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Gorlin-Goltz Syndrome - Case Report and Literature Review Emphasizing on Diagnostic Methods

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ABSTRACT

Gorlin-Goltz syndrome (GGS) is a hereditary cancer syndrome with dominant inheritance caused by mutations in the PTCH1 gene, responsible for encoding a transmembrane receptor that interacts with the SHH signaling protein. This Hedgehog signaling pathway is essential for cell division and growth, for controlling the development of vertebrates' organs, for differentiating fingers, and for the formation of the brain, spinal cord, eyes, and teeth. When the PTCH gene is homozygously inactivated, cancerogenesis ensues, resulting in the development of numerous basal cell carcinomas and other neoplasms. Other than major anomalies such as multiple basal cell carcinomas, odontogenic keratocysts of the jaw, multiple palmar or plantar pits, bilamellar calcifications of falx cerebri and tentorium, Bifid or fused, or markedly splayed ribs, more than 100 minor anomalies have been described so far. Radiological investigations and genetic testing plays a major role in early diagnosis of this syndrome. We have presented a 19-year-old male patient who presented with multiple odontogenic keratocyst and eventually diagnosed to be GGS. we have also summarized GGS anomalies recorded so far along with differential diagnosis.

Key Words:

Nevoid, Basal, Carcinoma, Odontogenic, Keratocyst, Syndrome

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1. Introduction

Gorlin syndrome, also referred to as Gorlin-Goltz syndrome (GGS), basal cell nevus syndrome (BCNS), or nevoid basal cell carcinoma syndrome (NBCCS), is a hereditary cancer syndrome with dominant inheritance [1]. GGS is a multisystem disorder which was first described by Gorlin and Goltz. Mutations in the PTCH1 gene, responsible for encoding a transmembrane receptor that interacts with the SHH signaling protein, are the underlying cause of GGS [2]. There is a high penetrance in the population, meaning the frequency of an allele appearing phenotypically is significant, with varying levels of expression [3]. De novo mutations account for approximately 20–30% of BCNS cases. Gorlin syndrome affects between 1:57,000 and 1:256,000 people [4]. The incidence at birth has been confirmed to be 1:18,976 [5]. Men and women are affected by the illness in an equal ratio (1:1.3) [6]. Despite the fact that the disease affects people of all races, African Americans and Asians account for only 5% of cases, and extracutaneous symptoms such odontogenic keratocysts (OKC) are more frequently identified than basal cell carcinomas (BCCs) [7, 8].

2. Case report

A 19- year-old male patient complained of yellow color fluid discharge in the right upper posterior region. Orthopantomogram revealed multiple radiolucencies involving impacted 18, 38 and 48 [Fig 1]. A well-defined lobulated cystic lesion noted arising from right maxillary alveolus with an impacted tooth within and extending into the right maxillary antrum and associated opacification of the right maxillary sinus is seen – likely Dentigerous cyst. Well defined cystic lesions noted around the crown of unerupted molar teeth on both sides, with extension into the left ramus of mandible on left side– likely dentigerous cysts. Lesions were excised and sent for histopathological evaluation. Results revealed multiple odontogenic keratocysts that were lined by stratified squamous epithelium containing abundant lamellated keratin [Fig 2]. Given the clinical, histopathological and radiological features, further evaluation was suggested to rule out GGS. Further clinical evaluation revealed multiple palmar pits in the patient's hands. Patient was counseled on the risks of GGS, advised on follow up visits for further investigations to look for other features of GGS.

