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

María José Zambrano-Mericq MD1 | Joseph M. Lam MD2,3

1Department of Dermatology, Pontificia Universidad Católica de Chile, Santiago, Chile
2Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, British Columbia, Canada
3Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence
María José Zambrano-Mericq, Department of Dermatology, Pontificia Universidad Católica de Chile, Santiago 8331150, Chile.
Email: mjzambranom@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. Although uncommon, it can be triggered by viral infections in children. 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. 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. Many other manifestations have been linked to COVID19, including pityriasis rosea-like eruptions, oral mucosa abnormalities, ocular/periocular involvement, and EN in adults. 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. There have been 10 reports of EN associated with COVID19 vaccines, including one pediatric patient (three Oxford/AstraZeneca, four Pfizer/BioNTech, two Modena, and one Medigen) (Table 2).

**TABLE 1** Reported cases of erythema nodosum secondary to COVID19 infection

| Country         | Age (years) | Fever with EN | PCR COVID/ result | Relation to onset of COVID/Symptoms | Biopsy | Treatment for EN |
|-----------------|-------------|---------------|-------------------|------------------------------------|--------|------------------|
| Switzerland     | 62 F        | Yes           | Yes/+             | 12 days after fever, headache, fatigue, dry cough (concomitant) | No     | Betamethasone cream, compression, paracetamol and tramadol |
| Spain           | 57 F        | Yes           | Yes/+             | 8 days after admission to hospital with bilateral pneumonia | Yes    | Naproxen 500 mg BID, then prednisone 20 mg daily (2 weeks course) |
| United States   | 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 | Yes    | Prednisone taper 3 weeks, betamethasone cream bid, acetylsalicylic acid |
| United States   | 50 F        | Yes           | Yes/+             | 72 hour before EN onset | No     | Loxoprofen sodium hydrate, acetaminophen |
| Japan           | 10 F        | Yes           | Yes/+             | EN started 4 days after onset of fever, dry cough, fever, arthralgias | Yes    | Bamlanivimab |

**FIGURE 1** Erythematous nodules on bilateral shins

**Abbreviations:** --, negative; +, positive; F, female; M, male; NS, not specified.
### TABLE 2  Reported cases of erythema nodosum secondary to COVID19 vaccinations

| Country        | Vaccination                      | Age (years) and sex (M/F) | Fever with EN | PCR COVID/result | Relation to vaccination | Biopsy | Treatment for EN                                                                 |
|----------------|----------------------------------|---------------------------|---------------|------------------|-------------------------|--------|----------------------------------------------------------------------------------|
| Taiwan         | Medigen (MVC-COV1901)            | 27 M                      | Yes           | Yes/–            | 3 days after first dose | Yes    | Oral prednisolone, colchicine, and topical fluocinonide                           |
| Morocco        | AstraZeneca/Oxford (ChAdOx1nCoV-19) | 66 F                     | NS            | No               | 2 days after second dose | Yes    | Vitamin C, antihistamine, emollient and topical steroids                           |
| Saudi Arabia   | Pfizer/BioNTech                  | 22 F                      | NS            | No               | 1 day after first dose  | NS     | Oral ibuprofen 600 mg QID                                                        |
| Singapore      | Pfizer/BioNTech                  | 37 F                      | No            | No               | 1 day after second dose | Yes    | Colchicine 500 μg BID 1 month                                                    |
| Italy          | AstraZeneca/Oxford (ChAdOx1nCoV-19) | 64 F                     | NS            | No               | 2 days after first dose | No     | Methylprednisolone 16 mg                                                         |
| United States  | Moderna mRNA-1273                | 66 F                      | NS            | Yes/–            | 10 days after first dose | Yes    | none                                                                             |
| India          | AstraZeneca/Oxford (ChAdOx1nCoV-19) | 25 F                     | Yes           | Yes/–            | 7 days after first dose | Yes    | Topical mometasone, oral acetaminophen.                                          |
| NS             | Moderna mRNA-1273                | 44F                       | No            | Yes/–            | 7 days after second dose | NS     | Nonsteroidal anti-inflammatory                                                   |
| United States  | Pfizer/BioNTech                  | 17F                       | No            | No               | 3 weeks after second dose | No     | Rest and nonsteroidal anti-inflammatory                                          |
| Germany        | 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 (IFNγ, IL-12), granulocyte colony-stimulating factor, and monocyte chemoattractant protein-1.

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. Ordieres-Ortega et al. have postulated that COVID19-associated EN may be related to this dysregulated immune response and patients with polymorphisms of TNF-α. 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.

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.

ORCID
Maria José Zambrano-Mericq https://orcid.org/0000-0003-2435-3786
Joseph M. Lam https://orcid.org/0000-0001-7808-3369

