Unilateral monomorphic hypopigmented macules: A variant of Darier disease

Sir,

Darier disease was first described by Morrow in 1886 and independently, by Darier and White in 1889. Usually expressed clinically as hyperkeratotic lesions, primarily on the seborrheic areas, Darier disease has also been reported to have various morphological variants.[1] We describe one such case presenting with monomorphic hypopigmented macules, distributed diffusely on the left half of the body.

A 39-year-old Indian woman presented with multiple non-scaly, non-tender 5 mm to 1 cm sized hypopigmented macules and papules, confined to the left side of the body and nail dystrophy [Figure 1a and b], except for a midline crossover to the right side, in the abdominal area [Figure 2a and b]. The lesions were noticed a decade ago, over the left side of her trunk and arm, later progressed distally to involve the ipsilateral lower limb and have been static since 4–5 years. Some finger and toe nails were dystrophic and showed a V-shaped notch at the free edge of their nail plates [Figure 1b]. Face, palms, soles and mucosae showed no abnormality. These lesions being asymptomatic

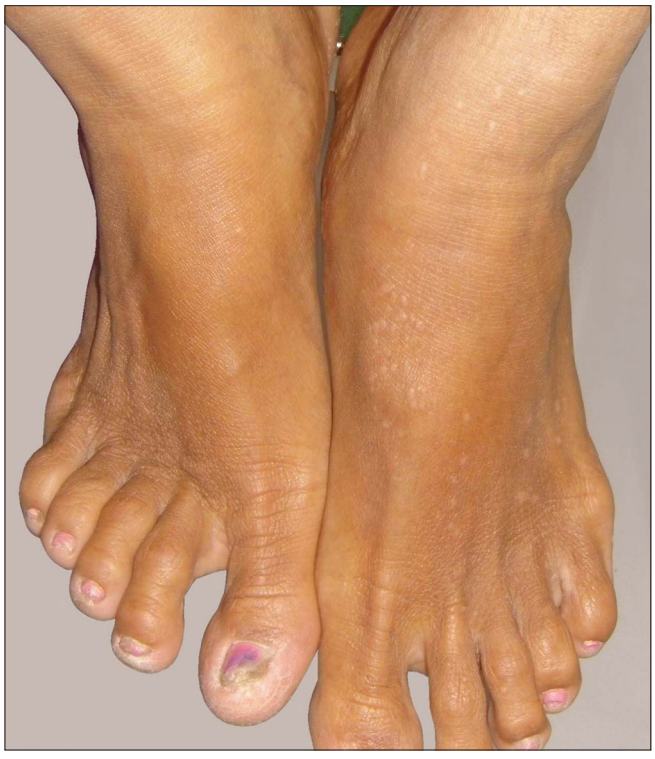

Figure 1a: Guttate leukodermic macules localized to the left lower limb with nail dystrophy

