








CASE REPORT

Erythema nodosum induced by Covid-19 Pfizer-BioNTech mRNA vaccine: A case report and brief literature review

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Erythema nodosum (EN), the most common form of panniculitis, is a reactive inflammation of the subcutaneous fat clinically presented with a sudden onset of painful, erythematous, nodular, subcutaneous lesions, typically localized to the pretibial area. EN is commonly caused by numerous infections (especially beta-haemolytic streptococcal infections), autoimmune diseases (sarcoidosis), inflammatory bowel conditions and drugs. EN induced by Covid-19 vaccines is rarely reported. We describe an original clinical observation of a 75-year-old woman who presented with EN after receiving the second dose of BNT162b2, an mRNA vaccine.

KEYWORDS

BNT162b2, Covid-19, erythema nodosum, mRNA vaccine, side effects, vaccination

1 | INTRODUCTION

Erythema nodosum (EN) is a reactive inflammation of the subcutaneous fat clinically characterized by painful, tender, nodular and erythematous lesions located symmetrically on pretibial surfaces. EN subsides classically in 3-6 weeks with mild hyperpigmentation.¹

The pathogenesis is thought to be related to deposition of immune complexes in venules of the deep dermis and adipose tissue.² EN is commonly caused by numerous infections (especially beta-haemolytic streptococcal infections), autoimmune diseases (sarcoidosis), inflammatory bowel conditions and drugs.³ Up to 10% of EN cases are attributed to medicines, particularly antibiotics and oral contraceptives.⁴ However, EN associated with vaccines has been rarely reported.⁵ Since March 2020, the Coronavirus disease 2019 (Covid-19) pandemic has affected and caused the death of millions of people all over the world and vaccines are considered the most effective strategy to end it.⁶ A wide variety of skin reactions occurring after Covid-19 vaccination has been described in the literature mainly urticaria, angioedema and maculo-papular eruption.⁷ Nevertheless, there

is currently a paucity of literature on EN associated with Covid-19 vaccines.⁸⁻¹¹ We describe here a clinical observation of EN induced by BNT162b2, an mRNA vaccine.

2 | CASE REPORT

A 75-year-old woman presented with diffuse erythematous painful and nodular lesions, located symmetrically over her legs. Six days before, she had received the second dose of Covid-19 vaccine (BNT162b2 [Pfizer-BioNTech]), which was followed by a sudden asthenia, polyarthralgia, throbbing and oedema over her lower limbs. She had a medical history including type-2 diabetes, hypertension and psoriasis. She had no known drug allergy. She had been given the first dose of the same Covid-19 vaccine 29 days prior to the second without incident. General physical examination was normal. Skin examination showed multiple, tender, erythematous and nonulcerative nodules, which ranged from 10 to 30 mm in diameter symmetrically located over the tibial area (Figure 1). Laboratory tests including a complete blood count, renal and hepatic tests, antistreptolysin O titer, and antinuclear antibody and thyroid tests were carried out and were negative. Chest radiograph and PCR were performed with normal results. Histopathology showed a slight perivascular and periadnexal

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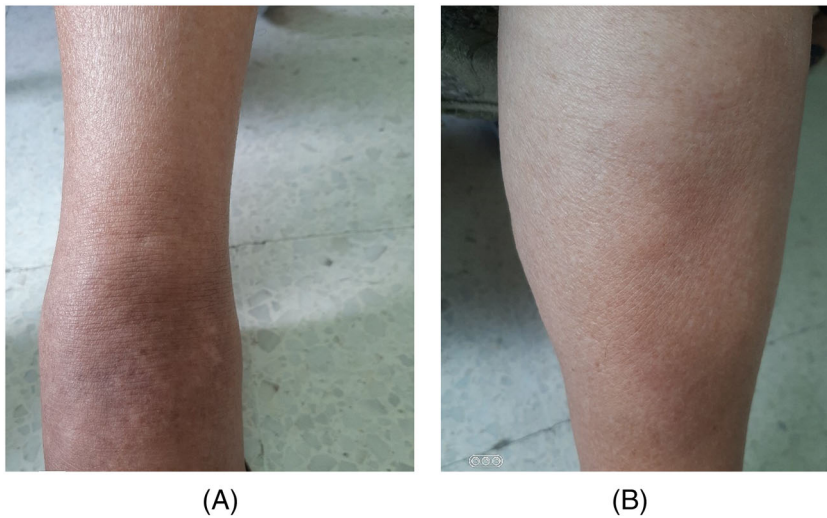


FIGURE 1 (A) Multiple erythematous nodules. (B) Multiple erythematous nodules over the leg

