Atypical erythema nodosum triggered by COVID-19 infection

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Key words: atypical EN; coronavirus; COVID-19; erythema nodosum; panniculitis; SARS-CoV-2; septal panniculitis.

INTRODUCTION

With the emergence of the novel SARS-CoV-2, we have learned a great deal about the potential cutaneous sequelae following infection. The variable dermatologic complications reported from viral infection thus far include pernio type lesions, urticarial eruptions, vesicular eruptions, and more.[1-3] Here, we report an atypical presentation of erythema nodosum (EN) following infection with SARS-CoV-2. To our knowledge, there have only been 3 other reports of EN secondary to SARS-CoV-2 infection, also known as COVID-19.[4-6]

Abbreviations used:

COVID-19:	coronavirus disease 2019
EN:	erythema nodosum
HIV:	human immunodeficiency virus
IL:	interleukin
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2

CASE REPORT

A 63-year-old woman presented for evaluation of a 3-week history of painful, red, swollen skin nodules on her bilateral lower extremities. Her past medical history was significant for a recent COVID-19 infection diagnosed using rapid nasal swab polymerase chain reaction 7 weeks prior to the presentation. Her symptoms due to the COVID-19 infection included 3 weeks of nausea, fatigue, cough, and shortness of breath. The patient first noticed tender nodules developing on the lower portion of her legs 3 weeks after she was tested positive for COVID-19 infection. She reported that the nodules were painful and interfered with her ability to ambulate. By the onset of nodule development, all other known COVID-19 infection symptoms had resolved. Physical examination revealed tender erythematous subcutaneous nodules involving the anterior and posterior aspects of bilateral lower extremities (Fig 1).

Prior to the presentation to the dermatology department, the Doppler ultrasound finding of bilateral lower extremity was negative for venous occlusion. We performed a 4-mm punch biopsy from the left distal calf that showed septal panniculitis without vasculitis, consistent with EN (Figs 2 and 3). Chest radiograph was negative for acute cardiopulmonary disease, antistreptolysin O titers were negative, and although she had traveled to Southern California in the preceding 3 months, *Coccidioides* antigens were absent in the patient's serum. She was treated with a 3-week prednisone taper and betamethasone 0.05% cream twice daily to the affected areas on her lower extremities. Most of her symptoms and discomfort cleared following the prednisone taper, and she was continued on the treatment with topical betamethasone to be used as needed.

DISCUSSION

EN is characterized by the clinical and histopathologic findings of acute onset of erythematous, painful, subcutaneous nodules on the anterior "pretibial" area of the lower extremities with a biopsy showing septal panniculitis.[7] EN is a delayed-type hypersensitivity reaction that can be idiopathic or associated with underlying autoimmune conditions or infectious etiology, most commonly reported following streptococcal infection. EN has also been

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;14:91-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.06.016

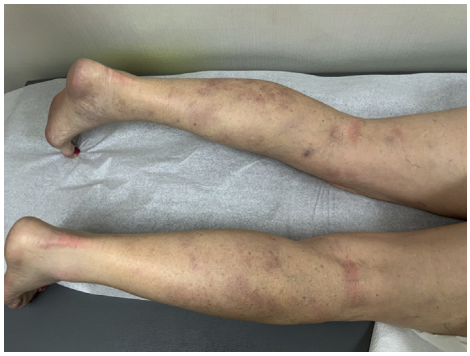

Fig 1. Erythematous nodules on the lower portion of bilateral legs.

