Case Report

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Gorlin–Goltz Syndrome with Eyelid Coloboma and Café au Lait Macule: Case Report and Literature Review

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ABSTRACT

Gorlin–Goltz syndrome (GGS), also known as Nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin syndrome, is a rare autosomal dominant inherited genodermatosis characterized by multiple nevoid basal cell epitheliomas at an early age, multiple jaw cysts, bifid ribs, and a multisystem developmental abnormality mostly affecting the skin, jaw, and central nervous system. Additionally, it includes a predisposition to neoplasms. The estimated prevalence varies from 1/57,000 to 1/256,000, without gender predominance. Cases have been reported from many countries except Yemen. We present a 42-year-old male patient who has presented with a coarse face, frontal bossing, synophrys, mandibular prognathism, multiple BCCs from the age of 15 years, palmoplantar pits, bifurcation and splaying of the left third rib, odontogenic keratocysts of the mandible, and calcifications of both the falx cerebri and the tentorium cerebelli. Additionally, he showed coloboma of the left lower eyelid and a café-au-lait (CAL) macule over the right waist area. He was diagnosed with Gorlin syndrome based on the presence of four major and four minor diagnostic criteria. Our case is unique as the patient presented with coloboma of the left lower eyelid, which has never been reported before, and a CAL macule, which has been reported only three times previously in association with Gorlin syndrome.

Keywords

Acitretin, Coloboma, Gorlin–Goltz syndrome, Nevoid basal cell carcinoma.

Introduction

Gorlin–Goltz syndrome (GGS), also known as Gorlin syndrome (GS), or Nevoid basal cell carcinoma syndrome (NBCCS), is a rare autosomal dominant inherited genodermatosis caused by mutations in the hedgehog signaling pathway. In the majority of cases (>90%), these mutations occur in the Patched 1 (PTCH1) tumor suppressor gene; these mutations occur less frequently in the PTCH2 gene or the suppressor of fused (SUFU) gene. GGS is characterized by multiple nevoid basal cell epitheliomas at an early age, multiple jaw cysts, bifid ribs, multisystem developmental abnormalities, and a predisposition to neoplasms, primarily affecting the skin, jaw, and central nervous system (CNS) [1-4]. The hedgehog signaling pathway is essential for embryogenesis and tumorigenesis, and its loss of function results in the manifestations of GSS. The syndrome has a high level of penetrance and variable expressivity, with an estimated prevalence ranging from 1/57,000 to 1/256,000, without gender predominance [5,6]. Black individuals represent only 5% of cases, and only 15% of them develop more than two BCCs, compared to 80%–90% of white individuals who develop multiple BCCs [7]. The high variability of GGS may delay diagnosis; most patients are diagnosed between 17 and 35 years of age [8].

Nowadays this disorder is named NBCCS, as suggested by Professor Gorlin, because this syndrome results from mutations in the PTCH1 gene [4].

Although Gorlin and Goltz defined the term GSS in 1960, the first case was reported by Jarisch and White in 1894 in a patient with multiple BCCs, scoliosis, and learning disability [9,10]. In 1939, Straith described three familial cases in which multiple basal cell

carcinomas and jaw cysts appeared [11]. In 1953, Gross presented the case of a patient who showed additional symptoms, such as synostosis of the first left rib and bilateral bifurcation of the sixth rib [12]. Bettley and Ward were the first to associate the presence of palmar and plantar pits with the syndrome [13]. The classic triad of this syndrome (multiple BCCs, keratocysts in the jaws, and bifid ribs) was defined in 1960 by Professor of Oral Pathology Robert Gorlin and dermatologist Robert Goltz [14,15]. In 1977, these criteria were modified by Rayner, who suggested that the presence of cysts, along with calcification of the falx cerebri or palmar and plantar pits, are necessary for diagnosis.[10] GGS manifests with multiple or early-onset BCCs, odontogenic keratocysts of the jaw, palmoplantar pits, calcification of the falx cerebri, and skeletal anomalies [16].

BCCs may develop during childhood, but they usually appear after puberty [17]. The number of BCCs in a single patient varies from a few to more than a thousand, and their size ranges from a pinpoint to >5 cm [17].

