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Gorlin Goltz Syndrome -A rare Disease reported in Bangladesh

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ABSTRACT:

A rare multisystemic disease with an autosomal dominant characteristic, Gorlin Goltz syndrome has a wide range of expressivity and complete penetrance. Gorlin Goltz Syndrome is a rare autosomal disorder with a high penetrance level that is characterized by an elevated propensity for basal cell carcinoma. Here, we present a case of a 60-year-old patient who had positive results for the Gorlin-Goltz syndrome. The emphasis of the following study is on the identification of all relevant clinical diagnostic criteria, radiological manifestations, and potential genetic testing that must be carried out in order to establish an appropriate treatment strategy.

Keywords: Gorlin Goltz Syndrome, Odontogenic Keratocyst, PTCH Gene

INTRODUCTION

An uncommon autosomal dominant variant condition known as Gorlin Goltz Syndrome is brought on by a mutation in the PTCH (patched) gene on chromosome arm 9q. A rare multisystemic disease with an autosomal dominant characteristic, Gorlin Goltz syndrome has a wide range of expressivity and complete penetrance.[1] There have been very few reports of Gorlin Goltz Syndrome in Bangladesh. Other names for this condition include Jaw cyst Bifid Rib Syndrome, Multiple Nevoid BCC Syndrome, Gorlin Syndrome, and Multiple Nevoid Basal Cell Epithelioma. According to several research, the estimated prevalence ranges from 1/57,000 to 1/256,000 with a male to female ratio of 1:1.[1]

Numerous intracranial ectopic calcifications of the falx cerebri, multiple odontogenic keratocysts (OKC), multiple BCCs, skeletal, dental, ophthalmic, and neurological abnormalities, as well as facial dysmorphism, are its defining features.[4]

Many major and minor criteria can be used to diagnose Gorlin Goltz syndrome.The presence of 2 major and 1 minor criteria or presence of 1 major and 3 minor criteria are necessary for establishing the case .[2,4,7] To avoid the severe consequences that can follow skin cancer and other tumors linked to the condition, an early diagnosis is crucial. Additionally, our example highlights the importance of a dental surgeon in developing a timely diagnosis and providing patient care. multidisciplinary approach.

CASE REPORT

A 60-year-old male patient was reported to the oral and maxillofacial surgery OPD at Update Dental College and Hospital in Turag , Dhaka. The patient complained of swelling in his lower jaw, which was accompanied by some creamy discharge from the gingival sulcus of his teeth.

Patient was a known case of hypertension which he was undergoing treatment. Patient was asked about other Cardiovascular disorder, neurological abnormalities, allergies with no relevant history. Without further investigation, however ,family history revealed a 13 year old boy with identical frontal and parietal bossing, a larger fronto-occipital circumference and a mild mandibular prognathism (figure 4).

Patient's face is bilaterally symmetrical with frontal and parietal bossing and slight mandibular prognathism with diffuse extra oral swelling.(figure 1)Flattened Nasal Bridge, hypertelorism, and increased fronto-occipital circumference (60 cm) are revealed from frontal view and lateral view accordingly.

Figure 1 (left side): Patient's extra oral examination showing Wide nasal Bridge and diffuse anterior mandibular swelling. Figure 2- Lateral view of the patient showing slight mandibular prognathism and increased fronto-occipital circumference

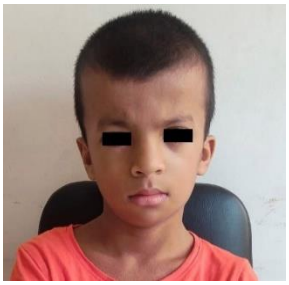

Figure 3 (left side): Front view showing frontal bossing and mandibular diffuse swelling in the left anterior side of the mandible. Figure 4: Patient's Son showing similar frontal bossing with increased frontal occipital circumference and wide nasal bridge

On Intra oral examination of the mandible there was pus present in gingival sulcus (figure 5)and no evidence of any carious teeth and internal swelling have been reported. Patient was also suffering from chronic gingivitis with poor oral hygiene.

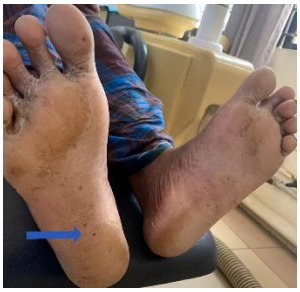

Figure 5 (Left side) : Intraoral examination showing pus in the gingival and buccal sulcus with gingival swelling. Figure 6: 3-4 plantar pits found on both plantar area.

