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CLINICAL LETTER

Erythema multiforme following vaccination for SARS-CoV-2: Report of a case and review of the literature — Secondary Publication

Dear Editor,

As more people are being vaccinated for SARS-CoV-2, its cutaneous adverse reactions are increasing. The majority of these adverse reactions are immediate-type hypersensitivity reactions;[1] however, a few cases of delayed-type, including erythema multiforme (EM), have been reported. Herein, we report a case of EM following the SARS-CoV-2 vaccination (BNT162b2; Pfizer–BioNTech), with a lymphocyte transformation test (LTT) result and summarize the previous literature reports.

A 77-year-old man was referred to our department with eruptions over his entire body, which had started 2 days after the second dose of BNT162b2. At the first visit, 3 weeks after the vaccination, non-pruritic annular oedematous erythema had extended and coalesced the trunk and extremities with target-like lesions (Figure 1a–d). He had no adverse reactions after the first dose. Laboratory test results were within the reference ranges, except mild eosinophilia and renal failure, and no triggers of EM were identified. Anti-streptolysin O titre was normal, antibodies for hepatitis C virus and Mycoplasma pneumoniae were absent, and serology revealed no reactivation of human herpesviruses. A skin biopsy revealed mild liquefaction degeneration (Figure 1e) and perivascular lymphocytic/eosinophilic infiltration in the superficial dermis (Figure 1f). The lack of mucosal involvement, bullae, erosion, and histological absence of individual cell necrosis made Stevens-Johnson syndrome/toxic epidermal necrolysis less likely as differential diagnoses. The LTT, covered by Japanese insurance as standard-of-care, was negative for the medications he had taken (candesartan cilexetil, amlodipine besylate and nifedipine), and the eruptions resolved without discontinuation of these medicines. Collectively, the diagnosis of EM was established, and BNT162b2 was suspected as the cause. Of note, the possibility of generalized fixed-drug-eruption cannot be excluded, and the distribution of the eruption should be carefully examined at the time of recurrence.

Information regarding patients' age and sex were obtained in 12 of 17 previously reported cases of EM after SARS-CoV-2 vaccination (age: 27–91 years; median: 66 years; nine women; Table 1) Nine had received BNT162b2. All symptoms occurred within 10 days of vaccination and improved without recurrence. Only three cases required systemic corticosteroid therapy.

We performed the LTT for BNT162b2 as an ex vivo diagnostic method to detect T-lymphocytes against the drug, but the result was negative (Table S1) (stimulation index [SI]: 121%; SI ≥1.8 is regarded positive in Japan[2]). We cannot exclude the possibility that the LTT was falsely negative due to inappropriate timing of the test (imbalance of T-lymphocyte subset), improper lymphocytes culture system (T-cell reaction against SARS-CoV-2 vaccine has been detected in IFN − γ ELISpot[3] and rapid expansion protocol[4]), or use of a different lot number from the vaccine used for immunization. However, Hashiguchi et al. reported that positivity rates of LTTs using the hepatitis B or influenza vaccine are high in the population after immunization.[5] We performed the LTT with a blood sample of a healthy individual who received two doses of BNT162b2, and the result was closely positive (SI: 178%) (Table S1), suggesting that the results of LTT against the SARS-CoV-2 vaccine require careful interpretation.

We reported a case of EM following the BNT162b2 vaccination with the result of LTT. As more individuals received the third dose of SARS-CoV-2 vaccination, more cases of EM are expected to be reported. Further accumulation of cases is required.

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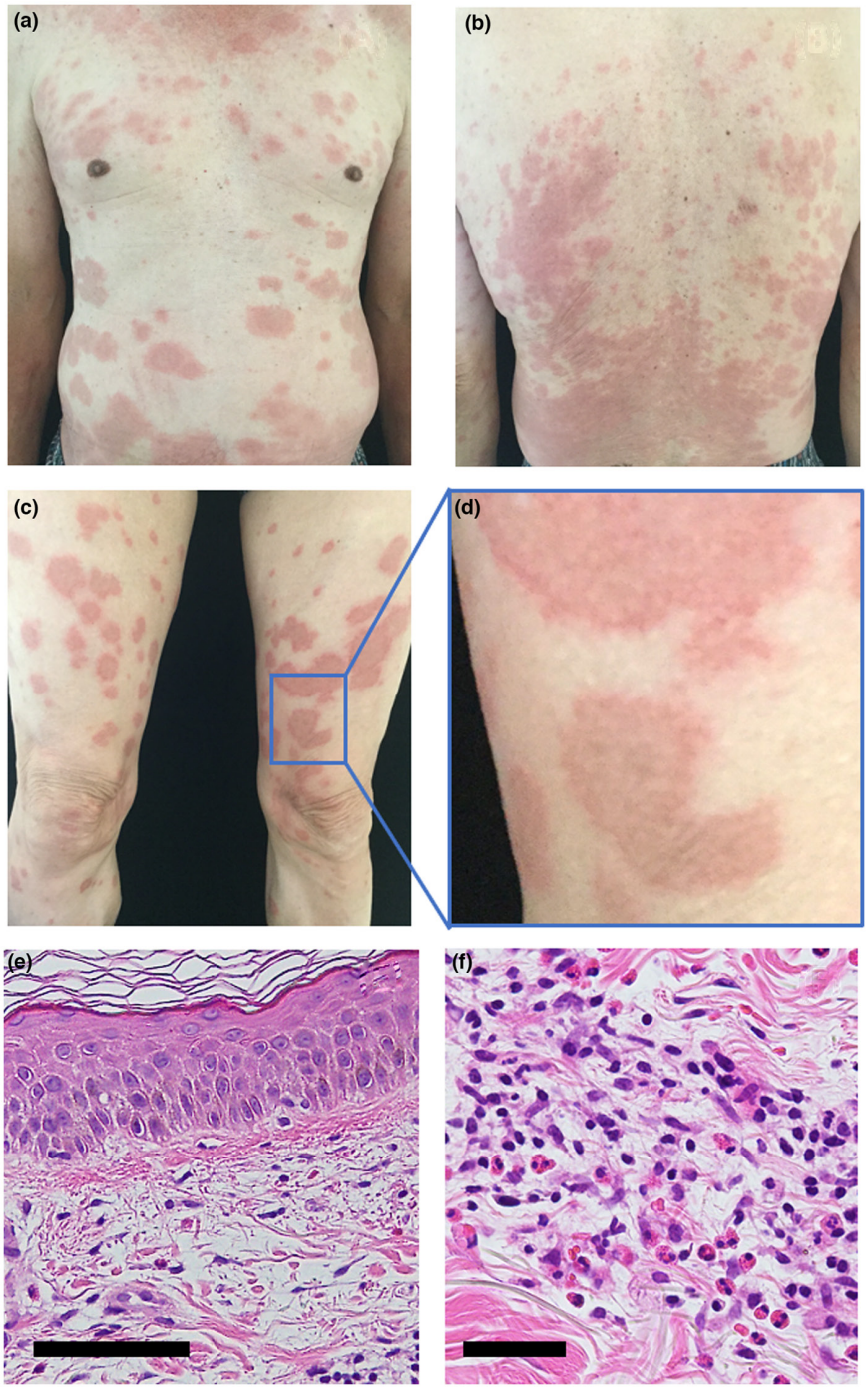

