fact, these skin reactions would suggest a hemosiderin pigmentation but resolves too rapidly to be explained as such. Therefore, another mechanism was proposed, which is local capillary leakage due to the vaccination and some type of immunologic reactions located in the dermis/epidermis junction.[1] However, despite the benign character and the harmless evolution of this side effect of the vaccines, its understanding is important to avoid unnecessary investigations and reassure the patient.

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Conflict of interest

All authors declare that there is no conflict of interest.

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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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Generalized erythema multiforme-like skin rash following the first dose of COVID-19 vaccine (Pfizer-BioNTech)

Dear Editor,

Since the outbreak of COVID-19 in December 2019, more than 4 million people have died worldwide. The global pandemic of COVID-19 has prompted each country to issue an emergency use authorization for COVID-19 vaccines. In South Korea, the Ministry of Food and Drug Safety authorized the administration of four vaccines: Pfizer-BioNTech (BNT162b2, New York, NY, USA), Moderna (mRNA-1273, Cambridge, MA, USA), Oxford–AstraZeneca (ChAdOx1, Cambridge, UK) and Johnson & Johnson's Janssen (JNJ-78436735, Beerse, Belgium). Although these vaccines were presumed to be safe, several nonspecific skin eruptions have been reported after the health system initiated public COVID-19 vaccination.[1] Here, we report a patient who developed *de novo* erythema multiforme (EM) following COVID-19 vaccination with BNT162b2.

A 78-year-old previously healthy woman presented to our clinic with a 2-day history of multiple targetoid erythematous plaques with severe itching over the entire body (Fig. 1). The patient received the first dose of COVID-19 vaccine (Pfizer-BioNTech) 12 days ago. Ten days after the vaccination, a skin

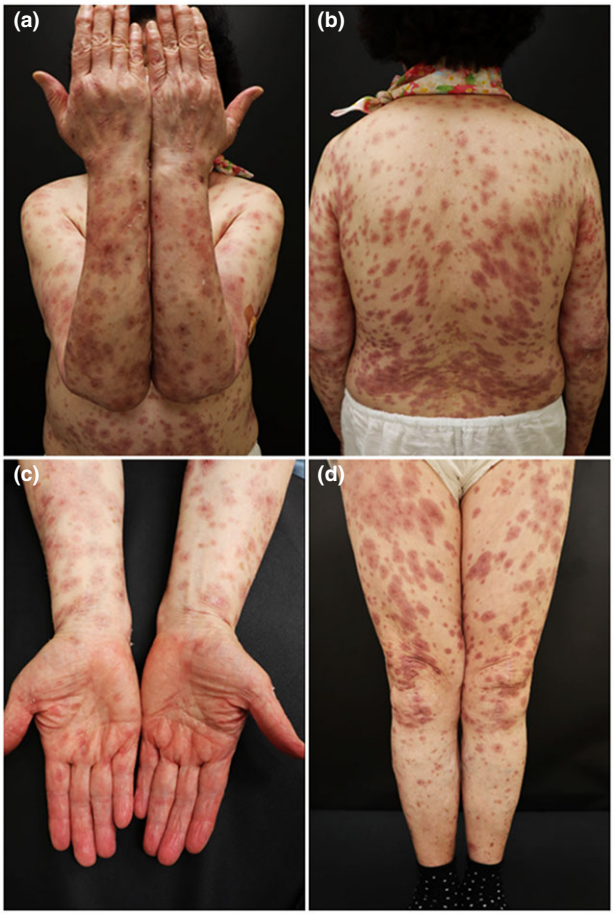

Figure 1 Multiple erythematous papules and concentric plaques on the (a) trunk and upper extremities, (b) back, (c) palms and (d) lower extremities.