Patient have been examined thoroughly and the evidence of skin lesions in the form of Plantar pits (figure 6) have been reported with no sign of basal cell carcinoma. The Orthopantomogram (OPG) shows(figure 7) multiple radiolucency in the anterior mandible of both left and right side in relation to 31,32,33 and 41,42,43,44, 45 and also radiolucency found in posterior maxilla of both side associated with unerupted 3rd molar.

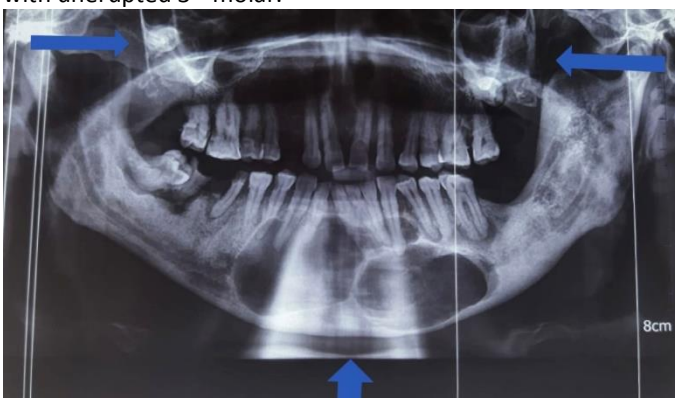

Figure 7: OPG showing multiple radiolucency with corticated margin in anterior mandible and also radiolucency with impacted 3rd molar in maxilla of both side.

Falx cerebri calcification is seen in the axial view of a CT scan of the maxillofacial region (Figure 8). Additionally, a PA view of the patient's chest X-ray was taken; however no sign of fused/bifid ribs have been found.

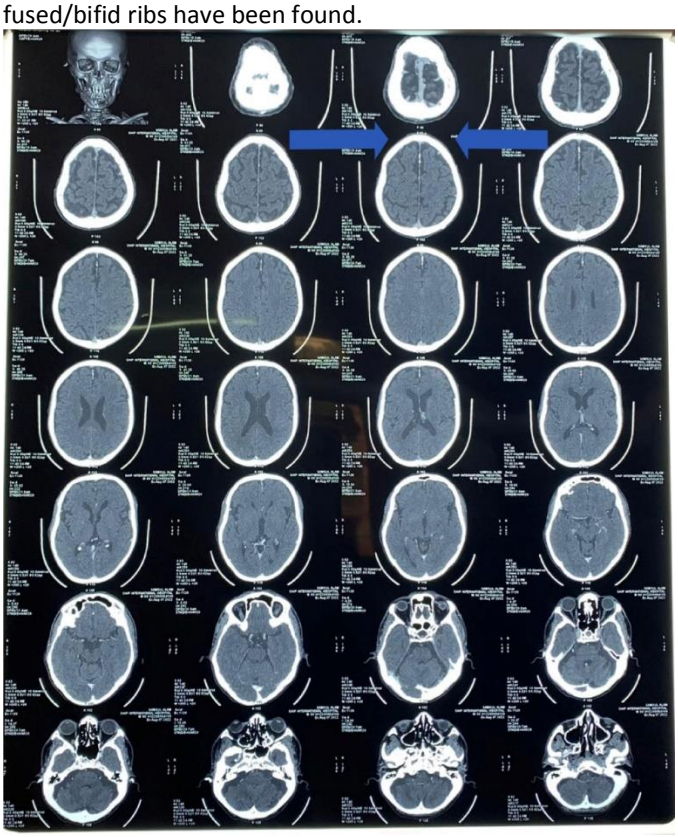

Figure 8: Axial View of the CT scan of the skull showing calcification of falx cerebri in the 3rd column of the 2nd row.

A provisional diagnosis of Gorlin Goltz syndrome based on

Patient's history, clinical findings, and radiological findings have been given. Regular hematological and biochemical investigation has been conducted. The patient was admitted to the hospital. Under all aseptic precaution General Anesthesia was administrated. Local Anesthesia with adrenalin was injected and crevicular incision was given followed by reflection of flaps intraorally both in maxilla and mandible. A surgical bony window was created using slow speed micromotor using tungsten carbide burs with frequent irrigation of normal saline.

