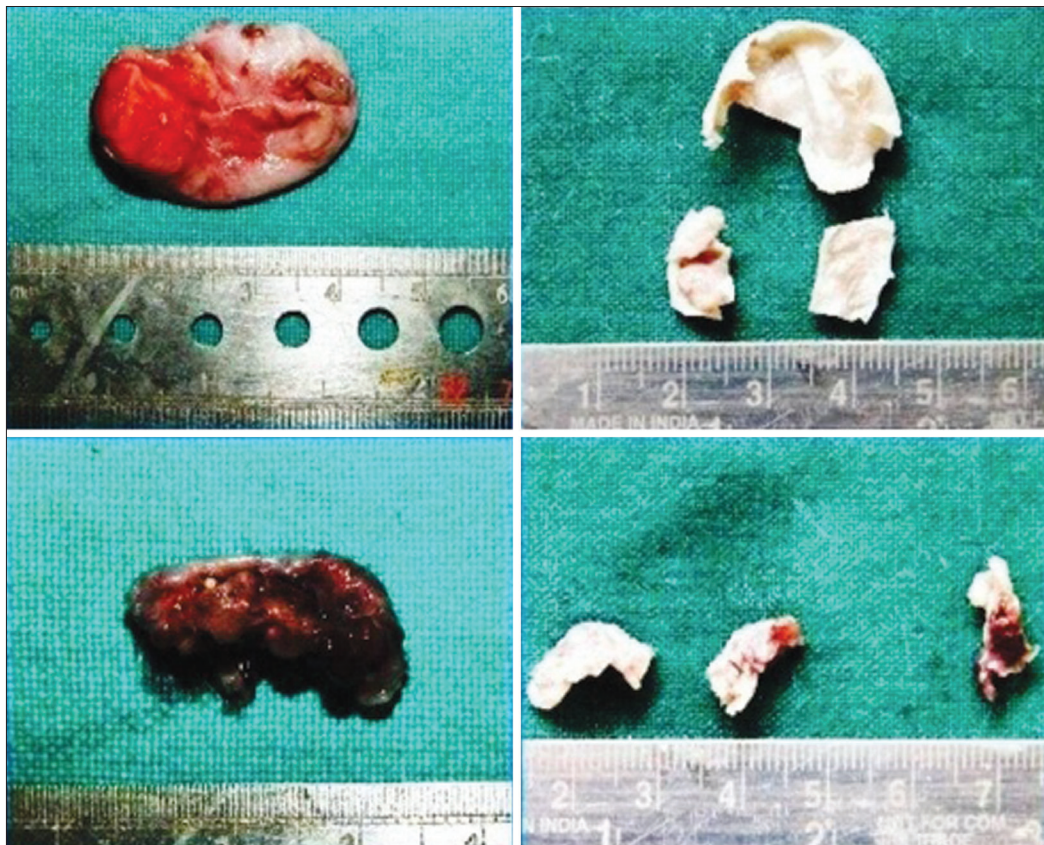


Figure 6: photographs of excised tissue

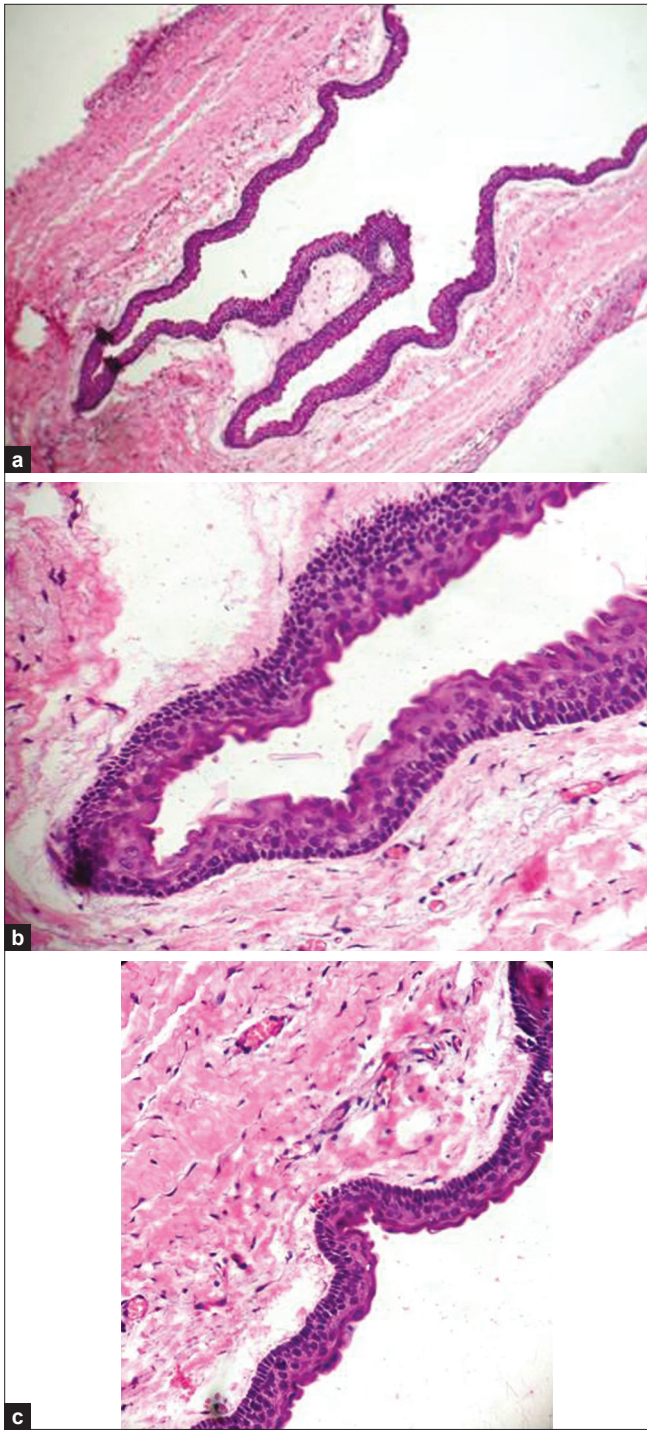


Figure 7: H and E stained photomicrographs of OKC [10× (a) and 40× (b and c)]

of two major and one minor or one major and three minor criteria are necessary to establish diagnosis.^[6,7]

Major criteria

- Multiple basal cell carcinomas or one occurring under the age of 20 years.
- Histologically proven OKCs of the jaws.
- Palmar or plantar pits (three or more).