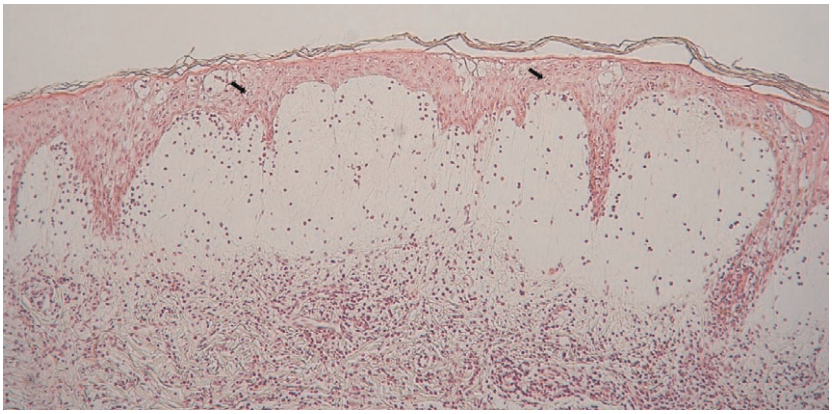

Figure 2 Haematoxylin and eosin (H&E, original magnification ×100) staining of a skin biopsy sample showing necrotic keratinocytes (black arrows), subepidermal bullae filled with lymphocytes and eosinophils, and dermal infiltration of numerous lymphocytes attacking the interface.

rash appeared on the upper chest and spread rapidly to the remaining parts of the body, including oral mucosa, with bullous change and oozing. She also developed high fever and myalgia. She denied ever having herpes simplex virus (HSV) infection-related symptoms and did not take any new medication around the time of vaccination. She was hospitalized, and a 3-mm punch biopsy of the skin was performed. Pathologic examination revealed necrotic keratinocytes and subepidermal bullae with numerous lymphocytes infiltration in the dermoepidermal junction (Fig. 2). Clinically and histologically, the patient was diagnosed with EM. Systemic corticosteroid treatment with topical agents and oral antihistamine was started, and she was discharged after 1 week of treatment. During the subsequent 2-month treatment period, she experienced gradual resolution of the rash although post-inflammatory hyperpigmentation remained. She decided not to receive the second dose of COVID-19 vaccine because of concerns about the recurrence of severe skin rash.

Erythema multiforme is a skin disease triggered by infection or medication. In most cases, EM is associated with HSV infection; therefore, antiviral agents can be considered for treating recurrent cases.[2] Recently, Lavery *et al.*[3] reported a flare-up of pre-existing EM after COVID-19 vaccination with BNT162b2. Their patient had a history of recurrent herpes labialis treated with antiviral medication, and the lesions were limited to hands and feet. In contrast, our patient had no history of HSV infection and presented with a generalized EM eruption.

Some cases of EM have been reported after other vaccinations, including diphtheria/pertussis/tetanus, human papillomavirus and measles–mumps–rubella.[4–6] Su *et al.*[7] analysed post-vaccination surveillance data, collected from 1999 to 2017, for EM, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Of 466 027 cases, EM accounted for 0.2%. The median time from vaccination to the onset of EM was 6 days. Most adverse events occurred within 14 days of vaccination. Therefore, the temporal association between the COVID-19 vaccine and EM in our case cannot be excluded.

It is unclear how vaccines trigger EM/SJS/TEN. Vaccine antigens are thought to induce cell-mediated inflammation and stimulate immune reactions. The activation of T helper type 1 cells leads to cytokine secretion, which is responsible for keratinocyte necrosis, subsequent epidermal antigen exposure and T-cell recruitment.[8] The same cascade is involved in the pathophysiology of EM/SJS/TEN, although the specific causative antigen or predisposing factor in affected patients is still unknown. Although these diseases may be life-threatening, considering the number of vaccinated people, the incidence is rare. There is evidence suggesting that the second dose of vaccine may cause the same adverse events, although they are mild in most cases.[1,9] Therefore, it cannot be the reason for prohibiting or discouraging vaccinations, and surveillance of skin adverse events should be continued.

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Conflicts of interest

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Data availability statement

Data openly available in a public repository that issues datasets with DOIs.

