Reumatismo, 2022; 74 (1): 36-40

Erythema nodosum after COVID-19 vaccine

B. Maranini[1], G. Ciancio[1], M. Corazza[2], F. Ruffilli[1], G. Galoppini[1], M. Govoni[1]

[1]Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Italy;
[2] Section of Dermatology, Department of Medical Sciences, University of Ferrara, Italy

SUMMARY

The current coronavirus disease 2019 (COVID-19) pandemic is a global challenge with strong medical and socioeconomic implications. Hopes have been placed in the development of various vaccines. As the vaccination campaign is in progress, adverse effects need to be monitored closely. Possible side effects range from minor events to more serious manifestations.

In this article, we describe two cases of erythema nodosum (EN) after COVID-19 vaccination in two previously healthy female patients of 59 and 51 years, respectively. Most of the usual etiologies of EN were excluded by laboratory testing. EN was successfully treated with corticosteroids. Remarkably, in the first case, a relapse occurred 48 hours after the second dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.

In this case series, we describe two unusual occurrences of EN after vaccination with an mRNA COVID-19 vaccine and a viral vector vaccine, respectively, and we discuss the available related literature.

Key words: *Erythema nodosum; dermatology; vaccine; COVID-19; coronavirus.*

Reumatismo, 2022; 74 (1): 36-40

INTRODUCTION

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, vaccines gained an increasingly relevant role. Possible vaccine-related side effects range from minor events such as pain, redness, and/or swelling at the injection site to more prominent manifestations such as high fever, chills, headache, nausea, and anaphylactic reactions (1).

A heterogeneous spectrum of cutaneous reactions has been reported to date, ranging from local injection site reactions to urticarial and morbilliform eruptions, pernio/chilblains, and zoster flares. Moreover, most patients with first-dose reactions did not experience a second-dose reaction (2).

Here, we describe two unusual cases of erythema nodosum (EN) after vaccination with an mRNA coronavirus disease 2019 (COVID-19) vaccine and a viral vector vaccine, respectively.

Corresponding author:
Beatrice Maranini
Rheumatology Unit
Department of Medical Sciences
University of Ferrara, Italy
Email: beatrice.maranini@edu.unife.it

CASE REPORTS

First case

A 59-year-old Caucasian patient was referred to the local Emergency Department with a clinical picture characterized by four extensive red and painful nodular lesions in the lower limbs, bilaterally around the knee and at the level of the distal tibia (Figure 1A), fever up to 38°C, malaise and severe fatigue started 10 days after the first dose of an mRNA-COVID-19 vaccine.

Past medical history revealed mild scalp psoriasis since the age of 30 without other significant comorbidities or allergies; no medication was chronically taken at home. Laboratory findings showed elevated inflammatory markers (C reactive protein, CRP 2.3 mg/dL, normal values <0.50 mg/dL) and mild neutrophilic leukocytosis (WBC 14,000 cells/microL, cut-off <11,000; neutrophils 9,500 cells/microL, cut-off <7700) with normal liver and kidney function. An extensive infectious panel, viral hepatitis

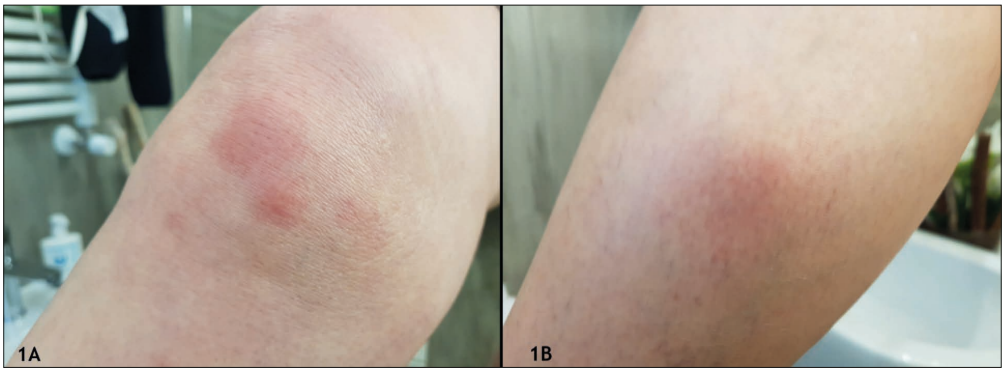

Figure 1 - Erythema nodosum. Lumpy red rash of the lower legs following mRNA-COVID-19 vaccine: skin lesions after first COVID-19 vaccine dose (1A) and recurrence after second COVID-19 shot (1B).

