Basal Cell Carcinoma with Flexural Predilection in Basal Cell Nevus Syndrome

Sir,

A 43-year-old male, presented with multiple greyish-black lesions on his face, scalp, and flexural areas. These lesions had onset around puberty and had since been increasing in size and number. Some of the lesions had been excised at private clinics but had not been investigated. Seven years back, he had also been diagnosed to have odontogenic keratocysts (2 in number) in his jaw, which was surgically removed along with molar tooth extraction. There was no family history nor was there a history of congenital malformations, skeletal abnormalities, or any other systemic manifestations including the nervous system.

On examination, he was found to have multiple, greyish-black papules, and plaques with rolled edges on the scalp, face, axillae, and inguinal region. Discrete milia were seen peri-orbitally and on the forehead [Figure 1a-c]. Palmar pits were present. Dental examination was normal. MRI of the head and neck revealed a small left maxillary odontogenic cyst and a partially empty sella turcica. Other intracranial structures and skeletal radiographs were normal. Histopathological examination of the skin lesion revealed a tumor arising from the basal layer of epidermis with characteristic peripheral palisading and demonstrating basaloid differentiation [Figure 2a-c], consistent with basal cell carcinoma (BCC). Tumor cells were diffusely positive for CK5/6 immunostain. Molecular analysis for gene mutation could not be performed due to resource constraints.

In view of three major criteria being fulfilled, a diagnosis of basal cell nevus syndrome (BCNS) was made. The patient was advised photoprotection and given topical 5% imiquimod for BCC (he refused surgical resection) with partial response.

BCNS, also called Gorlin-Goltz syndrome and nevoid basal cell carcinoma syndrome is an autosomal dominant, multisystem disorder. Most patients have mutations in the tumor suppressor gene, *PTCH-1*, with de novo mutations reported in 20−30% cases.[1] Multiple basal cell carcinomas are hallmark, with onset before 20 years of age in most cases. Though the lesions commonly involve photo-exposed areas, photo-protected areas may also be involved. A study by Tom *et al*. found males with BCNS to have more lesions on the face, upper back, and upper limbs, while females were found to have more lesions on the scalp, back, and lower limbs.[2] Though the involvement of axilla and groin has been described, predominant localization of lesions to flexures has not been described so far. Heckmann *et al*. proposed that the altered skin texture in the form of low skin tension and dermal thickness in skin folds result in altered expression of metalloproteases that play a role in tumor expansion.[3] Pigmented BCCs are more common in darker skin types, as was seen in our patient.[2]

Other cutaneous findings include palmo-plantar pits, melanocytic nevi, milium cysts, and epidermoid cysts.

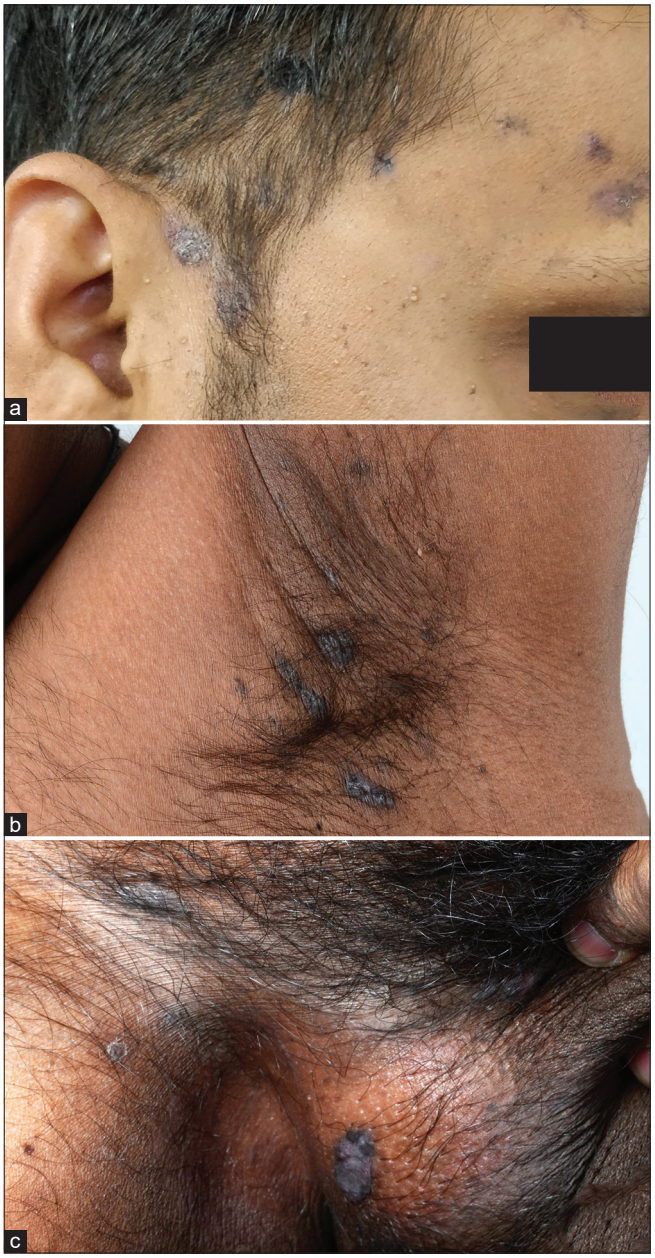

Figure 1: A case of basal cell nevus syndrome. (a) Discrete, greyish-blue papules, and plaques on the temporal region and hairline. Few milia can also be appreciated. (b) Grey-brown plaque of basal cell carcinoma on axilla, and (c) groin fold

