

CASE REPORT

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¹Department of Dermatology, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

²Medical Intern College of Medicine, King Faisal University, Alhasa, Saudi Arabia

³Department of Pathology, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

⁴Medical Intern, College of Medicine, Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia

⁵Medical Intern, College of Medicine, Najran university, Najran, Saudi Arabia

Corresponding author: Mohammed Almutairi, Medical Intern, College of Medicine, King Faisal University, Alhasa, Saudi Arabia. Phone: +966505921303. E-mail address: M.t.mutairi0@gmail.com. ORCID ID <https://orcid.org/0000-0002-6116-4960>.

Atypical Presentation of Erythema Nodosum Following Pfizer-BioNTech COVID-19 Vaccine

Nasser Alzoabi¹, Jamal Alqahtani¹, Bader Algamdi¹, Mohammed Almutairi², Jumana Alratroot³, Saud Alkhalidi⁴, Shatha Alqahtani⁵, Omar Alakloby¹

ABSTRACT

Background: Erythema nodosum (EN) is a common form of panniculitis that could be triggered by numerous conditions including infectious and non-infectious conditions. So far, few cases of EN caused by COVID-19 vaccine had been reported. **Case Report:** We report a case of atypical presentation of EN mimicking cellulitis in a patient who received the first dose of the Pfizer-BioNTech COVID-19 vaccine. A 38-year-old healthy woman who developed painful swelling on the left leg one week after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine. Skin biopsy was revealed septal panniculitis. Due to the temporal association and the absence of other identifiable causes, Pfizer-BioNTech COVID-19 vaccine-related EN would be the most likely explanation. **Conclusion:** COVID-19 vaccines could be associated with rare side effects that should be reported for a better understanding of related outcomes of COVID-19 vaccination. This case was reported to keep in mind that EN can have atypical presentation as a rare side effect of COVID-19 vaccines.

Keywords: COVID-19, Erythema Nodosum, COVID-19 vaccine.

1. BACKGROUND

The novel coronavirus disease 2019 (COVID-19) which causes Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), appeared at the end of 2019 in Wuhan city in China (1). Covid-19 has high ability of transmission from human to another human. Subsequently, COVID-19 has become an epidemic in China, and due to its fast spread globally the World Health Organization (WHO) announced that COVID-19 is pandemic disease on March 11, 2020 (2, 3).

EN is one of the most common forms of panniculitides presents as subcutaneous tender nodules with overlaying erythema commonly affected pretibial area of the lower legs. It is regarded as a reactive process to many various antigenic stimuli. Many precipitating factors has been linked to EN; these include infections, drugs, vaccines, pregnancy, some systemic diseases such as inflammatory bowel diseases, sarcoidosis and hematological malignancy (4, 5). Few case reports recently associated EN with either COVID-19 infection or vaccines. We report a case of atypical presentation of EN mimicking cellulitis in a patient who received the first dose of Pfizer-BioNTech COVID-19 vaccine.

2. CASE REPORT

A 38-year-old Saudi lady who presented to the dermatology clinic with painful swelling on her left leg for one month duration. Patient did not have fever, cough, chest pain, or GI/GU symptoms. She was not on any regular medications or contraceptives pills. However, she reported getting her first dose of Pfizer vaccine one week prior to the appearance of these lesions. Before her presentation to our clinic, she had received multiple courses of antibiotics, as she was suspected to have cellulitis, but without any improvement. Clinical examination revealed tender, erythematous, subcutaneous nodules over the left shin (Figure 1). The rest of systemic examination was unremarkable. Complete blood count, liver function test, renal function test all within normal limit. Chest X-ray was clear and tuberculin skin test was negative. A 4mm punch biopsy was done which showed septal infiltration composed of lymphocytes, histiocytes, and eosinophils, admixed with multinucleated

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No.	Country	Age	Interval Period	Location of Rash	Type of Vaccine	Vaccine dose	Reference
1	Taiwan	27	3 days	Bilateral LL	Medigen	1 st dose	(8)
2	Saudi Arabia	22	1 day	Bilateral LL	Pfizer	1 st dose	(9)
3	Morocco	66	2 days	All 4 limbs	Astrazeneca	2 nd dose	(10)
4	Italy	64	2 days	Bilateral LL	ChAdOx1-S nCoV-19	1 st dose	(11)

Table 1. Summary of literature review of erythema nodosum following various COVID-19 Vaccine

giant cells (Figure 2). Hemorrhage and edema were also noted in the hypodermis with mild septal fibrosis. The described features are suggestive of the clinical diagnosis erythema nodosum. Due to the absence of other identifiable causes and the temporal association with COVID-19 vaccine dose, the diagnosis of Pfizer-BioNTech COVID-19 vaccine-related EN was made. The patient was prescribed ibuprofen 600 mg twice per day for 2 weeks with complete recovery after 4 weeks.

