Case study

Peri-apical sinus, a leading edge of Gorlin–Goltz syndrome: Case report

ABSTRACT

Gorlin–Goltz syndrome is an autosomal dominant disorder, with mutations in the patched tumor suppressor gene (PTCH1) leading to a wide range of developmental anomalies and neoplasms of cutaneous, dental, osseous, ophthalmic and neurological origin. It commonly presents as multiple keratocystic odontogenic tumors (KCOTs) of the jaws, basal cell carcinomas (BCC) of skin, calcifications of the falx cerebri, ocular hypertelorisms, palmar-plantar pits, bridging of sella turcica and macrocephaly. In addition to these major criteria, more than 100 minor criteria have been described. We hereby, present one such case of Gorlin-Goltz syndrome reported to our dental clinic in Jabalpur, India. A 20 year old male patient presented with complaint of foul fluid discharge from a peri-apical sinus of an over retained, mobile Deciduous Maxillary left canine tooth. Patient’s general physical examination revealed macrocephaly, wide nasal bridge, ocular hypertelorism, numerous naevi and a sebaceous cyst. Panoramic and CT examinations revealed presence of multiple keratocystic odontogenic tumors (KCOT) in both the jaws, bridging of sella turcica, patchy calcifications of falx cerebri and tentorium cerebelli.

Though, multi-disciplinary examination revealed no evidence of neoplasm, multi-disciplinary treatment along with genetic counseling was provided to the patient. Life long surveillance was offered to prevent future morbidity and mortality associated with this syndrome. This case, illustrates the importance of thorough dental and physical examination including examination of draining oral sinuses, missing teeth, deciduous teeth, macrocephaly and frontal bossing. Additionally, detailed investigations in patients with lesions suggestive of aberrant phenotypic characteristics are mandatory.
Keywords: Gorlin-Goltz syndrome; Keratocystic odontogenic tumor; Basal cell carcinoma, NBCCS

1. INTRODUCTION

Gorlin–Goltz syndrome (GGS) also known as nevoid basal cell carcinoma syndrome (NBCCS) is a rare hereditary condition characterized by a wide range of developmental anomalies and predispositions to neoplasm [1]. Multiple keratocystic odontogenic tumors (KCOT), basal cell carcinomas (BCC), palmar/plantar pits, ectopic calcifications of the falc cerebri, bridging of sella turcica are some of the pathognomonic major criteria. Additionally, more than 100 minor criteria like hypertelorism, syndactyly and dermoid cysts have been described [1]. Recent genetic studies have suggested the markers such as patched tumor suppressor gene (PTCH1, PTCH2) and suppressor of fused homolog (SUFU) to be responsible for this syndrome. Mutation in specifically, PTCH1 gene has been established as primary etiologic factor for this syndrome [2].

The estimated prevalence varies from 1/57,000 to 1/256,000, with a male-to-female ratio of 1:1 [1]. This syndrome has been reported in all the ethnic groups [3]. We hereby report one such case of Gorlin-Goltz syndrome with a variety of interesting clinical, radiographic and microscopic features.

2. PRESENTATION OF CASE

A 20 year old male patient reported to one of the author’s private dental clinic in Jabalpur (M.P), India (Fig. 1A). He presented with the chief complaint of foul fluid discharge from upper left anterior teeth region since one month with an accompanying symptom of moderate pain since 7 days. Past medical history and family history were non-contributory. Clinical examination revealed over retained Deciduous Maxillary left canine tooth with grade I mobility and it was suspected to be the source of infection. Permanent Maxillary left canine (Fig. 1B) and Mandibular right canine teeth (Fig. 1C) were missing on clinical examination. Retained Deciduous Maxillary left canine tooth was extracted under local anesthesia. In addition; both Mandibular third molars were also missing. For further evaluation both, peri-apical and panoramic radiographs were advised. Panoramic radiograph revealed presence of multiple cystic lesions in both the jaws (Fig.2). Permanent Maxillary left canine tooth was found to be impacted and lying very high in the cystic cavity involving left maxillary sinus. Permanent
Mandibular right canine tooth was also found to be impacted and lying in the cystic cavity which crossed the midline. Oral radiologist opinioned in favor of Gorlin-Goltz syndrome and advised few more radiographic examinations along with CT examination of head and neck.