REFERENCES
1. Leung AKC, Leong KF, Lam JM. Erythema nodosum. World J Pediatr. 2018;14(6):548-554. doi:10.1007/s12519-018-0191-1
2. Trapani S, Rubino C, Lodi L, Resti M, Indolfi G. Erythema nodosum in children: a narrative review and a practical approach. Children. 2022;9(4):511. doi:10.3390/children9040511
3. Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue. Br J Dermatol. 2020;183(3):431-442. doi:10.1111/bjd.19264
4. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: part 1. Clin Exp Dermatol. 2021;46(3):444-450. doi:10.1111/ced.14481
5. Conforti C, Dianzani C, Agozzino M, et al. Cutaneous manifestations in confirmed COVID-19 patients: a systematic review. Biology. 2020;9(12):449. doi:10.3390/biology9120449
6. Suter P, Mooser B, Thien HPPH. Erythema nodosum as a cutaneous manifestation of COVID-19 infection. BMJ Case Rep. 2020;13(7):e236613. doi:10.1136/bcr-2020-236613
7. Ordieres-Ortega L, Toledo-Samaniego N, Parra-Virto A, Fernández-Carracedo E, Lavilla-Olleros C, Demelo-Rodríguez P. Atypical erythema nodosum in a patient with COVID-19 pneumonia. Dermatol Ther. 2020;33(4):e13658. doi:10.1111/dth.13658
8. Sipflle N, Bridwell RE, Roper J. Erythema nodosum-like rash in a COVID-19 patient: a case report. Am J Emerg Med. 2021;40:227. doi:10.1016/j.ajem.2020.07.063
9. Pile H, Harp T, Altman D. Atypical erythema nodosum triggered by COVID-19 infection. JAAD Case Rep. 2021;14:91-93. doi:10.1016/j.jdercre.2021.06.016
10. Kuriyama Y, Shimizu A, Oka H, et al. Erythema nodosum-like eruption in coronavirus disease 2019: a case report and literature review of Asian countries. J Dermatol. 2021;48(10):1588-1592. doi:10.1111/1346-8138.16071
11. Parker ER, Fitzpatrick A. A case report of COVID-19-associated erythema nodosum: a classic presentation with a new trigger. Fam Pract. 2022;cmab177. doi:10.1093/fampra/cmab177
12. Servestani AA, Ghotbabadi SH. Case report: post SARS-CoV2 infection erythema nodosum. 2021. doi:10.21203/rs.3.rs.819447/v1
13. Hsu HT, Su HA, Chen YC. Erythema nodosum, after Medigen vaccination against COVID-19? J Formos Med Assoc. 2022;121(3):723-724. doi:10.1016/j.jfma.2021.10.002
14. Hali F, Marnech C, Chiheb S, Alatawna H. Erythema nodosum manifestation post COVID-19 vaccine: a case report. World J Vaccines. 2021;11(3):33-38. doi:10.4246/wjv.2021.11.3005
15. Aly MH, Alshehri AA, Mohammed A, et al. First case of erythema nodosum associated with Pfizer vaccine. Cureus. 2021;13(11):e19529. doi:10.7759/cureus.19529
16. Wu X, Lim JHL, Lee JS, Chio MTW. Recurrent erythema nodosum after the second dose of the Pfizer-BioNtech BNT162b2 COVID-19 messenger RNA vaccine. JAAD Int. 2022;6:107-108. doi:10.1016/j.jidin.2021.12.009
17. Cameli N, Silvestri M, Mariano M, Benardo L, Nisticò SP, Cristaudo A. Erythema nodosum following the first dose of ChAdOx1-nCoV-19 vaccine. J Eur Acad Dermatol Venereol. 2022;36(3):e161-e162. doi:10.1111/jevd.17762
18. Teymour S, Ahram A, Blackwell T, Biate C, Cohen PJ, Whitworth JM. Erythema nodosum after Moderna mRNA-1273 COVID-19 vaccine. Dermatol Ther. 2022;35(4):e15302. doi:10.1111/dth.13502
19. Mehta H, Handa S, Malhotra P, et al. Erythema nodosum, zoster duplex and pteryiasis rosea as possible cutaneous adverse effects of Oxford–AstraZeneca COVID-19 vaccine: report of three cases from India. J Eur Acad Dermatol Venereol. 2022;36(1):e16-e18. doi:10.1111/jevd.17678
20. Herrera M, West K, Holstein H. Erythema nodosum-like rash after SARS-CoV2 vaccination: a case report. Chest. 2021;160(4):A1380. doi:10.1016/j.chest.2021.07.1261
21. Hafer J, Soumekh L, Tang C. Erythema nodosum after COVID-19 vaccination in a pediatric patient. JAAD Case Rep. 2022;23:12-14. doi:10.1016/j.jdcr.2022.03.009
22. Niebel D, Wenzel J, Wilsmann-Theis D, Ziob J, Wilhelmi J, Braegelmann C. Sinusitis and erythema nodosum associated with Pfizer vaccine. Cureus. 2020;12(1):e7759. doi:10.7759/cureus.7759
23. Mehta H, Handa S, Malhotra P, et al. Erythema nodosum, zoster duplex and pteryiasis rosea as possible cutaneous adverse effects of Oxford–AstraZeneca COVID-19 vaccine: report of three cases from India. J Eur Acad Dermatol Venereol. 2022;36(1):e16-e18. doi:10.1111/jevd.17678
24. Herrera M, West K, Holstein H. Erythema nodosum-like rash after SARS-CoV2 vaccination: a case report. Chest. 2021;160(4):A1380. doi:10.1016/j.chest.2021.07.1261
25. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636-1643. doi:10.1038/s41591-020-1051-9
26. McGonagle D, Sharif K, O’Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19(6):102537. doi:10.1016/j.autrev.2020.10.2537
26. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan. China Clin Infect Dis. 2020;71(15):762-768. doi:10.1093/cid/ciaa248

27. Labunski S, Posern G, Ludwig S, Kundt G, Bröcker EB, Kunz M. Tumour necrosis factor-alpha promoter polymorphism in erythema nodosum. Acta Derm Venereol. 2001;81(1):18-21. doi:10.1080/00015550116912

How to cite this article: Zambrano-Mericq MJ, Lam JM. Erythema nodosum associated with COVID19 infection: A pediatric case report and review of the literature. Pediatr Dermatol. 2023;40(1):166-170. doi:10.1111/pde.15096