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Darier disease: A fold (intertriginous) dermatosis

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Abstract Darier disease, also known as Darier-White disease, is characterized by yellow to brown, oily keratotic papules and plaques in the seborrheic areas of the face and chest. This disorder may show different clinical manifestations, such as palmoplantar pits and nail abnormalities. The trigger factors are mechanical trauma, heat, humidity, ultraviolet B, and pyogenic infections. The disease usually becomes apparent in the second decade of life. The ATP2 A2 (SERCA2) gene mutation was detected in all patients. Histopathologic changes include epidermal adhesion loss, acantholysis, abnormal keratinization, eosinophilic dyskeratotic cells in the spinous layer known as corps ronds, and the presence of grains in the stratum corneum. Although the treatment for Darier disease is unsatisfactory, some relief has been achieved with the use of corticosteroids and retinoids.

Introduction

Darier disease, or Darier-White disease, also known as keratosis follicularis, is an autosomal dominantly inherited keratinization disorder affecting the skin, mucosal membranes, and nails.[1–3] Scaly, hyperkeratotic yellow to brown papules and plaques in the seborrheic regions and flexural areas are characteristic clinical features of the disease. The other associated findings include palmoplantar papules, white papules in the oral mucosa, and nail changes. Neuropsychiatric abnormalities may coexist.[3–7] Mutations in the sarcoplasmic/endoplasmic reticulum calcium ATPase isoform 2 (SERCA2 b) are identified in all cases.[8,9] This mutation causes abnormalities in the calcium ion signal system, and, as a result, apoptosis and the loss of adhesion among the suprabasillary cells occur.[4]

History

The disease was first reported in 1889 by the French dermatologist Jean Darier (1856-1938) and also described by the first American professor of dermatology, James Clarke White (1833-1916), independently. It was described as a foul-smelling skin disorder with greasy and scaly brownish follicular lesions.[4,7,10] Darier named the disease *psorospermose folliculaire vegetante*. White claimed that it might be an inherited disease due to the similarity of skin lesions in the affected mother and daughter.[4] A localized form of the disease was reported in 1906.[6,11] A patient was diagnosed for the first time ever with oral manifestations in 1917.[5]

Epidemiology

Darier disease is a rare, autosomal, inherited disease. The disease can be found in both sexes equally, and no ethnic group differences have been identified.[3,7,8] The prevalence of the disease has ranged from 1 in 30,000 to 1 in 50,000.[7] Darier disease has been reported in various different clinical expressions in affected family members.[3,7,12] Also, sporadic mutations are common.[7] Despite the inherited characteristic of the disease, 47% of the patients do not have any family history of it. This could be ascribed to the fact that mild forms may have been overlooked.[5]

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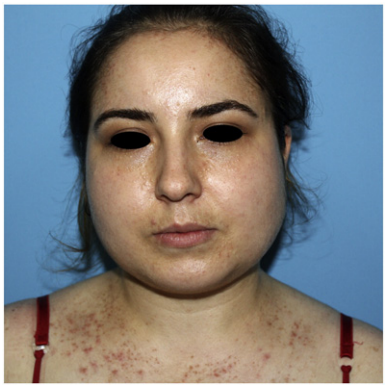

Fig. 1 Greasy papules over the oily areas of the face.

Pathogenesis

Darier disease is caused by a mutation in the ATP2 A2 (SERCA 2) gene located in the chromosome 12, q23-24.1 regions.[13–16] SERCA 2 is a pump that transports calcium ions into the endoplasmic reticulum and maintains high calcium concentrations in the lumen.[1,4] In this way, SERCA2 plays a crucial role in the synthesis and post-translational modifications of proteins. It has two isoforms: 2 a and 2 b. SERCA 2 b is the major isoform expressed in the epidermis. Insertion/deletion mutations in the SERCA 2 b isoform give rise to abnormal protein production and a loss of desmosomal adherence, which causes Darier disease. At least 120 ATP2 A2 mutations have been reported, and the majority of them are missense mutations (50%).[7]

Clinical features

Darier disease generally occurs between ages 6 and 20, with a peak in puberty for most patients. It is characterized by keratotic papules with a yellow to brown, greasy appearance in the seborrheic areas of the face, scalp, and chest (Figures 1 and 2).[1,2,4] These papules may coalesce to form fissured vegetative plaques and become bad-smelling lesions with secondary infections, especially in areas where folds occur.[7,8] The clinical severity of the disease is associated with factors such as mechanical trauma, heat, humidity, ultraviolet B, and pyogenic infections. Pruritus is a common symptom.[4,14] Nail abnormalities include longitudinal white or red lines, grooves and characteristic V-shaped notches on the distal ends of the nail plates (Figure 3). Palmoplantar pits and keratotic papules on the dorsum of the hands and feet can be seen.[1,3,17]

In spite of the fact that mucous membrane involvement is not common, white papules may be located on the oral mucosa, the esophagus, the vulva, and the rectum.[7,18] Up to 50% of patients with Darier disease have oral mucosa lesions, and the most affected site is the hard palate. Whitish papules with central depression may form irregular plaques mimicking the appearance of nicotinic stomatitis.[18–20] Also, gingivae buccal mucosae and tongue are the places in the mouth that can be affected. Parotid salivary glands may also be involved. Periductal fibrosis and ductal obstruction cause intermittent swellings in up to 30% of patients.[19] Oral lesions are considered to have no malignant potential,[20] but one squamous cell carcinoma case has been reported in a patient with Darier disease.[5,19,21]

In the literature, rare clinical variants of Darier disease have been reported. These include a cornifying type, an acral hemorrhagic form, a zosteriform pattern, and comedonal Darier disease. There is a case report of a patient who had three variants together: comedonal, cornifying, and a hypertrophic type.[22] Acral forms may be confused with acrokeratosis verruciformis of Hopf.[15,23,24] Localized forms of the disease occur in 10% of patients.[6,11] The clinical appearance is unilaterally located linear lesions following the Blaschko lines without family history.[6] Kaposi-Juliusberg syndrome is a severe generalized cutaneous herpetic infection as a rare complication of Darier disease.[19]

Neuropsychiatric disorders such as epilepsy, major depression, bipolar disorder, schizophrenia, and learning difficulties may accompany Darier disease.[3,25]

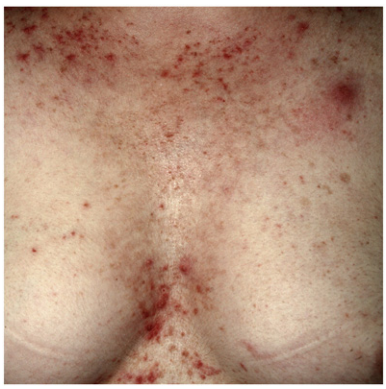

Fig. 2 A close-up view shows erythematous keratotic papules with greasy appearance in seborrheic areas of the chest.

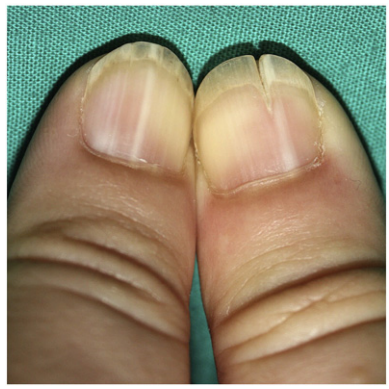

Fig. 3 Characteristic V-shaped notch on the distal end of the nail plate.