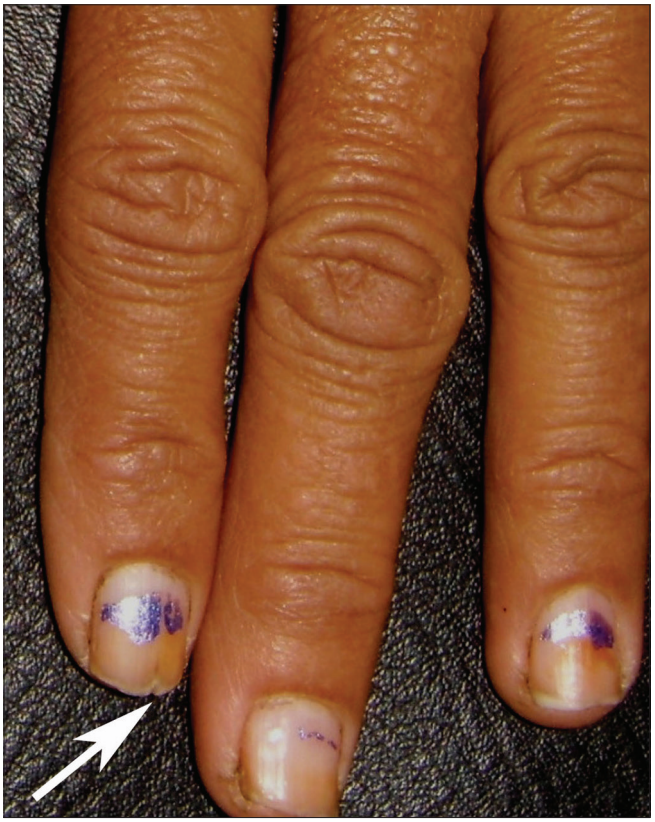

Figure 1b: Nails showing dystrophy and V-shaped nicks

and unaltered over the years, no medical advice was sought. There was no history of similar lesions in the family. No systemic complaints were noted. Differential diagnoses included lichen sclerosus, Grover's disease, leukoderma punctata, epidermodysplasia verruciformis and idiopathic guttate hypomelanosis. Histopathological examination of the punch biopsy from the hypopigmented macules revealed hyperkeratosis, parakeratosis, suprabasilar separation, acantholytic dyskeratosis and corp ronds with grains [Figure 3a-c] – all consistent with the diagnosis of Darier disease. Melanocytes in the basal epidermal layer were decreased in number, owing to the reduced number of vacuolated cells. To screen for the causative mutation, we performed a whole exome sequencing in the patient, but the analysis did not reveal any pathogenic mutation in the ATP2A2 gene. In addition, further in-depth analysis of the whole exome data could not reveal any pathogenic variations, which could even partially explain the phenotype. Therefore, we suggest that the underlying molecular defect could have arisen out of a somatic event. The patient was started on treatment with low-dose acitretin and is kept under follow-up.

Darier disease, also known as keratosis follicularis, is an autosomal dominant genodermatosis that occurs as a result of mutation in the ATP2A2 gene, located on chromosome 12q23-24.1. It encodes the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATP isoform 2 protein, which is a calcium pump that transports calcium ions from the cytosol into the sarcoplasmic/endoplasmic reticulum, catalyzing the hydrolysis of adenosine triphosphate.[2] It is classically characterized by follicular and nonfollicular skin colored to reddish brown hyperkeratotic papules, primarily on the seborrheic areas, along with a cobblestone appearance of the buccal mucosa and white/red longitudinal bands on the nail plates that frequently end in V-shaped notching.[1] Zosteriform or linear, cornifying, vesiculobullous, isolated acral hemorrhagic,[3,4] acrokeratosis verruciformis of Hopf,[5] comedonal and hypopigmented/leukodermic macules[1,3,4] are its rare morphological variants. The last one was seen in our case.

Hypopigmented macules in people of color with Darier disease were first described by Goddal and Richmond in 1965. Cattano, in 1968, postulated these to be postinflammatory. However, the lack of any preceding inflammatory lesions led Cornelison *et al*., in

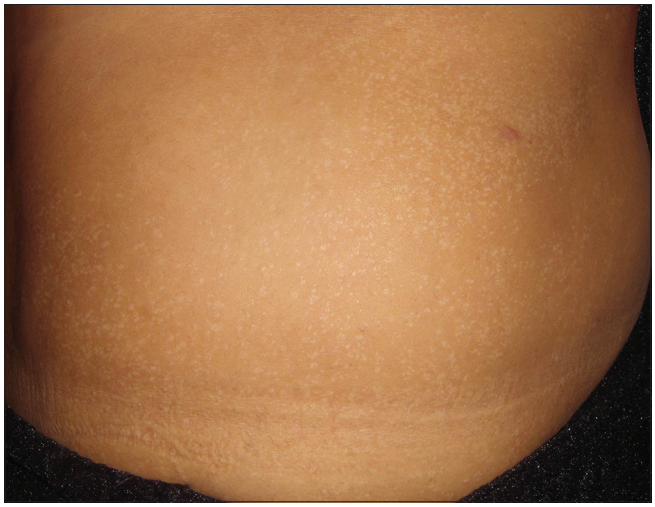

Figure 2a: Hypopigmented macules on left side of abdomen with a cross over to the right

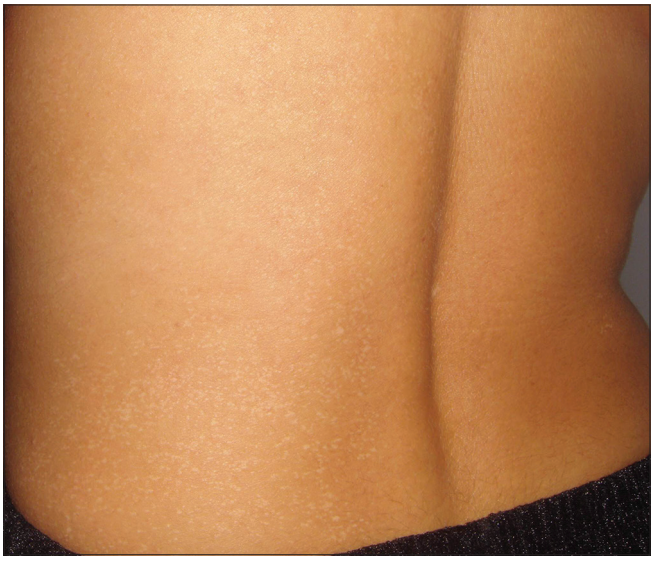

Figure 2b: Segmental hypopigmented macules localized to the left side of the back

