Acral hemorrhagic Darier disease: A case report of a rare presentation and literature review

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Key words: Acral hemorrhagic lesions; *ATP2A2*; Darier disease.

INTRODUCTION

Acral hemorrhagic lesions are an extremely rare feature of Darier disease (DD) that may present in the first 2 decades of life. Clinically, this manifestation of DD is characterized by irregular, jagged-shaped, minute hemorrhagic vesicles on the hands and feet. Histopathology shows irregular acanthosis and suprabasal acantholysis with dyskeratosis (corps, grains, and ronds), which are the characteristics of non-hemorrhagic DD lesions, along with extensive accumulation of intact erythrocytes in suprabasal clefts, which is unique to this unusual presentation. Although a mutation in exon 15 of the sarcoplasmic/endoplasmic reticulum calcium-ATPase 2 (*ATP2A2*) gene, which encodes a sarcoplasmic/endoplasmic reticulum calcium-ATPase pump (SERCA2), is found in 71% of genetically tested patients with DD and acral hemorrhagic lesions, few cases have reported conflicting genetic results, and no specific genotype-phenotype correlation has been established (Table I).[1-15] This feature has also been observed in patients with DD after they receive systemic retinoids. Herein, we report 2 cases of familial DD with acral hemorrhagic features and review other cases reported in the literature.

Abbreviations used:

DD: Darier disease
SERCA2: sarco/endoplasmic reticulum calcium-ATPase pump

CASE REPORT

A 41-year-old man presented with multiple, focal, black hemorrhagic vesicles with jagged borders on the dorsal and palmar aspects of both hands and feet. In addition, subtle red and white streaks as well as distal nicking were noted in his nails. The patient reported having this condition for several years and had used triamcinolone ointment 0.1%, with mild improvement. A punch biopsy of the left palm showed a hemorrhage in the cornified layer with suprabasal acantholysis; therefore, the patient was diagnosed with acral hemorrhagic DD. Notably, the patient's mother had a similar rash affecting the hands and feet (Fig 1). The patient was employed for maintenance at a fast-food restaurant and experienced repeat trauma to his hands, which exacerbated the condition. Genetic testing revealed a p.N676S mutation in the *ATP2A2* gene, a mutation that has not been previously found in patients with acral hemorrhagic DD.

Acitretin at 25 mg daily and betamethasone dipropionate ointment 0.05% were initiated for the patient. Because of mild improvement after 2 months of treatment, the acitretin dose was increased to 50 mg/d; however, an eruption resembling classic DD soon developed on his face and chest, which caused him to discontinue acitretin.

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Table I. Literature review of case reports and case series