Fig.1. A. Frontal view of the patient. B. Maxillary arch with a missing left canine tooth. C. Mandibular arch with a missing right canine tooth

Fig.2. Panoramic radiograph showing multiple KCOT's with impacted teeth
Patient’s general physical examination revealed macrocephaly, wide nasal bridge and ocular hypertelorism (Fig. 1A). Dermatologist confirmed the presence of numerous nevi on the chest (Fig. 3A) and sun exposed areas of face (Fig. 3B). Additionally, skin tags were also present around the neck (Fig. 3C). Otolaryngologist confirmed the presence of single well defined sebaceous cyst over left pinna (Fig. 3D).

Fig. 3. A. Multiple naevi on chest. B. Multiple naevi on face. C. Sebaceous cyst on Pinna. D. Skin tags on the neck

Conventional radiography and imaging science revealed presence of five (multiple) well circumscribed, unilocular, corticated KCOTs of various sizes with impacted teeth in both the jaw bones. Furthermore, CT images also demonstrated bridging of sella turcica (Fig. 4A), patchy calcifications of falx cerebri and tentorium cerebelli (Fig. 4B).
Fig. 4. A. CT scan showing bridging of *sella turcica* and calcifications of medulla. B. CT scan showing calcification of *falx cerebri* (arrow) and *tentorium cerebelli*.

Oral surgeon enucleated all the KCOT's (multiple) and specimens were subjected to histopathological examination. Oral pathologist confirmed the presence of multiple KCOT's. Histopathological features demonstrated presence of connective tissue wall enclosing a cystic space lined by *para-keratinized stratified squamous* epithelium of uniform thickness with tall columnar hypochromatic and pallisaded basal cells. Surface corrugations were also evident (Fig. 5).

Fig. 5. Histo-pathological examination depicting features of para-keratinized KCOT.

Based on history, clinical, radiographic and microscopic data; a diagnosis of Gorlin-Goltz syndrome was established. However, imaging played a pivotal role in diagnosis of this syndrome.
3. DISCUSSION

Gorlin-Goltz syndrome was first recognized in 1894 by Jarisch and White [2]. Later on Dr. Robert Gorlin and Dr. Robert Goltz (1960) studied its clinical features [5]. This remarkable syndrome is also known by other names. The common names are Nevoid basal cell carcinoma syndrome (NBCCS), Gorlin syndrome, Basal cell nevus syndrome (BCNS) and fifth phacomatosis [1].

GGS often presents itself in an early age. Multiple basal cell carcinomas (usually on the face, beginning early in life) and multiple KCOTs (also beginning early in life) are the main hallmarks of this syndrome; however, there are other manifestations that are grouped into the following five categories [1].

(A) Cutaneous anomalies: basal cell nevus, other benign dermal cysts and tumors, palmar/plantar pitting, palmar/plantar keratosis and dermal calcinosis.

(B) Dental and osseous anomalies: multiple keratocystic odontogenic tumors (KCOTs), mild mandibular prognathism, frontal and temporo-parietal bossing, kypho-scoliosis or other vertebral defects, bifurcated ribs, spina bifida and brachy-metacarpalism.

(C) Ophthalmic anomalies: hypertelorism, wide nasal bridge, dystopia canthorum, congenital blindness and internal strabismus.

(D) Neurological anomalies: mental retardation, dural calcification, bridging of sella, agenesis of corpus callosum, congenital hydrocephalus, occurrence of medulloblastoma.

(E) Sexual anomalies: hypogonadism and ovarian tumor-like fibrosarcoma.