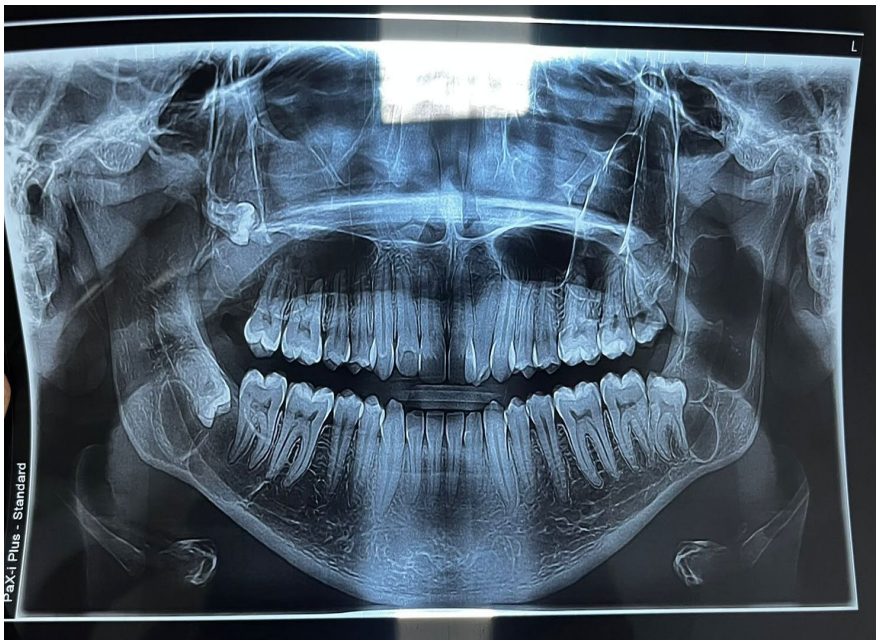

Fig 1: Radiographic appearance of multiple radiolucent lesions in the jaw for odontogenic keratocysts

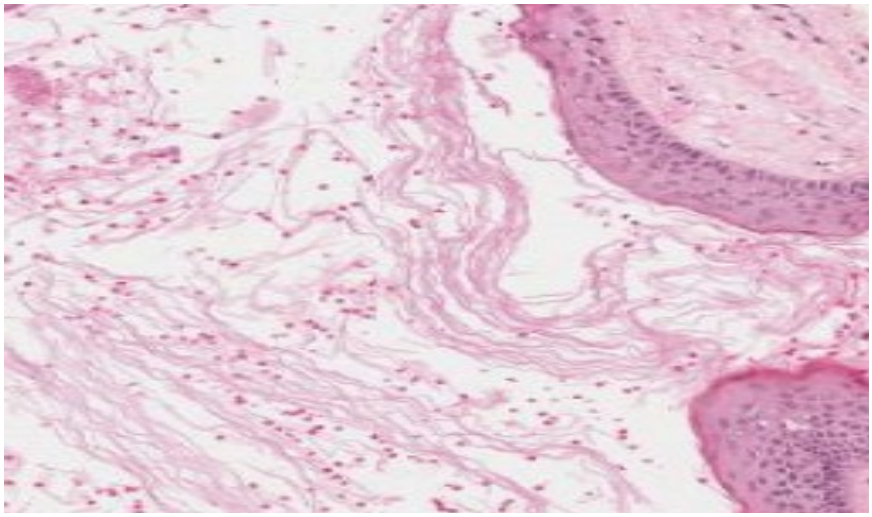

Fig 2: Cyst lined by stratified squamous epithelium containing abundant lamellated keratin

3.Discussion

Etiopathogenesis (Genetics)

A mutation in the tumor suppressor gene PTCH1, which is found on chromosome 9q22.32, causes Gorlin syndrome. The Hedgehog (Hh) protein, which is encoded by SHH, the gene located on chromosome 7q36.3, is recognized by a transmembrane receptor protein that is produced by the PTCH gene. This signal transduction route, known as the Hedgehog signaling pathway, has evolved through time and is implicated in more than 50% of cancer types [9]. The three hedgehog homologues found in mammals are the Desert Hedgehog (DHH), Indian Hedgehog (IHH), and the most extensively researched Sonic Hedgehog (SHH) [10]. The Hh protein, a polypeptide ligand found in fruit flies of the species Drosophila, is responsible for the name of this intracellular signaling pathway. It is said that fruit fly larvae without the Hh gene resemble hedgehogs [11].

As seen in Figure 3, upon reaching the targeted cell, SHH attaches itself to the patched-1 receptor (PTCH1). A downstream protein in the pathway called Smoothened (SMO) is inhibited by PTCH1 in the absence of such a ligand. It has been proposed that PTCH controls the intracellular location of a small protein that regulates SMO. Sterol-sensing domain (SSD), a sterol binding domain present in PTCH1, has been shown to be crucial for the inhibition of SMO activity [12]. According to a recent concept, PTCH functions as a sterol pump to remove the oxysterols produced by 7-dehydrocholesterol reductase, hence regulating SMO. This pump is inhibited when there is a connection between SHH and PTCH1 or when there is a mutation in the PTCH1 SSD domain, enabling the oxysterols to build up near SMO [13]. The nuclear transcription factors glioma-associated oncogene homolog GLI1 and GLI2, activators, and GLI3, repressor, are activated as a result of this accumulation, which enables SMO to activate or stay on the membrane for an extended period of time. The nucleus becomes overpopulated with activated GLI, which regulates the transcription of target genes [14]. Apart from PTCH1, mammals also possess PTCH2, a hedgehog receptor that binds SHH and shares 54% of its gene sequence with PTCH1. On the other hand, PTCH2 mediates DHH signaling and is the most expressed in the testis. PTCH2's capacity to inhibit SMO is diminished when it is not bound to the ligand, and its overexpression does not compensate for the mutant PTCH1 in BCC [14, 15]. This path is essential for cell division and growth, for controlling the development of vertebrates' organs, for differentiating fingers, and for the formation of the brain, spinal cord, eyes, and teeth. The SHH protein is in fact required for the development of the forebrain, helping to define the midline for the ventral or lower region of the forebrain. Additionally, it forms the cerebral hemispheres in conjunction with other signaling