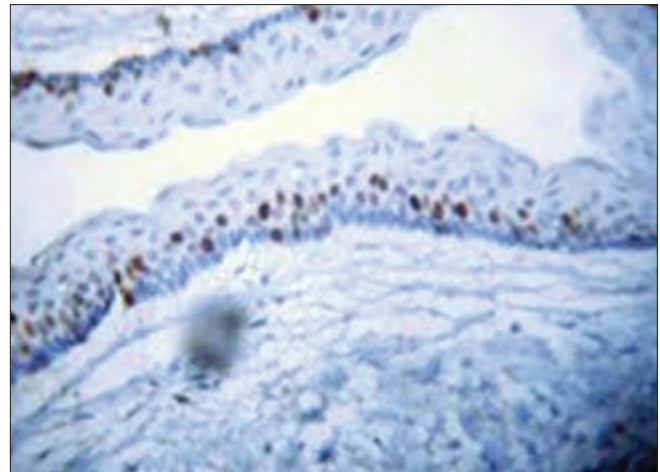


Figure 8: Ki 67 immunopositive

- Bilamellar calcifications of the falx cerebri.
- Bifid, fused, or markedly splayed ribs.
- First degree relative with nevoid basal cell carcinoma syndrome.

Minor criteria

- Macrocephaly (adjusted for height).
- Congenital malformation: Cleft lip or cleft palate, frontal bossing, coarse face moderate or severe hypertelorism.
- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
- Radiological abnormalities: Bulging of sella turcica, vertebral anomalies such as hemi vertebrae, fusion or elongation of vertebral bodies, modeling defects of the hands and feet, or flame-shaped hands or feet.
- Ovarian fibroma.
- Medulloblastoma.

Gorlin-Goltz syndrome is an autosomal dominant disorder with a high penetrance and variable expressivity. It 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. More recent investigations reveal the role of the *Hh* pathway in cell cycle regulation in adults. In the *Drosophila* model, the primary receptor for the *Hh* signaling pathway has two

transmembrane protein components: Patched (Ptc) and Smoothed (Smo). In the absence of Hh protein, the Ptc protein inhibits the Smo. Under normal conditions, Hh, when present, binds Ptc, releasing Smo to affect downstream events such as cell growth and differentiation. Based on this model, inactivation of Ptc or constitutive activity of Smo or Hh could lead to overactivity of Smo, resulting in neoplasm formation.^[5]

Woolgar *et al.* in 1987 concluded that mean age group for syndromic cases is 10 to 30 years and females are more affected than males. In syndromic cases, more commonly maxillary molar area is affected. Recurrence rate is higher in syndromic cases (63%).^[14] Woolgar *et al.* have also noted significant differences histologically. OKC associated with Basal Cell Nevus Syndrome showed more number of satellite cyst, solid islands of epithelial proliferation and odontogenic rests within the capsule, and increased mitotic figures in the epithelium lining the main cavity.^[14]

OKC's falling in the category of Keratocystic Odontogenic Tumor (KCOT) may be associated with Gorlin-Goltz Syndrome in the form of multiple cystic lesions.^[3,11] Katase *et al.* analyzed the neoplastic nature and biological potential of sporadic and nevoid basal cell carcinoma syndrome (NBCCS)-associated KCOT.^[15] Heparanase is an endo-d-glucuronidase enzyme that specifically cleaves heparan sulfate and the increase of its level in tumors promotes invasion, angiogenesis, and metastasis. In his study, all odontogenic cysts have shown positive immunoreactions for the heparanase for the heparin protein in various intensities. Intense gene and protein expressions have been observed in KCOT associated with NBCCS, as compared with sporadic ones and dentigerous cyst. So, heparanase expression may be correlated with the neoplastic properties of KCOT, particularly in NBCCS-associated cases.^[3,11]

Apart from surgical enucleation for cystic lesions, adjunctive therapies like chemical cauterization is useful to prevent recurrence by fixing the daughter cyst or remnants of epithelial lining that are not removed during the enucleation procedure. Carnoy's solution is a phenolic compound with tissue fixative properties.^[13] Voorsmit *et al.* have demonstrated that Carnoy's solution penetrates the bone to the depth 1.54 mm following a 5 minutes application without any damage to the inferior alveolar nerve.^[16]

CONCLUSION

Gorlin-Goltz syndrome is a well-known Autosomal Dominant disorder. The incidence reported worldwide ranges from 1 in 50,000 to 1 in 150,000. Not many cases have been reported in India, and hence we report here a rare case and importance of multidisciplinary approach in management of the syndrome. Thorough extraoral and intraoral examinations along with OPG, skull and chest radiographs help in proper diagnosis of the condition. This investigation prompts an early verification of the disease, which is very important to prevent recurrence and better survival rates from the existent diseases. OKC of the jaws which can cause disfigurement of the face, mobility and even loss of teeth can be avoided by early detection and treatment of the same.

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