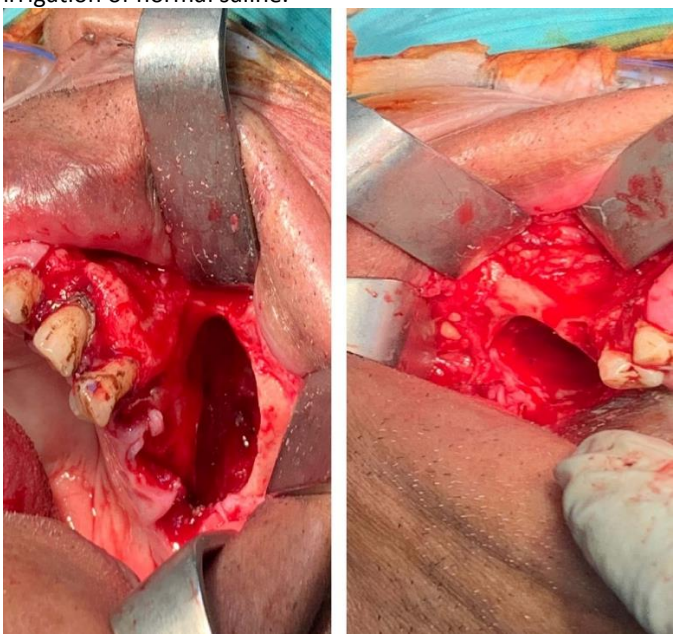

Figure 9: Enucleation of the maxillary cysts of both side with extraction of impacted 3rd molar.

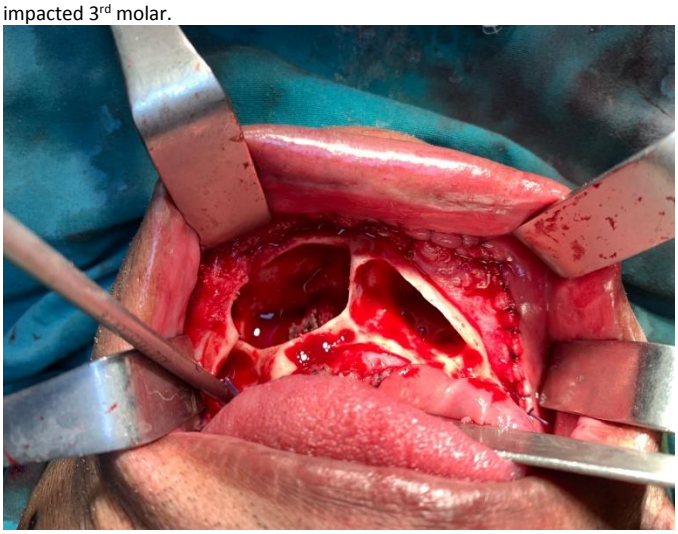

Figure 10: Enucleation of mandibular cysts.

Cysts were then enucleated along with its complete lining from maxilla (both side) and mandible(Figure 8&9) followed by extraction of teeth in the mandible from lower right 3rd molar to lower left 1st molar (due to lesion involvement and poor periodontic condition) and the unerupted maxillary 3rd molars.

The Specimen from both maxilla and mandible were fixed in 10% formalin and sent to the Pathology department for histological examination. All the specimens were sectioned and studied using hematoxylin and eosin stains. And all three lesions were diagnosed as Odontogenic Keratocysts.

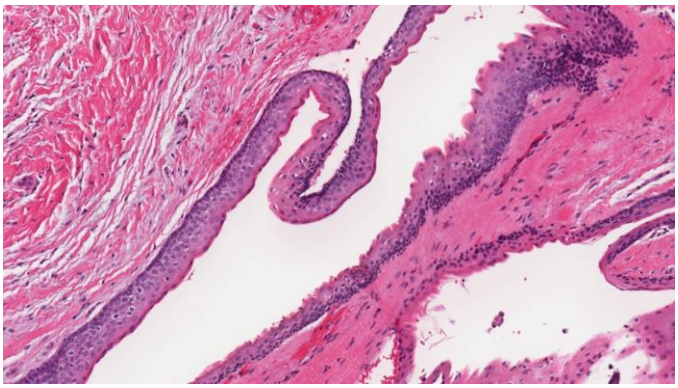

Figure 11 : H&E stained photomicrograph showing cystic lumen lined by corrugated parakeratinized stratified squamous epithelium of 6-8 cell thickness with epithelial folding with basal palisading nuclei.

