Contents

SECTION II Lentigines, Nevi, and Melanoma

1 Nevoid basal cell carcinoma syndrome

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Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin–Goltz syndrome (GS), is an inherited autosomal dominant condition with high penetrance and variable expressivity.[1] NBCCS is caused by a germline mutation of the gene *PTCH1* on chromosome 9q22.3–q31.[2]

It is characterized by a triad of clinical manifestations: multiple basal cell carcinomas (BCCs), odontogenic jaw keratocysts and bifid ribs.[1] Besides this classic triad described by Gorlin and Goltz, a wide spectrum of developmental defects and tumors can be variably found in patients affected by this syndrome: calcification of the falx cerebri, palmar and plantar pits, spine anomalies, relative macrocephaly, facial milia, frontal bossing, ocular hypertelorism, medulloblastoma, ovarian fibroma, cleft lip or palate and the development of mental abnormalities.[3–5]

The incidence of NBCCS in the general population varies between 1:57,000 and 1:164,000, with a male-to female ratio of 1:1.[6,7]

The diagnosis is made when a series of established major and minor criteria are present, and it should be confirmed by DNA analysis.[7,8]

The cutaneous manifestations of the syndrome are the presence of multiple BCCs and acral pits.

The finding of multiple BCCs in a young person should raise the suspicion of NBCCS. In addition to their early onset during life (they typically appear during puberty) and their high

number, BCCs of the NBCCS are less related to sun exposure than ordinary BCCs in nonsyndromic patients. Exposure to radiation therapy may lead to thousands of BCCs in the radiation field.[9] Although NBCCS represents only 0.4% of all cases of BCCs, early diagnosis is important for appropriate genetic counseling, avoidance of radiation, and timely adoption of photoprotection.[9,10]

Both nonsyndromic and syndromic BCCs are more commonly observed in patients with lighter skin. While BCCs occur in over 90% of whites with NBCCS, only 38%–44% of African Americans develop these tumors.[7,11]

Clinically, these lesions appear as pearly, flesh-colored or pigmented smooth papules, pedunculated lesions, nodules or plaques, sometimes covered by small blood vessels (Figures 1.1 and 1.2).[12,13] They can vary in number from just a few up to thousands, ranging in size from 1 to 10 mm or more in diameter, and tend to appear in unusual sites, like non-sun-exposed areas, the eyelid or the upper lip.[3,4,14,15]

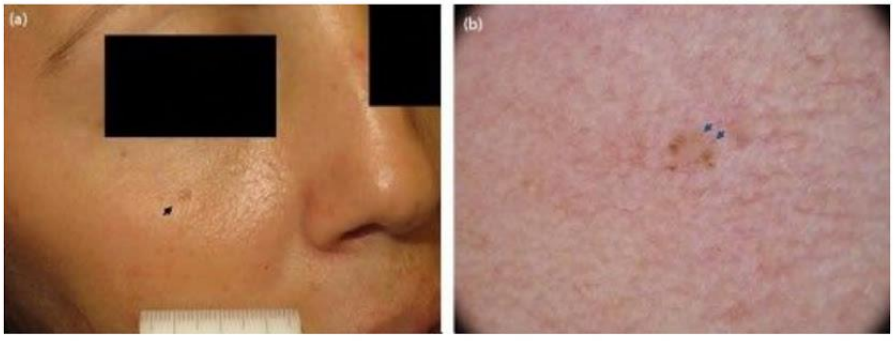

Figure 1.1 (a) A light brown smooth papule (arrow) on the right cheek of a 33-year-old woman affected by nevoid basal cell carcinoma syndrome. (b) In dermoscopy the lesion shows brown, black and some gray-blue dots (blue arrows), in the absence of additional specific BCC criteria (×20 original magnification).

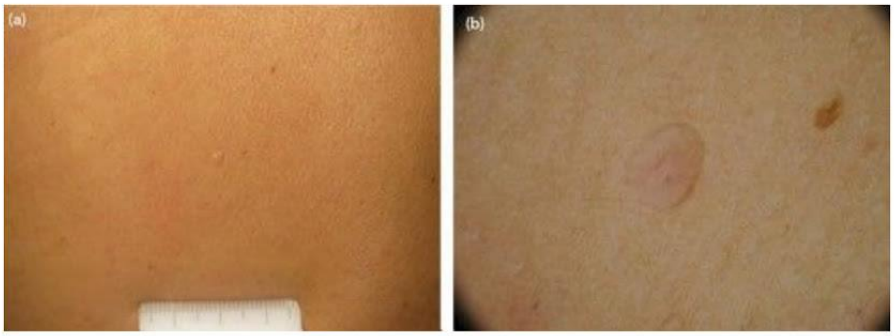

Figure 1.2 (a) The same patient presented, on her upper back, a translucent papule clinically resembling a dermal nevus. (b) The dermoscopic image of this papule shows arborizing vessels strongly suggestive for nodular BCC (×20 original magnification).