Case no.	Age, y	Sex, race	Location	Initial presentation	Triggers	Treatments	*ATP2A2* mutation	Author, year published
1*	35, 14	Female, White	USA	Both	Trauma	N/A	N/A	Jones et al,[1] 1964
2	56	Male, White	USA	Both	Trauma	N/A	N/A	Jones et al,[1] 1964
3	58	Female, White	USA	Both	Trauma	N/A	N/A	Jones et al,[1] 1964
4	43	Female	UK	Hemorrhagic	Trauma and UV	N/A	N/A	Coulson and Misch,[2] 1989
5	47	Female, White	UK	Classic	Retinoid	25 mg/d of etretinate		Gebauer et al,[3] 1990
6*	N/A	N/A	USA	N/A	Trauma	N/A	N/A	Foresman et al,[4] 1993
7*	48, 32, 12	Female	Italy	Classic	N/A	N/A	p.N767S	Regazzini et al,[5] 1996
8	76	Female	Germany	Classic	Trauma and UV	N/A	N/A	Jörg et al,[6] 1997
9*	N/A	N/A	Scotland	N/A	N/A	N/A	p.N767S	Ruiz-Perez et al,[7] 1999
10*	N/A	N/A	Italy	N/A	N/A	N/A	p.N767S	Ruiz-Perez et al,[7] 1999
11*	N/A	N/A	Sweden	N/A	N/A	N/A	C268F	Ruiz-Perez et al,[7] 1999
12	28	Male	Croatia	Classic	UV	40 mg/d acitretin, topical antiseptics, and keratolytics	No mutation in exon 15	Pećina-Šlaus et al,[8] 2003
13*	34	N/A	Japan	Both	Friction	N/A	p.N767S	Hamada et al,[9] 2007
14	48	Male	Spain	Classic	Summer trauma	10 mg/d of acitretin, antihistamines, 5-fluorouracil cream, and topical tazarotene		Sánchez-Salas et al.[10] 2011
15	84	Female	Italy	Classic	Retinoid	Acitretin	No mutation in *ATP2A2*	Zavattaro et al,[11] 2014
16	38	Female	USA	Hemorrhagic	N/A	N/A	N/A	Boes et al,[12] 2016
17	65	Female	Canada	Hemorrhagic	N/A	Topical tretinoin	N/A	Vender and Vender,[13] 2016
18*	50, 28	N/A	Spain	Both	Trauma	25 mg of acitretin, topical tretinoin, and 20 mg/d of isotretinoin	N/A	Flores-Terry et al,[14] 2017
19	60	Female	Spain	Classic	Trauma	N/A	N/A	Flores-Terry et al,[14] 2017
20	40	Male, Maltese	Australia	Classic	Retinoid trauma	10 mg of acitretin 3 times/wk	N/A	Nguyen et al,[15] 2018
21*	41	Male, Hispanic	USA	Hemorrhagic	Trauma	25 mg/d of acitretin, bethametasone dipropionate ointment 0.05%	p.N676S	Our case

ATP2A2, Sarcoplasmic/endoplasmic reticulum calcium-ATPase 2; *N/A*, not available; *UK*, United Kingdom; *USA*, United States of America.
*Case reported in a kindred.

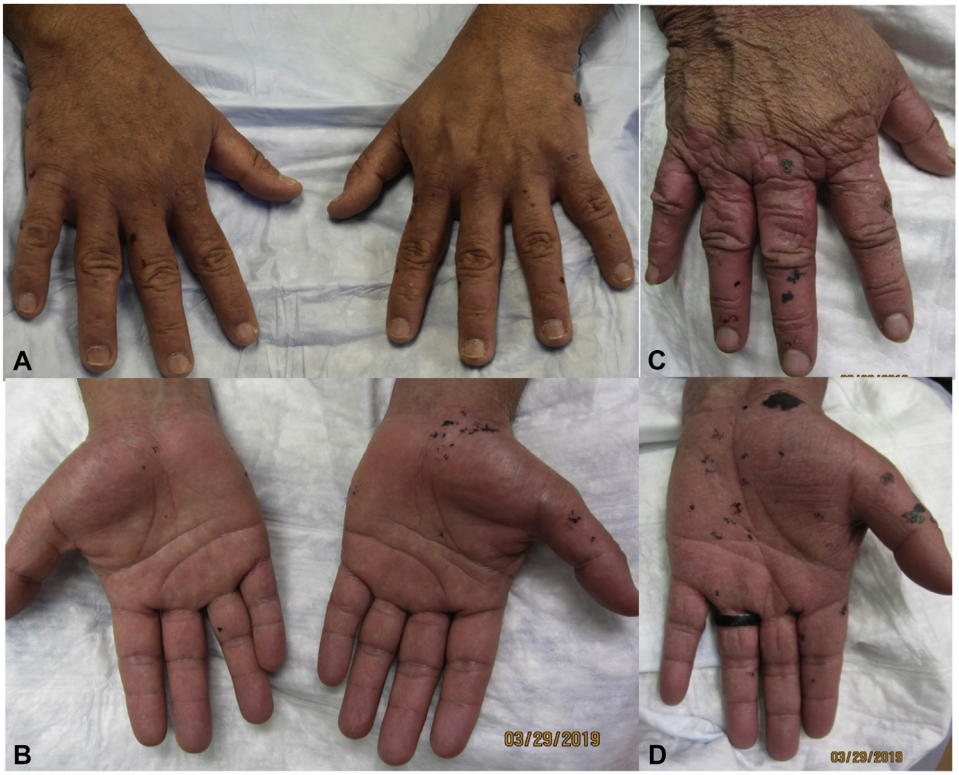

Fig 1. Dorsal and palmar aspects of the hands and fingers of (**A, B**) the patient and (**C, D**) the patient's mother covered with erythematous lichenified plaques and black hemorrhagic vesicles with red and white streaks in the nails.

