A Unique Case of Gorlin–Goltz Syndrome with Associated Sotos Syndrome

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Abstract

Both Gorlin–Goltz syndrome and Sotos syndrome are rare genetic conditions showing variable expressiveness. They both are inherited in an autosomal dominant pattern. Since these conditions tend to be multisystemic disorders, the familiarity of various medical specialists with its manifestations may reduce the time necessary for providing a diagnosis, better differentiation of these two conditions, or even the co-existence of two syndromes.

Keywords: Bifid rib, muscle hypotonia, odontogenic keratocyst

Introduction

In 1960, Robert James Gorlin and William Goltz described a case with a triad of skeletal abnormalities, presence of multiple (OKC), and basal cell carcinoma.[1,2] It was designated as Gorlin–Goltz syndrome, and later numerous names were coined such as bifid rib syndrome, basal cell nevus syndrome, multiple basal cell carcinoma syndrome, and fifth phacomatosis.[3,4] The prevalence of this syndrome is about 1/60,000 live births.[5]

While in 1964, Juan Sotos first described five patients with early excessive growth and distinctive facial appearance calling it cerebral gigantism, later known as Sotos syndrome. It is caused by a gene deletion with an autosomal dominant pattern of inheritance. Characteristic features of Sotos syndrome are cerebral gigantism, hypotonia, and joint hyperextensibility. The incidence of Sotos syndrome is 1/10,000–1/15,000 live births with an autosomal dominant pattern of inheritance.[6]

Case Report

This case report is a nine year old child patient who reported on September 13, 2018, to the Department of Oral and Maxillofacial Surgery of a teaching dental hospital. The chief complaint of the patient as reported by the patient's parents was missing teeth and swelling in the front region of the lower jaw of the mouth for 2 years. The patient had a history of visiting a multispecialty postgraduate institution, when he was around 6 months old in June 2009 because of the disproportionately large head of the patient compared to his body and delayed milestones. He was examined systemically, and was found to have hypotonic muscle, macrocephaly and hepatosplenomegaly. While no seizure activity was observed, an auditory examination revealed that the patient did not respond to verbal stimuli but on subsequent follow-ups his auditory response improved. Computed tomography (CT) scan of the patient revealed thin and gracile corpus callosum and cerebral atrophy. The provisional diagnosis of the patient was Sotos syndrome/overgrowth syndrome or glutaric aciduria Type 1. Based on clinical examination and CT scan, the patient was diagnosed with Sotos syndrome and remained under follow-up there till the age of 2 years [Figure 1].

When the patient was examined in our department [Figure 2], he was found to be well oriented to time, place, and person. No behavioral abnormalities such as autism, phobias or aggression was noted. On general physical examination, he had frontal bossing, increased fronto-occipital

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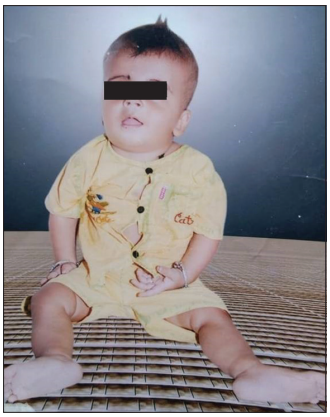

Figure 1: Disproportionate body proportions of the patient

Figure 2: Appearance of the patient when he presented to our department (showing frontal bossing, broad chin)

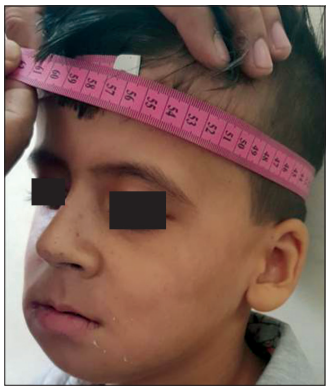

Figure 3: Increased fronto-occipital circumference

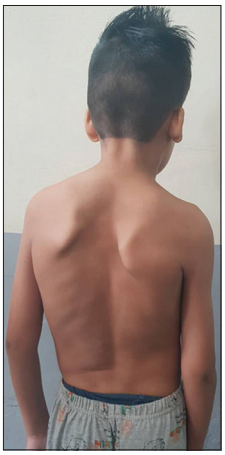

Figure 4: Scoliosis

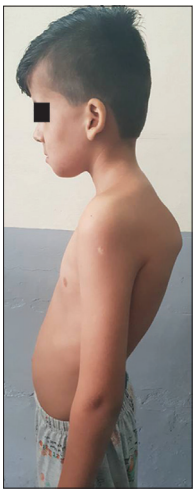

Figure 5: Kyphosis

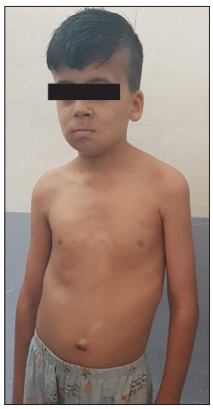

Figure 6: Anterior view of chest and abdomen showing de-pigmented patch near umbilicus

