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Case Report

Darier-White disease: A rare genetic disorder

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Abstract

Background: The clinical manifestation of Darier-White disease, an autosomal dominant genodermatosis, are greasy hyperkeratotic papules in seborrheic regions with nail abnormalities and mucous membrane changes due to a defective sarcoendoplasmic calcium pump. The clinical appearance and unpleasant odor in some sites of the lesions may cause psychosocial disturbances and pose a major morbidity.
Case Illustration: We report a case of a 20-year old female with clinical manifestations of multiple erythematous to hyperpigmented hyperkeratotic papules, multiple flesh-colored keratotic papules with red and white longitudinal bands on dystrophic fingernails, as well as plantar pits. Skin punch biopsy was performed to support the diagnosis. Urea-containing emollients and acitretin at a dose of 0.3 mg/kg/day were prescribed for the patient.
Discussion: Our case showed the classic clinical manifestations of Darier's Disease. The skin punch biopsy result is also consistent with Darier's disease. We provided the patient with emollients and acitretin, a systemic retinoid, which are found to be the most effective treatment for DD. While no relationship is established between Darier's disease and other medical problems, the patient developed anxiety and social isolation due to the clinical appearance and odor, creating a negative impact on her quality of life.
Conclusion: Comprehensive and holistic management should be the goals for the management of this rare genetic disorder

Keywords: *acantholytic disease, Darier-White disease, genodermatosis*

Background

Darier's disease (DD) is a rare autosomal dominant genodermatosis resulting from a defect in ATP2A2 gene on chromosome 12q23-23.1, creating aesthetical implications. The incidence of disease is reported to be 4 new cases per million, over 10 years.[1] It is a chronic disease whose exacerbations and remissions may be initiated by various triggering factors. Accompanying neuropsychiatric problems have also been reported in some cases. Treatment is both challenging and unsatisfactory. Due to its rarity, we report herein a case of DD who exhibited classic clinical and histopathologic findings.

Case Illustration

A 20-year old female presented with a 12-year history of multiple flesh-colored, asymptomatic papules over the dorsal surface of the hands and feet, palms and soles, multiple erythematous to hyperpigmented, hyperkeratotic papules on the anterior neck, axillary, inframammary and inguinal areas, and dystrophic fingernails with red and white longitudinal bands (Figure 1). These lesions were associated with malodorous smell on the axillary, inframammary and inguinal areas, more pronounced during summer months from March to May. There was no associated comorbidity. Similar lesions were seen on her father. The patient's quality of life has been negatively-affected due to the bothersome odor and unsightly lesions. Due to the anxiety and emotional stress experienced by the patient, consultation was done at our institution.

Skin punch biopsy showed suprabasal acantholysis with a presence of round acantholytic cells with mild superficial perivascular inflammatory infiltrate of lymphocytes and eosinophil (Figure 2). Referral to a psychiatrist for counseling was advised. The patient was treated with urea-containing emollients and acitretin at a dose of 0.3 mg/kg/day. However, the patient did not return for follow up. Thus, treatment outcome is unknown.