At histopathologic examination, BCC associated with NBCCS does not differ from BCC arising in nonsyndromic patients.[5] About 30% of GS cases have two or more types of BCC histopathologic patterns (morphea-like, solid, superficial, cystic, adenoid, fibroepithelial or pigmented).[9,16]

The differential clinical diagnosis for these tumors includes melanocytic nevi, seborrheic keratosis, acrochordons, hemangiomas or molluscum contagiosum (Figure 1.2).[3]

Acral pits are another hallmark of NBCCS. They are observed in almost 50% of patients and are more common on the hands than on the feet.[12] They appear as pale, flesh-colored, pink or red millimetric depressions (Figure 1.3), which are totally asymptomatic and persist from their onset throughout life. Palmar pits are considered, by some authors, precursor lesions for BCCs.[17,18]

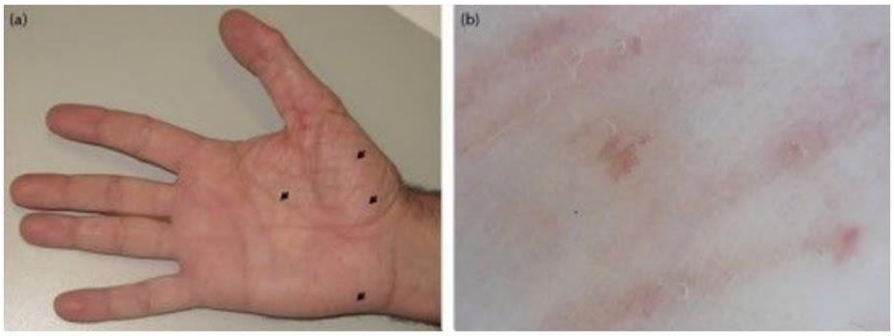

Figure 1.3 (a) The volar surface of the right hand of a 46-year-old man affected by NBCCS shows several white to red small depressions (arrows), known as "palmar pits." (b) On dermoscopy, the palmar pits show red globules regularly distributed in a linear fashion (×20 original magnification).

Although sporadic BCCs are generally managed with excisional surgery, considering the number and the recurrent nature of these lesions in NBCCS, several alternative approaches have been proposed, including ablative laser therapy, electrocoagulation, cryosurgery, photodynamic therapy, topical imiquimod and 5-fluorouracil. The development of oral hedgehog pathway inhibitors has raised a new dimension to the current treatment of BCCs for patients affected by NBCCS.[19]

DERMOSCOPY

BCCs associated with NBCCS cannot be differentiated from those arising in nonsyndromic patients.[5] Then, BCCs in GS can be detected in early stages by the presence of typical, but often subtle, dermoscopic features of BCC.

BCCs in patients affected by NBCCS usually show arborizing vessels, ulceration and fine telangiectasias, in addition to blue-gray ovoid nests, dots and globules when pigmented.[20,21]

However, BCCs in these patients, especially when very small, may display a subtle dermoscopic aspect that makes diagnosis

more difficult. Several authors, for example, described patients whose BCCs were typified only by dark brown and/or blue-gray dots or globules, without any vascular pattern (Figure 1.1).[15,21–23] In longer-standing lesions, blue ovoid nests and arborizing vessels (Figure 1.2) are often observed. Also the presence of maple-leaf-like areas and spoke-wheel structures has been described.[15,21]

Acral pits show, on dermoscopy, small red or pink depressed lesions with sharp borders. Additional findings are red globules (Figure 1.3) that show a regular linear distribution, usually along the furrows.[21]

Jarrett and colleagues described two morphologically distinct types of pits: type 1 pits are composed of blue structures and microarborizing vessels and are more frequently seen in childhood; type 2 pits are characterized by a predominant vascular pattern of dotted vessels and are more frequently seen in adulthood.[24]

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