INTRODUCTION

Gorlin-Goltz syndrome (GGS) is an infrequent multisystemic disease with an autosomal dominant trait, with complete penetrance and variable expressivity, though sporadic cases have been described. Its clinical features arise in the first, second or third decade of life, affecting multiple organ systems which include skeletal, eye, skin, reproductive and neural system, although all the features are rarely observed in a single patient. This syndrome has been termed with several names such as, basal cell nevus syndrome, GGS, nevoid basal cell carcinoma syndrome (NBCCS), multiple basal cell carcinoma (BCC) syndrome, multiple basalioma syndrome, jaw cyst basal cell tumor skeletal anomalies syndrome, jaw cyst bifid rib basal cell nevus syndrome, nevoid basalioma, odontogenic keratocysts skeletal anomalies syndrome and fifth phacomatosis. This syndrome has been termed with several names such as, basal cell nevus syndrome, GGS, nevoid basal cell carcinoma syndrome (NBCCS), multiple basal cell carcinoma (BCC) syndrome, multiple basalioma syndrome, jaw cyst basal cell tumor skeletal anomalies syndrome, jaw cyst bifid rib basal cell nevus syndrome, nevoid basalioma, odontogenic keratocysts skeletal anomalies syndrome and fifth phacomatosis. This syndrome has been termed with several names such as, basal cell nevus syndrome, GGS, nevoid basal cell carcinoma syndrome (NBCCS), multiple basal cell carcinoma (BCC) syndrome, multiple basalioma syndrome, jaw cyst basal cell tumor skeletal anomalies syndrome, jaw cyst bifid rib basal cell nevus syndrome, nevoid basalioma, odontogenic keratocysts skeletal anomalies syndrome and fifth phacomatosis.

This article describes a case of GGS in a 15-year-old male patient. It also provides literature review of GGS.

CASE REPORT

A male patient aged 15 years reported to the Department of Oral and Maxillofacial Pathology with a chief complaint of swelling in the right side of the upper and lower jaws. It had started as a small swelling that increased in size over 10 months. On examination, the swellings were found to be firm and slightly tender.

An orthopantomograph [Figure 1] revealed multiple radiolucent lesions on both sides of the maxilla and the right side of the mandible. Impacted teeth were present on both sides of the maxilla and on the right side of the mandible that were displaced by the enlarging cysts [Figures 1 and 2]. He also had hypertelorism and synophrys [Figure 3]. Computed tomography (CT) scan of the brain did not reveal calcification of the falx cerebri [Figures 4 and 5]. Skin lesions like basal cell nevus or keratosis were absent. However, a chest radiograph showed the presence of a bifid rib on the right side [Figure 6]. The presence of multiple cysts in the jaws and extra oral features raised suspicion of GGS. Routine biochemical and hematological evaluations were carried out and the patient was hospitalized. Under all aseptic precautions, general anesthesia was administered. Local anesthesia with adrenaline was injected and flaps were raised intraorally in all quadrants one after the other. A surgical window was needed only in the third quadrant to reach the cyst. No vital structures were seen near the lesions. A slow speed straight hand piece (E-type Nosecone; NSK) with tungsten carbide burs (tapering fissure and flame shaped) and a surgical curette.
were used with saline irrigation for enucleating the cysts. Curettage was done using a curette and a round bur. The remnants of the cysts were removed using chemical cautery with Carnoy’s solution (2.5%) for 3 min without chloroform followed by irrigation with saline. The cysts were enucleated from all four quadrants followed by extraction of impacted teeth 17, 18, 28, 38 and 48. The tissues removed were put in separate bottles containing formalin and the corresponding quadrant number was noted. As bone regeneration in children is faster, bone grafts were not used. The enucleated tissues were sent for histopathological evaluation. All three lesions were sectioned and studied using hematoxylin and eosin stains. The sections showed a cystic lining of corrugated parakeratinized stratified squamous epithelium consisting of 6–10 layers of uniform thickness. The basal layer showed palisading nuclei and tombstone appearance [Figure 7]. Epithelial connective tissue separation was seen [Figure 8]. The underlying