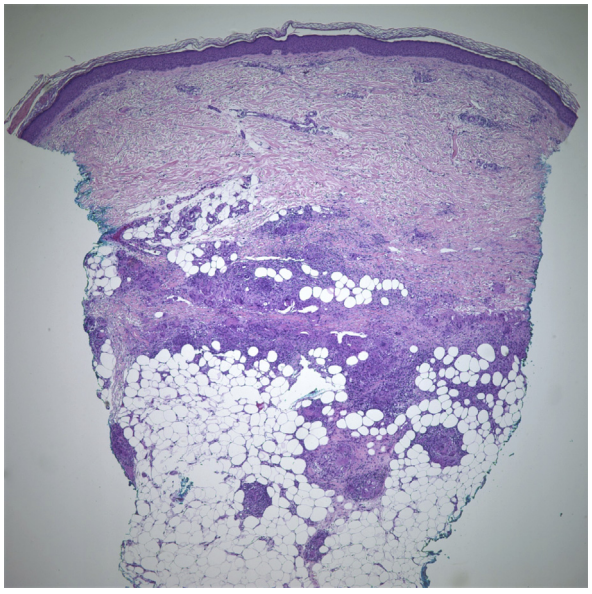

Fig 2. Low-power punch biopsy from the left distal calf demonstrated septal panniculitis.

associated with various viral infections such as Epstein-Barr virus, hepatitis B and C, HIV, and herpes simplex virus. Workup includes a chest x-ray to exclude pulmonary infections such as tuberculosis, coccidioidomycosis, histoplasmosis, and sarcoidosis; antistreptolysin O titers; and complete blood counts to rule out malignancy. Our patient presented with the classic characteristics of EN but also had significant involvement of the posterior aspects of her lower extremities, which is atypical. Given the time course of the presentation and lack of other identifiable causes, her EN was likely secondary to her COVID-19 viral infection; however, it may have also been idiopathic. Of the 3 other reported cases of EN secondary to COVID-19, 1 also describes an atypical distribution involving the arms, face, and lower portion of the back.[4] In the documented cases

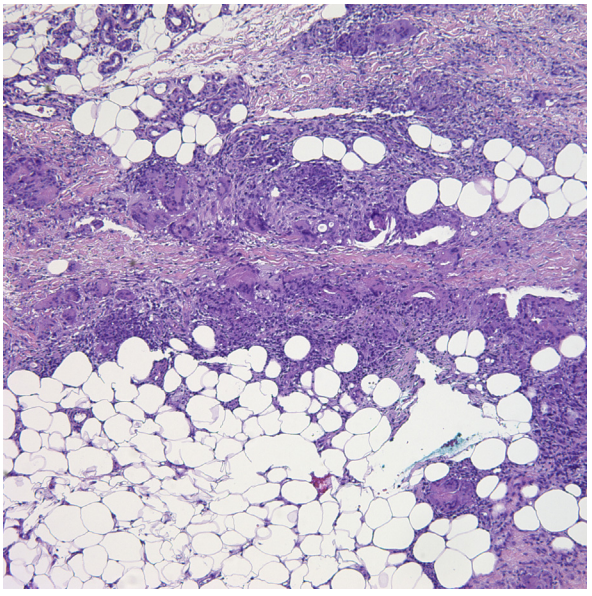

Fig 3. High-power punch biopsy from the left distal calf demonstrated septal panniculitis with a polymorphous infiltrate composed of histiocytes, lymphocytes, and multinucleate giant cells.

of EN associated with COVID-19 infection, 1 patient reported symptoms of painful tender nodules developing as early as 72 hours after being diagnosed with COVID-19, whereas the other 2 cases experienced symptoms of the lower portion of the leg such as pain, tenderness, swelling, and redness 1 to 2 weeks after their respiratory symptoms started.[4-6] The pathophysiology leading to typical and atypical presentations of EN in the setting of COVID-19 remains unclear. However, Ordieres-Ortega et al[6] have postulated that the development of EN in COVID-19 may be due to the dysregulated immune response caused by the virus, specifically including the case of elevated interleukin (IL) 1, IL-2, IL-6, and IL-7 in predisposed patients with polymorphisms of IL-1 and IL-6 promoter genes. Future studies are required to investigate this further. Although there are only 3 other known reports of EN triggered by COVID-19 infection, cutaneous manifestations are estimated to occur at a rate of 20.4% and include erythematous papular, vascular, vesicular, and urticarial eruptions.[8] Other atypical skin presentations following COVID-19 infection include generalized pruritis, Sweet syndrome, Kawasaki disease-like presentation, polymorphic patterns, and in our case, atypical EN.[1] Our understanding of cutaneous reactions following COVID-19 infection continues to expand, and this case emphasizes that COVID-19 infection should be included among the list of triggers for EN.

Conflicts of interest

None disclosed.

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