workup, and HIV screening were negative. Immunological panel testing for vasculitis and connective tissue diseases, including anti-nuclear antibodies (ANA), antibodies to extractable nuclear antigens (ENA), anti-double-stranded DNA antibodies (dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA), complement, lupus anticoagulant (LAC), anti-cardiolipin and anti-beta2 glycoprotein antibodies, rheumatoid factor and anti-cyclic citrullinate antibodies were all negative. Additionally, antistreptolysin antibodies, angiotensin-converting enzyme (ACE), and Interferon-gamma release assay were also negative. As to potential cancer-related causes, no suspicious symptoms were present including intestinal disorders, weight loss, or systemic B symptoms, and the patient regularly followed population cancer screenings.

The consultant dermatologist found the lesions on both legs to be consistent with EN and started therapy with prednisone 25 mg, subsequently gradually tapered and suspended, with complete regression of fever and fatigue in 2-3 days and an almost complete resolution of lower limb skin lesions within 15 days. No skin biopsy was performed due to high clinical suspicion and a complete response to steroid therapy.

Afterwards, the patient underwent the second vaccine dose and 48 hours later fatigue and painful cutaneous lesions on both lower limbs reappeared, although less extended than the previous ones (Figure 1B), without fever. The patient was then referred to our Rheumatological Unit. After accurate clinical inspection, recurrence of EN in both legs and dactylitis of the right hand were diagnosed, the latter being also confirmed by ultrasound. No other signs or symptoms of peripheral joint and tendon inflammation were present. All symptoms disappeared within 15 days of a new course of prednisone 12.5 mg daily, which was gradually tapered and withdrawn without any recurrence.

Second case

A 51-year-old Caucasian patient was referred to our Rheumatological Clinic by her GP for the occurrence of indurated painful plaques, spreading in the upper limbs and to a smaller extent in the lower limbs (Figure 2) accompanied by fever up to 38.5°C, widespread severe myalgias and asthenia started on day 7 after the first ChAdOx1 nCoV-19 vaccine dose. COVID-19 PCR test was performed and found negative.

The patient was then hospitalized for further examinations and appropriate management. She had no known previous comorbidities and was not on any chronic therapy. Laboratory findings showed elevated inflammatory markers (CRP >11 mg/dL, cut-off values <0.50 mg/ds) and mild neutrophilic leukocytosis, without altered liver or kidney function. Again, infectious screening was negative. Complete immunological panel testing was performed, including ANA, ENA, ANCA, C3, C4, LAC, anti-cardiolipin, anti-beta2 glycoprotein antibodies, rheumatoid factor, and anti-cyclic citrul-

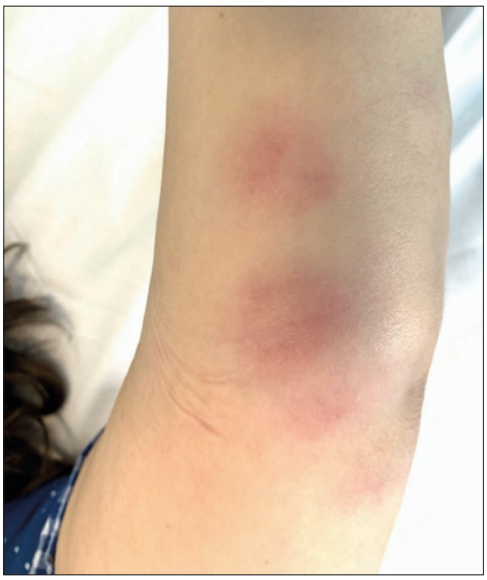

Figure 2 - Erythema nodosum. Erythematous plaques of arms following ChAdOx1 nCoV-19 vaccine.

linate antibodies, which were all negative. Due to high inflammatory markers and suspicion of sarcoidosis, chest X-ray examination was performed and found negative for lung lesions or lymphadenopathy.
The patient was already under low dose glucocorticoid therapy at the time of the first visit at our center, which was prescribed by her primary care physician but did not lead to any improvement of skin lesions. Skin biopsy was then performed: a histopathologic finding of septal panniculitis with mixed cellular infiltrate of lymphocytes, histiocytes, and giant cells was found, in the absence of vasculitis. Prednisone 25 mg was then started and gradually tapered, with complete regression of fever and fatigue within a few days and a significant reduction of cutaneous lesions during the first 5 days of hospitalization. The patient was then discharged with the indication of tapering the steroid dose until discontinuation, which occurred without relapses. Considering the rapid response to steroid therapy and the absence of recurrence, we did not perform any further oncological examination, since the patient had already undergone regular screening, postponing the decision to eventually perform it during follow-up evaluations.

