

Exacerbation of Darier's disease with COVID-19



Rachel Dykes, DO,^a Elizabeth Ergen, MD,^b Taylor Martin, BS,^c and Neil Coleman, MD^d

Key words: COVID-19 infection; Darier's disease; Darier's disease flare; dyskeratotic papules.

INTRODUCTION

Darier's disease (DD) is a rare genodermatosis, which is inherited in an autosomal dominant manner. It is characterized clinically by hyperkeratotic papules in a predominately seborrheic and intertriginous distribution with associated nail findings.¹ Mutations in the ATP2A2 gene, which encodes the 2b isoform of the Sarcoendoplasmic Reticulum Calcium-ATPase pump (SERCA2b), underlie the disease. This mutation leads to calcium pump dysfunction and ultimately epidermal acantholysis and apoptosis.^{2,3} Flares have been associated with heat, UV light, friction, lithium, interferon therapy, and infections such as staph, yeast, dermatophytes, and HSV.⁴⁻⁶ Here we report a case of a 38-year-old female with biopsy-proven DD who developed 2 distinct DD flares, each associated with a concurrent COVID-19 infection.

CASE REPORT

A 38-year-old woman with DD presented to the hospital with a widespread rash. Nine days prior to admission, she developed congestion and fatigue and tested positive for COVID-19. Concurrently, she noticed a widespread, painful, swollen, red, bumpy rash on her body, arms, and legs. This was more severe than prior flares of DD. She was treated for COVID-19 with azithromycin, prednisone, and a monoclonal antibody infusion. Her rash did not improve. Prior flares of DD had been associated with methicillin-resistant staphylococcus aureus skin colonization or infection, so she was treated with

Abbreviations used:

COVID-19:	coronavirus disease 2019
DD:	Darier's disease
IL:	interleukin
TNF:	tumor necrosis factor
SERCA2b:	Sarcoendoplasmic Reticulum Calcium-ATPase pump

oral linezolid. Her skin rash continued to worsen, and she presented to the hospital for evaluation.

Physical examination revealed extensive keratotic, erythematous, edematous papules and vesicles on the trunk and extremities (Fig 1). The face was spared. Chronic Darier nail changes were noted with splinter hemorrhages, longitudinal bands, and v-shaped nicks. Labs were unremarkable. A 4-mm punch biopsy was taken from the right thigh. The histology showed prominent acantholytic dyskeratosis with intraepithelial vesicle formation (Fig 2). Immunohistochemical staining for herpes simplex I, II, and varicella zoster virus antibodies was negative. A PAS stain was negative for fungus. The findings were most consistent with DD. She was treated with broad-spectrum antibiotics, prednisone, and ammonium lactate 12% lotion. Her rash subsided approximately 14 days after it began.

One year later, she developed a second COVID-19 infection and presented with the same extensive papulo-vesicular skin eruption. She was treated with doxycycline and topical steroids with minimal relief. The rash subsided spontaneously within 2 weeks.

From the Graduate School of Medicine, University of Tennessee Medical Center, Knoxville, Tennessee^a; Department of Dermatology, University of Tennessee Medical Center, Knoxville, Tennessee^b; Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee^c; Department of Pathology, University of Tennessee Medical Center, Knoxville, Tennessee.^d

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Correspondence to: Rachel Dykes, DO, Graduate School of Medicine, University of Tennessee Medical Center-Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. E-mail: Racheledykes1@gmail.com.

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Fig 1. Darier's disease flare clinical presentation. Hyperkeratotic, erythematous papules and vesicles on the trunk and extremities.

DISCUSSION

The appearance of new vesicular lesions in a patient with DD should prompt evaluation for a disseminated herpes viral infection (HSV I, HSV II, or VZV). Depending on the resources available, polymerase chain reaction, Tzanck smear, or immunohistochemistry may be used. A rare vesiculo-bullous variant of DD has been reported in the literature and should be considered when vesicular lesions are seen.⁷ We emphasize the case of a patient with DD who developed an exacerbation with papulo-vesicular lesions who did not have the vesiculo-bullous variant of Darier's disease and for whom testing for herpes viral infections was negative. The flare occurred concurrent with a COVID-19 infection and then recurred 1 year later with a second COVID-19 infection. This raises the question of whether COVID-19 caused the severe papulo-vesicular DD flares. To our knowledge, COVID-19-associated DD exacerbations have not yet been reported in the literature, although this may be due to underreporting and the rare nature of DD. Notably, Elbæk et al reported the case of a patient who developed a severe flare of DD with extensive dyskeratotic papules following the first dose of the COVID-19 vaccination.⁸