The odontogenic keratocyst (OKC) is a locally aggressive cystic lesion that affects the mandible twice as commonly as the maxilla, accounting for up to 15% of odontogenic cysts. These cysts form from tissues that are involved in odontogenesis and are capable of causing major destruction. They are highly recurrent, with a recurrence rate of up to 62.5% after surgical removal [18].

Case Report

A 42-year-old male patient presented to the dermatology clinic with multiple skin lesions on his face and trunk that had persisted for 27 years. Upon cutaneous examination, multiple skin-colored, brown to black papules and nodules were observed, primarily distributed across the central face, including the eyelids, and ranged in size from 2 mm to 12 mm in diameter (Figures 1A–1D). A black plaque was found on the right parietal scalp. Approximately 30 lesions, ranging from small papules to large flat plaques, and measuring 1 to 8 cm in diameter, exhibited colors from skin-toned, red, to black and were distributed across the patient's back, primarily on the upper back (Figure 1C). One blue to black nodule was seen on the dorsal aspect of the left thigh. Multiple small depressions were observed on both the patient's palms and soles, as well as to a lesser degree on their dorsal aspects (Figures 1D). A 10x15 cm café au lait patch was seen on the right side of the waist (Figure 1C). The patient's left lower eyelid lacked lashes and exhibited a loss of tissue on its middle margin, a typical presentation of eyelid coloboma (Figure 2A). Further, the patient showed macrocephaly, frontal bossing, a coarse face with synophrys, a broad nasal root, mandibular prognathism, and hypertelorism (Figure 2B). Oral examination revealed crowded conical and misaligned teeth (Figure 2C). No other family members had similar conditions. The patient was unaware of the risks associated with his condition.

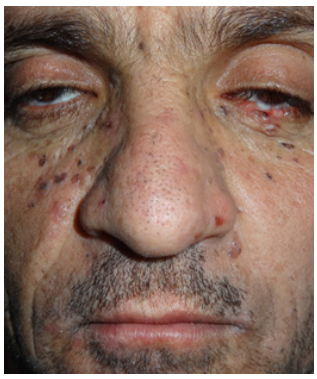

Figure 1A: Multiple BCCs over the forehead and periocular area. Coloboma of the left lower lid.

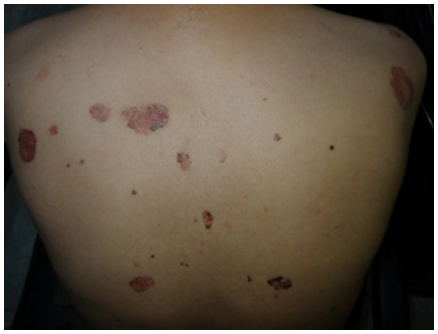

Figure 1B: Multiple BCCs of different sizes, and colors over the upper back.

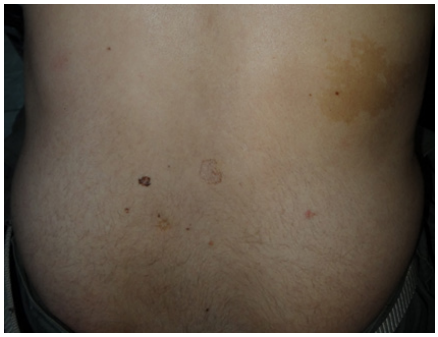

Figure 1C: CAL nevus over the right side of the mid back, along with many BCCs over the lumbar area.

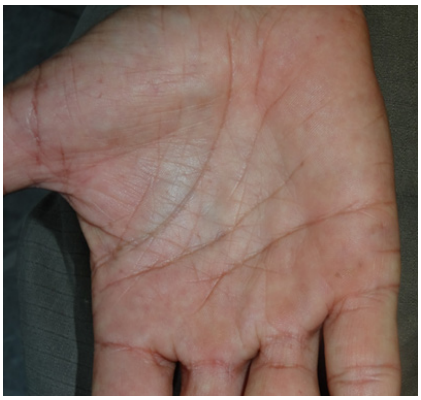

Figure 1D: Pits over the right palm.