Gorlin-Goltz syndrome is often diagnosed by the major and minor criteria proposed by Evans et al (1993), which were later modified by Kimonis et al (2004). According to them presence of two major criteria and one minor or one major and three minor criteria are necessary to establish the diagnosis [5, 6]. (Table 1)
### Table 1. Major and minor criteria for establishing the diagnosis of Gorlin-Goltz syndrome

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Multiple basal cell carcinomas or one occurring under the age of 20 years.</td>
<td>1. Macrocephaly (adjusted for height).</td>
</tr>
<tr>
<td><strong>2.</strong> Histologically proven KCOTs of the jaws.</td>
<td>2. Congenital malformation: cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism.</td>
</tr>
<tr>
<td><strong>3.</strong> Palmar or plantar pits (three or more).</td>
<td>3. Other skeletal abnormalities: sprengel deformity, marked pectus deformity, marked syndactily of the digits.</td>
</tr>
<tr>
<td><strong>4.</strong> Bilamellar calcification of the falx cerebri.</td>
<td>4. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemi-vertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet or flame shaped hands or feet.</td>
</tr>
<tr>
<td><strong>5.</strong> Bifid, fused or markedly splayed ribs.</td>
<td>5. Ovarian fibroma</td>
</tr>
<tr>
<td><strong>6.</strong> First-degree relative of nevoid basal cell carcinoma syndrome patients.</td>
<td>6. Medulloblastoma</td>
</tr>
</tbody>
</table>

The mutations in PTCH and SUFU gene have been seen to be involved in the etio-pathogenesis of GGS. PTCH1 gene is mapped to long arm of chromosome 9(q22.3-q31), with no heterogeneity. The PTCH1 gene provides instructions for producing the patched-1 protein, which functions as a receptor for a protein called sonic hedgehog, a ligand for this receptor. Together, they trigger signals that play a role in cell growth, cell specialization and determine the patterning of different parts of developing body. Mutation in PTCH1 gene prevents the production of patched-1 or leads to the production of an
abnormal version of the receptor. An altered or missing patched-1 receptor cannot effectively suppress cell growth and division. As a result, cells proliferate uncontrollably to form the tumors that are characteristic of GGS. In addition mutations in PTCH2 and SUFU gene (located on chromosome 10q24.32) have been associated with GGS in the absence of mutation in PTCH1 gene. As all of these three genes belong to sonic hedgehog pathway, whether mutations in a single gene or a combination of these genes is probably responsible for the various manifestations of NBCCS needs to be further studied. Furthermore, a new treatment strategy based on the understanding and inhibition of the hedgehog pathway can provide for specific drug treatment of disease in future, to suppress tumor growth [2, 7].

This case matched two major criteria (Viz. histologically proven multiple KCOTs of jaws and bilamellar calcification of the falx cerebri) and many minor criteria (viz. macrocephaly, wide nasal bridge, hypertelorism, multiple naevi, sebaceous cyst, impacted teeth, mandibular prognathism, high arched palate, bridging of sella turcica and calcification of tentorium cerebelli and meningis). There was more than adequate evidence for the diagnosis, in our case.

Ectopic calcifications of falx cerebri tend to occur in (70-85%) and tentorium cerebelli in (20-40%) of the patients according to the reports worldwide [8]. Around 85% of individuals with this syndrome will demonstrate palmar/plantar pits by the age of 20 years [9]. The case presented here, had two major criteria; however, BCCs and palmar/plantar pits were missing. BCCs are more common in the adult life; peak incidence would be third decade of life[10].

Multiple nevi would be present in 30-50% of patients under 20 yrs of age. Presence of skin tags around the neck is also one of the features of Gorlin-Goltz syndrome. Benign dermal cysts like sebaceous cyst can be found around the face in 30% of the cases [1]. Macrocephaly has been reported in 5-80% of the cases [1]. Hypertelorism is usually found in 6-78% of the patients with Gorlin-Goltz syndrome [11]. Though bridging of sella turcica (70-85%) and calcification of tentorium cerebelli (20-40%) is frequently reported; however spotting of meningeal calcifications in such patients is very rare in literature [8].

KCOTs are the most consistent and common feature of Gorlin-Goltz syndrome, evidenced in 65 to 100% of the affected individuals and are the first sign of GGS in 78% of the cases [1]. Although
benign, the recurrence rate after excision of KCOT is high, ranging from 12% to 62.5% and multiple recurrences does occur, often resulting into jaw deformities after multiple surgeries. Thus, an annual dental panoramic radiograph is usually suggested between the ages of 8 and 40 years. A recurring cyst can be a new cyst that originates from epithelial residue or a micro-cyst left behind in the overlying mucosa. It is believed that the aggressive behavior and high rate of recurrence of KCOT are due to a higher rate of proliferation of the epithelial lining [3].