Figure 1: Orthopantomograph revealing ectopic teeth present on both sides of the maxilla and on the right side of the mandible, displaced by cysts

Figure 2: Computerized tomography scan revealing ectopic teeth present on both sides of the maxilla and on the right side of the mandible, displaced by cysts

Figure 3: Extra-oral clinical image shows hypertelorism and synophrys

Figure 4: Computed tomography scan of the skull showing absence of calcification of the falx cerebri

Figure 5: Computed tomography scan of the skull showing an oval radiolucent lesion in the right mandibular ramus

Figure 6: Chest radiograph showing the presence of a bifid rib on the right side
connective tissue showed odontogenic epithelial islands, blood vessels and inflammatory cells. All three lesions were diagnosed as odontogenic keratocysts. The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) confirmed that our patient was a case of GGS. The patient is being followed up at 3-month intervals and no recurrence has been noted.

**DISCUSSION**

The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) helped us make a diagnosis of GGS in the patient. A literature review of GGS is as follows:

**History**

The first report of the syndrome was made in 1894 by Jarisch and White in a patient with multiple BCCs, scoliosis and learning disability. In 1939, Straith described a case with multiple basocellular carcinomas and cysts. Binkley and Johnson in 1951 and Howell and Caro in 1959 observed a relationship between basal cell epitheliomas and developmental malformations. Gross in 1953 presented a case with additional signs such as synostosis of the first left rib and bilateral bifurcation of the 6th ribs.

In 1960, Robert James Gorlin and William Goltz discovered the classical triad (multiple basocellular epitheliomas, keratocysts in the jaws and bifid ribs) that established the diagnosis of this syndrome. Later this triad was modified by Rayner et al., who established that cysts had to appear simultaneously, either with calcifications of the falx cerebri, or with palmar and plantar pits, in order to arrive at a diagnosis. The association of palmar and plantar pits with the syndrome was first described by Bettley and Ward.

**Incidence**

In the general population, the incidence of GGS is estimated at 1 in 50,000–150,000. Farndon et al. reported a minimum prevalence of 1 in 57,000 people. However, a prevalence from 1/57,000 to 1/256,000, with a male to female ratio of 1:1 has also been described. Shanley et al. in Australia and Muzio et al. in Italy estimated the prevalence as 1/64,000 and 256,000, respectively. Evans et al. reported a prevalence rate of 1/560,000 in the United Kingdom. The syndrome occurs with equal frequency in both sexes, but most reports have been in whites. It has both a sporadic and a familial incidence. Although detected in very young children, they are commonly expressed between the ages of 17 years and 35 years. New mutations are seen in 35% to 50% of cases. Nine variants of mutations have been reported in patients with GGS.

**Etiology**

Mutations of the human patched gene (PTCH1 gene), which is part of the hedgehog – signaling pathway, is the molecular basis of the syndrome. This gene was first isolated in 1996 as the human homologue of the Drosophila segment polarity PTCH1 gene, mapped to the long arm of chromosome 9q22.3–q31 with no apparent heterogeneity, in Australia and in the USA. This gene plays a role in tumor suppression, embryonic structuring and cellular cycle. Mutations in this gene results in loss of control of several genes known to play a role in organogenesis, carcinogenesis and odontogenesis thus resulting in the development of GGS. Pruvost-Balland et al. carried out a clinical and genetic study in 22 patients with GGS. PCH1 mutations were identified in 13 patients, out of which, six were familial cases, three were sporadic and in four patients, it was not possible to conclude if they were familial.
Features

Clinical manifestations of the syndrome can be grouped into the following nine categories.\textsuperscript{[9,18]}

