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Correspondence

Familial comedonal Darier s disease: a new ATP2A2 mutation with intra-family clinical heterogeneity

Dear Editor,

Darier s disease (DD) is an autosomal dominant genodermatosis caused by mutations in ATP2A2, which encodes sarcoendoplasmic reticulum CA2+-ATPases. Classic DD typically manifests follicular and extrafollicular greasy hyperkeratotic papules and plaques, arising primarily in seborrheic areas. However, there are other rare variants such as comedonal Darier s disease (CDD). It was first described in 1995, and 21 cases have been reported since then, with only three of them being familial. We report an additional case of familial CDD with a new ATP2A2 mutation.

A 45-year-old woman presented with comedo-like lesions, nodules, and cysts on the face and trunk since adolescence, diagnosed as acne vulgaris for years. Physical examination also revealed brownish papules on the backs of the hands, palmar pits, and longitudinal nail striae. She referred that her mother and maternal grandmother had the same skin lesions, and three of their four children had similar although not identical dermatosis (they were diagnosed as classic DD, without comedo-like lesions) (Figure 1). The histology of a facial lesion showed a comedone filled with a keratin plug and suprabasal acantholysis with villi and dyskeratotic cells (Figure 2). The genetic test in the proband showed a missense heterozygous variant c.287T>C (p.Leu96Pro) in ATP2A2. This variant has not been reported neither in the scientific bibliography nor in mutation databases; however, an ACMG classification catalogues the mutation as likely pathogenic under PP3, PM2, PP2, and PP4 criteria. Finally, the patient was diagnosed as CDD.

CDD is a peculiar variant of DD. It is clinically characterized by its prominent follicular involvement, which promotes the formation of large comedo-like lesions, mostly located on the face and scalp. Sixty percent of the cases presented other classic Darier s disease features. Lesions are usually oligo-symptomatic and persistent.[1] The cases present different grades of severity, from localized comedonal lesions to generalized comedones, nodules, and cysts like our case. The diagnosis can be challenging as it can be misdiagnosed as acne vulgaris, trichoepithelioma, familial dyskeratotic comedones, or warty dyskeratoma. Histopathologically, CDD is characterized by acantholytic and dyskeratotic cells located in the follicular adnexal epithelium of variable enlarged hair follicles.[1,2] The keratin profile in CDD has also been reported presenting similarities with both DD and acne vulgaris, although it is closer to DD.[3]

Regarding familial CDD, there are only three cases reported in the literature. Derrick et al.[4] reported a 55-year-old man who presented with typical warty papules of Darier s disease in combination with comedones whose mother and sister had evidence of DD. Chung et al.[2] reported a family with seven maternal relatives who presented also with typical features of DD and facial comedones. Guevara et al.[5] revealed a heterozygous missense mutation in ATP2A2 (c.1070C>A:p.T357K) in a CDD patient,

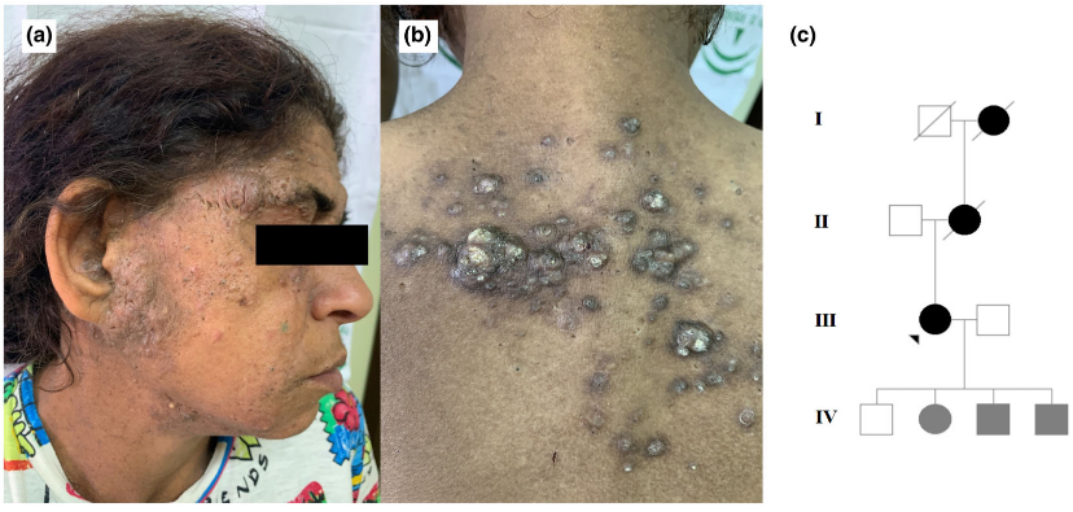

Figure 1 (a,b) Comedonal lesions, large nodules, and cysts on the face and back. (c) In the family pedigree, her mother and maternal grandmother seemed to have the same clinical manifestations (black: CDD), while three of their four children presented manifestations of classic DD only (gray: DD)

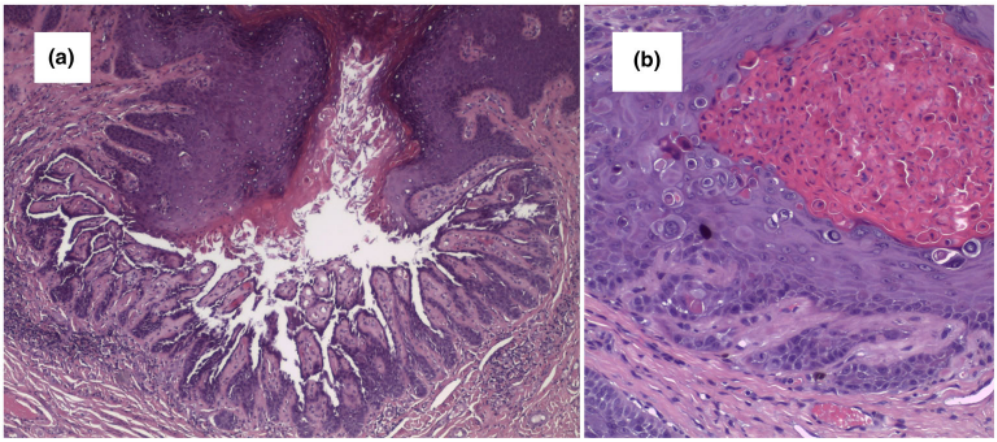

Figure 2 (a) Dilated hair follicle filled with keratin plug. The follicular adnexal epithelium shows suprabasal acantholysis with the formation of villi and dyskeratosis (hematoxylin eosin, 10). (b) Detail of dyskeratotic cells with corps ronds and grains (hematoxylin eosin, 20 magnification)

whose daughter manifested only nail abnormalities but the same mutation. These cases show that mutations in ATP2A can have a variable expressivity resulting in different members of the same family suffering different subtypes of DD (or, more rarely, CDD). Our case supports this idea, since the case proband manifested comedonal lesions and classic features of DD, while her children only had the characteristic signs of DD.

In conclusion, we report a case of familial CDD caused by a new mutation in ATP2A2, c.287T>C (p.Leu96Pro), and we highlight the importance of doing an exhaustive exploration to the relatives of a patient diagnosed as CDD due to its clinical variability.

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