DISCUSSION AND CONCLUSIONS

EN is the most common form of nodular septal panniculitis. The exact etiology is unknown although it appears to be a hypersensitivity reaction to a variety of antigenic triggers, such as infections (*e.g.* tuberculosis), chronic inflammatory diseases (*e.g.* sarcoidosis, Behçet disease, and inflammatory bowel disease), tumors and drugs (3) (Figure 3).
Suter et al. reported the first case of EN in the context of COVID-19 infection. EN was successfully treated with topic steroids, compression stockings, and appropriate analgesia, and disappeared completely within 2 weeks (4). Another case was described by Sipfle et al., pointing out that early identification of mild COVID-19 symptoms, such as dermatological manifestations only, could help in early detection of the viral infection, thus mitigating transmission (5). Ordieres-Ortega et al. reported a case of EN of the right leg that occurred 8 days after starting hydroxychloroquine and lopinavir/ritonavir for COVID-19 pneumonia (6). COVID-19 infection may induce a dysregulated immune response (7). Khan and colleagues observed that the spike protein potently induces inflammatory cytokines and chemokines (8). A complement-mediated destruction of cutaneous microvasculature, secondary to docking by SARS-CoV-2 spike protein, has been demonstrated (9). Since the mRNA COVID-19 vaccine promotes the production of the spike protein, the induction mechanism of the vaccine may be similar to that of infection. This could partially explain the relationship between COVID-19 and EN (10).
One of the first report of EN after the mRNA COVID-19 vaccine was by Aly et al. (11) in a 22-year old woman, who developed EN shortly after receiving the Pfizer vaccine; in the absence of laboratory or chest radiograph abnormalities, a vaccine-related EN was considered as the only possible explanation.
Regarding the case of EN following the viral vector COVID-19 vaccine, it is interesting to notice how the cutaneous adverse effects of the ChAdOx1 nCoV-19 described

Differential diagnosis	Clinical elements and examination
INFECTIONS • Group A β-haemolitic Streptococcus • Yersinia spp., Campylobacter, Salmonella, Mycoplasma, Chlamydia • Bacterial and viral infection (S. pyogenes, EBV, epatitis, Parvovirus B19) • Tuberculosis	• Throat culture, antistreptolysin-O titer, polymerase chain reaction assay • Stool cultures, genital and nasopharyngeal swab • Serology test • Interferon-gamma (IFN-γ) release assay
DRUGS • Antibiotics (Penicillin, Sulphonamides) • Contraceptive • Vaccine	• Pharmacological anamnesis
GRANULOMATOUS DISEASE • Sarcoidosis	• Chest X ray/computed tomography
ENTEROPATHIES • Inflammatory bowel disease (IBD) • Enteropathic arthritis	• Bowel symptoms (diarrhea, constipation, abdominal pain/bloating, mucus or blood in stool), occult blood test, faecal calprotectin, endoscopy
AUTOIMMUNE RHEUMATIC DISEASE • Rheumatoid arthritis • Systemic Lupus Erythematosus • Vasculitis (e.g. Bechet disease)	• Autoimmunity test, careful anamnesis for signs and symptoms related to rheumatological disorders (arthritis, photosensitivity, aftosis, xerostomia, xerophthalmia, purpura)
MALIGNANCY • Haematological disorders (lymphoma, leukemia)	• Systemic B symptoms, weight loss, blood tests
RARE/OTHERS • Cold panniculitis • α1-antitrypsin deficiency • Febrile neutrophilic dermatosis or Sweet's syndrome	• Anamnesis and cold exposure • Lungs, liver or pancreatin symptoms; genetic tests • Very high peripheral white cell count

Figure 3 - Differential diagnosis of erythema nodosum.

so far in the literature are mainly injection-site reactions rather than delayed effects like in our case. This finding is indirectly confirmed by the small number of biopsies that were necessary for diagnostic purposes (12). Only two recent papers by Mehta et al. (13) and Cameli et al. (14) described for the first time a case of EN following the ChAdOx1 nCoV-19 vaccine.