The large number and extensive distribution of the lesions prompted us to consider GGS. An orthopantomogram (OPG) of the teeth revealed multiple cysts on the mandible, with more on the left side, along with crowded and misaligned teeth (Figure 2D), which were confirmed by a CT scan (Figures 3A). A brain CT scan showed calcification of the falx cerebri and the tentorium cerebelli (Figures 3B). A CT scan of the chest revealed a bifurcated and splayed third left rib (Figure 3C) and scoliosis (Figure 3D). Three skin punch biopsies were taken: one from the upper back, one from the lower back, and one from palmar pits. These biopsies revealed BCC on the back and a defect in the stratum corneum on the palm (Figures 4A-4C). Our case is unique, as the patient presented with four major and four minor criteria for Gorlin syndrome, including coloboma of the left lower eyelid, which has never been reported before, and a CAL macule, which has been reported only three times previously [20-24]. Treatment is challenging; we administered oral acitretin (35 mg per day) for three weeks as chemoprevention. A few lesions around the patient's eyes were treated with electrodessication, while TCA chemical peels were used for large lesions on his back, and fluorouracil cream were used for smaller lesions on the face. A decrease in number and size of BCCs was observed on the 2 months follow up visit. The patient is under regular follow up every 3 months.

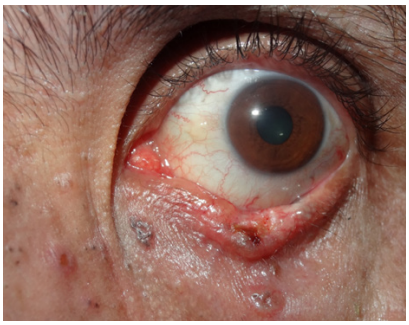

Figure 2A: Coloboma of left lower lid, along with many BCCs.

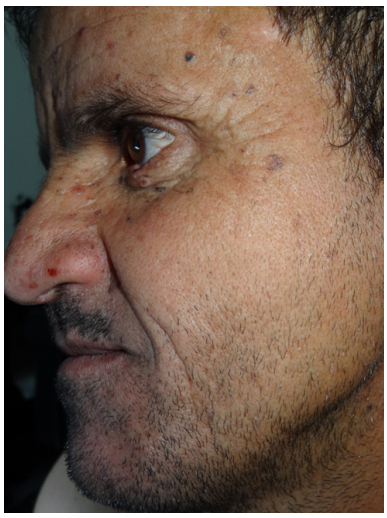

Figure 2B: Coarse facies with broad nasal bridge, hypertelorism, and synorphys. Note coloboma of left lower eyelid.

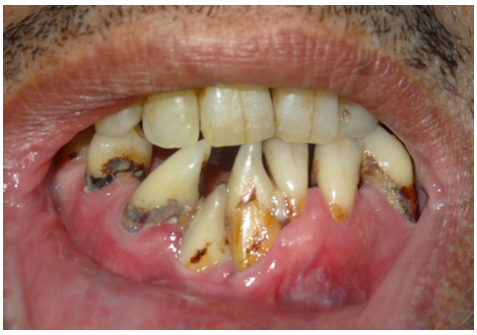

Figure 2C: Crowded conical, and misaligned genial teeth.

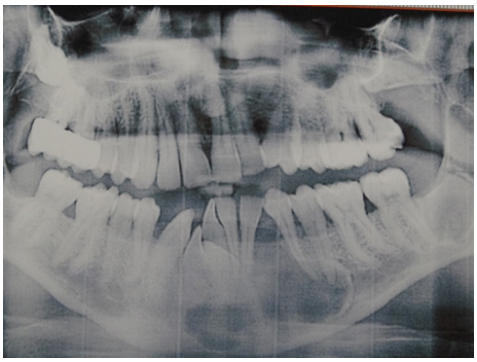

Figure 2D: Orthopantomogram, revealed multiple cysts in the mandible, more on the left side, crowded, and conical teeth.

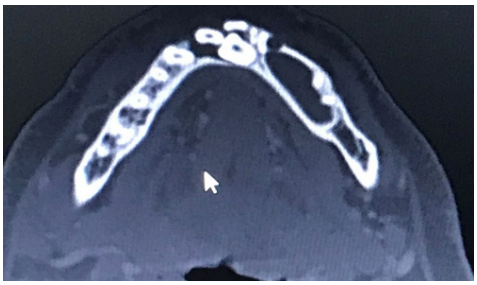

Figure 3A: Coronal view of Brain CT, with calcification of the falx cerebri, and tentorium cerebelli.