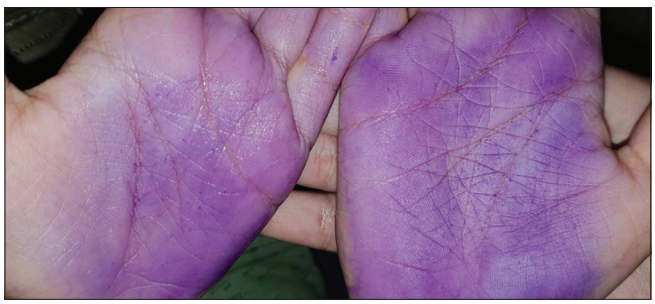

Figure 7: Palmar plantar pits

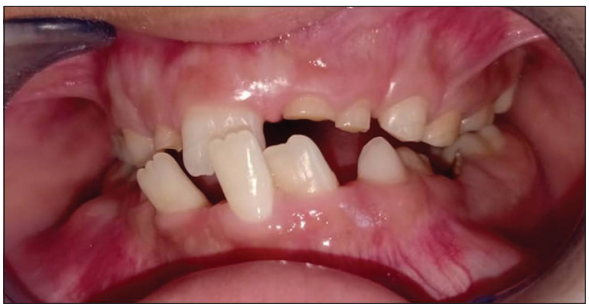

Figure 8: Intra-oral examination

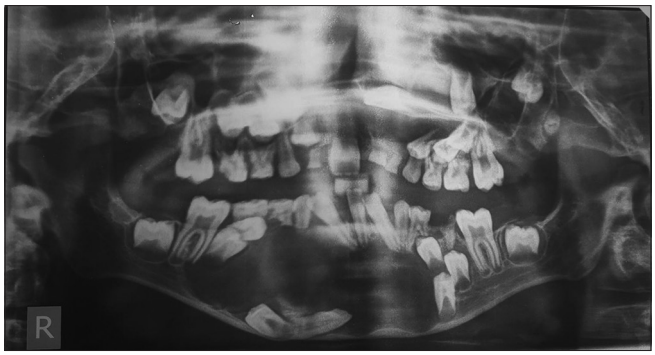

Figure 9: Preoperative orthopantomogram

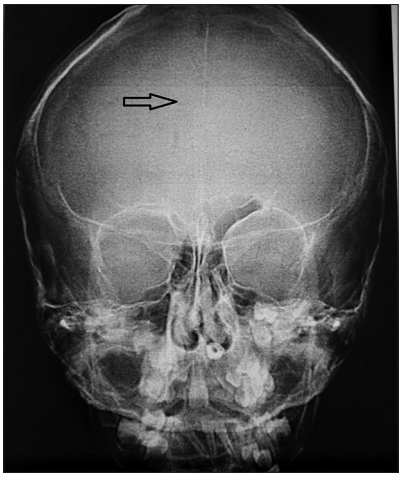

Figure 10: Anteroposterior view of the skull showing falx cerebri calcificatio

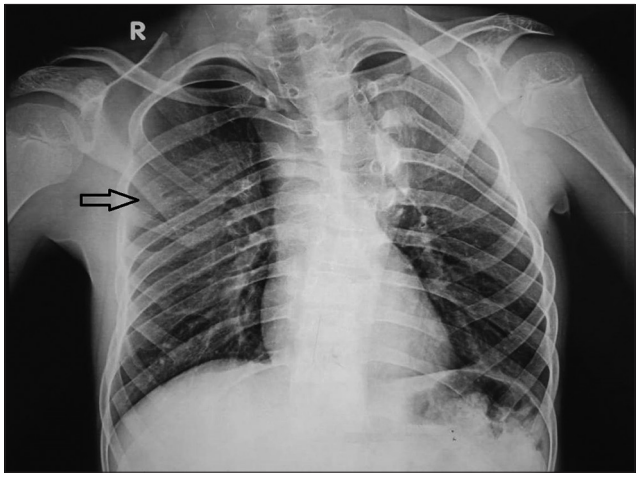

Figure 11: Chest X-ray showing 4th bifid rib on the right side

circumference (56 cm) [Figure 3], sparse hair at frontoparietal region, broad-square chin, kyphoscoliosis and mild pectus excavatus along with hypopigmented areas around his mid chest and umbilical regions [Figures 4-6]. The patient also had umbilical hernia [Figure 6], multiple palmar-plantar pits [Figure 7], muscle hypotonia, and right side testicular atrophy. Oral cavity [Figure 8] appeared to have several missing, decayed, and tilted teeth with overall poor oral hygiene and high-arched palate. The patient presented with swelling in the molar region bilaterally with vestibule obliteration, and the swelling was hard, nontender, and diffuse. The overlying mucosa was normal with no draining sinus.

Based on the clinical findings, differential diagnoses for our patient were Gorlin–Goltz syndrome, Sotos syndrome, Bannayan–Riley–Ruvalcaba syndrome, Cowden syndrome, Fragile X syndrome, glutaric aciduria Type 1, Weaver syndrome, Down syndrome, and Noonan syndrome. Then, radiographic examination was carried out to narrow down our list of clinical differential diagnoses.

The orthopantomogram (OPG) of the patient revealed a mixed dentition stage, a large cystic lesion in the front region of the lower jaw crossing midline with impacted teeth along the lower border of the lower jaw and small cystic lesion along the posterior region of upper jaw on the right side with a single impacted tooth. Upper canine and molars were still descending down toward occlusion and a supernumerary tooth (paramolar) was present in maxilla on the left side [Figure 9]. The lateral skull view and posterior-anterior view skull revealed falx cerebri calcification [Figure 10]. The chest X-ray of the patient revealed bifid and fused 4th rib on the right side [Figure 11].

