Gorlin syndrome in a patient with skin type VI

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Abstract

Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is a rare autosomal dominant disorder that is characterized by multiple basal cell carcinomas developing at a young age, keratocystic odontogenic tumors of the jaw, palmar or plantar pits, calcification of the falx cerebri, and skeletal abnormalities. Nevoid basal cell carcinoma syndrome is caused by mutations in the *PTCH1* or *SUFU* genes. Our patient with Fitzpatrick skin type VI was diagnosed with Gorlin syndrome based on the presentation of multiple major diagnostic characteristics. Although he is 33 years old, he has not developed any multiple basal cell carcinomas to date.

Keywords: Gorlin syndrome, nevoid basal cell carcinoma syndrome (NBCCS), Fitzpatrick skin Type VI

Introduction

Nevoid basal cell carcinoma syndrome is a rare hereditary disorder caused by mutations in the *PTCH1* or *SUFU* genes. The diagnosis of nevoid basal cell carcinoma syndrome (NBCCS) is established using major diagnostic criteria including: multiple basal cell carcinomas (BCCs), keratocystic odontogenic tumors, palmar or plantar pits, ectopic calcification of the falx cerebri, rib anomalies, and a family history of NBCCS. Because the potential of progression to BCCs and neoplasias is significant, diagnosing NBCCS early is crucial [1]. Based on a literature search of PubMed, to our knowledge this is a rare case of Gorlin syndrome in a black patient with Fitzpatrick Skin Type VI presenting without basal cell carcinomas. This case highlights the importance of considering NBCCS in darker-

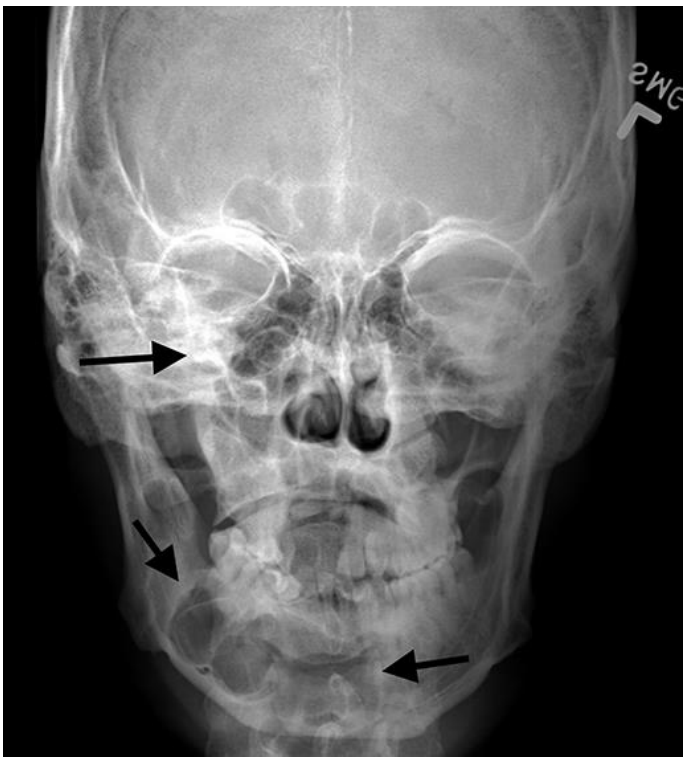

Figure 1. *Keratocystic odontogenic tumors: coronal head CT demonstrates expansile cystic lesions along the mandibular alveolar ridge, with thin well defined cortical margins (arrows). Cysts are most commonly seen in the mandible and maxilla, and may contain unerupted teeth and/or higher density proteinaceous material (not displayed in this image).*

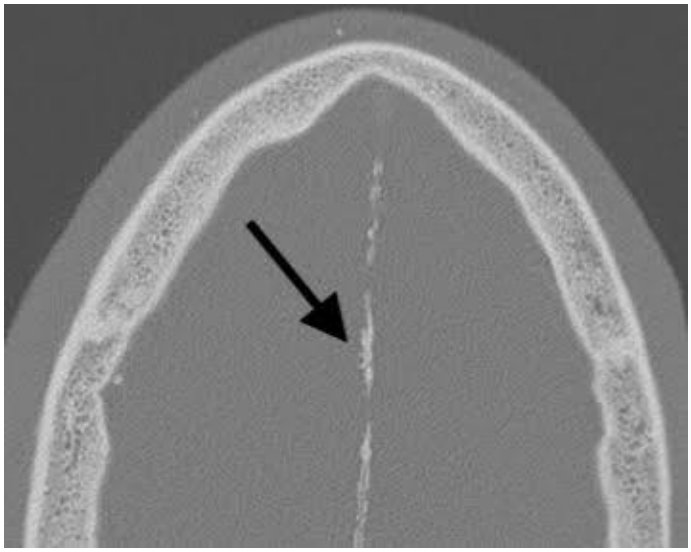

Figure 2. *Prominent dural calcifications: Axial head CT demonstrating prominent calcification along the cerebral falx (arrow).*

