

CASE REPORT

Erythema nodosum associated with COVID19 infection: A pediatric case report and review of the literature

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Email: mjzambrenom@gmail.com**Abstract**

Erythema nodosum (EN) is a common panniculitis characterized by tender erythematous nodules predominantly on the pretibial area and represents a hypersensitivity reaction to multiple triggers. COVID19 infection and vaccination have been associated with EN in the adult population. We report a pediatric case of EN following COVID19 infection and review the literature on COVID19 infection and COVID19 immunization-related EN.

KEYWORDS

COVID19 vaccines, dermatology, erythema nodosum, pediatrics, SARS-CoV-2

1 | INTRODUCTION

Erythema nodosum (EN) is the most common form of panniculitis in adults and children and is characterized by tender erythematous nodules, predominantly on the pretibial area. It is considered a hypersensitivity response to multiple triggers, such as infections, inflammation, neoplasia, and drugs. Although it is often idiopathic, the most frequent identifiable triggers are streptococcal infections, primary tuberculosis, sarcoidosis, Behçet disease, medications, pregnancy, and inflammatory bowel disease.¹ Although uncommon, it can be triggered by viral infections in children.² In recent years, COVID19 infection and vaccination have been reported as a trigger of EN. We report a pediatric case of EN following COVID19 infection.

2 | CASE REPORT

A previously healthy 6-year-old girl presented with a history of tender erythematous nodules over the pretibial skin which appeared 3 weeks prior to the visit (Figure 1). The lesions increased in size and number over the course of the first week and were tender, painful, and warm to touch. During this time, she also had fever without any other signs or symptoms of illness; she had no respiratory symptoms or loss of smell. Prior to the onset of the eruption, she had no medications, travel, vaccination for COVID19, and no sick contacts. Testing for SARS-CoV-2 was positive by PCR 5 days after the onset of the eruption. She had a throat swab that

was negative for group A *Streptococcus*. Laboratory investigations included a complete blood count with differential, erythrocyte sedimentation rate, chemistry panel, respiratory PCR panel, and anti-streptolysin O titers which were all normal. She had a slightly high C-reactive protein, and a normal chest radiograph. Over the course of 3 weeks, the eruption resolved with bed rest, ibuprofen, and acetaminophen.

3 | DISCUSSION

A variety of cutaneous manifestations have been described in association with COVID19 infection and Marzano et al.³ have proposed six main categories: urticarial rash, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis/racemosa-like pattern, and a purpuric “vasculitis” pattern. In children, certain presentations are more frequent. These include eruptions that are chilblains/chilblain-like (commonly named COVID toes and fingers), erythema multiforme-like, and manifestations of pediatric multisystem inflammatory syndrome in children (MIS-C) COVID19-related.⁴ Many other manifestations have been linked to COVID19, including pityriasis rosea-like eruptions, oral mucosa abnormalities,⁴ ocular/periorcular involvement, and EN in adults.⁵ Skin manifestations can occur in the absence of fever or respiratory symptoms and can serve as a sign of COVID19. Their pathophysiologic mechanisms are largely unknown and the role of COVID19 is still under study.

Since the outbreak of the COVID19 pandemic, several reports of erythema nodosum associated with COVID19 infection and vaccinations have been published (Table 1 and 2). A literature review of cases of EN in the setting of COVID19 infection found six patients reported, predominantly female (5/6) and between 30 and 63 years of age. The presentation of EN varied from 4 days before to 7 weeks after confirmation with a positive PCR. Most patients had concomitant fever (4/6) and the EN was located over the lower extremities (5/6). Two reports described elevation of inflammatory markers. None of the reported cases occurred in children, although there was one non-peer-reviewed paper that described EN in a 9-year-old boy with COVID19 infection.¹² There have been 10 reports of EN associated with COVID19 vaccines, including one pediatric patient (three Oxford/AstraZeneca, four Pfizer/BioNTech, two Moderna, and one Medigen) (Table 2).



