Images in Dermatology

Darier Disease

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A man in his 60s presented with a long-standing pruritic rash. His father and sons had a similar rash. Physical examination showed alternating white and red longitudinal streaks and distal V-shaped notching of several fingernails (**Figure**, A), yellow-brown greasy papules on the thighs and chest (Figure, B), and small white papules on the gingivae coalescing into cobblestoned plaques (Figure, C). Skin biopsy showed suprabasal acantholysis and dyskeratosis. The combination of nail, mucocutaneous, and histopathologic findings with family history was consistent with Darier disease. Treatment with acitretin improved the skin disease.

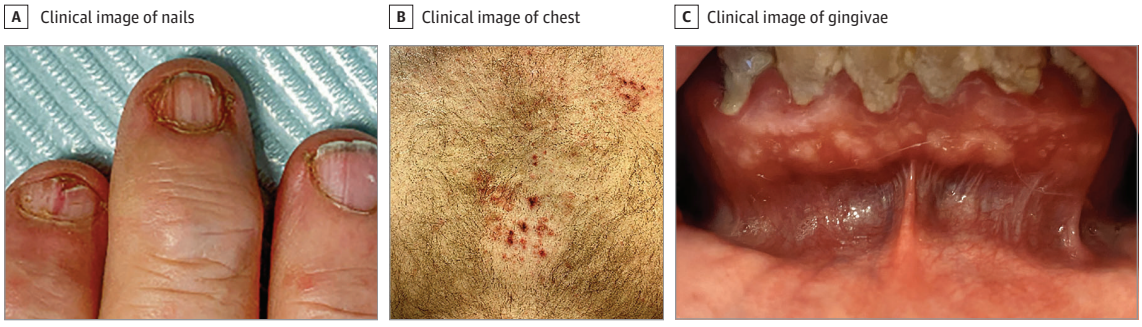
Darier disease is an autosomal dominant disorder involving the *ATP2A2* gene, which encodes sarco/endoplasmic reticulum calcium ATPase protein (SERCA2) responsible for pumping calcium from the cytosol into the endoplasmic reticulum. Alternative splicing of SERCA2 results in 3 isoforms: SERCA2a (expressed in myocardium), SERCA2b (ubiquitously expressed including skin), and SERCA2c. Several pathogenic variants of the *ATP2A2* gene, including missense, premature stop codons, and abnormal splicing,[1] result in reduced expression or dysfunctional SERCA2 and causing diminished endoplasmic calcium stores, endoplasmic reticulum stress, apoptosis (histologically seen as corps ronds and grains), and improper folding and trafficking of desmosomal proteins (histologically seen as acantholysis).[1]

Greasy keratotic yellow to brown papules in a seborrheic distribution are commonly seen. Less common cutaneous findings include palmoplantar pits, acral keratoses, and flat-topped papules. Extracutaneous manifestations can aid in diagnosis. Pathognomonic nail findings include V-shaped notching and alternating white and red longitudinal streaks, which are seen in up to 99% of cases.[2,3] Intraoral cobblestoning of the hard palate, buccal mucosa, tongue, and gingiva can be seen.[4] An association exists with neuropsychiatric disorders, but systemic manifestations are otherwise absent due to compensation from other SERCA isoforms.[5]

Occurrence around puberty and a chronic course are typical.[2] Medications like lithium and environmental factors including UV light, heat, friction, and sweating and moisture can induce flares, and secondary bacterial and viral infections can occur.[1,2] While family history can provide a useful clue in that the inherited form of the disease has nearly complete penetrance with variable expressivity, sporadic cases do occur. Postzygotic pathogenic genetic variants in patients with underlying germline variants result in loss of heterozygosity in specific areas and cause mosaic patterns of disease.

Treatment is difficult. General measures include sun protection, avoidance of heat, and minimization of friction.[2] Topical antimicrobial washes can help decrease the bacterial load and associated risk of superimposed infection. Corticosteroids reduce inflammation but do not alter the disease course. Low-dose naltrexone and topical and systemic retinoids have been used in some cases.[2] Refractory cases can be treated surgically.[2]

Figure. Clinical Images



A, V-shaped notching and alternating white and red longitudinal streaks on the fingernails. B, Greasy keratotic papules and plaques on the chest. C, Cobblestoning of the gingivae.

ARTICLE INFORMATION

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