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CASE REPORT

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Erythema nodosum after COVID-19 vaccine: Report of two pediatric cases

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Abstract

With the introduction of large-scale COVID-19 vaccination programs, a variety of cutaneous manifestations have been described. We present two girls (ages 12 and 5 years) who developed erythema nodosum (EN) 3 and 14 days after Pfizer-BioNTech COVID-19 vaccination, respectively. While EN after COVID-19 vaccination has been reported in adults, it is can also occur in children.

KEYWORDS

Astra Zeneca, Covid-19, cutaneous side effects, erythema nodosum, Medigen, Moderna, mRNA vaccine, Pfizer, SARS-CoV-2, vaccines

1 | INTRODUCTION

A total of 163.23 doses of COVID-19 vaccines per 100 population globally have been administered.[1] In the United States, 9% of children aged 6 months to 4 years, 38% aged 5 –11 years, and 67% aged 12–17 years have received the initial dose of COVID-19 vaccine.[2] Cutaneous manifestations related to COVID-19 vaccines include local injection-site reactions, urticaria, angioedema, herpes zoster, morbilliform, papulovesicular, and pityriasis rosea-like eruptions, chilblain-like lesions, erythema multiforme, and delayed inflammatory reactions to dermal hyaluronic acid filler.[3] To date, 8 cases of COVID-19 vaccine-induced erythema nodosum (EN) have been reported,[4–11] all in adults. We present two children with EN occurring after mRNA COVID-19 vaccination.

2 | CASE REPORTS

2.1 | Case 1

A 12-year-old girl, otherwise healthy and with no family history of autoimmune disease, developed multiple erythematous, deep-seated nodules on the pretibial aspects of both legs, 3 days after receiving the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine. The patient denied taking any medication in the previous month. There was no history of fever, sore throat, diarrhea, arthralgias, or any other symptoms in the 4 weeks prior to vaccination. No sick contacts were recalled. The lesions were tender to palpation and there were no systemic complaints or fever. Blood cell counts and serum chemistry were unremarkable, except for a slightly elevated erythrocyte sedimentation rate. Serologic tests for hepatitis B and C viruses were

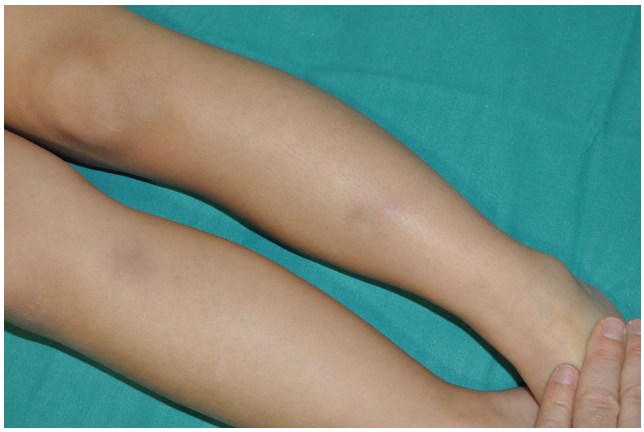

FIGURE 1 Erythematous to brownish subcutaneous nodules on the pretibial aspects of both legs on patient 2.

TABLE 1 Characteristics of reported cases of COVID-19 vaccine-induced erythema nodosum (EN). F, female; M, male; NS, not specified.

Author	Patient age (years)/sex	Vaccine	Time until EN following vaccination (days)	Recurrence of EN following 2nd dose/time (days)	Diagnosis	Underlying disease ruled out	Evaluation for underlying disease	Treatment	Time until resolution (weeks)
Teymour et al.[4]	66/F	mRNA-1273 (Moderna)	10 after 1st dose	No	Clinical and histopathological	Yes	Blood cell counts, serum chemistry, COVID-19 PCR nasopharyngeal swab, autoimmunity profile, serologic tests, QuantiFERON tuberculosis immunoassay	None	2
Hsu et al.[5]	27/M	MVC-COV1901 (Medigen)	3 after 1st dose	NS	Clinical and histopathological	Yes	Blood cell counts, serum chemistry, autoimmunity profile, COVID-19 rapid antigen test, QuantiFERON tuberculosis immunoassay, chest X-ray	Oral and topical corticosteroids, colchicine	10, improvement
Mehta et al.[6]	25/F	ChAdOx1-S (AstraZeneca)	7 after 1st dose	No	Clinical and histopathological	Yes	Serum chemistry, COVID-19 PCR nasopharyngeal swab, rest NS	Topical corticosteroids, paracetamol	2
Aly et al.[7]	22/F	BNT162b2 (Pfizer-BioNTech)	1 after 1st dose	NS	Clinical	Yes	Laboratory investigations NS, chest X-ray	NSAIDs	2
Wu et al.[8]	37/F	BNT162b2 (Pfizer-BioNTech)	1 after 1st dose	NS	Clinical and histopathological	Yes	NS	Colchicine	4
Hali et al.[9]	66/F	ChAdOx1-S (AstraZeneca)	2 after 2nd dose	-	Clinical and histopathological	Yes	Blood cell counts, serum chemistry, fecal culture, chest X-ray	Topical corticosteroids, antihistaminics, vitamin C	10 days, improvement
Cameli et al.[10]	64/F	ChAdOx1-S (AstraZeneca)	2 after 1st dose	NS	Clinical	Yes	Blood cell counts, serum chemistry, autoimmunity profile, serologic tests, Mantoux test, chest X-ray	Oral corticosteroids	4, improvement
Damevska et al.[11]	62/M	BNT 162b2 (Pfizer-BioNTech)	14 after 1st dose	Yes, 4	Clinical	Yes	Serum chemistry, rest NS	Topical corticosteroids	3
Gonzalez-Canete et al. (present cases)	12/F	BNT 162b2 (Pfizer-BioNTech)	3 after 1st dose	-	Clinical	Yes	Blood cell counts, serum chemistry, antinuclear antibodies	NSAIDs	1, improvement
	5/F	BNT 162b2 (Pfizer-BioNTech)	14 after 1st dose	-	Clinical	Yes	Blood cell counts, serum chemistry, serologic tests, oropharyngeal swab	NSAIDs	1, improvement