skinned patients even if the characteristic clinical sign of BCCs at a young age is not present.

Case Synopsis

A 33-year-old black man with Fitzpatrick skin type VI and a past medical history of a left club foot at birth and keratocystic odontogenic tumors was referred to the dermatology clinic with concern for Gorlin syndrome, also known as NBCCS. He was being treated in the otolaryngology department for multiple keratocystic odontogenic tumors (**Figure 1**) and chronic osteomyelitis of the mandible. Calcification of the falx cerebri was incidentally found on CT scan (**Figure 2**) prompting the referral. Physical examination was significant for three palmar pits on the left hand (**Figure 3**). The patient had no evidence of BCCs. On review of radiographic imaging, he was found to have bifid ribs seen on chest radiograph (**Figure 4**). The patient presented with four major diagnostic criteria and these findings are consistent with the diagnosis of NBCCS. The patient underwent genetic testing and was found to have a heterozygous mutation in *PTCH1* at exon 21 creating a premature translational stop codon. The patient has no known family history of NBCCS, but his paternal aunt had jaw cysts and died in her fifties of unknown causes. His father and mother died of unrelated causes at ages 48 and 34, respectively. Interestingly, although

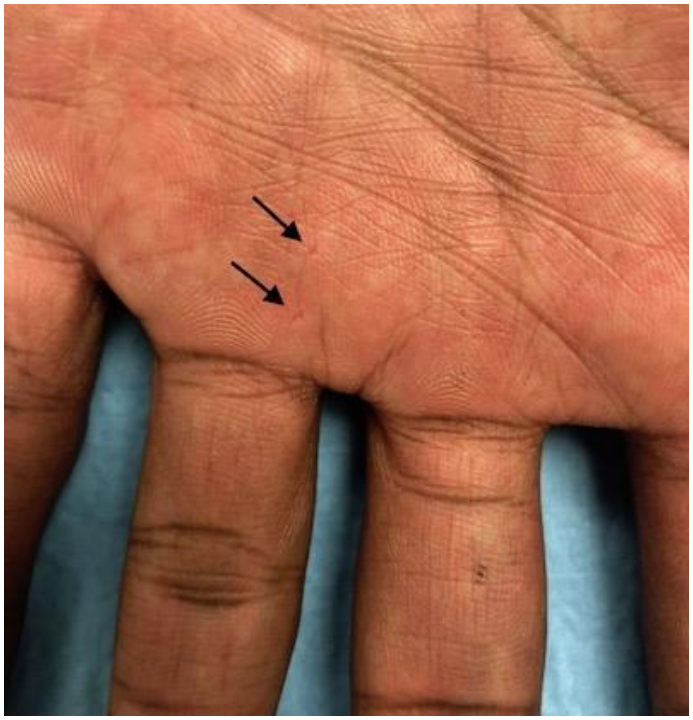

Figure 3. *Two of the three palmar pits of left hand (arrows).*

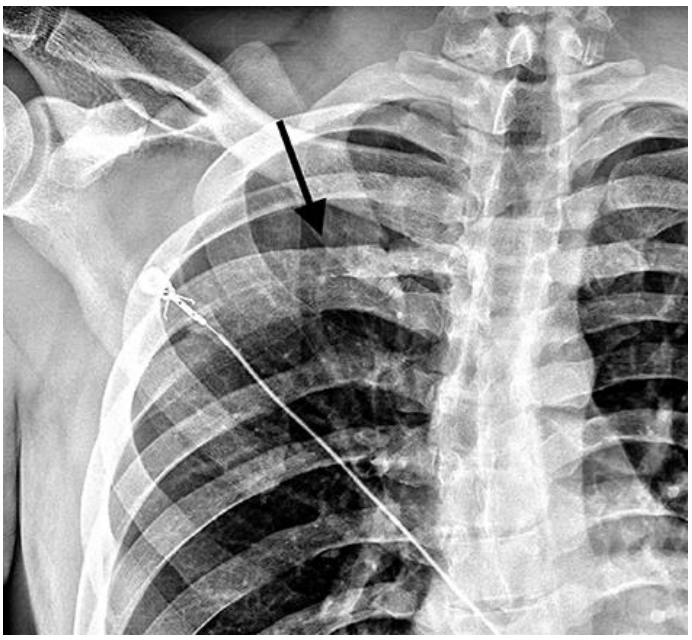

Figure 4. *Rib anomalies: PA chest radiograph demonstrated congenital fusion of the posterior right 4th and 5th ribs (arrow).*

patients with this condition usually develop BCCs at a young age, this patient has not had any to date.

Case Discussion

Gorlin syndrome is a rare hereditary disorder, typically characterized by developing BCCs at a young age [2], with a prevalence estimated to be 1:30,827 in the UK [3]. It is seen equally in males and females [4]. Gorlin syndrome is an autosomal dominant condition caused by mutations in the *PTCH1* or *SUFU* genes associated with a wide range of developmental abnormalities and a predisposition to neoplasias including BCCs. It has been estimated that 70%-80% of those diagnosed with NBCCS also have a parent with the disease. However, between 20%-30% have NBCCS as the result of a de novo mutation [3].