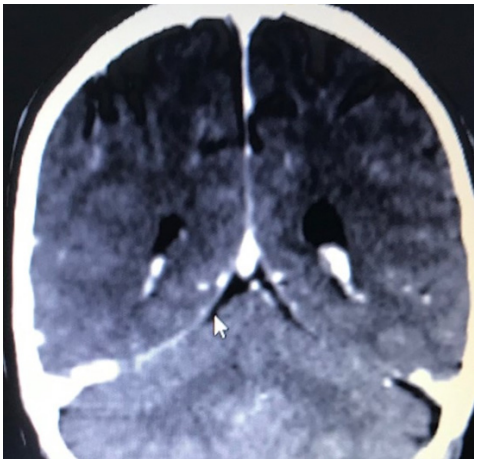

Figure 3B: Calcification of the falx cerebri, seen on an axial section of the Brain CT scan. A marked brain atrophy is also visible.

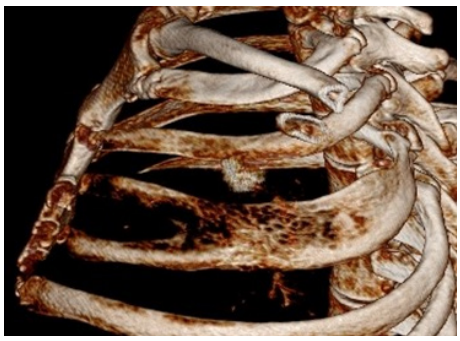

Figure 3C: Bifurcation and splaying of the 3rd left rib, viewed from left posterior-lateral.

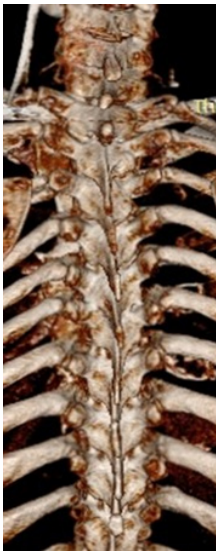

Figure 3D: Scoliosis on 3D CT scan of the chest

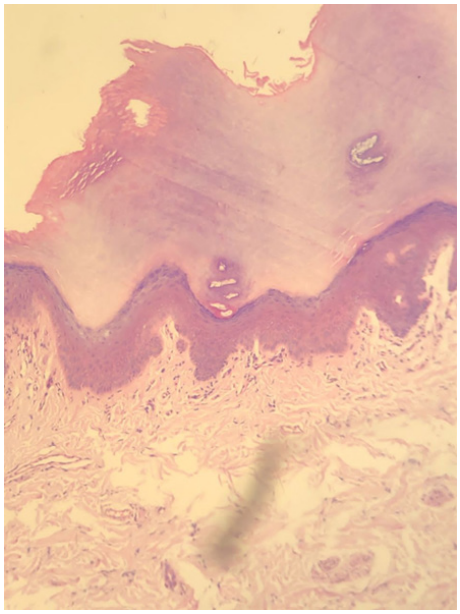

Figure 4A: Histology of a palmar pit, as a notch within the stratum corneum.

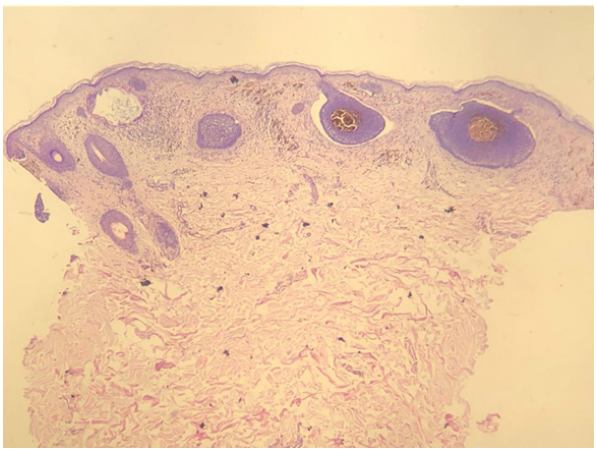

Figure 4B: Histology of the Superficial spreading BCC over the upper back.

