BJD
British Journal of Dermatology

Early-onset acral basal cell carcinomas in Gorlin syndrome

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Summary

Two patients are reported in whom early-onset, distal papules with a histopathological diagnosis of basal cell carcinoma were the first manifestation of Gorlin syndrome (GS). These lesions showed no progression and remained stable through follow-up. Two different *PTCH1* gene mutations were detected in the two patients, and thus a phenotype–genotype correlation of this manifestation of GS was not possible.

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Accepted for publication
6 May 2014

Funding sources
None.

Conflicts of interest
None declared.

DOI 10.1111/bjd.13118

What's already known about this topic?

- Gorlin syndrome (GS) shows a variety of basaloid hamartomatous lesions and basal cell carcinomas (BCCs).

What does this study add?

- Acral BCCs appearing at birth or in infancy may be the initial manifestation of GS.
- Acral BCCs are an unusual manifestation of GS.

Gorlin syndrome (GS) or naevoid basal cell carcinoma (BCC) syndrome is one of the tumour-prone genetic syndromes in humans that lead to the development of multiple BCCs of the skin. Other features of GS include macrocephaly, frontal bossing, hypertelorism, coarse facial features, keratocystic odontogenic tumours, calcification of the falx cerebri, palmar or plantar pits, vertebral or rib anomalies, polydactyly, ocular abnormalities and high incidence of tumours including childhood medulloblastoma and ovarian or cardiac fibromas.[1–3] GS shows a variable phenotype, ranging from patients with many of the typical manifestations to patients with minimal features. GS is due to mutations in the genes *PTCH1*, *PTCH2* and *SUFU* involved in the hedgehog pathway.[4–6] *PTCH1* mutations are by far the most common mutations found in patients with GS.[7]

We present two patients with a striking phenotype of acrally distributed BCCs starting in early infancy with *PTCH1* mutations and thus confirmed to have GS.

Case reports

Case 1 was a 2-year-old boy, without any familial or personal history. He was seen because of skin lesions on his hands and feet that had started by the age of 6 months. They had remained stable thereafter and new lesions had not appeared. They caused no pain or other symptoms. His general and neu-

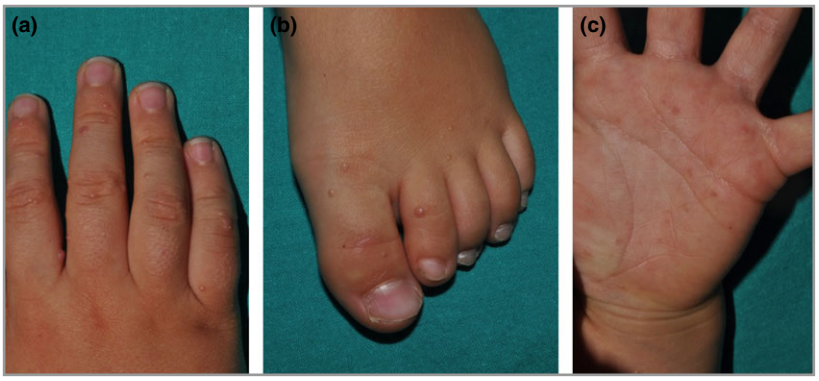

Fig 1. Patient 1. Lesions on (a) the dorsum of the hand; (b) the dorsum of the feet; and (c) the palms.

rological development was normal. On examination, multiple, 2–3 mm in diameter, pearly papules were seen on the dorsum and lateral aspects of his hands and feet (Fig. 1). Two isolated lesions were also seen on his right trunk and shoulder. Similar lesions, but with a slightly hyperkeratotic surface were present on his palms. Slight frontal bossing and closure of anterior fontanel were his only dysmorphic features. The rest of the clinical examination was unremarkable.

A skin biopsy showed a nodular dermal basal cell proliferation consistent with nodular BCC (Fig. 2). Immunohistochemistry staining with the follicular stem cell marker PHLDA1[8] was negative, thus suggesting that the lesion is unlikely to be a trichoblastoma. A cranial magnetic resonance imaging (MRI) scan showed no abnormalities. Gene testing for *PTCH1*, the main gene responsible for GS, was carried out. A mutation was identified in the first nucleotide of intron 17 (IVS17+1G>A), which alters the DNA reading frame and results in a premature stop codon and a truncated protein.

Case 2 was a 10-year-old boy who had three lesions on the dorsum of his right second and third toes and second right finger; one of them was present at birth and the other two appeared at the age of 6 months (Fig. 3). No new lesions identical to these had appeared thereafter. His family history was remarkable for multiple BCCs, palmar pits, syndactyly and jaw cysts in his father; he did not exhibit the acral lesions present in his son. Physical examination in the patient disclosed multiple papules on his palms, skin tags on the eyelids, macrocephaly and syndactyly in both feet. Orthopantomography showed a cyst on the right side of the mandible. A computed tomography scan, MRI scan, X-ray skeletal survey, and abdomen and ultrasound were normal. A biopsy from the lesion on the right finger showed features of nodular BCC. Gene testing showed a missense mutation c.1508T>G leading to a p.503Leu>Trp substitution in both the patient and his father.