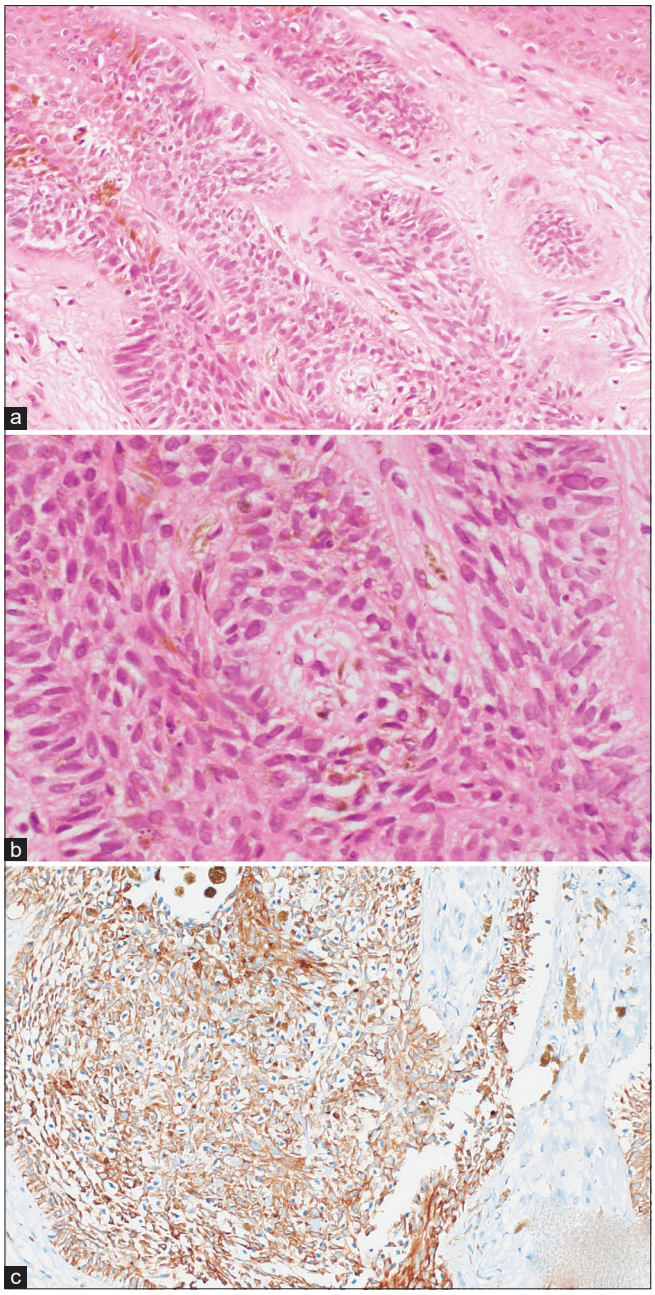

Figure 2: Histopathology of pigmented lesion on axilla. (a) Tumor cells are arising from the basal cell layer exhibiting peripheral palisading. Pigment laden macrophages can be seen in the dermis (H&E ×200); (b) Tumor cells with hyperchromatic nuclei, inconspicuous nucleoli, and scant amount of cytoplasm (H&E ×400). (c) Tumor cells strongly and diffusely positive for CK5/6 immunostain (immunoperoxidase ×200)

Extracutaneous findings include odontogenic keratocysts, calcification of falx cerebri, rib anomalies, macrocephaly, abnormal facies, and non-cutaneous tumors like medulloblastomas, ovarian or cardiac fibromas. Diagnostic criteria have been proposed by Kimonis *et al*.[4,5] and molecular diagnostic techniques to identify *PTCH-1* mutations are now available. Management requires detailed evaluation and multi-disciplinary approach. BCCs are managed in accordance with their size and location, with surgical excision, cryotherapy, ablative laser therapy, photodynamic therapy, and topical agents like 5% imiquimod and 5-flourouracil. Sonic hedgehog pathway inhibitors vismodegib, sonidegib, and saridegib are newer therapies with promising results.

To the best of our knowledge, this is the first report of BCNS with predilection of BCC localization to flexures. The occurrence of multiple BCCs should alert the physician, and prompt a detailed history taking and examination to rule out syndromic associations which may be life-saving in the long run.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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