DISCUSSION

Twenty cases of DD with acral hemorrhagic features, with 79% in female patients, have been reported in the literature (Table I). Eight of these cases described this phenotype to be transmitted within a kindred. Furthermore, only 3 of these cases reported purely hemorrhagic DD initially, similar to our patient and his mother, although these patterns of presentation depend on multiple factors, including the time of evaluation. In most cases, classic DD papules developed first in the individuals, and acral hemorrhagic lesions developed only later on in life or after treatment with a systemic retinoid.[3,5,6,8,10,11,14,15] Few others, such as our patient, had minimal physical findings of DD other than acrokeratosis verruciformis of Hopf and acral hemorrhagic lesions.[1,9,14] The majority of other patients with acral hemorrhagic features also had classic DD lesions.[2,4,12,13] Only 7 cases have reported the sequencing results of the *ATP2A2* gene in affected individuals. Although the acral hemorrhagic manifestation of DD has been associated with missense mutations in regions of the *ATP2A2* gene that encode transmembrane regions of the SERCA2 protein, a consistent phenotype-genotype correlation has not been determined.[7]

Oral acitretin and isotretinoin, topical 5-fluorouracil, and topical retinoids have been used to treat hemorrhagic lesions, with variable results. Acitretin, the most common treatment, resulted in mild improvement in some cases.[10,14] Notably, there have also been several cases of retinoid-induced acral hemorrhagic blisters in patients with DD successfully treated with etretinate and acitretin.[3,11,15] In our patient, acitretin improved the hemorrhagic lesions but exacerbated the classic DD lesions on nonacral sites.

In cases of the acral hemorrhagic presentation of DD, certain mutations in the *ATP2A2* gene may disrupt SERCA2 function in the vascular endothelium in addition to in keratinocytes or may produce a mutant SERCA2 protein that has a secondary effect in blood vessels.[7] The hemorrhagic phenotype may only present after local trauma, retinoid use, or UV radiation in the setting of reduced epidermal cohesion because these events impair calcium homeostasis beyond the compensatory ability of the normal allele and other mechanisms. Given the established relationship between retinoids and photosensitivity, it is likely that retinoid use and UV radiation are interrelated predisposing factors for acral hemorrhagic lesions. It has been suggested that retinoic acid

increases epidermal fragility and activates vascular endothelial growth factor gene transcription, modifying the permeability of endothelial cells and inducing the congregation of red blood cells into intraepidermal lacunae emptied via acantholysis and abnormal keratinization in patients with classic DD, leading to hemorrhagic blistering.[3,11] Hypoxia and UV radiation have also been shown to upregulate vascular endothelial growth factor in dermal fibroblasts and epidermal keratinocytes.[16,17] In 1 case, only acral hemorrhagic bullae developed in a patient who had taken 10 mg of acitretin daily 3 times weekly for 15 years after they endured trauma to the hands, suggesting that a combination of these factors is necessary to induce hemorrhagic blisters. Hemorrhagic lesions may not develop in patients who avoid these triggers, possibly explaining why some patients with *ATP2A2* mutations do not show the phenotype. Further investigation of the effects of oral retinoid treatment and other options, in addition to that of the genetic basis of acral hemorrhagic DD, is needed.

Conflicts of interest

Dr Choate has been an investigator for Alderya, Anaptsys, Galderma, Mayne, and Regeneron and a consultant with honorarium for AbbVie, Eli Lilly, Janssen, KrystalBio, Lifemax, Maybe, and Timber. Drs Hu, Posligua, and Durkin and Author Hong have no conflicts of interest to declare.

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