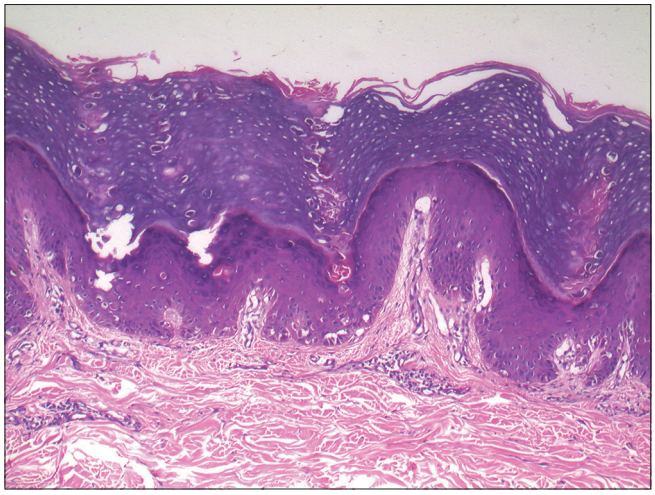

Figure 3a: Acantholytic dyskeratosis with overlying parakeratosis (H and E, ×100)

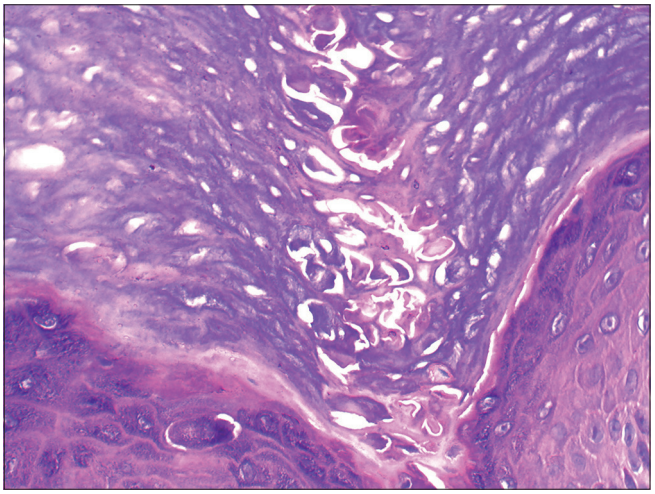

Figure 3b: Stratum corneum showing dyskeratotic and parakeratotic cells or corp grains (H and E, ×400)

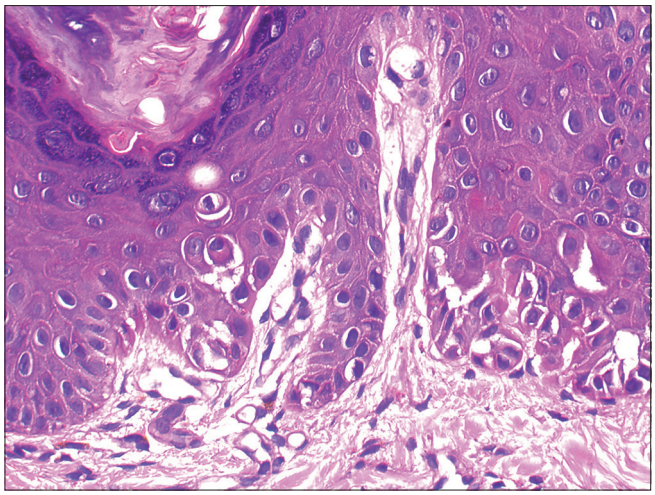

Figure 3c: Suprabasal split with some dyskeratotic acantholytic cells (H and E, ×400)

1970,[6] to suggest that these leukodermic macules corresponded to a "subclinical Darier disease," a view later supported by Berth-Jones and Hutchinson.[1,7,8] Since then, about 20-odd such cases of hypopigmented macules, predominantly on the trunk and proximal extremities have been reported in Darier disease, accompanying hyperkeratotic papules.[1,6-10] However, the absence of the classical warty lesions and diffuse segmental presence of the hypopigmented lesions on the left half of the body with cross over to the right side on abdomen (possibly due to partial mosaicism) appears to be a combination unique to this case, only once previously reported by Morin *et al*.[11]

Ultrastructural examination of such macules has revealed their melanocytes to be morphologically normal, containing mature melanosomes. However, in comparison to the perilesional skin, basal and suprabasal keratinocytes of these lesions show a considerable reduction in melanin granules, despite being surrounded by melanosome-filled dendrites.[12] A flawed keratinization interfering with the melanosome transfer with a disturbance in the "epidermal melanin unit" may contribute to this strange focal, macular depigmentation.[9] The unique absence of hyperkeratotic papules in the reported case and the absence of ATP2A2 gene mutation, raising the possibility of a somatic mutation, presented a diagnostic dilemma and motivated us to keep her under follow-up and to look out for any future development of hyperkeratotic papules.

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Conflicts of interest

There are no conflicts of interest.

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