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CASE REPORT

Two cases of COVID-19 vaccine-related erythema multiforme under the administration of immune checkpoint inhibitors

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ABSTRACT

The COVID-19 pandemic has increased mRNA vaccine usage and revealed various cutaneous adverse events, such as injection site reactions, urticaria, and morbilliform eruptions. Multiple centers have reported erythema multiforme (EM) as a COVID-19 vaccine-associated adverse event. Our center observed two cases of EM in patients receiving immune checkpoint inhibitors (ICI) after COVID-19 vaccination. Notably, ICI administration is known to cause cutaneous adverse events, including EM. A previous report indicated that administering COVID-19 vaccination to patients receiving ICI treatment could promote severe systemic symptoms. This raise concerns that COVID-19 vaccination might rapidly worsen skin rashes in these patients. Our report demonstrates that skin rash related to COVID-19 vaccine-induced EM in ICI-treated patients does not significantly differ from that of COVID-19 vaccine-related EM. Additionally, in both cases, the skin rash resolved without exacerbation. Further research is necessary to determine optimal management strategies. However, our findings provide reassurance that COVID-19 vaccination is safe in ICI-treated patients and should not be avoided.

Keywords: COVID-19 vaccine; erythema multiforme; immune checkpoint inhibitor

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1. Introduction

The global pandemic of COVID-19 has prompted each country to issue an emergency use for COVID-19 vaccines. Recently, several centers have reported multiple COVID-19 vaccine-related cutaneous adverse events[1–3]. COVID-19 vaccine-related cutaneous reaction patterns can be divided into type Ⅰ hypersensitivity reactions, type Ⅳ hypersensitivity reactions, autoimmune-related, and functional angiopathies based on pathogenesis[4]. Although erythema multiforme (EM) is an inflammatory skin condition classically linked to infections (herpes simplex virus and mycoplasma are the most common causes), several COVID-19 vaccines-related EMs have also been reported.

Immune checkpoint inhibitors (ICIs) are now being increasingly utilized in many more cancer types, and cutaneous immune-related adverse events (cirAEs) are also often observed in these patients. The cirAEs present a variety of clinical manifestations[5]. A case of cytokine release syndrome in a colorectal cancer patient recently treated with ICI and triggered by mRNA vaccination was reported[6]. The report indicated that administering COVID-19 vaccination to patients receiving ICI treatment could promote severe systemic symptoms. This raise concerns that COVID-19 vaccination might

rapidly worsen skin rashes in these patients. Here, we reported two cases of COVID-19 vaccine-associated EM under ICI administration.

2. Case synopsis

2.1. Case 1

A 68-year-old male came to our department because of his erythema and blisters. He had a history of recurrent gastric cancer and had been submitted to the fifth dose of nivolumab treatment. He also received the first dose of the COVID-19 vaccine six days later after nivolumab treatment. Ten days after nivolumab administration, erythema and blisters appeared. Clinical findings revealed scattered purple-red erythema on the extremities and trunk and edematous erythema and some tense vesicles on his hands (**Figure 1A**). Laboratory investigation revealed no abnormalities except for a mild deviation of liver enzymes. A skin biopsy of the hand erythema revealed hyperkeratosis, individual cell necrosis of keratinocytes in the epidermis, and vacuolar change at the epidermal-dermal interface were revealed (**Figure 1B**). Since there was no relapse of symptoms after re-administration of nivolumab and there were no episodes of viral infection or drug eruptions we diagnosed EM after COVID-19 vaccination. He was treated with topical steroid ointment of a very strong class, and the erythema quickly faded.

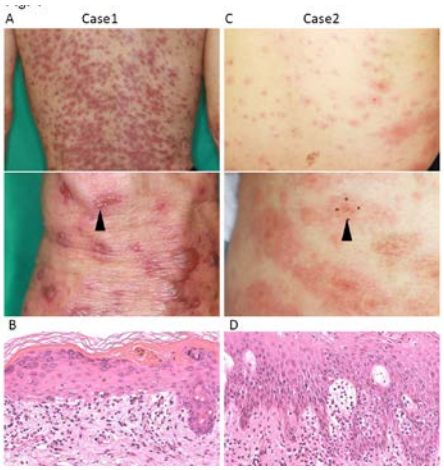

Figure 1. Clinical appearance and histology of two cases at initial examination. **(A)** clinical pictures of case 1 (the back and dorsal hand); the skin biopsy site is indicated by an arrow-head; **(B)** histology of H & E staining of case 1; **(C)** clinical pictures of case 2 (the back and abdomen); **(D)** histology of H & E staining of case 2.
(B)(D) scale bar is 100 mm.

