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Nevoid Basal Cell Carcinoma Syndrome: A Review

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ABSTRACT

Gorlin syndrome (GS) or nevoid basal cell carcinoma syndrome (NBCCS) is a rare genetic disorder characterised by development of multiple basal cell carcinomas (BCCs) at a young age. NBCCS occurs because of mutations in the PTCH1 gene, which functions as a tumour suppressor gene.

Patients with GS can have varied manifestations, both cutaneous and extra-cutaneous. The most notable cutaneous manifestations are BCCs, which are also the most characteristic tumours in GS, and palmar/plantar pits. esides the BCC, medulloblastomas are the second most characteristic malignant presentation.

There are a set of criteria for the diagnosis of GS, which have a high predictability in making an accurate diagnosis of GS. Genetic testing for PTCH1 gene is one of the diagnostic criteria, which is positive in about 60% of patients.

Patients with GS need a multidisciplinary approach. Mohs micrographic surgery is recommended for BCCs on high-risk areas. SMO receptor inhibitors such as Vismodegib and Sonidegib have been approved by FDA for the treatment of advanced BCCs.

Keywords: Gorlin syndrome, medulloblastoma, nevoid basal cell carcinoma syndrome.

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I. Introduction

Gorlin syndrome (GS), also known as naevoid basal cell carcinoma syndrome (NBCCS), is an autosomal dominantly inherited condition. It predisposes to multiple developmental defects and tumour formations, particularly basal cell carcinomas (BCCs) [1]. The syndrome is caused by mutations in the patched 1 (PTCH1) gene, which encodes the PTCH1 transmembrane receptor, involved in the sonic hedgehog (SHh) signaling pathway [2].

GS was first reported by [3] and has been reported from all over the world. There have been only two large epidemiological studies done for GS, one in UK and other in Australia, with respective prevalence of 1/30827 and 1/164000 [4].

Patients with GS have a reduced life expectancy with medulloblastoma being the most common cause of death [5].

II. Pathogenesis

NBCCS occurs because of mutations in the PTCH1 gene, which functions as a tumor suppressor gene, on chromosome 9q22. This mutation causes an up-regulation of SHh signaling pathway [6]. The Hh pathway was first described in the Drosophila fly and the signaling mechanisms are conserved from flies to humans. Mammalian Hh signaling includes:

1. Ligand: SHh, Indian Hh and desert Hh
2. Patches receptors: PTCH1 and PTCH2
3. Signal transducer smoothened (SMO)
4. Transcription factors: Gli1, Gli2 and Gli3 [7]

Genetic testing for PTCH1 mutation, being the gold standard, is utilized when there aren't enough clinical features to reach a clinical diagnosis of GS.

PTCH1 gene mutation is the commonest and is found in about 50-85% of patients with Gorlin syndrome [8], [9]. Mutations in PTCH causes over-activation of the Hh pathway, resulting in dysregulated cellular growth and differentiation.

III. Clinical Features

Patients with GS can have varied manifestations, both cutaneous and extra-cutaneous and for a long time there were no adequate diagnostic guidelines. However, in 2011, a consensus was released by the *First International Colloquium on Basal Cell Nevus Syndrome* (BCNS) regarding the diagnostic criteria. To confidently make a diagnosis of GS, 2 major, or 1 major and 2 minor criteria, or 1 major criteria with molecular confirmation need to be fulfilled [10].

Major criteria for diagnosis would include:

1. BCC before 20 years of age or BCCs out of proportion to sun exposure and skin type.
2. odontogenic keratocyst of the jaw in <20 years of age.
3. palmar or plantar pitting.
4. lamellar calcification of the falx cerebri.
5. medulloblastoma, typically desmoplastic.
6. 1st degree relative with BCNS. Minor criteria include:

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- rib anomalies
- other specific skeletal malformations and radiologic changes (i.e., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)
- macrocephaly
- cleft/lip palate
- ovarian or cardiac fibromas
- lympho-mesenteric cysts
- ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma).