proteins [16]. SHH is also crucial for the development of the eye as, in the early stages of development, the eye cells combine to create the ocular field, a single structure. This structure is located at the middle of the face. The ocular area splits into two independent eyes due to the sonic hedgehog signaling pathway [17]. When the PTCH gene is homozygously inactivated, cancerogenesis ensues, resulting in the development of numerous BCCs and other neoplasms. In addition to inheriting a faulty copy of the tumor suppressor gene (first hit), patients with Gorlin syndrome may also develop a mutation in the second healthy tumor suppressor, maybe as a result of exposure to ionizing radiation or UV light (second hit) [18].

Recently, it has been shown that people with Gorlin syndrome have altered versions of the suppressor of fused homolog (SUFU) gene, which is found on chromosome 10q24.32, and the PTCH2 gene, which is found on chromosome 1p34.1. Changes in the PTCH2 gene might not be definitive [19]. Functional deficiencies in the cytoplasmic protein SUFU are caused by changes in the SUFU gene. This is a significant inhibitor of the GLI1 protein, which is encoded by the GLI1 gene and also referred to as the glioma-associated oncogene [20]. The GLI1 protein binds to the SUFU protein, which sequesters it in the cytoplasm and inhibits its ability to translocate endonuclearly and, as a result, activate transcription. One of the most crucial mechanisms limiting Hedgehog signaling is lost when mutations in the SUFU gene result in the creation of an inactive protein [2]. Individuals with SUFU mutations in Gorlin syndrome are 20 times more likely to develop medulloblastoma (33%) than those with PTCH1 mutations (<2%) [22].

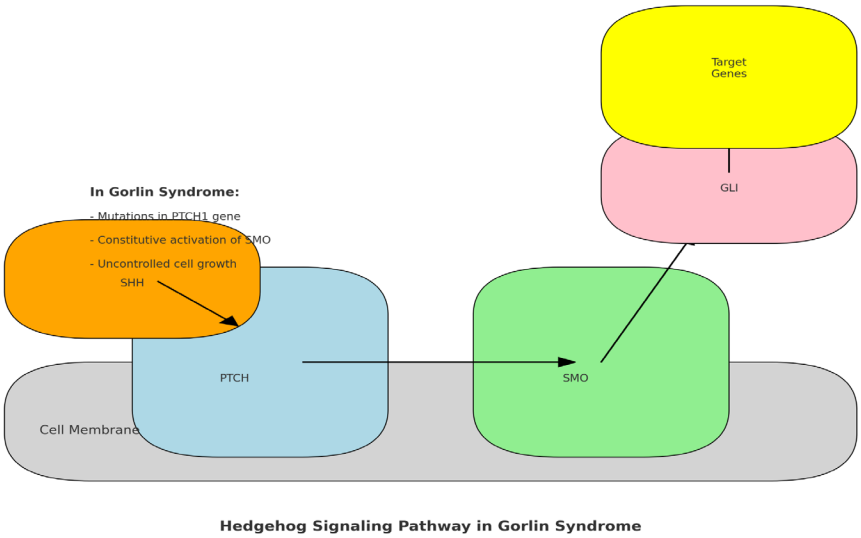

Figure 3: Hedgehog signaling pathway in Gorlin syndrome

Diagnostic criteria and other anomalies

GGS is rarely identified in very young kids, however it most commonly affects persons between 17 to 35 years. Because the symptoms develop gradually over the developing period, it is exceedingly difficult to detect in early childhood; nevertheless, early diagnosis is associated with a good prognosis [23]. The major and minor criteria for the diagnosis of GGS, as defined by Evans et al. in 1993, are displayed in Table 1.

Table 1: the major and minor criteria specified by Evans et al. in 1993 for the diagnosis of Gorlin-Goltz syndrome [7].