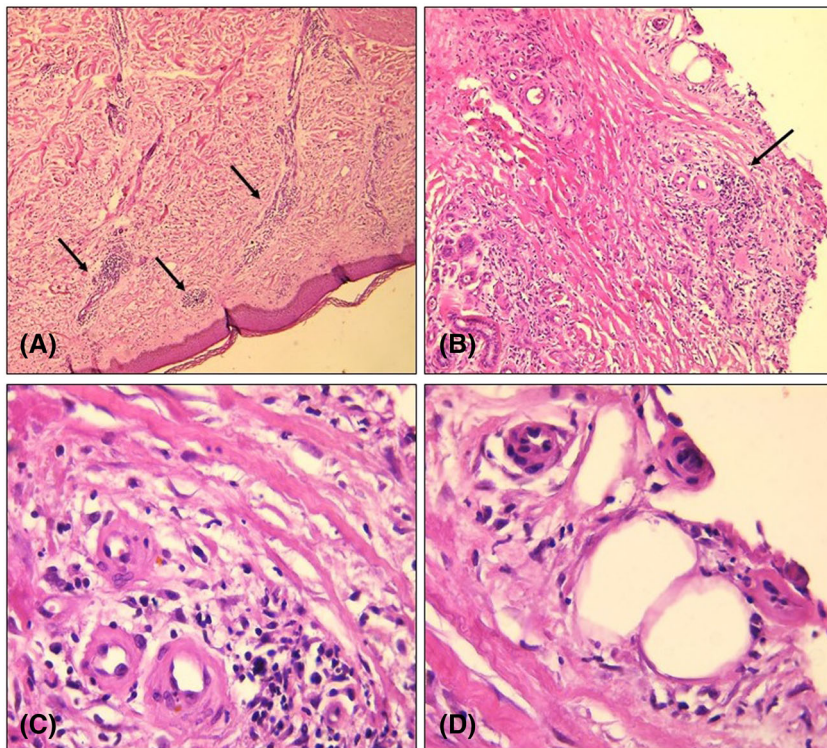


FIGURE 2 (A) (Haematoxylin and eosin [H&E] stain, original magnification $\times 40$ [HE $\times 40$]) and (B) (HE $\times 100$): biopsy specimen obtained from the skin lesions showing slight perivascular and periadnexal inflammatory cell infiltrate in the upper and the deep dermis (black arrow). (C) (HE $\times 400$): note the mononuclear infiltrate (lymphocytes and histiocytes) with marginating neutrophils attached to the vascular wall in the deep dermis. (D) (HE $\times 400$): adipose tissue is scant and a specific diagnosis cannot be made

inflammatory cell infiltrate in the upper and deep dermis with mononuclear cell infiltration with marginating neutrophils attached to the vascular wall in the deep dermis, consistent with EN (Figure 2).

Treatment with analgesics led to complete resolution of the lesion after 3 months. Three weeks later, on follow-up examination, the patient's symptoms had completely resolved and since then she has shown no relapse.

3 | DISCUSSION

We describe the clinical observation of a patient who developed EN thought to be related to the Covid-19 vaccine. In view of

the close temporal relationship between administration of the Pfizer vaccine and symptom onset, which was compatible, the spontaneous remission of symptoms and the absence of other attributable aetiologies of the eruption, the diagnosis of EN was retained. Based on the Naranjo scale, our case was assigned a score of 8, qualifying the diagnosis of EN to be probable. Consequently, the systemic reaction was probably related to the Covid-19 vaccine.¹²

EN is regarded as an immune-complex deposition disease affecting venules of the deep dermis and adipose tissue. In contrast to our patient, EN is most commonly observed in young women (between 20 and 50 years).¹³ The localization of the EN in the current case was typical since the extensor leg below the knee is the most frequent

location, but EN may also occur on other sites such as the upper limbs.²

The differential diagnosis of EN encompasses principally EN leprosum, which is a severe multisystem immune-mediated complication of leprosy,¹⁴ battered child syndrome, Henoch-Schönlein purpura, urticaria, erythema induratum and nodular fat necrosis.⁴

The majority of EN cases are believed to be idiopathic, but some cases are associated with conditions such as tuberculosis, sarcoidosis and inflammatory bowel disease.² Drugs are also involved in inducing EN, especially sulphonamides, analgesics, oral contraceptives and proton pump inhibitors.³ While vaccines are uncommon causes of EN, it has been described in association with vaccines for Bacille-Calmette-Guerin, hepatitis B, human papillomavirus, malaria, rabies, smallpox, tetanus, diphtheria, pertussis and typhoid, and cholera.^{5,15,16} Interestingly, our case suggests a relationship between the Covid-19 Pfizer vaccine and EN. Cutaneous adverse effects of Covid-19 vaccines have been described recently. Bellinato et al¹⁷ have summarized the available data related to cutaneous adverse reactions following Covid-19 vaccines but EN induced by Pfizer vaccine is lacking in this review. The most commonly reported side effects of Covid-19 vaccines are injection-site reactions, generally mild or moderate.¹⁸ Limited case series or sporadic case reports included exanthemas,¹⁹ vascular lesions,²⁰ urticaria,²¹ eczematous dermatitis,²² autoimmune bullous reactions²³ and severe cutaneous adverse reactions.²⁴ Moreover, the exacerbation of chronic immuno-mediated dermatoses (mainly psoriasis and atopic dermatitis) and reactivations of herpes infection have been reported.^{25,26} However, EN has been rarely described as a drug side effect to Covid-19 vaccines and to our knowledge it has been previously reported in four isolated cases.⁸⁻¹¹

Mehta et al⁸ were the first to report the case of a 25-year-old female patient who had developed EN 7 days after the first dose of Covishield (Oxford-AstraZeneca) Covid-19 vaccine. Cutaneous signs had resolved completely after 2 weeks. However, no recurrence was observed on receiving the second booster shot of vaccine.

