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DERMATOLOGIC THERAPY WILEY

LETTER

# Covid-19 vaccine associated erythema nodosum: Factors to consider

Dear Editor,

We read with great interest the letter by Teymour et al.[1] The authors describe a possible case of mRNA-1273 Covid-19 vaccine-associated erythema nodosum (EN) in a 66-year-old female. The patient subsequently received the second dose without the reappearance of EN.

We would like to report a further case of EN following the COVID-19 vaccination. Our patient is a 62-year-old non-obese male with a history of well-controlled hypertension. He received the first BNT162b2 mRNA vaccine on April 30, 2021. Two weeks post-vaccination, he noticed several tender nodules in his right ankle. A topical corticosteroid was prescribed for an assumed insect bite. He received his second dose on June 16, 2021; 4 days later, he experienced sudden onset of skin lesions accompanied by malaise and leg pain. Dermatological examination revealed subcutaneous nodules of 1–3 cm in diameter on the anterior lower legs and extensive redness and swelling at the vaccine injection site. Laboratory examinations revealed slightly elevated C reactive protein (10.5 mg/dl). Additional testing did not identify other etiologies for EN. We further assessed this association using the Naranjo adverse drug reaction causality scale.[2] Our patient had a score of 6, suggesting a probable adverse drug reaction. Three weeks later, most of the lesions regressed spontaneously (Figure 1). No skin biopsy was performed due to the typical clinical presentation and contusiform color evolution. No recurrence was observed at the 6-month follow-up. The patient is not eligible to receive a third vaccine dose.

EN is considered a hypersensitivity response to a variety of antigenic stimuli. Precipitating factors include infections, inflammatory diseases, neoplasia, and drugs. However, approximately 50% of cases are idiopathic.[3]

Eight vaccines have been associated with subsequent development of EN: tetanus, diphtheria, and acellular pertussis (DTaP), Bacille–Calmette–Guerin (BCG), hepatitis B, human papillomavirus, malaria, rabies, smallpox, typhoid, and cholera.[3] Time intervals between vaccine administration and the onset of EN are variable. They manifest within 24–48 h following vaccine administration (hepatitis B, typhoid and cholera vaccine, rabies vaccine, DTaP) or 2–4 weeks later (malaria, smallpox, BCG, and papillomavirus vaccine). The pathogenesis of vaccine-related EN may be linked to the antigen of the infectious disease or adjuvant components.[4]

COVID-19 vaccine-associated EN seems to be rare. In a large-scale study by McMahon et al, out of the 414 subjects, no cases of EN were reported.[5]

To date, there are seven reports of EN temporally associated with receipt of COVID-19 vaccine (Table 1).[1,6–11]

Our patient, with no history of COVID-19 infection, had mild EN after his first dose and severe relapse after the second dose. Interestingly, he showed injection site reaction, which has not been reported in the other cases. The absence of coincidental events leads us to support the potential role of the vaccine.

Our case and other mentioned cases are mainly based on a temporal relationship between the vaccine administration and the onset of EN.

However, the causality assessment requires complete information related to an individual case, such as evidence or history for herd immunity to SARS-CoV-2, type of vaccine, positive re-challenge,

