Case Report

Gorlin Goltz Syndrome: A Case Report and Discussion on Diagnosis and surgical management

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ABSTRACT

Gorlin Goltz syndrome (GGS) is a rare syndrome caused due to inheritance of autosomal dominant gene with the exception of sporadic mutation cases. The tumor suppressor gene known as Patched (PTCH) present in the 9q chromosome have been identified as the cause of GGS. Gorlin Goltz presents with a wide range of developmental anomalies and predisposition to neoplasm. It is of significance to rule out GGS in patients with multiple odontogenic keratocysts (OKT/OKC). To date, very few cases of GGS has been reported in India. We hereby present a case of multiple keratocysts in the mandible and maxilla, which on further evaluation revealed, various skeletal, facial and cutaneous anomalies leading to diagnosis of the Gorlin Goltz syndrome. This case report discusses clinical and radiological presentation of GGS and management of its different clinically presenting manifestations with special emphasis on OKT.

Keywords: Gorlin-Goltz syndrome; Odontogenic keratocysts; PTCH1gene; Falx cerebri calcification.

Gorlin Goltz syndrome is a rare multisystemic disease, which is inherited in an autosomal dominant way. It show penetrance of high level and variable expressiveness [1]. This syndrome is known by several different names such as "basal cell nevus syndrome" [2] and "nevoid basal cell carcinoma". Jarisch and White in 1894 was first to describe this syndrome but it was in 1960 when Gorlin and Goltz established a classic triad, which characterizes the diagnosis of this syndrome, basocellular epitheliomas, keratocysts in the jaws and bifid ribs [3]. Generally, multiple OKT may be the first presenting symptom for which a subject seeks physician advice, which are mainly dentists [4]. This syndrome affects all the ethnic groups with equal predisposition in male and female genders.

Goldstein et al has done extensive work on GGS and has compiled 22 case records till 2012 [5]. Prevalence varies according to the country [6]. Prevalence of 1 in 60,000 is accepted.

Studies have revealed wide spectrum of development defects and tumors associated with individual affected by Gorlin Goltz syndrome rather than the historical classical triad [6]. More than 100 minor features have been described as for this syndrome [7] and all the clinical manifestations of GGS is not necessary to be present for a diagnosis. It is seen with mutations in patched 1 gene (PTCH1) [8].

CASE REPORT

A 20-year-old female reported to the outpatient department of Dentistry with chief complaint of limited mouth opening and constant dull pain in both sides of the lower jaw. The subject was being treated elsewhere by general

physician for cysts in the jaw. She had a previous history of dental treatment where incisional biopsy and iodoform gauze packing of the bony lesion of the lower jaw was done. The subject was otherwise healthy and had no previous significant medical history. Although the face was bilaterally symmetrical, the frontal view showed flattening of the nasal bridge. There was a presence of frontal bossing.Intra oral examination revealed complete permanent dentition with missing third molars. DMFT score was zero and no other periodontal problems were diagnosed. Bilaterally in the retro molar region, medicated gauze packs were seen in the bony cavity, which foul smelled. Limited mouth opening was associated with muscle spasm due to secondary infection.

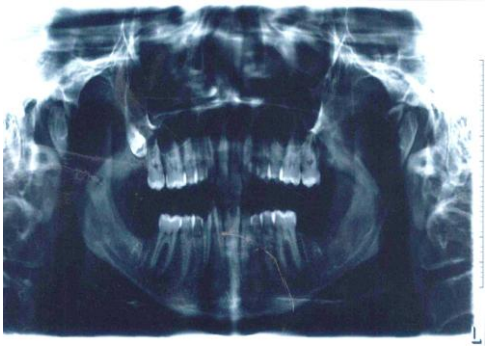

Figure 1 - Radiolucent areas with sclerotic border bilaterally in angle and body of mandible and the left side of maxilla, along with involving teeth