The most notable cutaneous manifestations are BCCs, which are also the most characteristic tumors in GS, and palmar/plantar pits. BCCs in patients with GS occur on both photo-exposed and non-exposed areas [1]. BCCs in GS tend to occur at early ages, usually below 20 years of age and their frequency increases with age. They mostly occur on the face and upper trunk (Fig. 1).

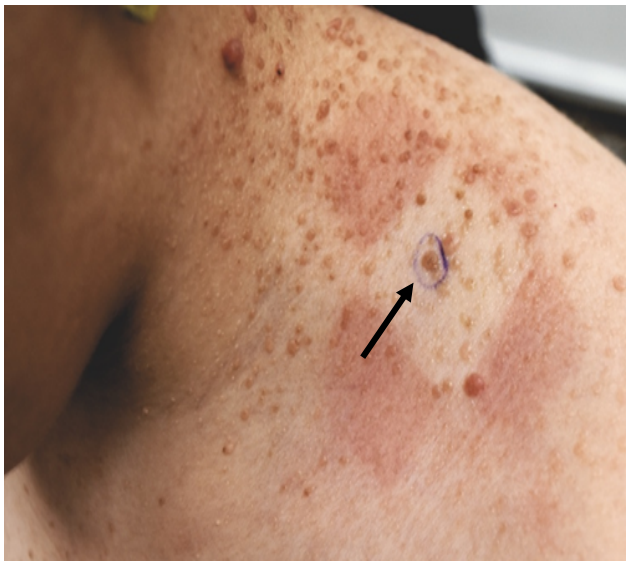

Fig. 1. cutaneous lesions including BCCs predominantly on the upper third of body.

Palmar/plantar are another frequent manifestation in GS and usually tend to occur before the age of 15 years [11].

Odontogenic cysts are the most notable extra-cutaneous feature seen in patients with GS. They occur mostly before the age of 20 years, are asymptomatic and may undergo malignant transformation.

GS has a wide variety of other clinical manifestations which are beyond the scope of this article, but a few notable ones are: calcification of falx cerebri, rib abnormalities such as bifid ribs and radiolucency's seen on hand roentgenograms [5].

Besides the BCC, medulloblastomas are the second most characteristic malignant presentation seen in patients with NBCCS and are often the presenting feature of the disease. They usually present at an age earlier than that of the general population, mostly around 2 years of age [11]. Medulloblastomas are the most common paediatric malignant brain tumour, and the usual line of treatment is surgical excision with radiotherapy and chemotherapy. Other uncommon malignancies are fibromas of the heart and ovaries.

Paediatric and teenage population with GS tends to have some peculiar features. They tend to be tall and have and increased head size since birth, with frontal, parietal and temporal bossing in most of them. Nearly half the patient <20 years exhibit development of naevi, however only about 14% develop BCCs [12].

In children with medulloblastoma, 3% of the children in all age groups and 10% in <2 years have GS. The average of presentation of medulloblastoma in GS is 5 years earlier than the isolated medulloblastomas [13]. Tumours in other organs have also been reported but rarely occur in children.

IV. Diagnosis

As mentioned above, there are a set of criteria for the diagnosis of GS, which have a high predictability in making an accurate diagnosis of GS. A thorough history and physical examination is a must in patients suspected of GS, including a detailed family history. BCCs are a clinical diagnosis whose clinical sensitivity can be increased using dermoscopy (Fig. 2).

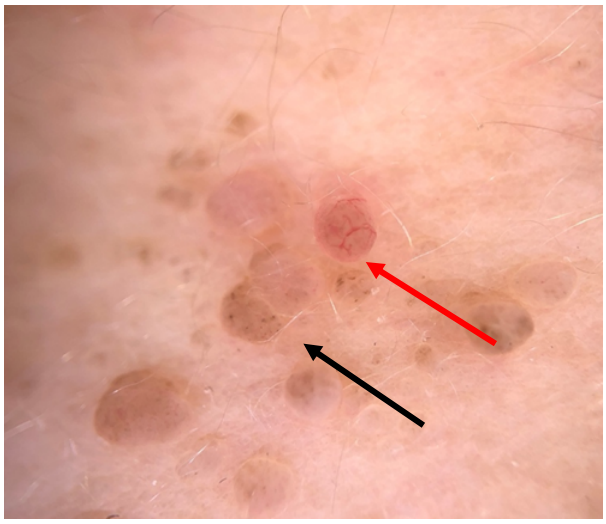

Fig. 2. Black arrow-dots and globules signifying seborrheic keratosis like lesion; Red arrow-arborising vessels suggesting BCC like lesion (Dermlite DL4, 10x).

