Hyperkeratotic Papules and Black Macules on the Hands

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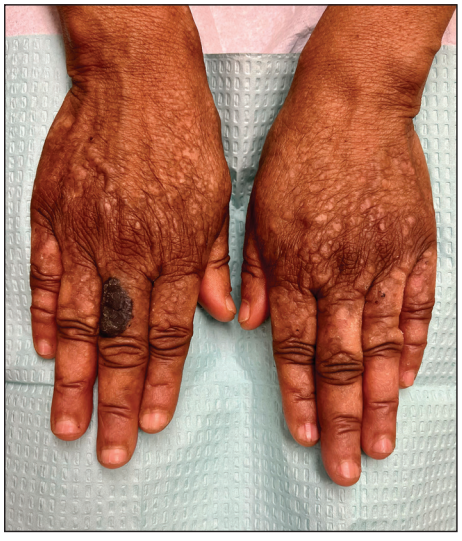

An elderly woman with a long history of hyperkeratotic papules on the abdomen, forearms, dorsal hands, and skinfolds presented with new lesions on the dorsal hands that had developed over the preceding few months after a lapse in treatment with her previous dermatologist. Her medical history was otherwise unremarkable. Physical examination revealed hyperkeratotic papules, black hemorrhagic macules with jagged borders, and a thin hemorrhagic plaque on the dorsal hands. Nail findings were notable for alternating white and red longitudinal bands with nicking of the distal nail plates. She also had scattered leucodermic macules over the trunk, feet, arms, and legs, as well as numerous hyperkeratotic papules coalescing into plaques over the mons pubis and in the inguinal folds.

WHAT'S YOUR **DIAGNOSIS?**

a. acral hemorrhagic Darier disease
b. acrokeratosis verruciformis of Hopf
c. bullous lichen planus
d. hemorrhagic lichen sclerosus
e. porphyria cutanea tarda

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Drs. Kovacs and Wan have no relevant financial disclosures to report. Dr. Patel is a advisor for Dermeleve and has received a research grant from the National Institutes of Health.
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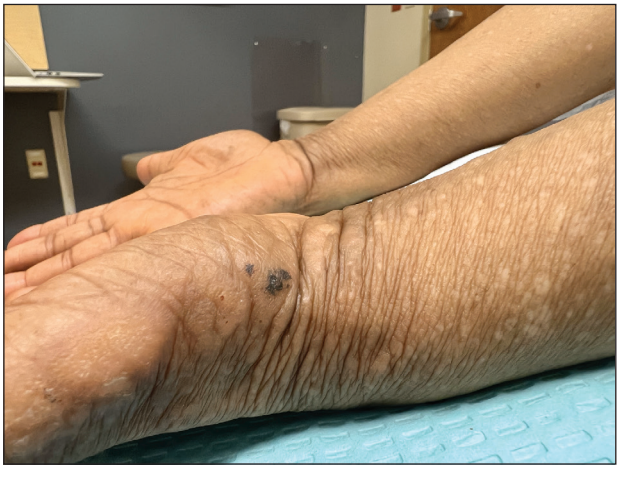
Cutis. 2024 October;114(4):E26-E28. doi:10.12788/cutis.1131

THE **DIAGNOSIS:** Acral Hemorrhagic Darier Disease

Darier disease (DD), also known as keratosis follicularis, is a rare autosomal-dominant genodermatosis caused by mutations in the ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2 gene (*ATP2A2*). This gene encodes the enzyme sarcoplasmic/endoplasmic reticulum calcium ATPase 2, which results in abnormal calcium signaling in keratinocytes and leads to dyskeratosis.[1] Darier disease commonly manifests in the second decade of life with hyperkeratotic papules coalescing into plaques, often accompanied by erosions and fissures that cause discomfort and pruritus. Darier disease also is associated with characteristic nail findings such as the classic candy cane nails and V-shaped nicking.

Acral hemorrhagic lesions are a rare manifestation of DD. Clinically, these lesions can manifest as hemorrhagic macules, papules, and/or vesicles, most commonly occurring following local trauma or retinoid use. Patients with these lesions are believed to have either specific mutations in the *ATP2A2* gene that impair sarcoplasmic/endoplasmic reticulum calcium ATPase 2 function in the vascular endothelium or a mutation in the sarcoplasmic/endoplasmic reticulum calcium ATPase protein itself, leading to dysregulation of mitochondrial homeostasis from within the cell, provoking oxidative stress and causing detrimental effects on blood vessels.[2] Patients with this variant can present with all the features of classic DD concomitantly, with varying symptom severity or distinct clinical features during separate episodic flares, or as the sole manifestation. Other nonclassical lesions of DD include acral keratoderma, giant comedones, keloidlike vegetations, and leucodermic macules (Figure).[3]

Acral hemorrhagic DD may appear either in isolation or in tandem with more traditional symptoms, necessitating consideration of other possible differential diagnoses such as acrokeratosis verruciformis of Hopf (AKV), porphyria cutanea tarda, bullous lichen planus (BLP), and hemorrhagic lichen sclerosus.



Leucodermic macules scattered over the left arm. A hemorrhagic macule with jagged borders was present on the left lateral wrist.

Sometimes regarded as a variant of DD, AKV is an autosomal-dominant genodermatosis characterized by flat or verrucous hyperkeratotic papules on the hands and feet. In AKV, the nails also may be affected, with changes including striations, subungual hyperkeratosis, and V-shaped nicking of the distal nails. Although our patient displayed features of AKV, it has not been associated with acral hemorrhagic macules, making this diagnosis less likely than DD.[4]

Porphyria cutanea tarda, a condition caused by decreased levels of uroporphyrinogen decarboxylase, also can cause skin manifestations such as blistering as well as increased skin fragility, predominantly in sun-exposed areas.[5] Our patient's lack of photosensitivity and absence of other common symptoms of this disorder, such as hypertrichosis and hyperpigmentation, made porphyria cutanea tarda less likely.

Bullous lichen planus is a rare subtype of lichen planus characterized by tense bullae arising from preexisting lichen planus lesions or appearing de novo, most commonly manifesting on the oral mucosa or the legs.[6] The bullae associated with BLP can rupture and form ulcers—a symptom that could potentially be mistaken for hemorrhagic macules like the ones observed in our patient. However, BLP typically is characterized by erythematous, violaceous, polygonal papules commonly appearing on the oral mucosa and the legs with blisters developing near or on pre-existing lichen planus lesions. These are different from the hyperkeratotic papules and leucodermic macules seen in our patient, which aligned more closely with the clinical presentation of DD.

Hemorrhagic lichen sclerosus presents with white atrophic patches and plaques and hemorrhagic bullae, which may resemble the leucodermic macules and hemorrhagic macules of DD. However, hemorrhagic lichen sclerosus most commonly involves the genital area in postmenopausal women. Extragenital manifestations of lichen sclerosus, although less common, can occur and typically manifest on the thighs, buttocks, breasts, back, chest, axillae, shoulders, and wrists.[7] Notably, these hemorrhagic lesions typically are surrounded by hypopigmented skin and display an atrophic appearance.

Management of DD can be challenging. General measures include sun protection, heat avoidance, and friction reduction. Retinoids are considered the first-line therapy for severe DD, as they help normalize keratinocyte differentiation and reduce keratotic scaling.[8] Topical corticosteroids can help manage inflammation and reduce the risk for secondary infections. Our patient responded well to this treatment approach, with a notable reduction in the

number and severity of the hyperkeratotic plaques and resolution of the acral hemorrhagic lesions.

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