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Case report

# Gorlin Syndrome in a type IV-skin person with a novel PTCH1 mutation: Case report and literature review

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**Abstract**

Nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin Syndrome, is an autosomal dominant multisystem disorder, characterized by multiple developmental abnormalities and inactivation germline mutations in the human homolog of the patched (PTCH) gene. We are presenting a case of NBCCS in a skin type 4 Saudi male with a novel PTCH1 gene mutation. To the best of our knowledge, this is the third case reported in Saudi Arabia but the first in adult population. Moreover, our patient harbors a novel heterozygosity mutation in patch1 gene.


*Keywords:* Basal cell carcinoma; Gorlin Syndrome

## 1. Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), basal cell nevus syndrome, or Gorlin Syndrome [OMIM, 109400] refer to the same rare genetic mulitsystemic disorder. Inheritance is autosomal dominant with near-complete penetrance and variable expression. It is characterized by multiple developmental abnormalities and inactivation germline mutations in the human homolog of the patched (PTCH) gene. NBCCS can involve skin, bone and the nervous system. Major features include multiple basal cell carcinomas (BCC); odontogenic keratocysts; palm and/or sole pits and calcification of the falx cerebri. Other features include as well cleft lip or palate, microphthalmos, a bifid or fused rib, scoliosis, tall stature, frontal bossing and medulloblastoma.

It is a rare condition in the dark skin population. To the best of our knowledge, herein, we report the third case of NBCCS in Saudi population and the first one in the adulthood with a novel PTCH1 gene mutation.

## 2. Case report

A 38 year-old male soldier from AlJouf, North of Saudi Arabia, presented with a history of multiple biopsy-proven pigmented BCCs overlying the abdomen, scalp, and right shoulder one year ago. Since then, he developed more BCCs over the same areas. He spent significant time outside without sun protection. There was no trauma, ionizing radiation, or exposure to chemicals. He is a heavy smoker. Family history is positive for non-consanguinity and a

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deceased mother with numerous skin tumors that remained undiagnosed.

Upon skin examination, multiple, >20 pigmented (black) papulo-nodular lesions were found on the scalp with variability in size, Fig. 1. Skin tags were present. There was frontal bossing, with confluent eyebrows (Fig. 1inset b) and tall stature (184 cm). There were numerous bilateral plantar (Fig. 1inset c) pits.

NBCCS was suspected based on the clinical presentation. X-rays of the face revealed well-defined lytic bony lesions involving the mandible. CT of the head suggested odontogenic bony keratocysts of the mandible and maxillary bones as well as extensive calcification of the falx cerebri. There was no evidence of cardiac fibromas on echocardiogram. Confirmation with a genetic study showed positivity for a haploinsufficiency with novel partial deletion (EXON 13) of the PTCH1 gene. Therefore, nevoid basal cell carcinoma syndrome was confirmed. BCCs were treated with surgical excision and curettage.

## 3. Discussion

NBCCS is a rare inherited multisystem condition caused by germline mutations in the PTCH gene (Cohen, 1999). Jarisch and White first described it in 1894, which was later followed by greater establishment of the syndrome by Gorlin and Goltz (1960). It has the estimated prevalence of 1:57000 to 1:164000 individuals. It affects both genders equally, with greater incidence in Caucasians and less in blacks and Asians (Goldstein et al., 1994; Ahn et al., 2004). Extensive literature review identified two pediatric cases in the Saudi population while our patient is the first case diagnosed in adulthood.