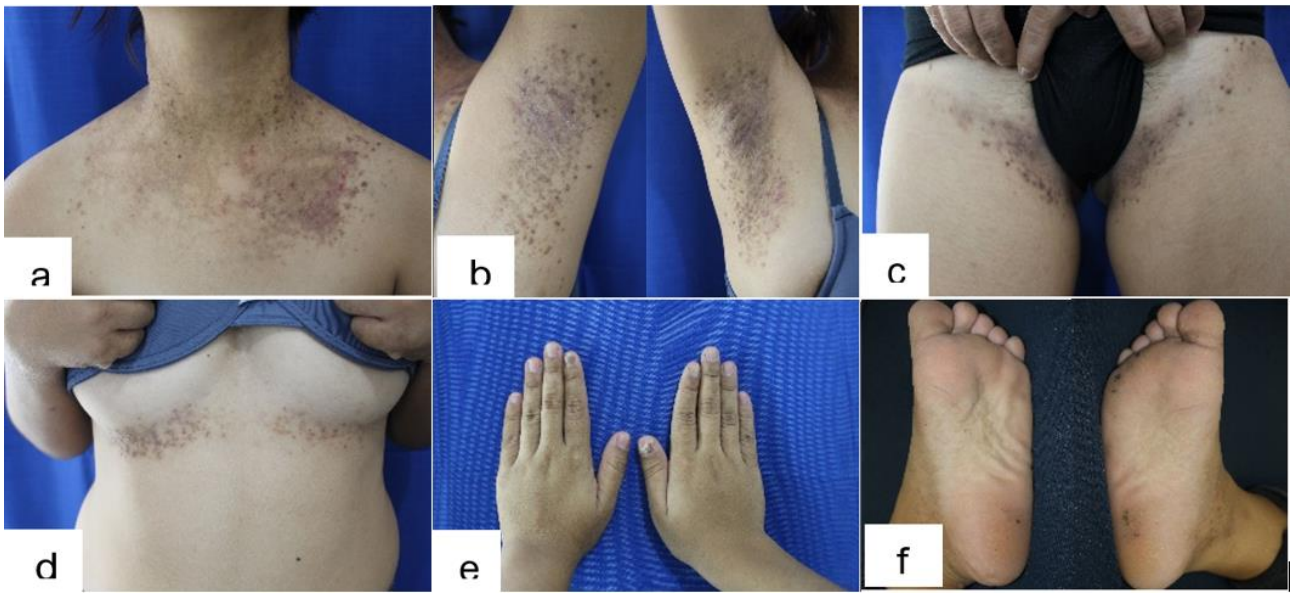

Figure 1. Multiple erythematous to hyperpigmented, hyperkeratotic papules on the (a) anterior neck, (b) axillary, (c) inguinal and (d) inframammary areas, (e) multiple flesh-colored, keratotic papules on the dorsal surface of hands with red and white longitudinal bands and dystrophic fingernails, (f) plantar pits

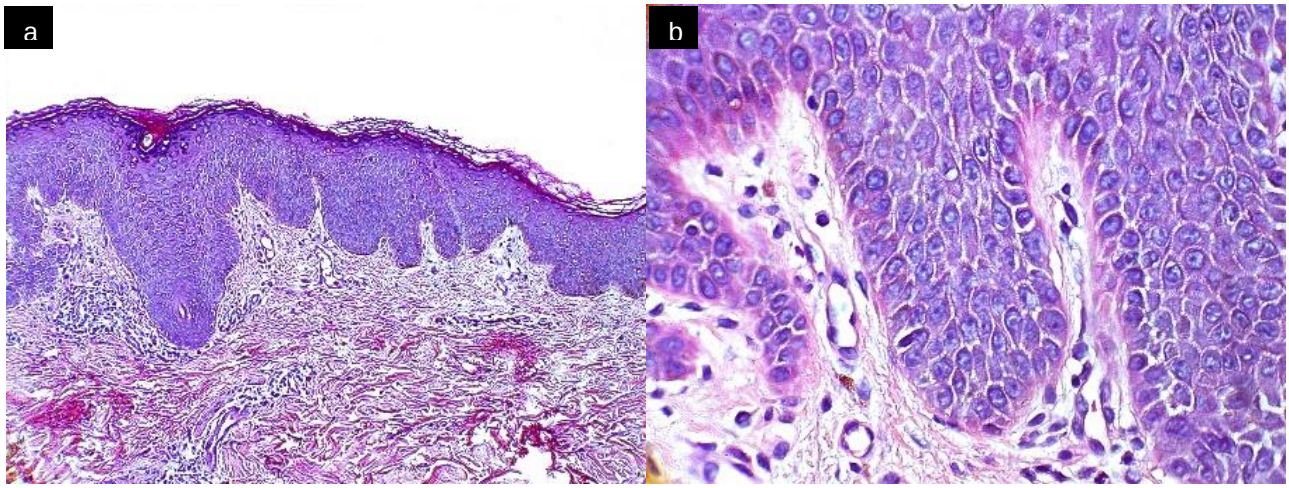

Figure 2. (a) Skin punch biopsy revealed suprabasal acantholysis with a presence of round acantholytic cells with mild superficial perivascular inflammatory infiltrate of lymphocytes and eosinophil (H&E, 100x), (b) (H&E, 400x)

Discussion

DD is a rare autosomal dominant genodermatosis with reported prevalence varying from 1 in 100,000 in Denmark to 30–35,000 in Northern England and Scotland. The average age of onset is during childhood or adolescence, with no sex predilection.[1] DD is caused by a defect in ATP2A2

gene on chromosome 12q23-23.1. ATP2A2 is a gene that encodes the sarcoplasmic/endoplasmic reticulum Ca2+ ATPase isoform 2 protein (SERCA2).[2] SERCA2's role is fundamental in cellular calcium homeostasis and in the active transportation of calcium ions from the endoplasmic reticulum's cytosol to the lumen, to achieve a low calcium level in the cytoplasma.[3] The mutation interferes with the normal internal calcium "signaling" that regulates processes such as cell proliferation, differentiation and adhesion between keratinocytes.[2] In a study by Dogan, *et al.,* it is believed that the mutation of this protein leads to loosening of the cell-cell adhesion by causing defect in the formation or maturation of the tonofilament-desmosome complex. The disrupted adhesion results in separation of the cells which contribute to particular focal suprabasilar acantholysis and dyskeratosis in keratinocytes known as corps ronds and grains histopathologically.[4]