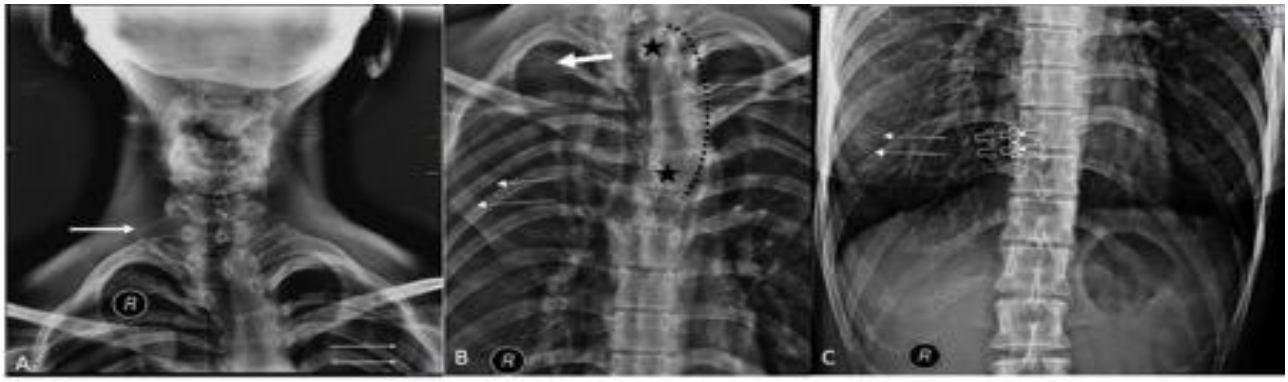

Figure II (a to c); showing skeletal changes; (a) plain radiograph of cervical spine, anteroposterior view, showing elongated transverse process on the right side (thick white arrow), bifid left fourth rib (double thin white arrows); (b) plain radiograph of upper thoracic spine, anteroposterior view, showing partial fusion of first to fifth thoracic vertebrae (black stars are on first and fifth thoracic vertebrae) with scoliosis having convexity to left side (curved line drawn along left border of vertebral column), bifid anterior end of second rib (double thin white arrows) and splayed posterior aspect of second rib (thick white arrow); (c) plain radiograph of lower thoracic spine, anteroposterior view, showing bifid anterior end of right sixth rib.

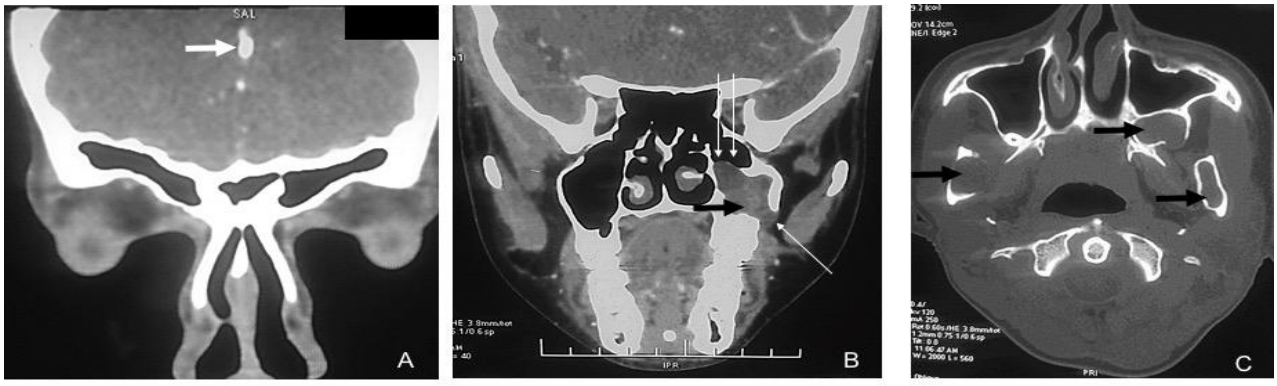

Figure III a to c; contrast CT craniofacial region (A) Coronal view of contrast CT showing falx calcification (arrow); (B) Coronal view of contrast CT showing lytic expansile lesion with a solid enhancing portion (black arrow) in left maxilla; the soft tissue lesion has breached the maxillary wall inferolaterally (single thin white arrow) and remodelled and uplifted the floor of the maxillary sinus (double thin white arrows); (C) axial section, bone window settings of CT scan, showing three expansile lytic lesions, one each in both mandibular rami and one in left maxilla (black arrows); there is no calcification within these lesions.