FIGURE 1 Erythematous nodules on bilateral shins

TABLE 1 Reported cases of erythema nodosum secondary to COVID19 infection

Country	Age (years) and sex (M/F)	Fever with EN	PCR COVID/ result	Relation to onset of COVID symptoms	Relation to medication	Biopsy	Treatment for EN
Switzerland ⁶	42 M	Yes	Yes/+	12 days after fever, headache, fatigue, dry cough (concomitant)	NS	No	Betamethasone cream, compression, paracetamol and tramadol
Spain ⁷	57 F	Yes	Yes/+	8 days after admission to hospital with bilateral pneumonia	8 days after hydroxychloroquine, lopinavir/ritonavir	Yes	Naproxen 500 mg BID, then prednisone 20 mg daily (2 weeks course)
United States ⁸	54 F	No	Yes/+	None, PCR+ 72 hour before EN onset	None	No	Naproxen and hydroxyzine
United States ⁹	63 F	No	Yes/+	3 weeks after nausea, fatigue, cough and shortness of breath, positive PCR 3 weeks before EN. COVID symptoms resolved prior to EN	NS	Yes	Prednisone taper 3 weeks, betamethasone cream bid
Japan ¹⁰	30 F	Yes	Yes/+	EN started 4 days before onset of fever, dry cough, fever, arthralgias	None	Yes	Loxoprofen sodium hydrate, acetaminophen
United States ¹¹	48 F	Yes	Yes/+	7 weeks after PCR +, complicated with pneumonia and fever	Bamlanivimab	No	Betamethasone cream bid 3 weeks, compression

Abbreviations: -, negative; +, positive; F, female; M, male; NS, not specified.

TABLE 2 Reported cases of erythema nodosum secondary to COVID-19 vaccinations

Country	Vaccination	Age (years) and sex (M/F)	Fever with EN	PCR COVID/result	Relation to vaccination	Biopsy	Treatment for EN
Taiwan ¹³	Medigen (MVC-COV1901)	27 M	Yes	Yes/–	3 days after first dose	Yes	Oral prednisolone, colchicine, and topical flucloxacillin
Morocco ¹⁴	AstraZeneca/Oxford (ChAdOx1nCoV-19)	66 F	NS	No	2 days after second dose	Yes	Vitamin C, antihistamine, emollient and topical steroids
Saudi Arabia ¹⁵	Pfizer/BioNTech	22 F	NS	No	1 day after first dose	NS	Oral ibuprofen 600 mg QID
Singapore ¹⁶	Pfizer/BioNTech	37 F	No	No	1 day after second dose	Yes	Colchicine 500 µg BID 1 month
Italy ¹⁷	AstraZeneca/Oxford (ChAdOx1nCoV-19)	64 F	NS	No	2 days after first dose	No	Methylprednisolone 16 mg
United States ¹⁸	Moderna mRNA-1273	66 F	NS	Yes/–	10 days after first dose	Yes	none
India ¹⁹	AstraZeneca/Oxford (ChAdOx1nCoV-19)	25 F	Yes	Yes/–	7 days after first dose	Yes	Topical mometasone, oral acetaminophen.
NS ²⁰	Moderna mRNA-1273	44F	No	Yes/–	7 days after second dose	NS	Nonsteroidal anti-inflammatory
United States ²¹	Pfizer/BioNTech	17F	No	No	3 weeks after second dose	No	Rest and nonsteroidal anti-inflammatory
Germany ²²	Pfizer/BioNTech	54F	No	NS	1 day after first dose	Yes	Prednisolone 1 mg/kg tapered over 3 weeks

Abbreviations: –, negative; +, positive; F, female; M, male; NS, not specified.

The mechanism underlying COVID19-associated EN is still unknown. It has been hypothesized that EN may be the result of the deposition of immune complexes in the venules of the septae of subcutaneous fat, causing a neutrophilic panniculitis. Patients with EN also expressed cytokines, growth factors, and chemokines involved in neutrophil recruitment and activation, including TNF- α , interleukin (IL)-1, IL-8, IL-6, Th1 cytokines (IFN γ , IL-12), granulocyte colony-stimulating factor, and monocyte chemoattractant protein-1.²³ Recent studies have suggested that in addition to the direct damage caused by the COVID19 virus, there is an uncontrolled inflammatory response that contributes to the disease severity. Many pro-inflammatory cytokines have been described, including elevated IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α .^{24–26} Ordieres-Ortega et al.⁷ have postulated that COVID19-associated EN may be related to this dysregulated immune response and patients with polymorphisms of TNF- α ,²⁷ IL-1, and IL-6 promoter genes may have a higher susceptibility to EN in situations of immune dysregulation, such as COVID19 infection. Of interest, while most infectious triggers of EN are bacterial, there have been a number of viruses linked with pediatric EN, including Epstein–Barr virus, cytomegalovirus, hepatitis B and C, parvovirus B19, human immunodeficiency virus, and varicella zoster virus.²

We report a pediatric case of EN following COVID19 infection and review the literature on EN associated with COVID19 infection and vaccination. While it is difficult to prove that COVID19 infection was the definite cause of EN in our patient, several factors point to this association: the timing of the eruption associated with a positive COVID19 test, similarity to other case reports, and the absence of other common triggers of EN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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