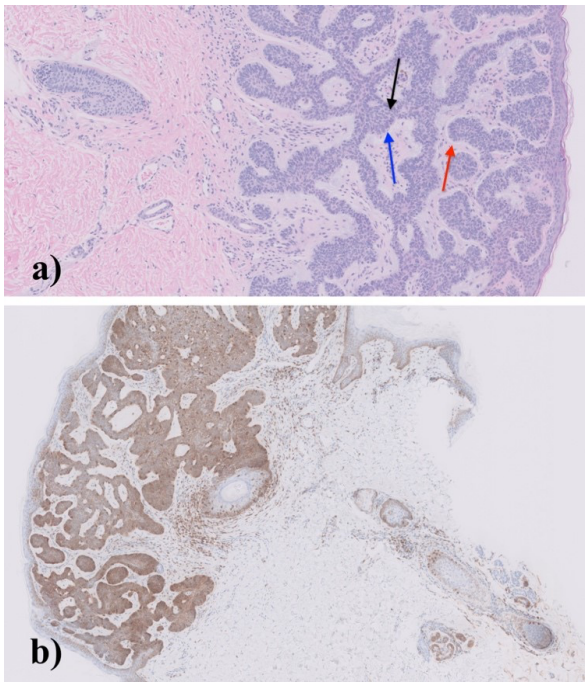

Fig. 3. a) Nests of cells (black arrow) with peripheral palisading (blue arrow) with stromal clefting (red arrow); b) Bcl-2 positivity throughout the dermal nests.

This can avoid the need for biopsy, especially in paediatric cases. However, some lesions may still pose a challenge and can be diagnosed using histopathology (Fig. 3).

V. Management

Annual neurological examination should be done in patients suspected with GS [5]. However, of note is that such patients should have minimal exposure to ionizing radiation because of their predilection for development of tumours.

Genetic testing for PTCH1 gene is one of the diagnostic criteria of special importance, which is positive in about 60% of patients with NBCCS [14]. X-rays of rib cage, spine, hands, feet and pelvis are helpful in diagnosing certain criteria of GS. Magnetic resonance imaging (MRI) of the head is important in early identification of medulloblastoma, to ensure early recognition and treatment of medulloblastoma. Panorex of jaw is required to diagnose odontogenic cysts of the jaw. Other investigations as may be needed for such patients should be undertaken based on the manifestations.

VI. Conclusion

Patients with GS need a multidisciplinary approach because of the multiple organ systems that may be involved. Preventive strategies that may help in reducing the occurrence are minimizing exposure to ionizing radiations, sun protection and even using oral retinoids.

Treatment of BCCs is based on the risk categorization, as is for sporadic BCCs. Mohs micrographic surgery is recommended for BCCs on high-risk areas while BCCs occurring in low-risk sites and are histologically less aggressive can be managed with curettage, electrocoagulation or cryotherapy. For multiple BCCs, photodynamic therapy (PDT), topical chemotherapy with 5-fluorouracil (5-FU) and imiquimod 5% can be used [5].

SMO receptor inhibitors such as Vismodegib and Sonidegib have been approved by FDA for the treatment of advanced BCCs. It has also been used for prolonged periods in the prophylactic prevention of BCCs in GS15. These are also useful in patients who are not fit candidates for surgery or radiotherapy. Itraconazole and Arsenic are other two therapeutic agents that respectively inhibit and impede SMO activation that may, alone or in combination, be used to inhibit the growth of medulloblastoma and BCCs, resistant to other drugs [16].

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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