- Cutaneous anomalies - Basal cell nevus/carcinoma (50–97%), other benign dermal cysts and tumors (21%), palmar/plantar pitting (90%), palmar and plantar keratosis and dermal calcinosis
- Dental anomalies - Multiple odontogenic keratocysts (75–100%), maxillary hypoplasia, mandibular prognathism, high arched palate or prominent palatine ridges (40%), cleft lip/palate (4%), impacted teeth and/or agenesis (3%), ectopic teeth and malocclusion
- Craniofacial anomalies - Calcification of falx (37–79%), tentorium cerebellum calcification (3%), bridged sella turcica (21%), macrocephaly (40%), brachycephaly, frontal bossing (25%), parietal and temporal bossing and coarse face (50%)
- Skeletal anomalies - Polydactyly (3%), syndactyly, scoliosis (15%), hemivertebrae or other vertebral defects, flame-shaped lucencies of hand/feet, spina bifida (3%), osteoporosis (3%), cervical/bifurcated/fused/splayed/absent/rudimentary ribs (26%), brachymetacarpalism and shortened fourth metacarpal (12%)
- Cardiac - Cardiac fibroma (3%)
- Ophthalmic anomalies - Hypertelorism (40%), dystopia canthorum, congenital blindness (15%), internal strabismus (15%), congenital amaurosis, exotropia, glaucoma (3%), ptosis and coloboma (3%)
- Neurological anomalies - Mental retardation (6%), dural calcification, bridging of sella, agenesis of corpus callosum, congenital hydrocephalus (3%), medulloblastoma (3–5%), agenesis/disgenesis of corpus callosum, meningioma (1% or less) and schizoid personality
- Sexual anomalies - Hypogonadism (3%), uterine and ovarian fibromas (15%), calcified ovarian cysts (3%) and supernumerary nipple
- Laboratory findings - Increased serum uric acid level (3%), increased levels of alkaline phosphate and cyclic adenosine monophosphate.

Investigations

Muzio had suggested the following investigation protocol.\textsuperscript{[44]}

- Family history - Past medical and dental history
- Clinical examinations - Oral, skin, central nervous system, head circumference, interpupillar distance, eyes, genitourinary system, cardiovascular system, respiratory system and skeletal system
- Genetic testing
- Radiographs - Chest, anteroposterior and lateral skull, panoramic radiograph, cervical and thoracic spine (anteroposterior and lateral), hands (for pseudocysts), pelvic (female), ovarian ultrasound (female) for ovarian fibroma and echocardiogram (children) for cardiac fibroma.

However, confirmation is by ultrasound and DNA analysis.\textsuperscript{[34]}

Diagnosis

Diagnosis of NBCCS may be difficult because of the variability of expressivity and because of different ages of onset for the different traits of this disorder.\textsuperscript{[31]} Early diagnosis of GGS is crucial for the affected children and their families, considering the risk of developing malignancies such as medulloblastoma and aggressive skin cancers.\textsuperscript{[45]} A negative family history could hamper the early clinical recognition of patients with GGS. However, it may be diagnosed during early childhood if the clinician is well aware of clinical signs of the disease.\textsuperscript{[37]} The diagnostic criteria for GGS was put forth by Evans et al. in 1991 [Table 1] and modified by Kimonis et al. in 1997 [Table 2].\textsuperscript{[26,29]} According to Kimonis, diagnosis can be established only when two major, or one major and two minor criteria are present.\textsuperscript{[26]}

Keratocystic odontogenic tumor and its treatment

Odontogenic keratocysts linked with GGS are now termed as “keratocystic odontogenic tumor” (KCOT).\textsuperscript{[40]} These are a constant feature present in about 75% of cases with GGS.\textsuperscript{[36]} KCOT are often the first sign of GGS in 78% of cases.\textsuperscript{[28,47]} They develop during the first decade of life, usually after 7 years and peak during the second and third decade.\textsuperscript{[4,19,32,47,48]} Their occurrence is approximately a decade earlier than that of odontogenic keratocysts not associated with the syndrome.\textsuperscript{[28,49-51]} The male to female ratio is 1:0.62 for conventional odontogenic keratocysts and 1:1 for KCOT.\textsuperscript{[52-54]}

