in the UK and Europe in January 2016. These groups recommend nicorandil be reserved as second-line treatment for angina due to the risk of severe skin, mucosal and eye ulceration. They also advise that nicorandil be ceased indefinitely if ulceration occurs. While an interrogation of recent monthly community prescription data from England demonstrates a 41% reduction in nicorandil prescriptions following this advice (from January 2015 to January 2021), nicorandil remains widely prescribed, with over 90,000 prescriptions dispensed in England in January 2021.

Nicorandil-induced skin ulceration typically presents as localised, painful, deep areas of ulceration with exiguous granulation tissue and no response to medical or surgical management. Histologically, non-specific inflammation with little granulation tissue is encountered. Fortunately, prognosis is excellent, with complete healing 2–6 months following nicorandil cessation. Thus, stopping nicorandil for 4 weeks is often diagnostic.

In summary, we present this case of nicorandil-induced delayed wound healing as a complication of MMS to raise awareness of this problem. Recognising nicorandil as a cause of delayed wound healing after excluding infective, inflammatory and malignant aetiologic factors followed by prompt cessation should result in rapid and complete healing.

**CONFLICT OF INTEREST**
None.

**CONSENT**
The patients in this manuscript have given written informed consent to publication of their case details.

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**REFERENCES**
1. Trechot P, Jouzeau JY, Brouillard C, Scala-Bertola J, Petitpain N, Cuny JF, et al. Role of nicotinic acid and nicotinamide in nicorandil-induced ulcerations: from hypothesis to demonstration. Int Wound J. 2015;12(5):527–30.
2. Lee M-TG, Lin H-Y, Lee S-H, Lee S-H, Lin HY, Lee SH, et al. Risk of skin ulcerations associated with oral nicorandil therapy: a population-based study. Br J Dermatol. 2015;173(2):498–50.
3. Medicines and Healthcare Products Regulatory Agency. Nicorandil (Ikorel): now second-line treatment for angina; risk of ulcer complications. Drug safety Update 2016.
4. NHS Business Services Authority. Prescription cost analysis – England 2020/21.
5. Sharma A, Orpin S, Goulding J, Kaur M. Two cases of nicorandil-induced ulceration mimicking skin malignancy. Br J Dermatol. 2014;171(3):662–3.

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**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; 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.

This article is a secondary publication of ‘Erythema multiforme following vaccination for SARS-CoV-2: report of a case with the result of lymphocyte transformation test’, published in the Japanese Journal of Dermatology. 132 (1):69–73, Jan 2022 (in Japanese).
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).
| 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          | 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              | Improved        |
|                         |         |                                 |               |                                |                           | Topical corticosteroid         |                 |
| 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.
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 re-activation 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 Japan3). We cannot exclude the possibility that the LTT was falsly 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 ELISpot3 and rapid expansion protocol4), 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.3 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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KEYWORDS
BNT162b2, COVID-19, Erythema multiforme, lymphocyte transformation test, SARS-CoV-2

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CONFLICT OF INTEREST
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Dear Editor,

Reports of cutaneous side effects due to a COVID-19 vaccine have increased with the expansion of vaccinations. Cutaneous side effects are more common in women, and the most frequent skin manifestations are delayed large local reactions, local injection site reactions, urticaria, and herpes zoster.1 There are few reports of a lichenoid reaction. We report a case of linear lichen planus triggered by the Pfizer-BioNTech COVID-19 vaccine.

A 57-year-old Japanese woman suffered from linear erythematous-brown papules along Blaschko's lines on her left upper extremity (Figure 1a). She had no personal or family history of inflammatory skin conditions. Apart from COVID-19 vaccination, she had not been exposed to any other medications, herbal therapy, or other vaccinations in the weeks or months prior to eruption developing. She noted that (i) she had received the third dose of the Pfizer-BioNTech COVID-19 vaccination at her left upper extremity 2 weeks earlier, and (ii) she had no skin symptoms after the first and second Pfizer-BioNTech COVID-19 vaccinations. The routine blood test results were unremarkable, including negative serology for hepatitis C. A skin biopsy revealed hyperkeratosis, basal liquefaction, Civatte bodies, and interface dermatitis with a perivascular infiltrate of lymphocytes (Figure 1b, c).

FIGURE 1  (a) Linear erythematous-brown papules along Blaschko’s lines on the patient’s left upper extremity. (b, c) Haematoxylin and eosin (H&E) staining show hyperkeratosis, basal liquefaction, and a band-like infiltrate of lymphocytes in the upper dermis and dermoepidermal junction with apoptotic keratinocytes. Scale bar: 100 μm.

REFERENCES
1. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, 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(1):46–55.
2. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy. 2007;62(12):1439–44.
3. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T H 1 T cell response. Nature. 2020;586(7830):594–9.
4. Taborska P, Lastovicka J, Stakheev D, Strizova Z, Bartunkova J, Smrz D. SARS-CoV-2 spike glycoprotein-reactive T cells can be readily expanded from COVID-19 vaccinated donor. Immun Inflamm Dis. 2021;9(4):1452–67.
5. Hashiguchi A, Matsuo K, Hirai H, Arai N, Hosoki K, Haida M. Utility of lymphocyte transformation test and Basophil activation test in identifying allergen by vaccine. Arerugi (Japanese Journal of Allergology). 2011;60(9–10):1430. (in Japanese).

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