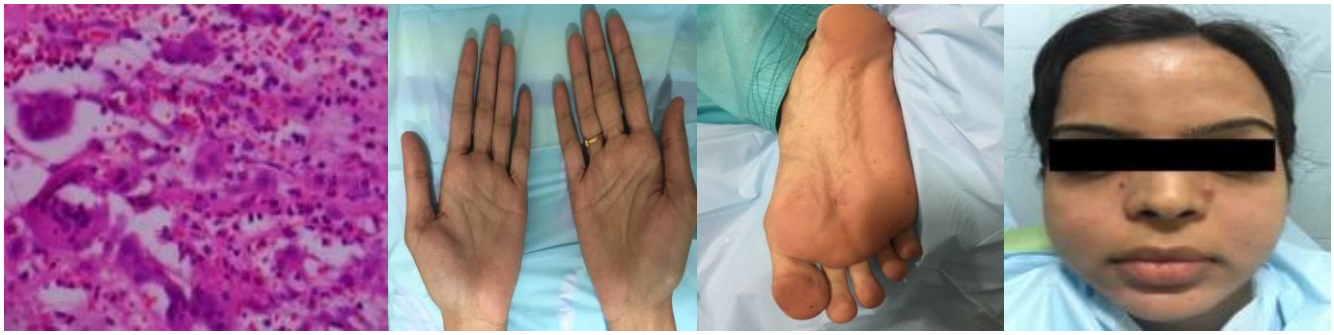

Figure 4 - Fibro collagenous tissue with moderate chronic inflammatory infiltrate and lined focally by stratified squamous epithelium. The luminal epithelial cells are para keratinized and produce an uneven corrugated surface. Figure 5a & 5b - Multiple palmer and plantar pits. Figure 6 - Frontal bossing

Orthopantomograph finding revealed radiolucent areas with sclerotic border bilaterally in angle and body of mandible and left side maxilla. All radiolucent lesions were multilocular (Fig. 1). X-ray chest revealed bifid left fourth rib (Fig. 2a), partial fusion of first to fifth thoracic vertebrae with scoliosis having convexity to left side, bifid anterior end of second rib and splayed posterior aspect of the second rib (Fig. 2b), bifid anterior end of right sixth rib (Fig. 2c). CT scan findings revealed calcification of the falx cerebri (Fig. 3a), and lytic expansile lesion in the left maxilla (Fig. 3b). Three expansile lesions in the both mandibular Rami and one in left maxilla (Fig. 3c) were also seen. A provisional diagnosis of GGS was made.

Biopsy was performed and histopathological examination revealed fibro collagenous tissue with moderate chronic inflammatory infiltrate lined focally by stratified squamous epithelium. Trabeculae of osteoid tissue were also present. The luminal epithelial cells were para keratinized and produced an uneven corrugated surface suggestive of odontogenic keratocyst (Fig. 4). An evaluation by dermatology was done, it revealed various classical signs, which included multiple palmer (Fig. 5a) and plantar pits (Fig. 5b). Frontal bossing was also an important diagnostic feature in our patient (Fig. 6).

The parents of the patient underwent radiological evaluation; neither of them showed any features of the Gorlin Goltz syndrome. In our patient the diagnosis of the Gorlin Goltz syndrome was confirmed by the presence of three major criteria (viz., multiple odontogenic keratocysts, calcified falx cerebri and bifid rib) and three minor criteria (viz., hypertelorism, Palmar/plantar pits, frontal bossing).

The surgical procedure was as follows: Under General Anesthesia, two cysts from mandibular & one cyst for left maxilla were enucleated and affected teeth associated with lesion were removed. Peripheral osteotomy was performed with surgical bur followed by application of cornoy's solution for 5 minutes in each cavity. Chemical cauterization and electro cauterization were done at sites where there was bone breach and the lesion extended up to the adjoining soft tissue. Hemostasis was achieved & primary closure done. The content of the cavity was sent for histopathological examination into three specimen samples. The patient is under surveillance of the disease and monitoring occurrence of any new lesion. Follow up clinically for one year is complete.

DISCUSSION

Diagnostic criteria, based on the most frequent and/or specific features of the syndrome, were defined by Evans et al. in the Journal of Medical Genetics in 1993, and modified by Kimonis et al. in 1997 [9] (Table 1.) Syndromes vary among individuals within the family as depending upon manifestation and severity of the phenotype. Molecular testing may be considered for confirmation by individuals with typical findings [10]. Molecular genetic testing for mutation in PTCH gene is unable to detect mutation in all affected individuals, So clinical examination and radiographic investigations remains the diagnostic standard for GGS. Comparison between syndromic and non-syndromic keratocysts have shown that keratocyst in GGS are normally multiple and have increased number of satellite cysts and solid island of epithelial proliferation. GGS Keratocyst are frequently parakeratinised [11]. Palmer and Plantar pits develop in the second decade of life and increase in number with age.

Current diagnostic criteria for GGS includes Clinical, histologic and family history and the treatment of the syndrome is the specific therapeutics for the clinical manifestations.OKC are the most consistent and representative sign of GGS in the first and second decade of life. The diagnostic criteria are based on clinical evidence, radiographic manifestation, and histological examination because molecular genetic testing for mutations in PATCH gene is unable to detect the mutation in all affected individuals [12].