The overall clinical and radiographic pictures were more supportive toward the provisional diagnosis of Gorlin–Goltz syndrome.

Under general anesthesia, the cyst was marsupialized extending from the mesial surface of 36 to the mesial surface of 46 and iodoform gauge pack given [Figure 12]. While enucleation of cyst was done with respect to the 17 region, the cystic contents and lining were sent for the histopathologic examination, which revealed lining epithelium, stroma with inflammatory infiltrate containing plasma cells and eosinophils [Figures 13-16]. The cyst was diagnosed as OKC with parakeratotic nature. The final diagnosis of Gorlin–Goltz was confirmed on the basis of major and minor criteria.

On follow-up visits, the iodoform pack was changed regularly on a weekly interval to help reduce the size of the cystic cavity such that enucleation can be done at a later stage. After 3 months, soft-tissue healing was satisfactory [Figure 17], and the patient's OPG revealed new bone formation around periphery of the cyst and the teeth that were previously present along the lower border of the mandible were starting to lift up and rise toward occlusion. An obturator was also given to the patient [Figure 18]. Five months later, complete soft-tissue healing was observed, and more new bone was formed on radiographic examination [Figure 19]. After 9-month follow-up, the cyst was regressed in size to be taken up for enucleation. Since the teeth that were supposed to come into occlusion after complete root formation were still embedded within the cyst with no signs of further change in their position, we had to remove them with the cystic lining [Figure 20].