Major criteria	Minor criteria
1. More than two basal cell carcinomas or one in patient <20-years-old 2. Odontogenic keratocysts of the jaw 3. Three or more palmar or plantar pits	1. Macrocephaly 2. Congenital anomalies (cleft lip or palate, frontal bossing, coarse facies, and moderate or severe hypertelorism)

4. Bilamellar calcifications of falx cerebri and tentorium 5. Bifid or fused, or markedly splayed ribs 6. First-degree relative with Gorlin-Goltz syndrome.	3. Other skeletal anomalies (Sprengel deformity, marked pectus deformity, and marked syndactyly of the digits) 4. Radiologic anomalies such as bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet 5. Ovarian fibroma or myeloblastoma.

Two major criteria or one major and two minor criteria are obligatory for diagnosis of Gorlin-Goltz syndrome [24]. In our case, diagnosis was confirmed with the presence of two major criteria (odontogenic keratocysts of the jaw and multiple palmar pits). Other than the features mentioned in the diagnostic criteria more that 100 minor features have been described [Table 2-9].

Skeletal anomalies
Bridging sella turcica
Syndactyly and/or oligodactyly
Scoliosis
Shortened 4th metacarpal Bifid rib
Splayed/fused ribs Occult bifid rib (cervical, thoracic or both)
Cervical ribs
Absent ribs
Sprengel scapular deformity
Hemivertebrae
Pectum excavatum, carinatum
Flatfoot
Pelvic calcification

Polydactyly
Arachnodactyly
Hallux valgus
Cortical defects in long bones

Table 2: Skeletal anomalies in GGS [25, 26]

Skin anomalies
Basal cell carcinoma
Milia, specially in limbs
Palmar and/or plantar pits
Comedones

Table 3: Skin anomalies in GGS [26, 27]

Craniofacial anomalies
Calcification of the cerebral falx
Brachycephaly Macrocephaly
Tentorium cerebellum calcification
Frontal bossing
Bridged in sella turcica
Coarse face
Coroidal cysts (3rd and 4th ventricles)

Table 4: Craniofacial anomalies in GGS [25, 26]

Sexual anomalies
Ovarian and uterine fibroids
Supernumerary nipple
Ovarian fibrosarcoma
Hypogonadism and cryptorchidism
Calcified ovarian cysts
Female distribution of the pubis hair, scarce beard in men and gynecomastia

Table 5: Sexual anomalies in GGS [28, 29, 30]

Neurological anomalies
Medulloblastoma
Agenesis/ disgenesis of corpus callosum
Meningioma
Schizophrenic personality
Mental retardation
Nervous deafness
Congenital hydrocephalus
Anosmia

Table 6: Neurological anomalies in GGS [31, 32, 33, 34, 35, 36]

Ophthalmic anomalies
Hypertelorism

Glaucoma
Exotropia
Choroidal and/or optic nerve coloboma
Congenital amaurosis
Congenital blindness and opaque cornea
Ptosis
Cataracts
Internal strabismus
Chalazion

Table 7: Ophthalmic anomalies in GGS [37, 38, 39, 40, 41, 42, 43, 44]

Orofacial anomalies
Odontogenic keratocysts
Palate or maxillary sinus fibroma
High–arched palate or prominent palatine ridges
Malocclusion (maxillary hypoplasia and mandibular hyperplasia, cleft palate)
Cleft lip and/or palate
Fibrosarcoma of the jaws
Impacted teeth and/or agenesis
Dental malocclusion
Ameloblastoma

Table 8: Orofacial anomalies in GGS [45, 46, 47, 48, 49]

Other anomalies
Abdominal defects (diaphragmatic hernia, hiatal hernia, umbilical hernia, and omphalocele) Renal Anomalies Lymphomesenteric Cysts Cardiac Fibroma

Table 9: Other anomalies in GGS [1, 35, 50]

Radiological investigations

Skeletal abnormalities, odontogenic keratocysts, and many basal cell nevi are the three characteristic symptoms of GGS. A crucial part of diagnosing GGS is radiological studies. Typical dysmorphisms including macrocephaly, a protruding forehead, and facial milia affect about 60% of patients [18]. Facial dysmorphisms such as cleft lip/palate, macrocephaly, and ocular anomalies may be present, along with skeletal abnormalities such as fused or cuneiform vertebrae, hemivertebrae, and kyphoscoliosis. There may be mandibular hyperplasia with varying prognathism and a hypoplastic appearance of the maxilla. Malocclusion and dental crowding, which are brought on by keratocysts and can result in root resorption, non-eruption, and displacement of the dental parts, are other less common skeletal defects [1, 7]. Several radiolucent lesions in both maxillary bones, some of which were connected to the dental apexes of the third molars, is common. This demonstrated the value of the radiographic study employing orthopantomography. Furthermore, the lesions caused thinning of the bone thickness [51].