The diagnosis of Gorlin syndrome is established in individuals using major diagnostic criteria including: BCCs (>5 in a lifetime or a BCC before age 30 years), [3], recurrent keratocystic odontogenic tumors of the jaw (in approximately 90% of patients), [4], three or more palmar or plantar pits, [5], (in approximately 85% of patients over the age of 20 years), [4], ectopic calcification of the falx cerebri (in more than 79% of affected individuals greater than 20 years of age), [5], rib anomalies (e.g., bifid ribs), [5], and a first degree relative with NBCCS [3, 5]. Additional minor criteria include: vertebral anomalies, brachymetacarpaly, hypertelorism or telecanthus, and frontal bossing [5]. Depending on the source, the clinical criteria for the number of major and minor criteria can differ. One source of diagnostic criteria for NBCCS establishes two major or one major and two minor diagnostic criteria [5]. The variability in expressivity and the difference in age of onset of the different characteristics of the disorder may cause difficulty in diagnosing patients [6]. Diagnosis can be confirmed by molecular genetic testing with the identification of a heterozygous germline pathogenic variant in *PTCH1* or *SUFU* [3].

Skin pigmentation and sun exposure can affect the generation of basal cell carcinomas. It has been suggested that increased skin pigmentation could provide protection to UV radiation, which in turn could decrease the number of BCCs [7]. BCCs are more likely to occur in patients with Gorlin syndrome who have lighter skin color with a Fitzpatrick skin type less than III [8].

A literature review utilizing PubMed and the search terms "Gorlin syndrome," "nevoid basal cell carcinoma syndrome," "NBCCS," "basal cell nevus syndrome," "BCNS," "African American," "Black," and "Fitzpatrick" was performed. The search yielded one case of NBCCS in Fitzpatrick skin type IV [9] and two cases in Fitzpatrick skin type V [10, 11]. Additionally, there are reports of darker-skinned persons being diagnosed with NBCCS, but there were no Fitzpatrick skin types noted (**Table 1**), [7, 12-17]. The percent of patients with NBCCS that are black is less than 5% [18]. In 80% of white American patients with NBCCS, BCCs occurred at a mean age of 21 years, however in black American patients BCCs appeared by 21 in only 38% [5]. It is recommended patients with NBCCS have skin examinations at least annually [3]. These recommendations do not specify management guidelines for patients with skin of color in the setting of Gorlin syndrome. Although, likely at less risk for BCCs, we plan to monitor our patient every three-to-six months initially, then progress to annual screening pending dermatologic findings. To our knowledge, no other cases of NBCCS have been reported in Fitzpatrick skin type VI. Our case highlights the importance of a multidisciplinary approach to patients with NBCCS, particularly in patients with skin of color that may present with other major diagnostic criteria prior to BCCs.