FIGURE 1 Clinical (a–d) and histopathological (e, f) features of the patients of EM after receiving BNT162b2 with the result of lymphocyte transformation test (f). (a, b) Coalesced multiple annular oedematous erythema up to 6 cm were observed on the trunk. (c, d) Targetoid lesions partially presented on extremities. (e, f) Mild liquefaction degeneration was observed at the dermal–epidermal junction and mild perivascular lymphocytic and eosinophilic infiltration were observed in the upper dermis. (haematoxylin–eosin; scale bar = 50 μm).

TABLE 1 17 cases of EM after SARS-CoV-2 vaccination.

Reporter	Age/Sex	Type of vaccine (Manufacturer)	Dose at onset	Time to onset from vaccination	Diagnosis	Treatment	Progress
McMahon DE, et al.	N/A	mRNA-1273 (Moderna)	First	N/A	EM	N/A	N/A
	N/A	mRNA-1273 (Moderna)	First	N/A	EM	N/A	N/A
	N/A	mRNA-1273 (Moderna)	First	N/A	EM	N/A	N/A
MJ Lavery, et al.	58/F	BNT162b2 (Pfizer–BioNTech)	First second	Within 0.5 day 1 day	Flair of pre-existing EM	Topical corticosteroid	Improved
NT Lopes, et al.	75/M	CoronaVac (Sinovac)	Second	5 days	EM	Topical corticosteroid Oral antihistamine	N/A
T. Gambichler, et al.	74/F	BNT162b2 (Pfizer–BioNTech)	First	1 day	Rowell's syndrome (SLE + EM)	Systemic PSL 150 mg/day	Improved
Scharf C, et al	27/F	BNT162b2 (Pfizer–BioNTech)	N/A	3 days	Nevocentric EM	Oral antihistamine	Improved
Borg L, et al	38/M	BNT162b2 (Pfizer–BioNTech)	Second	2 days	EM	Systemic PSL 40 mg/day	Improved
Zhang LW, et al	46/F	CoronaVac (Sinovac)	Second	4 days	EM	Oral antihistamine Topical corticosteroid	Improved
de Las Vecillas L, et al	47/F	BNT162b2 (Pfizer–BioNTech)	Second	1 day	EM minor	Oral antihistamine	Improved
Sechi A, et al.	76/F	BNT162b2 (Pfizer–BioNTech)	First	4 days	EM	Topical corticosteroid	Improved
Saibene AM, et al	58/F	mRNA-1273 (Moderna)	Second	1 day	EM major	Systemic mPSL 1 mg/kg	Improved
Kim MJ, et al	78/F	BNT162b2 (Pfizer–BioNTech)	First	10 days	Generalized EM-like skin rash	Systemic corticosteroid Topical agents Oral antihistamine	Improved
Buján Bonino C, et al	91/F	BNT162b2 (Pfizer–BioNTech)	Second	6 days	Atypical EM	Topical corticosteroid	Improved
Pourani MR, et al	N/A	N/A (Sinopharm)	N/A	N/A	EM-like eruption	N/A	N/A
	N/A	AZD1222 (AstraZeneca)	N/A	N/A	EM-like eruption	N/A	N/A
Present Case	77/M	BNT162b2 (Pfizer–BioNTech)	Second	2 days	EM	Topical corticosteroid Oral antihistamine	Improved

Abbreviations: EM, erythema multiforme; F, female; M, male; mPSL, methylprednisolone; N/A, not available or applicable; PSL, prednisolone; SLE, systemic lupus erythematosus.

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KEYWORDS

BNT162b2, COVID-19, Erythema multiforme, lymphocyte transformation test, SARS-CoV-2

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CONFLICT OF INTEREST

All authors disclose no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.