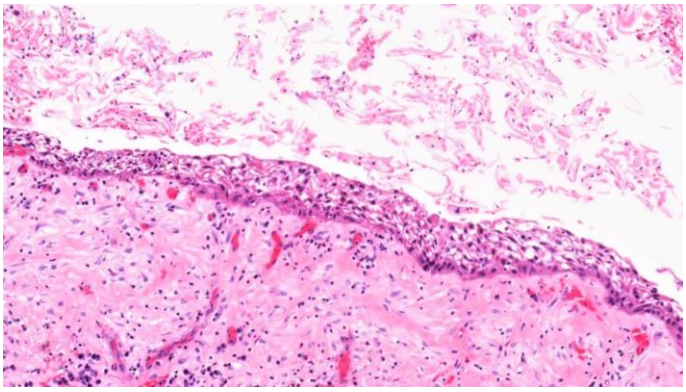

Figure 12 : H&E stained photomicrograph showing epithelial connective tissue separation where the connective tissue contains blood vessels and inflammatory cells.

DISCUSSION

There are numerous important diagnostic criteria that must be considered while making a diagnosis. The diagnosis is made after considering the major and minor clinical and radiological findings, which are ideally confirmed by Deoxyribonucleic acid (DNA) analysis.[4] Jarisch and White described the syndrome for the first time in 1894 in a patient with Multiple BCC, scoliosis, and learning disability. The classical triad was discovered in 1960 by Robert James Gorlin and William Goltz (Multiple basal cell epitheliomas ,keratocysts of the jaws and bifid ribs.) Rayner et al. later modified the triad to include the cysts appearing concurrently with calcification of the falx cerebri or palmar or planter pits in order to finalize the diagnosis. [8]

Fardon et al. estimated a prevalence of 1 in 57,000 people. According to Shanley et al. in Australia and Lo Muzio et al. in Italy, the prevalence is 1 in 64,000 and 256,000, respectively.

Whereas according to Evans et al., the prevalence rate in the United Kingdom is 1 in 560,000. [7,8,10]

The pathogenesis of Gorlin Goltz syndrome is thought to be the result of PTCH gene mutations. The loss of the PTCH1 gene (tumor suppressor gene), which is part of the *Hedgehog* signaling pathway, is attributed to be the primary cause of GGS. [1,2]This gene is involved in tumor suppression, the cellular cycle, and embryonic development.[12]The gene was discovered in 1996 as the human homologue *Drosophilia* , which was mapped to the long arm of chromosome 9q22.3-q3. Homozygous PTCH inactivation causes tumorigenesis and the development of BCC and other neoplasms. Recently, patients with Gorlin Goltz Syndrome were found to have suppressor of fused gene (SUFU) on chromosome 10q and PTCH2 on chromosome 1p.

The pathogenesis of Gorlin Goltz syndrome is attributed to be the consequences of the abnormalities in PTCH gene . The loss of PTCH1 Gene (tumor suppressor gene) which is a part of *Hedgehog* signaling pathway is caused to be the main reason of the molecular basis of GGS .[1,2]This gene plays an important role tumor suppression, cellular cycle and embryonic development.[12] The Gene was first isolated in 1996 as the human homologue *Drosophilia* mapped to the long arm of chromosome 9q22.3-q3. Homozygous inactivation of PTCH leads to tumorigenicity and the formation of BCC and other neoplasms. Recently suppressor of fused gene (SUFU) on chromosome 10q and PTCH2 on chromosome 1p have been found in patient showing the criteria of Gorlin Goltz Syndrome.[11] In general, two distinct episodes of DNA damage are required for a tumor suppressor gene to be inactivated.[3]The first hit involves a mutation in one allele that can be inherited dominantly and has no phenotypic effect. The second hit, such as ionizing radiation or ultraviolet light, involves the mutation of another allele. Inactivation of both alleles results in tumorigenicity. [1,3]

The clinical manifestation can be categorized in these following sections.[8]

A. *Cutaneous Anomalies :* Basal Cell Carcinoma (50-97%),other benign dermal cysts, palmar and plantar pitting (90%), palmar and plantar keratosis.

B. *Dental Anomalies :* Multiple odontogenic keratocysts , (75-100%),mild mandibular prognathism, cleft lip and palate, impacted teeth high arched palate.

C. *Craniofacial Anomalies :* Calcification of Falx cerebri(35-75%), bridging of Sella turcica (21%), macrocephaly (40%),parietal and temporal bossing and coarse face (50%).