Subsequently, Camely et al¹¹ described a second case of EN occurring in a 64-year-old woman 2 days after receiving the first dose of ChAdOx1 CoV-19 vaccine. The patient had heterozygous factor V Leiden mutation comorbidity. Resolution of symptoms was observed within 4 weeks after systemic therapy with methylprednisolone. Aly et al⁹ described the third case of a 22-year-old female patient who had EN 1 day after receiving the first dose of the Pfizer vaccine. Three days after receiving the oral ibuprofen, she improved, the nodules started to flatten and complete resolution of symptoms was observed 2 weeks later.

Finally, in December 2022, Wu et al¹⁰ reported a case of EN occurring in a 37-year-old woman 1 day after receiving the second dose of Comirnaty (Tozinameran) vaccination. The patient had a prior history of EN related to well-controlled pulmonary tuberculosis and underlying Hashimoto thyroiditis. The clinical course was marked by a complete resolution of her lesions achieved with colchicine treatment 1 month later.

Similarly, Rademacher et al²⁷ have described two cases of Löfgren's syndrome (associated with bilateral hilar lymphadenopathy,

EN and ankle peri-arthritis) after Covid-19 vaccination: The first patient was a 21-year-old woman who developed symptoms 3 days after a second dose of Moderna vaccine (the first dose was ChAdOx1, AstraZeneca). The second patient was a 27-year-old man who described symptoms 28 days after first vaccination by the adenoviral vector vaccine (ChAdOx-1, Vaxzevria, Astra Zeneca).

The time course of development of EN following exposure to a trigger is unpredictable and may occur between 5 days and 21 months,²⁸ could occur within a shorter duration. For instance, Cohen⁵ reported a case of EN occurring only 48 hours after combined reduced-antigen content tetanus diphtheria and acellular pertussis. In our patient, we ruled out Covid-19 infection as the explanation of the occurrence of EN. In fact, EN has been reported to be involved in the clinical features of Covid-19 infection.²⁹

In these previous cases of EN induced by Covid-19 vaccines, the median age was 26 years (interquartile range 21-64) and the majority of patients were women (sex ratio 5:1). The median time interval between vaccination and the onset of EN was 2.5 days. The Covid-19 vaccines inducing EN were mRNA (Pfizer-BioNTech [BNT162b2], N = 2; Moderna, N = 1) and viral vector (Oxford/AstraZeneca, N = 3).

Generally, cutaneous reactions to Covid-19 vaccines are slightly more common after the first dose compared to the booster (53% vs 46%, respectively),¹⁹ but in these reported cases of EN, the offending dose of Covid-19 vaccine was the first one in three of five patients and the median time to symptom resolution was 2 weeks. However, in the present case, the EN onset was after the second booster shot of mRNA Covid-19 vaccine and a complete resolution of symptoms was observed 3 months after the initial presentation.

The pathogenesis of EN secondary to vaccinations remains unclear, but it is thought to be related to a reaction to antigens of the infectious agent or a hypersensitivity reaction to components of the vaccine.⁵ Episodes of autoimmune disease flares following Covid-19 vaccination have been reported usually within a maximum of 1 week following vaccination.³⁰

In the previous reported cases of EN associated with Covid-19 vaccines, an underlying autoimmune disease was noted in one patient,¹⁰ who had Hashimoto thyroiditis. Our patient had a past history of psoriasis and type 2 diabetes. These underlying autoimmune conditions suggest an interaction between the immune system and the messenger RNA molecules and their lipid carrier particles.

We also suspect a genetic predisposition to EN, which may induce the EN's onset. Indeed, a possible genetic susceptibility may be a risk factor to developing EN. Up to 70% of patients with GATA2 mutations have dermatological features, mainly panniculitis or EN and lymphoedema.³¹

In conclusion, the current observation is the third case of EN particularly induced by the second dose of BNT162b2 (Pfizer-BioNTech) Covid-19 vaccine occurring in a 75-year-old patient. It is important for clinicians to be aware of this rare, yet potential, adverse effect to this vaccine. The literature is likely to reveal more cutaneous reactions induced by Covid-19 vaccination in the future.

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019a,b).

Our manuscript does not contain any targets and ligands that can be linked to the Guide to Pharmacology.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conceptualization and writing – original draft: K.A. and F.C. Data curation: M.Y., N.B.F., S.B.H. Supervision writing, review and editing: N.B.F., H.B.R., A.C.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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