2.2. Case 2

A 46-year-old female came to our department because of her erythema. She was receiving pembrolizumab (anti-PD-1 antibody) for primary lung cancer. She received a second dose of the COVID-19 vaccine (Moderna), and approximately 20 days later, she presented to our department with edematous erythema over most of her body (**Figure 1C**). A skin biopsy of the abdominal erythema revealed vacuolar lesions and interface dermatitis (**Figure 1D**). Based on the above, a case of EM was diagnosed. Erythema was mild, but there was concern about exacerbation due to previous cases[6]. Therefore, she started on prednisolone (PSL) 60 mg/day. PSL was then tapered off, but there was no flare-up of the skin rash.

In addition, immunohistochemical analysis was performed to examine the subset of T cells infiltrating into the skin in 5 cases of EM after COVID-19 vaccination (3 without ICI administration and 2 with ICI administration). In these cases, both CD4+ and CD8+ T cells infiltrated the epidermis and dermis and were also present around blood vessels in the dermis in two cases (**Figure 2A**). The number of CD4+ and CD8+ T cells infiltrating the skin at an average of 5 high-magnification views was similar regardless of ICI administration (**Figure 2B**).

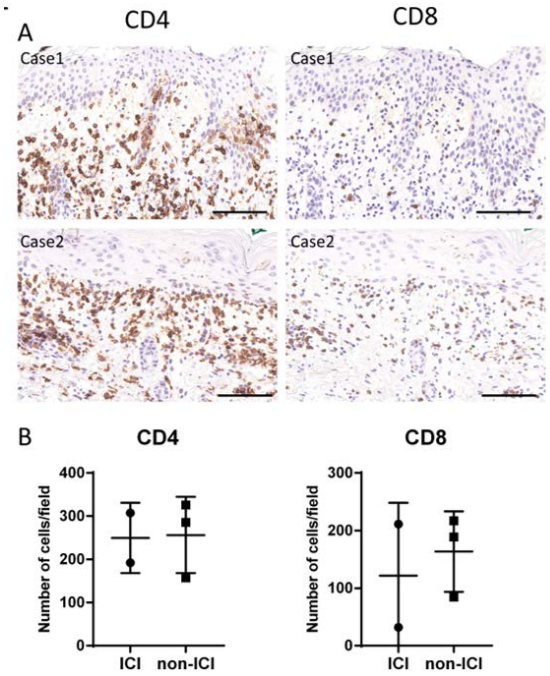

Figure 2. Immunohistochemistry of CD4 and CD8. **(A)** immunohistochemical analysis of CD4 and CD8 was performed in 5 cases of EM after COVID-19 vaccination (3 without ICI administration and 2 with ICI administration). The upper panel presents the immunohistochemistry of CD4 and CD8 in the two cases. The scale bar is 100 mm; **(B)** the lower graph shows the number of CD4+ and CD8+ cells infiltrating into the skin in the average of 5 high magnification fields among 5 cases of EM associated with the COVID-19 vaccine.

3. Case discussion

In the present study, we experienced two cases of EM that developed after COVID-19 vaccination under ICI administration. Although several case reports of EM associated with the COVID-19 vaccine have been published, the mechanism of erythema in COVID-19 vaccinees remains unclear. The infiltrating T cells in EM vary based on the underlying cause. HSV-specific CD4+ Th1 cells are recruited to the skin by viral antigens and trigger an inflammatory cascade, potentially leading to herpes virus-associated-EM[7]. In cases of ICI-induced cirAE leading to SJS/TEN, epidermal infiltration of CD8+ T lymphocytes and increased expression of PD-L1 in keratinocytes have been reported in skin tissues[8]. In our cases, there was no significant variation in the amount of CD4+ and CD8+ T cells on the skin between COVID-19 vaccine-induced EMs in the presence of ICI therapy and those caused by COVID-19. In case 2, where the rash was more severe, topical steroids were the only necessary treatment. Therefore, COVID-19 vaccine-related EMs under ICI treatment do not necessarily exacerbate skin rash symptoms in all cases, in contrast to COVID-19 vaccine-associated EMs. Further research is necessary to determine optimal management strategies. However, our findings provide reassurance that COVID-19 vaccination is safe in ICI-treated patients and should not be avoided.

Conflict of interest

The authors declare no conflict of interest.

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