Radiographs of the jaws often show multilocular radiolucent lesions with well-defined sclerotic borders. Keratocysts are asymptomatic and are fairly infrequent abnormalities, which may account for the delayed identification in some situations [52]. However, they can turn painful in the event of an infection, edema, nerve compression, or tooth movement. The mandibular body and upper jaw are less commonly afflicted, but the mandibular branch region is where they are more localized. Usually, a few satellite cysts encircle keratocysts [53]. It is recommended to follow up with radiographic examination because this characteristic, which is linked to increased epithelial mitosis in the presence of a thicker fibrous capsule, favors a high lesion recurrence following surgical excision [54]. Radiographic scans of the skull commonly show abnormalities to the sella turcica and bilamellar calcification of the falx cerebri, among other characteristic lesions [54].

Genetic testing

The following circumstances warrant PTCH1 genetic testing [55, 56]:

1. Verification of the diagnosis in patients not meeting enough clinical diagnostic standards
2. predictive testing for at-risk individuals who don't fit the clinical criteria but have a family relative who is affected
3. testing during pregnancy if a known family mutation exists

Molecular testing techniques can involve the utilization of a multigene panel, the serial testing of a single gene, and more extensive genomic testing [56, 57].

1. When doing a serial test on a single gene, the following order is advised:
2. Examination of the PTCH1 series
3. Analysis of deletions and duplications aimed at the PTCH1 gene
4. Analysis of the SUFU sequence
5. Analysis of deletions and duplications aimed at the SUFU gene
6. PTCH1 RNA analysis

Families with medulloblastoma and no maxillary keratocysts should have SUFU molecular testing first. One option may be to implement a multigene panel comprising PTCH1, SUFU, and additional relevant genes [58].

Differential diagnosis

If macrocephaly and other neonatal defects are present, the presence of Sotos syndrome, Beckwith-Wiedemann syndrome (BWS), and isolated hydrocephalus or megalencephaly should be

considered [59, 60]. If the initial clinical signs are multiple BCCs, clinical examination and radiographs should diagnose NBCCS. However, there are other inherited disorders with similar skin signs should be considered [Table 10].

Macrocephaly + neonatal defects		Features	Diagnosis
	Sotos syndrome [61]	Behavioral problems, advanced bone age, cardiac anomalies, cranial anomalies, joint hyperlaxity/pes planus, maternal preeclampsia, neonatal jaundice, neonatal hypotonia, kidney abnormalities, scoliosis, and seizures	Pathogenic variant of (NSD1) gene identification
	Beckwith-Wiedemann syndrome (BWS) [62]	Neonatal hypoglycemia, macrosomia, macroglossia, hemihyperplasia, omphalocele, embryonic tumors (e.g., Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma), visceromegaly, cytomegaly, corticosarcoma kidney (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney or Cacchi	Abnormal regulation of gene transcription in two gene domains imprinted on chromosome 11p15.5

		Ricci disease, nephromegaly), and folds/pits in the ears.	
	Isolated hydrocephalus or megalencephaly [63]		Clinical examination, family history, and x-ray
Multiple BCCs	Brooke-Spiegler syndrome (BSS)/ CYLD cutaneous syndrome (CCS) [64]	- autosomal dominant genetic disease - trichoepithelio mas, milia in sun exposed areas and cylindromas	CYLD gene mutation
	Bazex-Dupré-Christol syndrome (BDCS) [65]	- dominant genetic disorder linked to chromosome X - multiple BCCs, follicular atrophy on the back of the hands and feet hypohidrosis, and hypotrichosis	(ARP-T1)/ ACTRT1 gene mutations

	Rombo syndrome [66]	- dominant hereditary disease reported in a single family - vermiculate atrophoderma, milia, hypotrichosis, trichoepithelioma, BCC, and peripheral vasodilation with cyanosis - BCCs develop in adulthood	
	Autosomal dominant or X-linked syndrome with hypotrichosis and BCC [67]	Reported in single family	
	Autosomal dominant inheritance of multiple BCCs [68]	Absence of other features	

Table 10: Differential diagnosis of GGS

4. Conclusion

The treatment of a patient with Gorlin-Goltz syndrome requires a specific combined medical and dental strategy. An early diagnosis opens the door to appropriate therapy and successful complications prevention. Young patients can take protective measures to reduce their exposure to radiation if they do not have basal cell carcinoma. Since there is a documented recurrence of the lesions, patients that have already been identified and treated should be closely monitored.

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