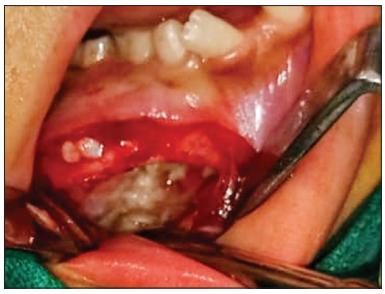

Figure 12: Marsupialization of cyst

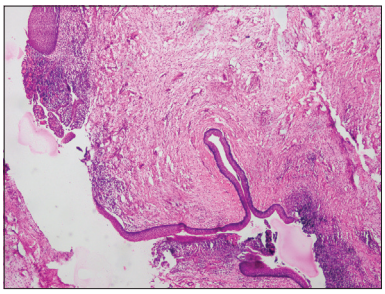

Figure 14: Histopathologic slide showing odontogenic keratocyst

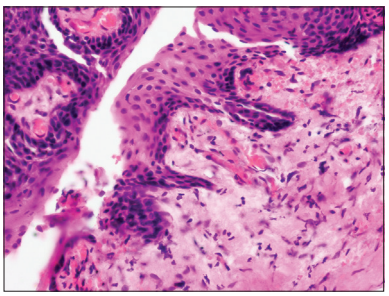

Figure 16: Histopathologic slide showing stroma with eosinophil cells

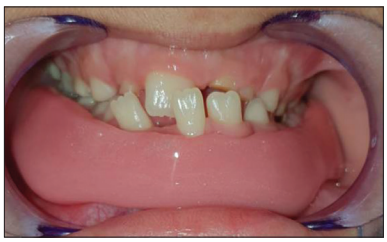

Figure 18: Obturator placed

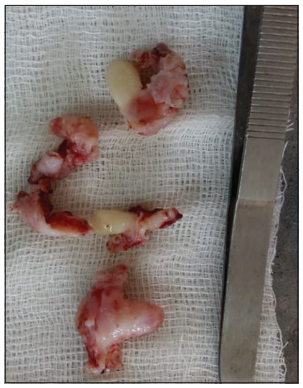

Figure 20: Enucleation of cyst done along with 33, 42, and 43 teeth

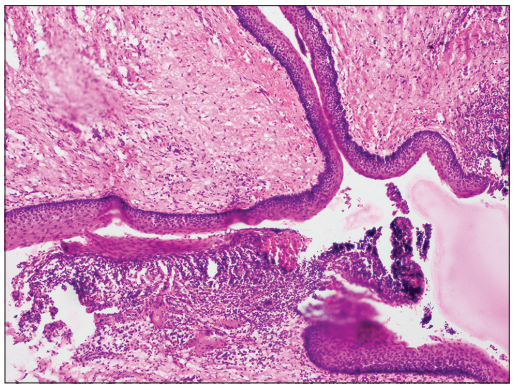

Figure 13: Histopathologic slide showing cyst lining

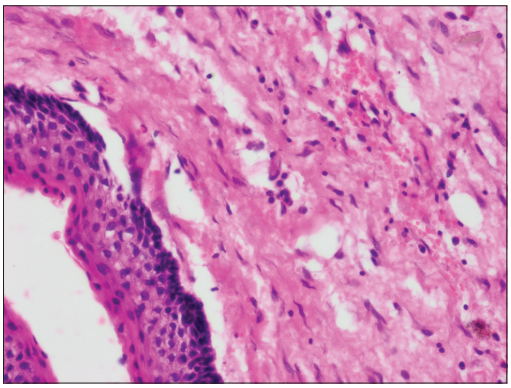

Figure 15: Histopathologic slide showing stroma with plasma cells

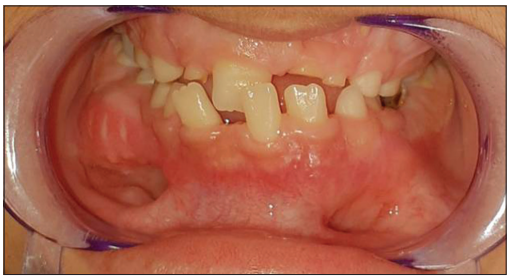

Figure 17: Soft-tissue healing after 3 months

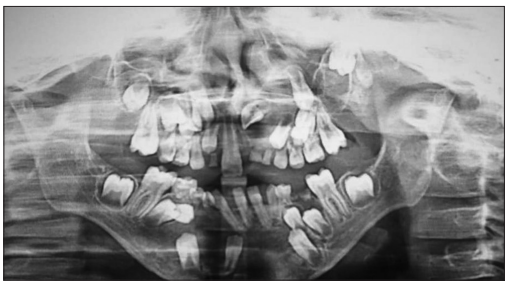

Figure 19: Postoperative radiograph after 5 months

Discussion

The diagnostic criteria for Gorlin–Goltz syndrome were established by Evans *et al*. and modified by Kimonis *et al*. in 1997.[7,8] According to them, the diagnosis of Gorlin–Goltz syndrome can be established when two major or one major and two minor criteria are present as described below.[7-9]

Major criteria

- More than two basal cell carcinoma or one basal cell carcinoma at younger than 30 years of age or ≥10 basal cell nevi
- Any OKC (proven on histology) or polyostotic bone cyst
- Three or more palmar or plantar pits (present in about 65% of patients)
- Ectopic calcification: Lamellar or early at younger than 20 years of age
- Falx cerebri calcification
- Positive family history of nevoid basal cell carcinoma.