Regarding possible mechanisms, DD patients have mutations in ATP2A2 gene, which encodes

the 2b isoform of the SERCA2b. Dysfunction of this calcium pump leads to epidermal acantholysis and apoptosis.^{2,3} COVID-19 infection produces a cytokine storm characterized by elevated levels of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-1 β .⁹ TNF-alpha and IL-6 act to downregulate ATP2A2 mRNA levels, which would decrease the capacity of an already dysfunctional SERCA2b calcium pump in DD patients.¹⁰ Furthermore, an abundance of TNF-alpha enhances necroptosis of epithelial cells of the epidermis, potentially compounding acantholysis and apoptosis in the epidermis.¹¹ Finally, it is possible that fever or sweating during COVID-19 infection triggered these exacerbations in our patient.

Since the beginning of the pandemic, numerous cutaneous manifestations have been reported with COVID-19 infections. There are limited data available, however, regarding genetic dermatologic conditions in the setting of COVID-19 and whether it can lead to flares or worsening of symptoms in these patients. We present this case of DD in the setting of a COVID-19 infection to make physicians aware of a possible association.

Conflicts of interest

None disclosed.

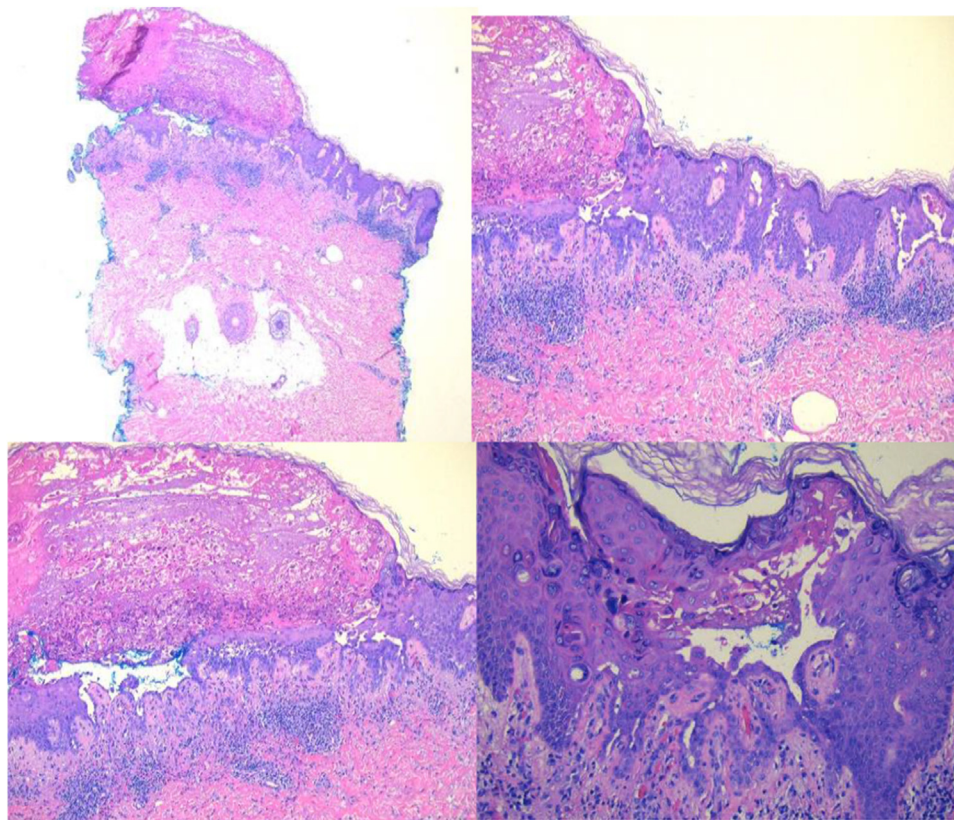


Fig 2. Darier's disease histopathology. Skin biopsy at varying magnifications showing prominent acantholytic dyskeratosis with intraepithelial vesicle formation. Hematoxylin and eosin stain.

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