Conclusion

This is a case of Gorlin Syndrome in a black American patient diagnosed using the clinical criteria and confirmed with genetic testing. A multidisciplinary team of physicians is important in management of this syndrome. Although our patient does not have any BCCs to date, it is recommended that he be evaluated yearly for the development of BCCs.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Summary of features of black patients with nevoid basal cell carcinoma syndrome (NBCCS), (also called Gorlin, basal cell nevus syndrome, BCNS) by age.*

Age/Gender Description	Skin Type	Features	Genetic Testing	Family History	Ref
2.5/M African-American	Not reported	Desmoplastic medulloblastoma, macrocephaly, bilateral rib fusion and segmentation anomalies, anteromedial temporal arachnoid cyst, mild ventriculomegaly with thinning of periventricular white matter, frontal and biparietal bosselation, hypertelorism, bilateral papilledema, right abducent nerve palsy, severe gait ataxia, and bilateral upper- and lower-extremity dysmetria. BCC: None reported	Novel mutation in the PTCH gene	NBCCS in the father; mother revealed large tumors were common in her family	[14]
4/F Black	Not reported	Pits of hands and feet and bilateral ovarian fibromas. BCC: Multiple	Not reported	Negative	[7]
7/M African-American	Not reported	Palmar pits, bifid ribs, hypertelorism, macrocephaly, spina bifida occulta, and epicanthal folds. BCC: None	Not reported	Positive	[7]
8/F African-American	Not reported	Bifid ribs, calcification of falx cerebri, hypertelorism, macrocephaly, broad nasal root, spina bifida occulta, and ovarian fibroma - right. BCC: None	Not reported	Positive	[7]
8/M African-American	Not reported	Medulloblastoma, palmar/plantar pits, large odontogenic keratocyst of mandible, slightly large head circumference, frontal bossing, ocular hypertelorism, and high-arched palate. BCC: Multiple in medulloblastoma treatment radiation field	Not reported	Mother had mandibular odontogenic keratocyst, calcification of falx cerebri, large head circumference, high-arched palate	[9, 12, 17]
11/M Black	Not reported	Expanding, cystic mass in left posterior alveolar ridge, exotropia appearing to be secondary to an impacted molar displaced into the orbit by an odontogenic keratocyst, and palmar/plantar pitting. BCC: Multiple	Not reported	Negative	[18]
11/M Black	Fitzpatrick type V	Large keratocysts from right maxilla, left maxilla, and right mandible, palmar/plantar pitting, calcifications along tentorium, frontal bossing, and autism. BCC: Multiple, pigmented	Hetero-zygous mutation, PTCH1 gene	No maternal family history; paternal family history was unknown	[10]
14/M Black	Not reported	Palmar/plantar pits, partial cleft lip and skin tag (repaired), subglottic web/narrowing, jaw cysts, calcification of falx cerebri and tentorium cerebelli, scoliosis, bifid, and fused ribs, Sprengel deformity, frontal bossing, dolichocephaly, Mandibular Prognathism, broad nasal root, pectus carinatum, epicanthal folds, and childhood seizures. BCC: 1	Genetic linkage study	Grandmother, mother, and female sibling with NBCCS	[7]

17/F Black	Not reported	Palmar/plantar pits, polydactyly bilateral, jaw cysts, calcification of falx cerebri, scoliosis, short 4th metacarpal, parietal bossing, and childhood seizures. BCC: None	Genetic linkage study	Grandmother, mother, and male sibling with NBCCS	[7]
19/F African-American	Not reported	Dermatosis papulosa nigra, palmar/plantar pits, Maxillary and mandibular cysts, (odontogenic keratocysts) frontal and parietal bossing, mandibular prognathism, hypertelorism, and calcification of falx cerebri. BCC: 2	Not reported	Positive	[7]
20/M African-American	Not reported	Maxillary and mandibular jaw cysts, malpositioned and malformed teeth, frontal bossing, broad nasal root, hypertelorism spina bifida (odculta), calcification of falx cerebri, hydrocephaly, and cleft lip and palate. BCC: None	Not reported	Positive	[7]
22/F African-American	Not reported	Hypertelorism, dura calcification, bilateral ovarian fibroma, and pigmented nevi. BCC: None	Not reported	Not reported	[7]
25/M partially African-American	Fitzpatrick type IV	Extensive palmar pitting since childhood, a recurrent jaw cyst, and inguinal hernia. BCC:11	Not reported	Family history was obscured by adoption	[9
26/F African-American	Not reported	Pits on palms, scoliosis, cataracts; uveitis; glaucoma; and vitritis, bullous keratopathy, retrocorneal and papillary membranes, intraocular lens fibrosis, and posterior chamber fibrosis. BCC: Multiple, pigmented	Not reported	Patient reported father had dark brown papules on his face	[13]
29/M Black	Not reported	Palmar/ plantar pits, jaw cysts and abnormal skull configuration. BCC: None	Genetic linkage study	Father, 4 male and 3 female siblings with NBCCS	[7]
30/M Black	Not reported	Palmar/plantar pits, skin cysts, milia, neurofibroma, jaw cysts, calcification of falx cerebri, scoliosis, missing and/or malformed ribs, and hypertelorism. BCC: 1	Genetic linkage study	Father, 4 male and 3 female siblings with NBCCS	[7]
31/F Black	Not reported	Multiple maxillary and mandibular jaw cysts and malocclusion, plantar and >50 palmar pits, bifid and fusion of ribs, scoliosis, Sprengel deformity with left scapula, biparietal bossing, hypertelorism, dural calcification of falx cerebri, petroclinoid ligament, tentorium cerebelli, lutencies of right radius and left humerus, bilateral fibrothecomatous nodules of ovaries, epicanthal folds, course face, strabismus of right eye (corrected), abnormal blind spot in left eye, cafe au lait spot, and neurofibroma. BCC: 3, found on back and axilla	Genetic linkage study	Father, 1 female and 5 male sibling with NBCCS	[7]