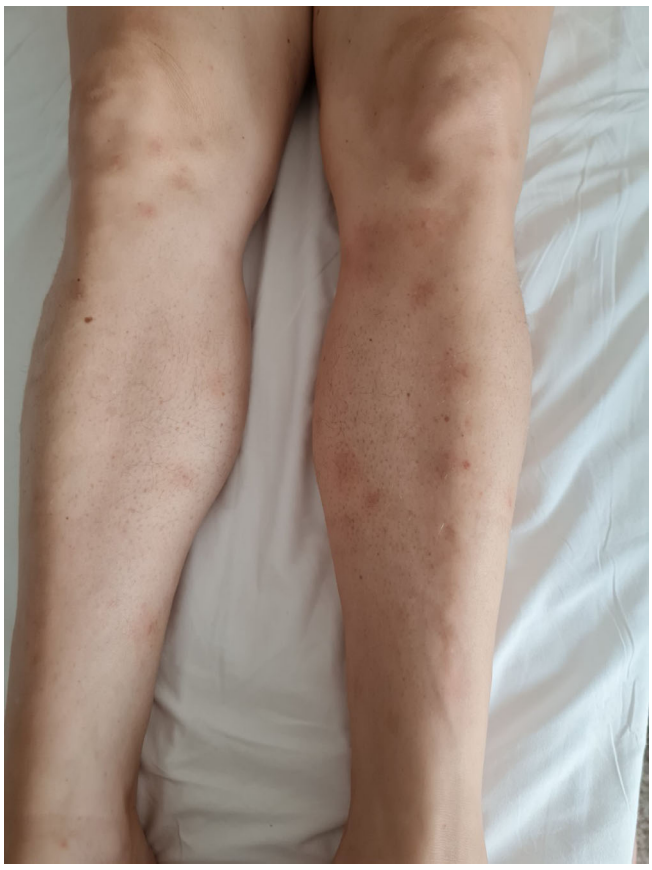

**FIGURE 1** Contusiform color evolution of nodules, 3 weeks after onset of erythema nodosum

**TABLE 1** Reported cases of COVID-19 vaccine-associated erythema nodosum

| Author | Patient age/sex | Vaccine | 1st dose-reaction | 2nd dose-reaction | Time | Lab/HP findings |
|---|---|---|---|---|---|---|
| Teymour et al[1] | 66/F | mRNA-1273 (Moderna) | Nodules on the bilateral anterior tibia | second inoculation without reappearance | 10 days | Unremarkable/compatible with EN |
| Hali et al[6] | 66/F | ChAdOx1-S (AstraZeneca) | NR | nodular lesions of the lower and upper limbs | 48 h | ↑ESR/septal hypodermitis, no vascular involvement, minimal granulomatous infiltrate |
| Mehta et al[7] | 25/F | ChAdOx1 nCoV- 19 (Covishield) | Low-grade fever, joint pains, and painful nodules over legs | No recurrence was observed on receiving 2nd dose after 4 weeks | 4 days | ↑inflammatory markers/ compatible with EN |
| Aly et al[8] | 22/F | BNT162b2 (Pfizer-BioNTech) | Nodules on both legs | NR | 24 h | Normal/NP |
| Wu et al[9] | 37/F | BNT162b2 (Pfizer-BioNTech) | No | Nodules on distal legs | 24 h | NR/ septal panniculitis with granulomatous aggregates |
| Hsu et al[10] | 27/M | Medigen MVC-COV1901 | Fever, malaise, headache, myalgia, nausea, swelling of the ankles, rash on the legs | NR | 72 h | ↑CRP/ septal panniculitis, lymphocytic infiltrates, and Miescher's granulomas |
| Cameli et al[11] | 64/F | ChAdOx1 nCoV-19 (AstraZeneca) | Painful, erythematous plaques on both lower limbs | NR | 2 days | Normal/NP |
| Damevska and Simeonovski (present case) | 62/M | BNT162b2 (Pfizer-BioNTech) | Several nodules | Malaise, nodules on lower limbs, Injection -site reaction | 14 days after the 1st dose, 4 days after 2nd dose | ↑CRP /NP |

Abbreviations: NP, not performed; NR, not reported.

follow-up information, other disease and drug interactions, and so on. Apart from clinical judgment, the use of algorithms, such as the Naranjo scale, could be of great assistance when assessing these conditions.[2,12]

We thank Teymour et al[1] for their important case description. Further studies are needed to evaluate the mRNA vaccine as a potential cause of EN. In our opinion, the correct conclusion from the current evidence should be that Covid-19 vaccine-associated EN is a rare, benign, and self-limiting condition.

We would like to emphasize that we have a professional obligation to detect and report cutaneous adverse events related to COVID-19 vaccines.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

Katerina Damevska
Viktor Simeonovski

*University Clinic for Dermatology, Faculty of Medicine, University Ss. Cyril and Methodius in Skopje, Skopje, Macedonia*

**Correspondence**
Katerina Damevska, University Clinic of Dermatology, Mother Theresa 17 St., Skopje 1000, Macedonia.
Email: kate_damevska@yahoo.com

## ORCID

*Katerina Damevska* https://orcid.org/0000-0003-4745-3747
*Viktor Simeonovski* https://orcid.org/0000-0003-2956-0928

## REFERENCES

1. Teymour S, Ahram A, Blackwell T, Bhate C, Cohen PJ, Whitworth JM. Erythema Nodosum after Moderna mRNA-1273 Covid-19 vaccine. *Dermatol Ther*. 2022;4:e15302. doi:10.1111/dth.15302
2. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2): 239-245.
3. Pérez-Garza DM, Chavez-Alvarez S, Ocampo-Candiani J, Gomez-Flores M. Erythema nodosum: a practical approach and diagnostic algorithm. *Am J Clin Dermatol*. 2021;22(3):367-378.
4. Cohen PR. Combined reduced-antigen content tetanus, diphtheria, and acellular pertussis (tdap) vaccine-related erythema nodosum: case

report and review of vaccine-associated erythema nodosum. *Dermatol Ther (Heidelb)*. 2013;3(2):191-197.
5. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85:46-55.
6. Hali F, Marmech C, Chiheb S, Alatawna H. Erythema nodosum manifestation post COVID-19 vaccine: a case report. *World J Vaccines*. 2021;11:33-38. doi:10.4236/wjv.2021.113005
7. Mehta H, Handa S, Malhotra P, et al. Erythema nodosum, zoster duplex and pityriasis 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/jdv.17678
8. 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
9. Wu X, Lim JHL, Lee JSS, Chio MT. 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.jdin.2021.12.009
10. 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
11. Cameli N, Silvestri M, Mariano M, Bennardo L, Nisticò SP, Cristaudo A. Erythema nodosum following the first dose of ChAdOx1-S nCoV-19 vaccine. *J Eur Acad Dermatol Venereol*. 2022;36(3):e161-e162. doi:10.1111/jdv.17762
12. Adverse Event Following Immunisation control guideline. https://www.health.nsw.gov.au/Infectious/controlguideline/Pages/adverse.aspx (Accessed January 22, 2021).