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Severe necrotizing myopathy after COVID-19 vaccine with BNT162b2 and regimen with ipilimumab plus nivolumab in a patient with advanced melanoma

Dear Editor,

Immune checkpoint inhibitors (ICIs) have dramatically changed the prognosis of advanced melanoma patients, but also exposed them to immune-related adverse events (irAEs).[1] Furthermore, with the combination ipilimumab (IPI) plus nivolumab (NIVO), some rare irAEs, such as myositis and neuromuscular diseases, are increasingly emerging.[2] Similar manifestations have been reported during coronavirus disease 2019 (COVID-19)[3] and more rarely with the vaccination.[4] Because cancer patients exhibit severe and fatal forms of the COVID-19 disease, vaccination is recommended.

Herein, we report a case of severe necrotizing myopathy after COVID-19 vaccination, in a man with advanced melanoma treated with IPI plus NIVO.

A 41-year-old man, without medical history, was diagnosed in November 2015 with stage IIIB melanoma (defined by the American Joint Committee on Cancer) on the left shoulder. He was subsequently enrolled in January 2016 in the EORTC MK-3475 trial.[5] He received pembrolizumab/placebo for 1 year, without any irAEs. In January 2021, computed tomography (CT) revealed unresectable, latero-aortic and common iliac lymph node masses; biopsy confirmed melanoma metastasis, and molecular testing revealed a *BRAFV600E* mutation. Despite unblinding revealed that he was in the pembrolizumab arm, we decided to initiate NIVO (1 mg/kg) plus IPI (3 mg/kg) every 3 weeks. He received his first and second injections on 25 February and 19 March 2021 respectively. On March 12, the first dose of COVID-19 vaccine (BTN162b2, Pfizer-BioNTech) was performed into his deltoid. Three days after the second infusion of ICIs, he was hospitalized for severe muscle pain, weakness of the limbs, bulbar symptoms and dyspnoea. Physical examination revealed asymmetric and severe weakness of the quadriceps, psoas, deltoids, biceps and neck flexor muscles. Blood tests revealed increased creatine phosphokinase (CPK) levels (12647 IU/L, normal, < 190 IU/L), without myocarditis. Autoantibodies associated with myasthenia gravis and paraneoplastic myositis were negative. Magnetic resonance imaging (MRI) was consistent with a myositis (Fig. 1a–d). Electromyography (EMG) showed severe myogenic syndrome in the four limbs (Fig. 1e), and muscle biopsy revealed a necrotizing myopathy (Fig. 2a–f).

Considering all these data, a diagnosis of necrotizing myopathy grade 4 according to the Common Terminology Criteria for Adverse Events ((version 4) was made. Immunotherapy was discontinued, and high dose of glucocorticoids (1 g/day intravenously) was administered for 3 days, followed by oral prednisone, progressively reduced. Daily physical examination revealed progressive improvement. The CPK levels, MRI and EMG were normalized within 2 months. In this context and as IgG against SARS-CoV-2 was highly positive (807 IU/L, normal, < 190 IU/L), the patient did not receive the second injection of the vaccine. Six months after, he had a near-complete clinical recovery and a partial oncological response.

Clinical trials with the BNT162b2 mRNA COVID-19 vaccine reported a good safety profile.[6] Nevertheless, several cases of myositis following COVID-19 vaccination with RNA vaccines (Pfizer-BioNTech or Moderna) and adenovirus vaccine (Oxford-AstraZeneca) have also been registered in the international pharmacovigilance database. To date, the relationship between COVID-19 vaccination and an increase of irAEs during ICI therapy has not been investigated. Data exist with the inactivated influenza vaccine (IV), but caution is warranted because they are contrasted.[7,8]

Myositis is a rare but already reported adverse event of IPI+NIVO treatment.[1] We cannot exclude that it is also the case in our patient. However, we hypothesize that vaccination by an immune-boosting effect acts as the trigger of necrotizing myopathy in our patient, with ICIs as the potential contributors. This scenario was remarkably exposed by Au *et al*.,

