

# A case report of COVID-19-associated erythema nodosum: a classic presentation with a new trigger

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## Abstract

**Background:** Over the course of the pandemic, cutaneous manifestations of SARS-CoV-2 infections have been increasingly characterized, yet only a few cases of erythema nodosum (EN) are reported in the literature and international registries.

**Case presentation:** In this report, we describe a case of tender, erythematous nodules that appeared acutely on the distal legs in a 48-year-old female with renal transplant following SARS-CoV-2 infection complicated by prolonged fevers and pneumonia. The patient was diagnosed with a classic presentation of EN arising from a new and emerging trigger—COVID-19 infection. The cutaneous lesions resolved with conservative management.

**Conclusions:** This report highlights the importance of clinician awareness of the potential association of COVID-19 with a classic clinical presentation of EN and underscores that these cases can be managed with the same therapeutic repertoire as EN due to other aetiologies. Of note, use of systemic agents was not employed in this case, as our patient improved with conservative therapy alone.

**Key words:** case report, COVID-19, erythema nodosum, panniculitis, skin manifestations

## Introduction

Erythema nodosum (EN) is a reactive panniculitis classically presenting with tender, erythematous, subcutaneous nodules on the anterior lower extremities.<sup>1</sup> EN has a strong female predilection and may be accompanied by fever and malaise.<sup>2</sup> Due to its distinctive appearance, EN is often distinguished on clinical grounds and, thus, infrequently biopsied.<sup>1</sup> EN is considered a cutaneous manifestation of systemic disease including inflammatory bowel disease, streptococcal and mycobacterial infections, sarcoidosis, malignancy, pregnancy, or medication induced, but many cases remain idiopathic.<sup>1,2</sup> While reports in the literature are limited, preceding COVID-19 infection should be considered among potential aetiologies for EN.

## Report of a case

A 48-year-old female with type 1 diabetes mellitus and renal transplant presented with a 2-week history of tender nodules on her legs. Seven weeks prior to presentation, she was diagnosed with COVID-19 by PCR. Despite treatment with bamlanivimab, her course was complicated by pneumonia and prolonged fever, lasting 16 days. On exam, multiple, coalescing, tender, ill-defined, erythematous, subcutaneous nodules were symmetrically distributed on the bilateral distal medial legs, clinically consistent with EN (Fig. 1). Due to a high clinical index of suspicion and the patient's reluctance to undergo a procedure, no skin biopsy was performed. We chose to avoid the use of systemic steroids and nonsteroidal anti-inflammatory drugs (NSAIDs) given her diabetes and

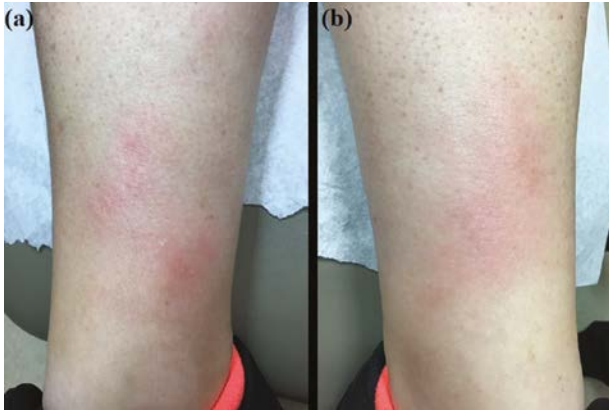
renal transplant, in favour of conservative therapy. She was treated topically with betamethasone dipropionate 0.05% cream twice daily for 3 weeks and compression stockings. She tolerated treatment well and was compliant with therapy, noting significant flattening of the nodules over the following month.

## Discussion

During the COVID-19 pandemic, multiple reports and registries have systematically documented the association of SARS-CoV-2 infection with specific cutaneous findings.<sup>3–5</sup> Dermatologic conditions reported in association with COVID-19 illness include petechial and morbilliform eruptions, vesicular and urticarial rashes, erythema multiforme-like lesions, livedo racemosa, acral pernio-like lesions, and retiform purpura secondary to acral vasculopathy.<sup>3–5</sup> Latency in the development of cutaneous eruptions following the onset of acute SARS-CoV-2 infection was observed in 44% cases.<sup>3</sup> Although EN is much more commonly associated with other infectious aetiologies, COVID-19 infection has emerged as a potential aetiology for EN, albeit infrequently documented. In 1 systematic review of dermatologic manifestations of 655 patients with confirmed COVID-19, 3 patients demonstrated an atypical EN eruption, while an international registry of 716 patients described 5 cases of EN.<sup>4,5</sup> An additional 4 reports in the literature observed individual cases of EN in the setting of COVID-19, developing 3–15 days after confirmation of SARS-CoV-2 infection.<sup>6–9</sup> In general, discordance between acute infection and subsequent onset of the cutaneous

## Key messages

- Erythema nodosum (EN) is a rare cutaneous manifestation of COVID-19 infection.
- In the absence of classic triggers, consider COVID-19 as the aetiology in EN.
- Cases of COVID-associated EN are managed similarly to those of classic EN.



