

Vesiculobullous Darier Disease Symptomatically Responsive to Cetirizine

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ABSTRACT

Darier disease is an autosomal dominant genodermatosis of abnormal keratinization characterized by hyperkeratotic papules and plaques with a predilection for seborrheic areas. We report a case of a rare vesiculobullous variant of treatment-resistant Darier disease in a 55-year-old woman that failed topical tacrolimus and topical and oral glucocorticoids. Cetirizine was initiated at 10 mg daily and increased to 40 mg daily over four weeks, with resultant marked improvement of the patient's burning sensation. A punch biopsy revealed a perivascular infiltrate of eosinophils. This patient's symptomatic improvement with cetirizine, which has antagonizing properties against eosinophils, highlights the potential role of eosinophils in the pathogenesis of vesiculobullous Darier disease. We suggest that major basic protein secreted by eosinophils may propagate blister formation in vesiculobullous Darier disease by disrupting desmosomes.

J Drugs Dermatol. 2019;18(2):213-214.

INTRODUCTION

Darier disease (DD), also known as Darier-White disease or keratosis follicularis, is an autosomal dominant genodermatosis of abnormal keratinization caused by mutations in the ATP2A2 gene and characterized by hyperkeratotic papules and plaques with a predilection for seborrheic areas.[1] Blisters rarely occur. We report a case of vesiculobullous DD with symptomatic improvement on cetirizine.

Case Report

A 55-year-old woman with a history of several years of DD presented with a recurrent, widespread, burning eruption of seven months' duration. Vesicles intermittently appeared, lasted for several weeks, and subsequently became crusts. She was initially treated with prednisone, tacrolimus ointment, and triamcinolone cream without improvement.

On physical examination, erythematous and hyperpigmented plaques with scale were present on the trunk and extremities. Scattered vesicles with an erythematous base were noted on these plaques and on non-erythematous skin (Figure 1).

A punch biopsy demonstrated intraepidermal bullae that were associated with acantholysis, focal dyskeratosis, and eosinophils in the blister cavity (Figure 2). There was a superficial, perivascular, infiltrate of lymphocytes and histiocytes with conspicuous eosinophils. The blister plane was predominantly through the spinous layer and focally suprabasilar. A direct immunofluorescence test did not show the deposition of C3, IgA, IgG, IgM, or fibrinogen. An indirect immunofluorescence test did not show the deposition of IgG or IgG4 in intercellular spaces or along the basement-membrane zone. Antibodies to desmoglein 1 and desmoglein 3 were absent with a serum ELISA test.

Prednisone and topical therapy were discontinued, and the patient was treated with cetirizine, with increases from 10 to 40 mg daily over four weeks. The patient's burning sensation decreased markedly over several weeks; however, her eruption persisted.

DISCUSSION

Vesiculobullous DD was first reported in 1939, with approximately 19 cases published since then.[2] Although it shares clinicopathologic features with Hailey-Hailey disease and various forms of pemphigus and pemphigoid, this rare variant of DD is a separate clinical entity.[1] Blisters in DD may be precipitated by heat, ultraviolet radiation, physical stress, surgery, high humidity, and prior treatment with oral retinoids.[3]

Reports typically demonstrate improvement with the use of systemic or local glucocorticoids or systemic retinoids.[1] One case reported control of disease with oral antihistamines, 5-fluorouracil cream, and topical tazarotene.[3] Although the mechanism of this rare vesiculobullous variant of DD has not been fully elucidated, our patient's symptomatic response to cetirizine highlights the possible role of eosinophils in the disease process. Eosinophils secrete major basic protein (MBP), which has effects that can be mimicked with synthetic poly-L-arginine.[4] In an in vitro study of cultured human bronchial epithelial cells exposed to poly-L-arginine, decreased immunoreactivity to plakoglobin, a major cytoplasmic component of desmosomes, was found in the cell membrane.[4] This indicates that MBP disrupts desmosomes,[4] which results in loss of keratinocyte adhesion in the stratum spinosum, which, in turn, leads to intraepidermal bullae formation. This supports our hypothesis that eosinophils are a mediator of vesiculobullous DD. Thus far, the presence of eosinophils in vesiculobullous DD

FIGURE 1. On the left thigh were erythematous and hyperpigmented plaques with scale. Overlying these plaques and non-lesional skin were scattered vesicles measuring 2-to-4 mm. There were few erosions with hemorrhagic crusts. The biopsy site is outlined in black pen.

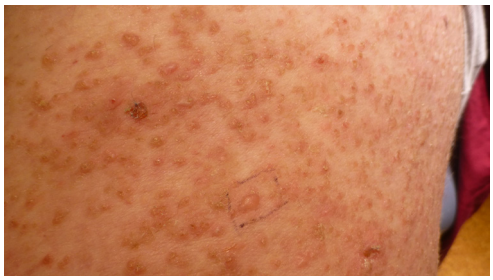
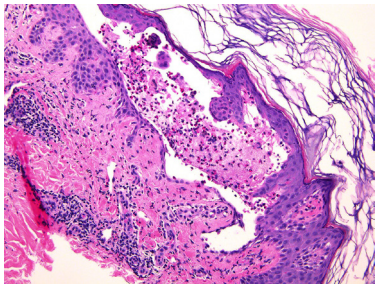


FIGURE 2. There is a suprabasilar cleft containing eosinophils and acantholytic keratinocytes with a perivascular infiltrate of lymphocytes and eosinophils (hematoxylin-eosin, original magnification x100).



only has been described in patients that are responsive to treatment with systemic or topical glucocorticoids.[1]

Cetirizine, which is a second-generation antihistamine that selectively antagonizes the histamine H1 receptor, is minimally sedating and has a markedly decreased anticholinergic effect.[5] In addition to its blockade of H1, cetirizine inhibits both platelet-activating factor-induced and N-formyl-methionyl-leucyl-phenylalanine-induced eosinophil chemotaxis as well as superoxide anion generation, which attenuates eosinophil migration into human skin.[5] Cetirizine is effective in treating the symptoms of Kimura's disease by inhibiting eosinophils,[6] and, therefore, indirect evidence would suggest that cetirizine also might inhibit eosinophils in vesiculobullous DD.

We suggest that treatment with second-generation antihistamines, specifically those with antagonizing properties against eosinophils, should be considered for symptomatic relief in vesiculobullous DD.

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