DD has cosmetic and aesthetic implications.[1] It is a chronic disorder, which may exacerbate and go into remissions. Exacerbations have been reported to be triggered by heat, sunlight, UVB, lithium, oral corticosteroids, mechanical trauma and menstruation.[1] The diagnosis of DD can be made through clinical observations of persistent greasy hyperkeratotic papules and plaques, usually found around seborrheic areas, accompanied with characteristic nail abnormalities.[4]Changes to the nail include short and wide nails, with white and red longitudinal bands, V-shaped notch and scalloping of distal nail plate and subungual hyperkeratosis. The palmar pits are pathognomonic. Mucus membranes may show asymptomatic papules with central depression or cobblestone papules on palatal and alveolar mucosa in 50% of cases. Plane wart-like lesions on the dorsal surface of hands and feet and guttate leukoderma may be early features of the disease.[1]

In our case, the presence of multiple erythematous to hyperpigmented hyperkeratotic papules on the anterior neck, axillary, inguinal, and inframammary areas, and multiple flesh-colored, keratotic papules on the dorsal surface of the hands with red and white longitudinal bands on dystrophic fingernails and plantar pits show classic clinical manifestations of Darier's Disease. Suprabasal acantholysis with the presence of round acantholytic cells and mild superficial perivascular inflammatory lymphocytes and eosinophils infiltrate seen in the patient's skin punch biopsy are also histopathologic findings consistent with Darier's disease.

The treatment of DD may pose a challenge and often difficult and unsatisfactory.[3] The principles of the treatment of DD includes heat and sunlight avoidance and emollient use.[5] For mild DD, elimination of exacerbating factors and the use of sunscreen and emollient substances such as urea or lactic acids may be beneficial. For more severe cases, topical and oral retinoids, lactic acid, salicylic acid, topical steroid, and oral antibiotics can be used.[6] A study by Cassals, *et al*. found topically applied adapalene to be effective. Short contact 0.1% tazarotene gel for 6 weeks treated the disease successfully. In a study by Dogan, *et al*., topically applied 0.1% tretinoin cream treated the lesions after twice daily application for 4 weeks.[4] O'Malley, *et al*.'s study reported 38% (15 out of 40) of the patients treated with topical tretinoin showed partial or complete response.[6] There are other local treatment options reported for Darier's disease including 5-FU, cryotherapy and photodynamic therapy, although these alternatives are not as cost-effective when compared to short-term topically applied retinoids.[4]

Systemic retinoids, including isotretinoin, acitretin, and alitretinoin, are found to be the most effective treatment for DD.[3] Retinoids are believed to have antiproliferative effects on keratinocytes: modulating keratinocyte differentiation, normalizing abnormal differentiation, and down-regulating epidermal growth factor receptors and hyperproliferative keratins.[4] However, their use is limited due to their potentially detrimental side effects.[3] In a case report by Santos-Alarcon, *et al.,* partial improvement was seen after one month of 0.5 mg/kg/d of oral isotretinoin (30 mg/day), but the patient experienced adverse effects including cheilitis, epistaxis, and xerosis, which the patient was not able to tolerate.[7] In this case, the patient was given urea-containing emollients and acitretin at a dose of 0.3 mg/kg/day. Due to the patient's non-compliance with the follow-up schedule, treatment response cannot be ascertained.

The risk of transmission of generalized disease will depend on whether the germ line is affected.[2] Data from several large, multigenerational pedigrees have revealed that the disease is passed down in an autosomal dominant fashion and has complete penetrance.[8] More than 113 familial and sporadic mutations in ATP2A2 have been identified. Investigations on the correlations between genotype and phenotype have not been successful. Identical ATP2A2 mutations in family members can show various degrees of clinical severity, which suggests the expression of Darier's disease may be affected by other genes or environmental factors.[1] Although there were claims

of having similar lesions on the patient's father, there was no evidence that they were the same. Genetic transmission cannot be proven.

No relationship is established between Darier's disease and other medical problems in the current literature. However, the accompanying neuropsychiatric problems have been reported in some families.[5] Although the existing literature scarcely reports about the association of Darier's disease with specific psychiatric disorders, any skin disease with visible lesions may cause psychiatric sequelae such as anxiety, depressive symptoms, or social isolation. One study argued that suicidal ideations were observed to be a problem in patients with Darier's disease.[8] No suicidal ideation manifested in our patient. However due to the clinical appearance and odor, the patient developed anxiety and social isolation, creating a negative impact on her quality of life.

Conclusion

Reduction of triggers, treatment of skin lesions, prevention of infection, and careful evaluation of the psychiatric and emotional status should be the goals for the management of this rare genetic disorder.

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