KCOT characteristically grows along the cancellous bone with very little cortical expansion. Intraluminal hyperosmolality, active epithelial proliferation, collagenolytic activity of the cyst wall and synthesis of interleukin-1 (IL-1) and Interleukin-6 by keratinocytes are the various theories for its pathogenic expansion. These stimulate secretion of keratocyte growth factor and tumour necrosis factor, which in turn increases levels of prostaglandins and parathyroid related proteins. It has also been seen that the release of inflammatory cytokines such as IL-1 from the epithelial cells tends to activate the resorption of bone around the lesions by stimulating osteo-clastogenesis and activation. Additionally, autophagy, activated during tumour development, and having a significant role in anti-apoptosis and proliferation of tumour cells is a significant finding in KCOTs [12].

There is little evidence that IHC is helpful in the diagnosis of KCOT or GGS in particular. The profile of cytokeratin (CK) expression in KCOT is similar to that found in other odontogenic cysts (high molecular weight CKs and CK19 are common). Furthermore, they express CK1 and CK10, which are markers of cornification. KCOT show increased mitoses and Ki-67 expression compared to other cyst types with expression above the basal layers being characteristic. This finding and evidence of reduced PTCH protein expression may be a marker for KCOT, which may provide evidence of neoplastic origin, or may distinguish syndromic from non-syndromic cysts. There is some evidence emerging that anti-apoptotic markers, including bcl-2 and BAX, may be specifically increased in KCOT, but this needs confirmation and their diagnostic value has not been established [13].

The neoplastic nature and biological potential of sporadic and nevoid basal cell carcinoma syndrome (NBCCS)-associated KCOT were analyzed. 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. Intense gene and protein expressions have been observed in KCOT associated with NBCCS, as compared with sporadic ones. So, heparanase expression may be correlated with the neoplastic properties of KCOT, particularly in NBCCS-associated cases [14, 15].
The importance of this syndrome lies in some of its serious prognosis. Morbidity in GGS is associated with the complications. The main problem is related to the aesthetic aspect, in relation to the development of multiple skin tumors which can cause a significant deformity of the face. The cosmetic concern may cause low self-esteem in the patient and may result to social dilemmas. Ameloblastomatous and carcinomatous changes are known to have developed in the jaw cysts, but GGS rarely results in premature death (10%), if it does, the death is usually caused by medulloblastoma. Although seen in 2-5% of GGS patients, most of the associated medulloblastoma are desmoplastic lesions with a milder course and better prognosis [16]. In addition, X-ray therapy of invasive basal cell carcinomas leads to secondary dissemination and re-initiates carcinogenesis of skin lesions, which in effect increases the mortality in such cases [3].

More aggressive form of management, enucleation with meticulous curettage was performed. Genetic counseling was provided to the patient. Patient is on life-long surveillance, physical examination after six month of surgery revealed no evidence of recurrence or any associated morbidity. Panoramic radiographs and a multidisciplinary examination are scheduled for 1 year, post-operatively (to prevent unnecessary radiation exposure). Pre-cautiously, patient was advised to stay away from prolonged sun exposure (to avoid ultraviolet radiations). In addition, regular follow up by multi-specialists team was explained to be mandatory to prevent secondary morbidity and complications.

This is a rare case report from India, well-consistent with the clinical features of GGS. In the absence of official data regarding the prevalence of GGS in India, Medline search reported 48 cases of the Gorlin-Goltz syndrome published from India, till now [2, 3, 17, 18]. This most probably represents rarity in incidence or under-recognition due to inadequate dental facilities in rural areas or incomplete examination by the clinicians in our country.

4. CONCLUSION

This case illustrates the importance of a thorough examination and detailed investigations in our routine patients to prevent them from secondary morbidities and mortalities.

8. CONSENT
All authors declare that written informed consent was obtained from the patient for publication of this case report with accompanying images.

9. ETHICAL APPROVAL

The Health Research and Ethical Committee of the Hitkarini Dental College and Hospital gave approval for this report to be written. Written informed consent of the patient in question, was obtained before proceeding.

10. REFERENCES