33/M African-American	Fitzpatrick type VI	Bilateral clubfeet at birth, multiple keratocystic odontogenic tumors, chronic osteomyelitis of mandible, calcification of falx cerebri, three palmar pits on left hand, and bifid ribs. BCC: None	Hetero-zygous mutation, PTCH1 at exon 21	No known family history; but paternal aunt had jaw cysts	CR
35/M Black	Not reported	Palmar/plantar pits, jaw cysts, calcification of falx cerebri, missing and/or malformed ribs, short 4th metacarpal, frontal bossing, and brachycephaly. BCC: None	Genetic linkage study	Father, 4 male and 3 female siblings with NBCCS	[7]
37/F Black	Not reported	Palmar/plantar pits, jaw cysts, calcification of falx cerebri, mandibular prognathism, and palate: slight torus. BCC: None	Genetic linkage study	Mother, 1 male and 1 female child with NBCCS	[7]
38/M Black	Not reported	Palmar/plantar pits, jaw cysts, scoliosis, frontal bossing, abnormal skull configuration, skin tags and pseudofolliculitis barbi. BCC: 3	Genetic linkage study	Father, 4 male and 3 female siblings with NBCCS	[7]
40/F Black	Not reported	Palmar/ plantar pits, jaw cysts and malocclusion, calcification of falx cerebri, scoliosis, short 4th metacarpal, brachycephaly, Mandibular Prognathism, cortical cysts, modeling, and synophrys. BCC: None confirmed	Genetic linkage study	Father, 1 female and 5 male siblings with NBCCS	[7]
48/F African-American	Not reported	Multiple palmar and plantar pits. BCC: >12 pigmented BCC, found 1 in each axillae	Not reported	Mother had BCNS	[16]
50/F Black	Fitzpatrick type V	Pits on palms and soles and clinodactyly. BCC: Multiple, the umbilical BCC was pigmented	Not reported	Mother had palmar and plantar pits, clinodactyly	[11]
60/M Black	Not reported	Palmar and plantar pits, jaw cysts, skin cysts, and synophrys. BCC: None confirmed	Genetic linkage study	2 daughters and 5 sons with NBCCS	[7]
61/F Black	Not reported	Palmar and plantar pits, skin cysts, hypopigmented areas, edentulous, and scoliosis. BCC: None	Genetic linkage study	Daughter, male and female grandchild with NBCCS	[7]
Adult/F African-American	Not reported	Milia, dermal devi, palmar and plantar pits, mandibular cysts, frontal and parietal bossing, mandibular prognathism, and hypertelorism. BCC: None	Not reported	Positive	[7]
80/M Black	Not reported	Palmar pits, and mandibular cysts, and midline calcified falx cerebri. BCC: Multiple, developed when he was 77	Not reported	Negative	[15

Note: Fitzpatrick skin typing classification was not developed until 1975, therefore a Fitzpatrick skin type for Black or African-American patients is not available in articles prior to that year and have not been included in this table.
Duplication of patients among studies was eliminated.
CR- Case Report