Interestingly, more than one hundred clinical findings have been reported in the English literature. The diagnosis is clinical, and is supported by the presence of two major, or one major and two minor criteria (Table 1) Evans et al. (1993). Major manifestations are found in 75–80% of cases, and include early development of basal cell carcinomas; odontogenic keratocysts; palm and/or plantar pitting; ectopic calcification of the falx cerebri; and family history of NBCCS (Evans et al., 1993). Minor criteria include bifid ribs; craniofacial anomalies such as coarse facial features, macrocephaly, frontal bossing, confluent brows, and hypertelorism; early onset midline medulloblastoma; ovarian or cardiac fibromas; lymphomesenteric cysts; and congenital malformations like cleft lip or palate, polydactyly, eye abnormalities, cataracts, glaucoma, and coloboma (Evans et al., 1993). Diagnosis can be difficult in young patients, and atypical cases in persons with dark complexion.

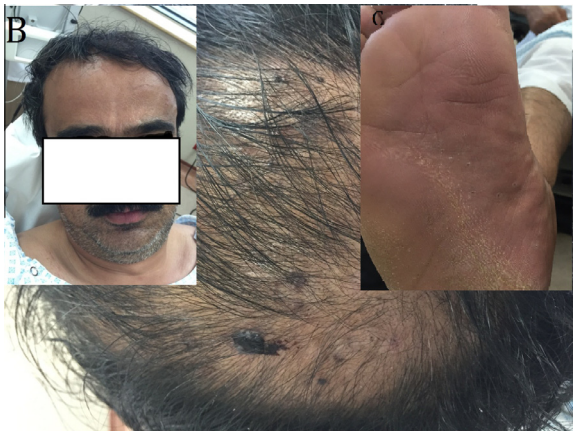


Fig. 1. Multiple BCCs over the scalp. Inset b: frontal bossing. Inset c: plantar pits.

Skin manifestations include BCCs, palmoplantar pits, milia, hemangiomas, and skin tags (Walling et al., 2004). BCC occurs in approximately 75% of NBCCS Caucasian patients and are multiple (Kimonis et al., 1997). Interestingly, one-third of all sporadic basal cell carcinomas have mutations in the PTCH gene (Gailani et al., 1996). In NBCCS, the age at first diagnosis ranges from three to 53 years with the mean average of 20–21 (Kimonis et al., 1997). The histopathological examination of gorlins' BCCs is indistinct from sporadic cases (Gorlin, 2004). In this syndrome, BCCs are largely evident in Caucasians (80%) than in black (30–40%) or Asian individuals (Goldstein et al., 1994; Ahn et al., 2004; Kulkarni et al., 2003). This finding is principally expected because darker skinned populations are intrinsically resistant to UV light.

Palmoplantar pits are a common feature. They are secondary to partial or complete absence of the horny cell layer of the skin (Howell and Mehregan, 1970). Odontogenic keratocysts occur mainly in the mandible, and unlike BCCs, share no racial predilection (Goldstein et al., 1994). Ectopic calcification occurs in the falx cerebri in 65% of patients with rates increasing to 90% in those over 40 years old (Kimonis et al., 1997). Our patient had all major and some minor criteria for diagnosis in addition to tall stature, frontal bossing, and coarse facial features were present.

NBCCS must be distinguished from other rare genodermatosis with malignant potential e.g., Bazex, Rombo, Muir-torre syndrome, Xeroderma pigmentosum and Basaloid follicular hamartomas (BFH). Bazex syndrome is a X-linked condition characterized by multiple BCCs, hypotrichosis, hypohidrosis and acral follicular atrophoderma (Hauck and Manders, 1994). Rombo syndrome is characterized by multiple BCCs, vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas and peripheral cyanosis (Hauck and Manders, 1994). Muir-Torre syndrome is an autosomal dominant condition with various skin sebaceous neoplasms and visceral malignancies (Hauck and Manders, 1994).

NBCCS results from mutations in the PTCH gene, the human homolog of Drosophila. It exhibits autosomal dominance with near-complete penetrance but is variably expressed (Anderson et al., 1967). The patched gene is located in the long arm of chromosome 9 (Farndon et al., 1992). The transcribed PTCH protein is part of a receptor complex (with Smoothened, SMO) for the hedgehog protein, part of the sonic hedgehog-signaling pathway (Stone