Table 1: Diagnostic criteria by Evans et al. in 1991

| Major criteria | Minor criteria |
|----------------|--------------|
| More than 2 BCCs, one BCC in patients younger than 30 years of age or more than 10 basal cell nevi | Congenital skeletal anomaly (e.g., bifid, splayed, fused or missing rib, or bifid wedged or fused vertebra) |
| Any odontogenic keratocyst (proven by histology) or polyostotic bone cyst | Occipital-frontal circumference greater than the ninety-seventh percentile, with frONTAL bossing |
| Three or more palmar or plantar pits | Cardiac or ovarian fibromas |
| Ectopic calcification in patients younger than 20 years of age (lamellar or early falx cerebri calcification) | Medulloblastoma |
| A positive family history of NBCC | Lymphomesenteric cysts |
| BCCs: Basal cell carcinomas, NBCC: Nevoid basal cell carcinoma |

BCCs: Basal cell carcinomas, NBCC: Nevoid basal cell carcinoma
Table 2: Diagnostic criteria by Kimonis et al. in 1997

| Major criteria                                                                 |   |
|------------------------------------------------------------------------------|---|
| More than 2 BCCs or one BCC in patients younger than 20 years of age          |   |
| Odontogenic keratocysts of the jaw (proven by histologic analysis)            |   |
| Three or more palmar or plantar pits                                         |   |
| Bilamellar calcification of the falx cerebri                                 |   |
| Bifid, fused or markedly splayed ribs                                         |   |
| A first degree relative with NBCCS                                           |   |

| Minor criteria                                                               |   |
|------------------------------------------------------------------------------|---|
| Macrocephaly                                                                 |   |
| Congenital malformations (e.g., cleft lip or palate, frontal bossing, coarse faces and moderate or severe hypertelorism) |   |
| Other skeletal abnormalities (e.g., sprenzel deformity, marked pectus deformity and marked syndactyly of the digits) |   |
| Radiological abnormalities (e.g., bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped luencies of the hands and the feet) |   |
| Ovarian fibroma or medulloblastoma                                           |   |

**BCCs:** Basal cell carcinomas, **NBCCs:** Neviod basal cell carcinomas

KCOT have a greater predilection for the mandible (69%) than the maxilla (31%).[28,53-55] In the mandible, 43% of KCOT occur in the molar-ramus region, followed by 18% in the incisor-canine region and 7% in the premolar region. In the maxilla, 14% occur in the incisor-canine region, followed by 12% in the molar tuberosity region and 3% in the premolar region.[54]

Their high mitotic index and increase in proliferating cell nuclear antigen suggests the greater proliferative potential of the epithelial lining leading to cyst expansion.[48,56] Heparanase is an endo-d-glucuronidase enzyme that specifically cleaves heparan sulfate and its increased level in tumors promotes invasion, angiogenesis and metastasis. Katase et al. suggested that heparanase expression may be correlated with the neoplastic properties of KCOT.[57]

In young patients, the cysts may be associated with unerupted teeth and cause tooth displacement and root resorption. They are asymptomatic unless secondarily infected and rarely cause pathological fractures. Ameloblastoma and squamous cell carcinoma have risen from these cysts.[49] On the orthopantomograph, KCOT may show a unilocular or multilocular pattern and the cystic spaces may have smooth or scalloped border.[44,49] Multiple odontogenic keratocysts may be confirmatory of the syndrome.[32] Histologically, in comparison to conventional odontogenic keratocysts, syndromic KCOT show more number of satellite cysts, solid islands of epithelial proliferation, intramural epithelial remnants, odontogenic rests within the capsule, increased parakeratinization and mitotic figures in the epithelium.[53,58-60] Moreover, syndromic KCOT have shorter epithelial height and smaller nuclei when compared with solitary odontogenic keratocysts.[59] Immunohistochemical analysis has shown that cytokeratins CK17 and CK19 are overexpressed in odontogenic keratocysts.[61]

**CONCLUSION**

The presence of two major signs (bifid rib and multiple odontogenic keratocysts) and one minor sign (hypertelorism) confirmed that our patient was a case of GGS. It is important to make an early diagnosis of GGS, as the case presents malignant predisposition and hence can be managed appropriately. Health specialists like pediatricians, dentists, maxillofacial
surgeons, dermatologists, etc., must have good knowledge of the features of GGS so that the patient can be treated early and further monitored.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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