Therefore, the recent vaccination could be considered in both our cases the potential trigger of EN. Diffuse arthralgias were present in our first case, although these symptoms may be less specific and also present in many other clinical conditions. However, the occurrence of the first episode of dactylitis, confirmed by ultrasound, in a patient with a history of scalp psoriasis can lead us to hypothesize, albeit only as a speculation, the possible role of the vaccine as a trigger of immune-mediated reaction in a predisposed subject. The two aforementioned elements, history of psoriasis and current dactylitis, are not sufficient to satisfy the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria for psoriatic arthritis diagnosis (15). The follow-up of the patient will allow us to clarify any further evolution towards psoriatic arthritis, or inflammatory bowel disease (IBD), since EN and psoriasis are important comorbidities of IBD, potentially anticipating it and belonging to the broad '*psoriatic spectrum disease*' (16).

However, our case series have some limitations: first, skin biopsy was not performed in the first case, which may be described as EN-like skin lesions. According to the consultant dermatologist, skin biopsy was not performed due to the high clinical suspicion and complete resolution following steroid therapy. Moreover, it is interesting to notice that the EN-like eruption recurred after SARS-CoV-2 second shot, making a mere coincidence unlikely and at difference with other case reports in which recurrence did not happen (17). In addition, since the diagnosis of EN is usually clinical, it is now a general practice to reserve the biopsy for difficult to diagnose or atypical cases, in which skin lesions do not follow the typical pattern of erythema nodosum (*e.g.*, if the nodules appear in atypical areas, or persist beyond 8 weeks, or ulcerations develop). In addition, more than ever, with the current global vaccination campaign in progress,

we are asked to quickly detect potential adverse events, even extremely rare and mild ones, in order to monitor the safety of the COVID-19 vaccination campaign and in an effort to reassure the general population. Therefore, we decided to present these cases due to the possible clinical impact they may have in relation to autoimmune manifestations following SARS-CoV-2 vaccination.
Further reports are needed to understand possible underlying mechanisms of immunological skin reactions after the COVID-19 vaccine, as already claimed (18, 19). Most importantly, these above-mentioned adverse reactions are not serious and should not discourage people from completing the vaccination cycle.

Acknowledgments
The patients described in this manuscript have given written informed consent to the publication of the case details.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020; 383: 2603-15.
2. 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.
3. Perez-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: 367-78.
4. Suter P, Mooser B, Pham Huu Thien HP. Erythema nodosum as a cutaneous manifestation of COVID-19 infection. BMJ Case Rep. 2020; 13: 7.
5. Sipfle DN, Bridwell Md RE, Roper DJ. Erythema nodosum-like rash in a COVID-19 patient: A case report. Am J Emerg Med. 2021; 40: 227, e1- e2.
6. Ordieres-Ortega L, Toledo-Samaniego N, Parra-Virto A, et al. Atypical erythema nodosum in a patient with COVID-19 pneumonia. Dermatol Ther. 2020; 33: e13658.
7. 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: 762-8.
8. Khan S, Shafiei MS, Longoria C, et al. SARS-CoV-2 spike protein induces inflammation via TLR2-dependent activation of the NF-kappaB pathway. Elife. 2021; 10.
9. Magro CM, Mulvey JJ, Laurence J, et al. Docked severe acute respiratory syndrome coronavirus 2 proteins within the cutaneous and subcutaneous microvasculature and their role in the pathogenesis of severe coronavirus disease 2019. Hum Pathol. 2020; 106: 106-16.
10. 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: 102537.
11. Aly MH, Alshehri AA, Mohammed A, et al. First case of erythema nodosum associated with Pfizer vaccine. Cureus. 2021; 13: e19529.
12. Blumenthal KG, Saff RR, Freeman EE. Delayed large local reactions to mRNA vaccines. reply. N Engl J Med. 2021; 384: e98.
13. 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. 2021 [Epub ahead of print].
14. Cameli N, Silvestri M, Mariano M, et al. Erythema nodosum following the first dose of ChAdOx1-S nCoV-19 vaccine. J Eur Acad Dermatol Venereol. 2021 [Epub ahead of print].
15. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006; 54: 2665-73.
16. De Simone C, Sollena P, Coco V, Caldarola G. Psoriasis and erythema nodosum: two comorbidities of inflammatory bowel diseases. G Ital Dermatol Venereol. 2013; 148: 175-84.
17. Teymour S, Ahram A, Blackwell T, et al. Erythema nodosum after Moderna mRNA-1273 COVID-19 vaccine. Dermatol Ther. 2022: e15302.
18. Burlando M, Russo R, Cozzani E, Parodi A. COVID-19 "second wave" and vaccines: the dermatologists' perspective. Int J Dermatol. 2021; 60: 889-90.
19. Maranini B, Ciancio G, Cultrera R, Govoni M. Herpes zoster infection following mRNA COVID-19 vaccine in a patient with ankylosing spondylitis. Reumatismo. 2021; 73: 1445.