D. *Skeletal Anomalies:* Bifid/fused/splayed ribs(26%), scoliosis, polydactyly ,syndactyly,.

E. *Opthalmic Anomalies :* hypertelorism (40%), wide nasal bridge ,congenital blindness, dystopia canthorum and internal strabismus.

F. *NeurologicalAnomalies :* Mental retardation, dural calcification, congenital hydrocephalus, medulloblastoma.

G. *Sexual Anomalies:* Hypogonadism, ovarian tumor like fibrosarcoma.

Diagnosis is usually based on major and minor criteria which were first established by Evans et al. and later were modified by Kimonis et al.in 2004.[10] The presence of 2 major and 1 minor or 1 major and 3 minor criteria are essential for establishing the diagnosis.[2,4,7] The major and minor criteria are described below.[4,8,10]

Major Criteria :

1. Multiple Basal cell carcinoma or one occurring under the age of 20 years.
2. Histologically proven OKCs of the jaws.
3. Palmar or plantar pits (three or more)
4. Bilamellar calcification of the falx cerebri.
5. Bifid ,fused or markedly splayed ribs
6. First degree relative with nevoid Basal Cell Carcinoma Syndrome.

Minor Criteria :

1. Macrocephaly (adjusted for height)
2. Congenital malformation :Cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism.
3. Other skeletal abnormalities :sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
4. Radiological abnormalities**:** bridging of the sella tursica , vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet or flame shaped hands or feet.
5. Ovarian fibroma
6. Medulloblastoma

Genetic testing of PTCH1 is suggested for the following reasons [6]

1. Diagnosis confirmation in patients lacking sufficient clinical diagnostic criteria
2. Predictive testing for patients at risk with an affected family member but not meeting clinical criteria
3. Prenatal testing if there is a known familial mutation

The suggested Molecular genetic tests in Gorlin Goltz Syndrome are [6]

1. Gene Sequence Analysis of PTCH1
2. Gene Deletion/duplication analysis of PTCH1
3. Gene Sequence analysis of SUFU
4. Gene deletion/duplication analysis of SUFU

Investigation protocol suggested by Muzio[8,9]

- Family History-past medical and dental history
- Clinical Examination- Oral, skin, head circumference, interpupillary distance, respiratory system, skeletal system, genitourinary system, cardiovascular system
- Genetic testing

- Radiographs-Chest anteroposterior (AP)view and lateral skull view, panoramic radiograph, cervical and thoracic spine (AP and lateral), ovarian ultrasound (female) for ovarian fibroma and echocardiogram(children) for cardiac fibroma.

Diagnosis is established in our patient based on 3 major criteria (Presence of Multiple OKC of the jaws -histologically proven, calcification of falx cerebri and presence of plantar pits) and 3 minor criteria (frontal bossing, wide nasal bridge and hypertelorism) following the above mentioned investigations.

Appropriate Gorlin Goltz syndrome management is dependent on early diagnosis, a complete family history, and a thorough evaluation of clinical and radiological findings. In the case of OKC, various techniques may be used to prevent recurrence, which can occur in up to 62% of cases. The following factors must be considered when deciding which treatment technique to use: lesion size, extension, location, patient age, possible cortical and soft part damage, and whether the lesion is primary or recurrent. The treatment method can range from simple enucleation to curettage, curettage with peripheral osteotomy, or osseous resection.

Based on the understanding of the Hh signaling pathway and the premise that tumors arise as a result of its overactivity. A new treatment strategy proposes that inhibiting this pathway with specific pharmacological treatment may suppress tumor growth.[12]

CONCLUSION

GGS is a rare autosomal dominant disorder involving multiple systems. Not many cases have been reported in Bangladesh, hence we report here this rare case and the methodical approach in the management of the case through proper intraoral, extraoral examination along with proper evaluation of radiological and histological findings. Genetic Counselling in family members of patient with GGS as in the above mentioned case who have a son of similar symptoms in whom diagnosis is possible but not confirmed helps to detect necessary diagnostic criteria and also helps in early diagnosis followed by improving the survival through proper directed treatment.

DECLARATION OF CONSENT OF THE PATIENT

The authors attest that they obtained all necessary patient consent forms. The patient has given his consent in the form for his images and other clinical information to be published in the journal. The patients are aware that their names and initials will not be published, and that all reasonable efforts will be made to keep their identities hidden.

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