Discussion

BCCs are a hallmark of GS. They usually begin to appear in the early teens, but can occur much earlier in patients who have been treated with radiation for medulloblastoma.[9,10] The median age of onset is about 25 years, but the first lesions may be delayed up to 65 years. The initial sites for development of BCCs in GS are the face and the nape of the neck, and the most commonly involved areas are the face, back and chest.[9,10] They are rarely seen below the waist. There seems to be a significant association between the number of BCCs in GS and the skin pigmentation and sun exposure.[9,10] Our patients showed a striking early onset of BCCs, but did not experience any progression thereafter. Sun exposure does not seem to have played any role because of their age and the absence of lesions on their faces; furthermore, the dorsum of feet or the palms are not areas of increased

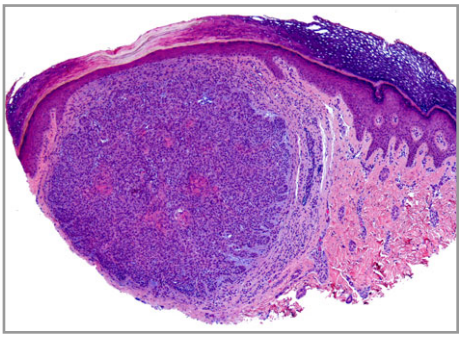

Fig 2. Patient 1. A basaloid proliferation with stromal retraction in the dermis (haematoxylin and eosin staining; original magnification × 40).

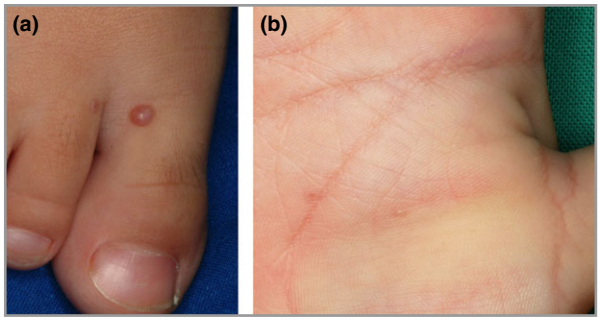

Fig 3. Patient 2. (a) Lesion on the dorsum of the toes; (b) a papule on the right palm.

sun exposure. The acral distribution of BCCs in our patients is unusual in GS, as is the presence of palmar BCCs.[11,12] Although we did not biopsy palmar papules in our patients, they had a very similar appearance to the dorsal papules, and they did not show a pitted appearance of typical palmar pits of GS. Finally, our patients showed many lesions of BCC in the absence of other typical lesions of GS, and only the gene testing or other manifestations of GS appearing later in life allowed for a diagnosis.

The type of *PTCH1* gene mutation may have played a role in the development of the unusual manifestations in our patients. Many different types of *PTCH1* gene mutations lead to GS, including deletions, insertions, splice site alterations, nonsense and missense mutations.[9] However, no evidence for a genotype/phenotype correlation has been demonstrated in GS, and thus the type of mutation and its position do not seem to have any impact on the number of BCCs and their age of onset.[7,9] The mutations we found in our patients have not been previously described in other patients with GS, and thus we cannot establish if the phenotype in our patients is the result of a specific type of gene mutation. However, because both patients exhibited different types of mutations, this hypothesis seems unlikely.

Long-term management of GS implies prevention strategies for sun and radiation exposure.[13] Because both of our patients have shown no progression and their BCCs do not seem to behave aggressively, we have decided to establish a watching attitude.

References

1 Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis* 2008; **3**:32.

2 Kimonis VE, Goldstein AM, Pastakia B *et al.* Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet* 1997; **69**:299–308.

3 Evans DGR, Ladusans EJ, Rimmer S *et al.* Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet* 1993; **30**:460–4.

4 Bale AE, Yu K-P. The hedgehog pathway and basal cell carcinomas. *Hum Mol Genet* 2001; **10**:757–62.

5 Smyth I, Narang MA, Evans T *et al.* Isolation and characterization of human patched 2 (PTCH2), a putative tumour suppressor gene in basal cell carcinoma and medulloblastoma on chromosome 1p32. *Hum Mol Genet* 1999; **8**:291–7.

6 Pastorino L, Ghiorzo P, Nasti S *et al.* Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet* 2009; **149A**:1539–43.

7 Wicking C, Shanley S, Smyth I *et al.* Most germ-line mutations in the nevoid basal cell carcinoma syndrome lead to a premature termination of the PATCHED protein, and no genotype–phenotype correlations are evident. *Am J Hum Genet* 1997; **60**:21–6.

8 Sellheyer K, Cribier B, Nelson P *et al.* Basaloid tumors in nevus sebaceous revisited: the follicular stem cell marker PHLDA1 (TDAG51) indicates that most are basal cell carcinomas and not trichoblastomas. *J Cutan Pathol* 2013; **40**:455–62.

9 Jones EA, Sajid MI, Shenton A, Evans DG. Basal cell carcinomas in Gorlin syndrome: a review of 202 patients. *J Skin Cancer* 2011; **2011**:217378.

10 Manfredi M, Vescovi P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: a review of the literature. *Int J Oral Maxillofac Surg* 2004; **33**:117–24.

11 Holubar K, Matras H, Smalik AV. Multiple palmar basal cell epitheliomas in basal cell nevus syndrome. *Arch Dermatol* 1970; **101**:679–82.

12 Golitz LE, Norris DA, Luekens CA Jr. Charles DM. Nevoid basal cell carcinoma syndrome. Multiple basal cell carcinomas of the palms after radiation therapy. *Arch Dermatol* 1980; **116**:1159–63.

13 Lam C, Ou JC, Billingsley EM. 'PTCH'-ing it together: a basal cell nevus syndrome review. *Dermatol Surg* 2013; **39**:1557–72.