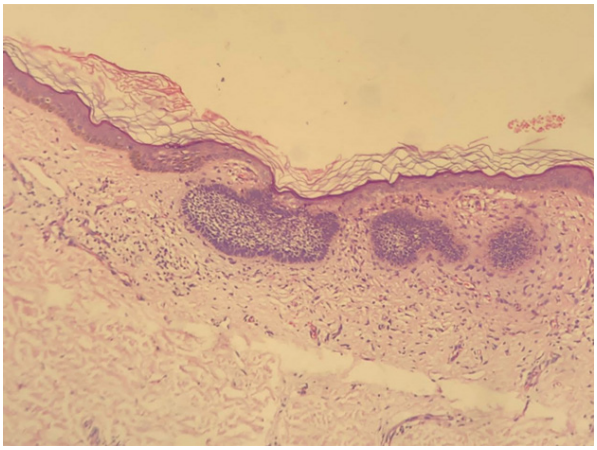

Figure 4C: Histology of Superficial spreading BCC over the sacral area.

Discussion

GSS is a multisystem genodermatosis that can involve almost every organ. A multidisciplinary team consisting of a dermatologist, a dentist, a geneticist, and a neurologist is essential for improving a patient's overall survival rate. Before 1963, some researchers believed that nevoid basal cell carcinoma, epithelioma adenoides cysticum of Brooke, and trichoepithelioma were the same disease, until Gray and Helwig proved that epithelioma adenoides cysticum is similar to solitary trichoepithelioma, as both show similar characteristic histopathologic and histochemical changes, recognizing NBCC as a separate entity.

The clinical features of GGS are divided into the following groups:

1. Cutaneous features: multiple BCCs, palmoplantar pits, milia, comedones, cysts, dermal calcifications, and CAL macules
2. Dental features: multiple odontogenic keratocysts (OKCs)
3. Craniofacial features
4. Ocular features: congenital cataract, congenital blindness, internal strabismus, coloboma, and glaucoma
5. Musculoskeletal and radiographic features: temporo-parietal,

frontal bossing giving a pagetoid appearance, broad nasal root, hypertelorism, prominent supraorbital ridge giving the eyes a sunken appearance, dystopia canthorum, mild mandibular prognathism, cleft lip, and cleft palate. Other features include bifid, synostosic, or splayed ribs, involving more than one rib unilaterally or bilaterally, as well as cervical rudimentary rib, kyphoscoliosis, fusion of vertebrae, spina bifida, shortened fourth metacarpals (Albright's sign), enlarged hands, extra metatarsals, and polydactyly.

6. Oncologic features: medulloblastoma, cardiac, and ovarian fibromas.
7. Endocrine features: hypogonadism in males and ovarian tumors in females.
8. Neurologic features: medulloblastoma, calcification of dura, falx cerebri, tentorium cerebelli, mental retardation, agenesis of corpus callosum, congenital hydrocephalus, and schizophrenic behavior.

BCCs may develop during childhood but usually appear after puberty [17]. Their number in a single patient varies from a few to more than a thousand, and their size ranges from pinpoint to >5 cm [17]. Lesions may vary from flesh-colored papules to ulcerating plaques. They occur in 90% of white individuals but only 40% of black individuals. BCCs are most commonly located in the midface area but often appear on skin that is not exposed to sunlight.

Palmar and plantar pits occur in 65% to 85% of patients, increasing with age [25]. They appear as punctiform, asymmetric depressions in the skin of palms and soles of feet, measuring 2 to 3 mm in size and 1 to 3 mm in depth. These depressions can be flesh-colored, pink, or red and are caused by a partial or complete lack of the stratum corneum. They were first described in 1960 by Ward [26], who called them "dyskeratosis of the palms and soles." The existence of BCCs within palmar pits has been reported [27,28]. The presence of three or more palmar pits is considered a major diagnostic criterion, although these pits can be found in other genodermatoses, such as generalized follicular hamartoma, reticulate acropigmentation of Kimura, Cowden's syndrome, and Darier disease [27].