The recurrent jaw cyst is the main oral sign, being present in 90% of patient [13]. Keratocysts appear in the tooth bearing area of the jaws, and believed to arise from the dental lamina [14]. Most non –NBCCS Keratocysts are isolated lesions, but in NBCCS the keratocysts are commonly multiple, from 1to30, and the average number is 5. In NBCCS patients, there is continued development of new and recurring cysts until about age 30, when the rate of development tends to decrease. The most common site in the mandible is a molar ramus region (44%) followed by incisor canine region (18%). In contrast, the majority of maxillary cyst occurs in incisor- canine (15%) and molar tuberosity (13%). The most common symptoms presented by half of the patients are swelling, a quarter with mild pain. During the past years, advancement has been taking place in the knowledge of the genetic characteristic of the syndrome, existing clinic pathologic variations and its different manifestations. A two hit model [15] for developmental defects in Gorlin Syndrome. 1) The syndrome associated OKC, presumably must have originated from precursor cell containing the hereditary (1^{st} Hit). 2) Additional somatic mutation or loss of heterozygosity, epigenetic silence of the other allele may act as a second hit, which can make PTCH inactive. The 2 hit is necessary for various tumors, hamartomas like BCC, OKCs, meningioma and ovarian fibromas. But, other lesions, for example, palmar pits require 1 hit. Preliminary diagnosis and treatment of the Gorlin Goltz syndrome, as well as family screening for the syndrome and genetic counselling are essential, as it may be associated with 10% of the patients with aggressive basal cell carcinoma and malignant neoplasia. High concentration of melanocytes has been associated with a decreased chance of (BCC) basal cell carcinoma proliferation owing to protect from UV radiation. Lack of BCC may further delay diagnosis of early GGS without affording protection from syndromes other manifestations.

Among skeletal manifestation mean height of the subject is found to be increased (183 cm in males 174 cm in female) and about 15% of patients are extremely tall [16] About 70% of affected individuals have eyes which appear wider apart due to abnormal growth of the skull. Other skeletal signs are scoliosis (40%) and abnormalities are such as bifid, wide, fused, partially missing ribs under developed ribs (30-60%) [13]. Other developmental defects proved to be prominent features of GGS include pits of palm and soles, [30-65%] by the age of 10 years and percentage rising to 80% by the age of **15** [17**].** These can be considered a very useful diagnostic trait of GGS as pointed out by Kimonis et al and also present in our case.

In CT scan Ectopic calcification of central nervous system have been reported: lamellar calcification of the falx cerebri (70-85%) [13], the calcification of the falx cerebi can appear very early in life, and is often strikingly apparent from late childhood. Other features detected are cyst of choroid plexus of the third and lateral ventricles of the brain, agenesis of corpus callosum [18], meningioma, medulloblastoma [19]. Precise differential diagnosis needs exclusion of some rare dermatological syndrome, such as Bazex syndrome (characterized by basal-cell carcinoma associated with hyportrichosis, hypohidrosis, milia and folliculare atro-phodermia), trichoepithelioma papulosum multiplex (named also epithelioma adenoids cysticum), or Torre's syndrome (Muir-Torre's syndrome). One of the most problematic aspects is 60% rate of recurrence following surgery. This may be due to incomplete removal of the cyst that is from retention of epithelial island and/or satellite micro cysts, which occur with great frequency in the connective tissue capsule, or from the proliferation of the basal layer of epithelium. Several specialists are required to treat various manifestations of the disease. The acceptable surgical treatment modalities for OKC are: 1. Decompression & marsupialization. 2. Enucleation with & without adjuncts. 3. Enucleation & treatment of bony defect with cornoy's solution. 4. Enucleation and liquid nitrogen cryotherapy. 5. Block resection with or without preservation of continuity of jaw.

The choice of treatment should be based on multiple factors; patient age, size and location of the cyst, soft tissue involvement, history of previous treatment and histological variant of the lesion. The goal is to choose the treatment modality that causes the lowest risk of recurrence and the least morbidity.There have been reports of ameloblastoma arising in odontogenic keratocyst or

rarely squamous cell carcinoma. Tollers suggested that the OKC may be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behaviour .WHO reclassify the lesion based on its behaviour, histopathology and genetics.

CONCLUSION

The presence of multiple odontogenic keratocyst should alert clinician to suspect GGZ and look into other features of the Gorlin Goltz syndrome. It is advisable to carry out all radiographic investigations to confirm the syndrome to make diagnosis at an early stage of life and make early diagnosis of associated neoplasia. If once, detected close relatives should be carefully examined for possible hereditary risks of the condition and subjected to genetic counseling.

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