**Fig. 1.** Panel a depicts the right lower extremity, and Panel b depicts the left lower extremity. These clinical images demonstrate a classic presentation of erythema nodosum with coalescing, erythematous subcutaneous nodules symmetrically distributed on the bilateral distal medial legs.

lesions of EN is commonly seen. Specifically, streptococcal-induced EN typically presents 2–3 weeks after resolution of pharyngitis, while tuberculosis-associated EN is thought to develop 3–8 weeks after infection.<sup>2,10</sup> While the lag time between acute COVID-19 symptoms and the onset of EN in our patient was longer than the handful of other case reports, it is not outside the typical timeframe of EN due to infectious aetiologies, nor that of other reactive cutaneous phenomenon such as pernio that are well reported in COVID-19.<sup>11</sup> While few case reports currently link EN to COVID-19, recent SARS-CoV-2 infection as a causative agent in EN could be considered once other classic aetiologies are eliminated.

While the intricacies of the pathogenic mechanisms have yet to be fully elucidated, EN is thought to represent a delayed-type hypersensitivity reaction to an antigenic stimulus, resulting in immune complex deposition in the subcutis and a subsequent inflammatory cascade that produces a neutrophilic septal panniculitis.<sup>1,12</sup> A robust cytokine response produced in SARS-CoV-2 infection results in upregulation of tumour necrosis factor- $\alpha$  and interleukin-1 and -6.<sup>6,13</sup> This pathway may be involved in development of panniculitis in the setting of COVID-19-associated EN.<sup>6</sup> Interestingly, to the authors' knowledge, only 2 cases of vaccine-induced EN are reported. In the first case, a 25-year-old female in India developed EN 1 week after receiving the Covishield COVID-19 vaccine (Oxford–AstraZeneca), and in the second report, a 27-year-old male developed EN 3 days after the first dose of the MVC-COV1901 COVID-19 vaccine (Medigen Vaccine Biologics Corporation, Taiwan).<sup>14,15</sup> COVID-19 vaccine-associated EN appears very rare. In a registry for adverse cutaneous reactions to Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines, no cases of EN were described among the 414 reported reactions.<sup>16</sup> Similarly, in an

Ethiopian registry examining adverse reactions following administration of the Oxford–AstraZeneca COVID-19 vaccine to 672 health professionals, there were no reported instances of EN.<sup>17</sup> In general, it is postulated that vaccine-related cutaneous reactions are related to host immune response; however, the precise immunologic mechanisms contributing to the development of EN following COVID-19 infection or vaccine administration require further elucidation.<sup>5,6,16</sup>

Most cases of EN either spontaneously resolve or improve quickly with symptomatic care, rarely requiring aggressive systemic treatment.<sup>1</sup> Commonly used systemic therapies include corticosteroids, NSAIDs, potassium iodide, colchicine, dapsone, and antimalarials.<sup>12</sup> The management of EN in the setting of COVID-19 is similar. In 1 prior report, EN was successfully treated with topical steroids and compression, as was the case described herein.<sup>7</sup> Another case of COVID-associated EN resolved with use of NSAIDs, and a more extensive presentation demonstrated rapid resolution of lesions with oral steroids.<sup>6,8</sup> Our report describes COVID-19-associated EN successfully treated with conservative therapy, contributing to the expanding catalogue of cutaneous manifestations of COVID-19 documented in the medical literature. Given its high infectivity and potential for considerable morbidity and mortality, recognition of the dermatologic presentations of COVID-19 may aid in the early identification, treatment, and quarantine of infected patients.<sup>9</sup> We hope this case underscores EN as a potential dermatologic sequela of COVID-19.

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## Ethical approval

The patient provided written consent for permission to publish this case.

## Conflict of interest

None declared.

## Data availability

There are no data to share.

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