Odontogenic keratocyst (OKCs) are locally aggressive cystic lesions that affect the maxilla or the mandible; they originate from dental lamina remnants and account for up to 10% of odontogenic cysts. These cysts form from tissues involved in odontogenesis and are capable of causing major destruction. They are highly recurrent, with up to 62.5% recurrence after surgical removal [18]. OKCs are observed in up to 90% in patients with GGS [29-32]. They were first identified and described in 1876 by Mikulicz and further classified by Philipsen in 1956. In 1962, Pindborg and Hansen suggested the histological criteria necessary to diagnose them [33].

Evans first proposed diagnostic criteria for GGS in 1993; these criteria were modified by Kimonis in 1997 and most recently revised by Bree in 2011 [16]. According to a recent publication, for an established diagnosis of GGS, one of the following conditions must be fulfilled: (i) one major criterion and genetic confirmation, (ii) two major criteria, or (iii) one major criterion and two minor criteria (Table 1) [34].

Table 1: Diagnostic criteria of Gorlin syndrome.

Major Criteria	Minor Criteria
1. BCC before the age of 20 years or extreme quantity of BCCs not proportional to skin photo type, or previous sun exposure	1. Costal malformations
2. Jaw Odontogenic keratocyst before the age of 20 years.	2. Other peculiar skeletal deformities and x-ray changes (e.g., vertebral deformities, kyphoscoliosis, postaxial polydactyly, short fourth and fifth metacarpals)
3. Palmoplantar pits.	3. Megalocephaly
4. Lamellar petrification of the falx cerebri, and /or tentorium cerebelli.	4. Split lip/palate
5. Medulloblastoma	5. Fibroma of the ovaries/myocardium
6. First-degree relative with GGS	6. Cysts of the mesenteric Lymph nodes
	7. Ophthalmic malformations (e.g., hypertelorism, strabismus, glaucoma, congenital cataracts, coloboma)

Ocular manifestations in GGS are frequent, albeit rarely reported, with an estimated incidence of 4%–23% [35]. Such manifestations in relation to the syndrome were reported with the following frequencies in the literature: hypertelorism (45.5%), congenital cataract (18%), nystagmus (9%), colobomas (9%), highlights strabismus (63%), epiretinal membranes (36%), and myelinated optic nerve fiber layers (36%) [36]. Colobomas are substance defects that can involve any part of the eye, including the iris, retina, and eyelid. The term “coloboma” is derived from the Greek word “koloboma,” which means a hole or a tissue defect. An eyelid coloboma is a congenital full-thickness defect of the eyelid margin and may also involve different structures of the eye: eyelids, iris, lens, ciliary body, choroid, retina, or optic nerve. The defect may vary from a small marginal notch to a full-thickness absence of the entire eyelid margin involving one-third to half of the eyelid. Usually, the upper eyelid is more commonly affected, and the most common site is the junction between the medial and middle third of the upper eyelid. Eyelid colobomas represent an incomplete form of cryptophthalmos. Cryptophthalmos is a congenital condition in which there is a failure of differentiation of eyelid structures.

Eyelid colobomas involve the upper lid more commonly than the lower one, and the most common site is the junction between the medial and middle third of the upper eyelid. They can be unilateral or bilateral, isolated or associated with other malformations. The case presented is unique, as it involves a lower eyelid coloboma, which has not been reported previously in association with GGS [37].

Synophrys, the fusion of eyebrows above the bridge of the nose, can be found in other genodermatoses, including Cornelia De Lange syndrome and Waardenburg syndrome [38].

Below are the diagnostic criteria for GSS suggested by Bree and Shah [34].

Major Criteria

1. BCC prior to 20 years old or excessive numbers of BCCs out of proportion to prior sun exposure and skin type
2. Odontogenic keratocyst of the jaw prior to 20 years of age
3. Palmar or plantar pitting
4. Lamellar calcification of the falx cerebri
5. Medulloblastoma
6. First-degree relative with GGS

Minor Criteria

1. Rib anomalies
2. Other specific skeletal malformations and radiologic changes (e.g., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)
3. Macrocephaly
4. Cleft lip/palate
5. Ovarian/cardiac fibroma
6. Lymphomesenteric cysts
7. Ocular abnormalities (e.g., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)

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