3. DISCUSSION

Erythema nodosum is a type of panniculitis, characterized by erythematous painful rounded nodules symmetrically localized on the extensor surfaces of the legs. These lesions tend to resolve spontaneously within 2–8 weeks without leaving scars. Erythema nodosum is usually diagnosed clinically but biopsy can be done when clinical diagnosis is uncertain. The histopathological signs of erythema nodosum are characterized by septal inflammation of the subcutaneous fat tissue (4, 5).

Erythema nodosum can occur due to various conditions including infections, drugs, malignancy, inflammatory bowel disease, pregnancy and sarcoidosis. The most frequent causes of erythema nodosum are infections. The second frequent cause is sarcoidosis which account for 11% to 25% of the total cases, followed by drugs (3% to 10%), pregnancy (2% to 5%), and enteropathies, (1% to 4%) (6).

EN is known to be associated with various infections and vaccines. Few case reports have been written in which EN was associated with COVID-19 infection or vaccinations. Philipp Suter et al, report the first case of EN in patient with acute COVID-19 infection who was spontaneously improved with resolution of COVID-19 infection in addition to analgesia and topical corticosteroid (7). Other cases report occurrence of EN in patients who received different types of COVID-19 vaccine including Medigen vaccine, AstraZeneca, Vaxzevria COVID-19 vaccine, ChAdOx1 nCoV-19 vaccine and Pfizer-BioNTech vaccine (8-11).

In our case, the patient, who was a healthy 38-year-old woman, has developed erythema nodosum manifestations one week after receiving her first dose of Pfizer BioNTech COVID-19 vaccine. Her condition was compatible with Pfizer-BioNTech COVID-19 vaccine-related EN due to the absence of other causes and temporal as-



Figure 1. Single ill-defined, non-blanchable, erythematous, and painful subcutaneous nodules over the left shin.

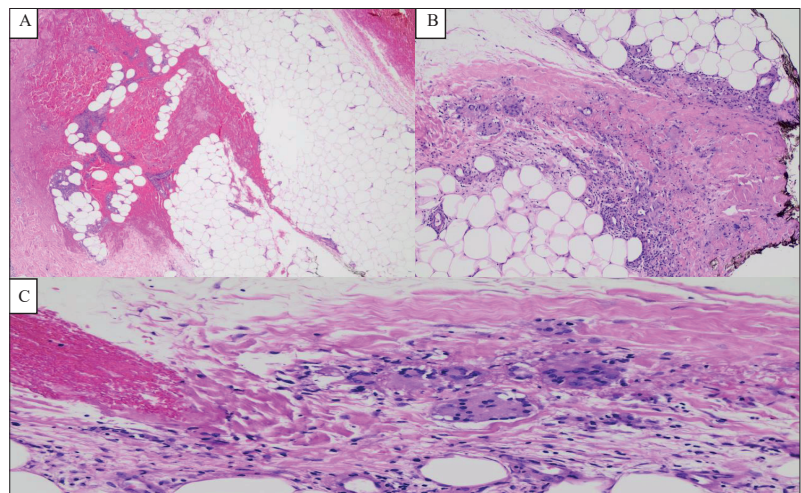


Figure 2. (A) Low power view showing the hemorrhage and edema in the subcutaneous tissue. (Hematoxylin-eosin, original magnification × 40). (B) Low power view featuring the inflammatory infiltration and the fibrosis in the septa. (Hematoxylin-eosin, original magnification × 100). (C) Higher power view showing the multinucleated giant cell reaction. (Hematoxylin-eosin, original magnification × 200)

sociation between erythema nodosum and administration of first dose of Pfizer-BioNTech COVID-19 vaccine.

Pfizer-BioNTech COVID-19 vaccine has been associated with other cutaneous adverse effects. Early local injection site reactions were the most commonly observed adverse cutaneous effect related to Pfizer COVID-19 vaccine. Other rare cutaneous adverse effects are delayed local reactions, morbilliform rash, urticarial reactions, pityriasis rosea, Rowell's syndrome, and lichen planus (12).

Table 1 shows the results of our extensive literature review using PubMed search engine. In summary, there were four cases in total that involved EN as a new emerging sign following COVID-19 vaccine administra-

tion. The four cases were reported in different countries (Independent of Geographic region), two cases reported were patients in their 20's, and other two cases were in their 60's. Regarding the time interval between the vaccine administration and the onset of the rash, a range of 1-3 days was noted, with the lower limbs being the site of rash in all of cases. Furthermore, the incidence of rash was not confined to one type of vaccine, as it has been seen following Medigen, Pfizer, Astrazeneca, and ChAdOx1-S-nCoV-19 vaccines.

4. CONCLUSION

A 38-year-old healthy woman who developed painful swelling on the left leg one week after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine. Skin biopsy revealed septal panniculitis. Due to the temporal association and the absence of other identifiable causes, Pfizer-BioNTech COVID-19 vaccine-related EN was made. This case was reported to keep in mind that EN can have atypical presentation as a rare side effect of COVID-19 vaccines.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's Contribution:** All authors were involved in the preparation of this article. All Authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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