Some authors take plurilamellar appearance of the falx cerebri calcification as a pathognomic symptom of Gorlin–Goltz syndrome.[10]

Minor criteria

- Congenital skeletal anomalies such as fused, splayed, missing, or bifid ribs, wedged or fused vertebrae
- Occipitofrontal circumference ≥97%
- Cardiac or ovarian fibroma
- Medulloblastoma
- Lymphomesenteric cysts
- Congenital malformations such as cleft lip or palate, polydactylism, or eye anomalies (cataract, coloboma, and microphthalmos).

Other diagnostic findings in adults with Gorlin–Goltz syndrome are as follows:

i. Skeletal anomalies: Hemivertebrae, scoliosis, syndactyly, polydactyly, and shortened 4th metacarpal
ii. Craniofacial anomalies: Frontal bossing: Increased occipitofrontal circumference; brachycephaly; macrocephaly, coarse face, heavy fused eyebrows; broadened nasal root; calcification of the falxes; tentorium cerebella calcification; bridged sella turcica; low positioning of occiput; congenital blindness due to corneal opacity; congenital or precocious cataract or glaucoma; coloboma of iris, choroids, or optic nerve; convergent or divergent strabismus; and nystagmus
iii. Neurological anomalies: Agenesis/dysgenesis of the corpus callosum, congenital hydrocephalus, meningioma, mental retardation, and schizoid personality
iv. Oropharyngeal anomalies: Cleft lip/palate: high-arched palate or prominent ridges
v. Anomalies of the reproductive system
vi. Cardiac anomalies

The patients with Sotos syndrome present with excessive growth that is global and may reach two or more standard deviations of the percentile with an increased growth rate during the prenatal and first 5 years of life. Height usually normalizes in adulthood. The patients present with coarse face, prominent superciliary arches, antimongloid slant of the palpebral fissures, large and long head with the high bossed forehead, hypertelorism, a square and pointed chin, and macrocephaly.[11] The disorder is associated with developmental delay, hypotonia, joint hyperextensibility, and behavioral and learning disturbances often with mild mental retardation. Scoliosis has also been reported in Sotos syndrome.

The patient in this case report was suspected to have Sotos syndrome when he was around 6 months old at PGI, Chandigarh, where he visited till the age of 2 years. Now, the patient presents with features more pronounced in Gorlin–Goltz syndrome. Our patient satisfied the following criteria:

Major

1. Multiple OKC
2. Palmar and plantar pits (≥3)
3. Ectopic calcification – calcification of the falx cerebri.

Minor

1. Bifid and fused ribs
2. Large head with occipitofrontal circumference being 56 cm and frontal bossing.

Associated finding

1. Testicular atrophy
2. Corpus callosum thin and gracile
3. Scoliosis.

Gorlin–Goltz syndrome is autosomal dominant with high penetrance and variable expressivity. It may seem that the numerous symptoms of this disease make diagnosis a very simple task, but, in fact, it is quite difficult. In our patient, previous reports and diagnosis and present clinical findings are in favor of coexistence/overlapping of Sotos syndrome and Gorlin–Goltz syndrome. The incidence of scoliosis in Sotos syndrome is high, and muscle hypotonia is characteristic of the Sotos syndrome. Furthermore, our patient had associated features such as macrocephaly, increased occipitofrontal circumference, prominent jaw, sparse hair at the frontoparietal region, and high-arched palate. Conversely, this case report might add to the variable expressivity of the Gorlin–Goltz syndrome, that is, the presence of hypotonia of muscles.

Conclusion

Each case should be examined thoroughly to evaluate the variable expressivity of symptoms in both Gorlin–Goltz and Sotos syndrome. Dentist plays a crucial role in the diagnosis of Gorlin–Goltz syndrome since multiple OKC is pathognomonic to this syndrome and might be the first finding toward the investigation of the patient suffering from Gorlin–Goltz syndrome. Such patients must always be treated with a multidisciplinary approach that is a team approach of an oral and maxillofacial surgeon, orthodontist, orthopedic surgeon, dermatologist, and neurosurgeon should be considered. Patients suffering from Gorlin–Goltz syndrome should not have excessive sun exposure, as it triggers the formation of basal cell carcinoma. Periodic follow-up is essential in these patients, because OKC has a tendency to reoccur, especially

if it is parakeratotic in nature, and also we need to avoid basal cell carcinoma formation and further worsening of vertebral deformity in these patients. Follow-up at weekly intervals followed by regular intervals of six months for five years, followed by once annually for the entire life is mandatory for the patient to avoid any other symptom from emerging.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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