negative. An oropharyngeal swab was negative for beta-hemolytic *Streptococcus*. A clinical diagnosis of EN was made, and the parents and patient declined a skin biopsy. Treatment with oral ibuprofen was prescribed, and the skin lesions began to fade within 1 week and eventually disappeared. The patient has not received a subsequent vaccine dose.

2.2 | Case 2

A 5-year-old girl with no significant past medical history had a 1-week history of erythematous to brownish subcutaneous nodules appearing on the pretibial aspects of both legs (Figure 1). These lesions had appeared approximately 2 weeks after receiving the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine. No new medication was introduced in the prior weeks, and there was no contact with sick individuals. The nodules were painful, and the patient had no systemic symptoms or fever. Routine laboratory testing, including blood cell counts, serum chemistry, c-reactive protein, and antinuclear antibodies were normal or negative. A clinical diagnosis of EN was made. A skin biopsy was declined by her parents. The patient started treatment with oral ibuprofen with significant improvement within a week. Four weeks later her lesions had disappeared. The patient has not received a subsequent vaccine dose.

3 | DISCUSSION

EN is the most common type of panniculitis in children.[12] While a cause for EN is often not identified, reported causes and triggers of EN include bacterial and viral infections, malignancy, or inflammatory diseases. Vaccines are an unusual cause of EN.[13] COVID-19 vaccine-induced EN has been reported in 8 adults, ages 22–66 years of age.[4–11] Four patients were vaccinated with an mRNA vaccine, 3 with Pfizer-BioNTech[7,8,11] and 1 with Moderna.[4] Three cases occurred after vaccination with Oxford-AstraZeneca[6,9,10] and one after Medigen.[5] A relationship between EN and COVID-19 vaccine was based on the appearance of EN within 1–14 days after vaccination[4–11] and recurrence with a second dose of vaccine in one case.[11] In 5 cases, a skin biopsy was performed. showing septal panniculitis.[4–6,8,9] In the three remaining cases, the diagnosis was clinical. Underlying triggers, other than COVID-19 vaccination, were reasonably ruled out in most cases through medical history and laboratory investigations. Patients followed different treatments, such as oral or topical corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and colchicine, with lesions improving or resolving over 1–4 weeks. (Table 1).

The pathogenesis of COVID-19 vaccine-induced EN is unclear. EN is considered a delayed type of hypersensitivity eruption; therefore, humoral IgG and IgM responses elicited by vaccines may play a role.[4] It has been hypothesized that the strong TNF response induced by mRNA vaccines[14] might also play a role in the development of COVID-19 vaccine-induced EN.[8] Dysregulation of TNF-α is related to the formation of granulomas, and a correlation exists between a polymorphism in the promoter region of the gene encoding TNF-α and the development of EN associated with sarcoidosis.[15] This could explain the slightly higher incidence of EN reported after mRNA COVID-19 vaccination,[4,7,8,11] as in our two cases, compare with other COVID-19 vaccines, such as viral vector vaccines[6,9,10] or protein subunit vaccines.[5]

Literature is sparse regarding EN occurring in children after COVID-19 vaccination. However, it is reassuring that COVID-19 vaccine-induced EN appears to be transient and responds well to treatment, so the benefit of vaccination still outweighs the risks. In our patients, a skin biopsy was not carried out, although clinical features and evolution support the diagnosis of EN. In our cases, the exclusion by clinical history, examination, and lab tests of other known causes of EN, together with the close temporal sequence, makes vaccination a plausible etiology. However, it should be noted that about half of cases of EN are idiopathic,[12] and thus, this possibility cannot be ruled out. It is possible that cases of EN after COVID-19 may have been overlooked, and new cases are likely to appear with the introduction of large-scale COVID-19 vaccination programs in children.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article.

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