INTRODUCTION

Human beings are currently facing a pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with COVID-19 present symptoms to various degrees, with severe symptoms observed in elderly patients and in patients with certain underlying medical conditions. COVID-19 easily transmits by droplets and small airborne particles containing the virus and can spread globally. Like other health crises, this pandemic has triggered severe social and economic disruptions worldwide. Therefore, a preventive strategy has been desired since the early phase of the COVID-19 pandemic. Consequently, the COVID-19 vaccine improved the outlook of this health crisis and is currently essential to overcoming the COVID-19 pandemic. The current COVID-19 vaccines show high efficacy in the prevention of infection and impair the severity of symptoms. However, vaccination raises concerns, such as vaccine-associated adverse reactions, which are currently highlighted issues for clinicians. Delayed cutaneous hypersensitivity reactions are commonly observed in clinical patients, and medications are recognized as the representative causative agents. This type of cutaneous adverse reaction observed in COVID-19 vaccination makes it difficult for clinicians to decide whether patients with a history of adverse reactions to the COVID-19 vaccine are eligible for additional vaccination. Herein, we present previously reported cases of mild cutaneous adverse reaction following COVID-19 vaccine administration, which was successfully controlled by prior administration of the antihistamine agent fexofenadine 3 days before COVID-19 vaccination for 7 days.

CASE REPORT

2.1 Case 1

A 48-year-old female experienced a cutaneous adverse reaction 3 days after the second administration of the COVID-19 vaccine, as previously described. She exhibited generalized erythematous...
plaques on her trunk and extremities, without mucosal eruption. She desired a third administration of the BioNTech COVID-19 vaccine (Pfizer) to prevent infection. Administration of an antihistamine agent, fexofenadine 120 mg, occurred daily, 3 days before the third COVID-19 vaccine administration, in order to impair cutaneous adverse reactions to the COVID-19 vaccine. Although we carefully observed the occurrence of her skin eruption, she only recognized small macules on both arms without recurrent skin eruptions in other body sites while under continuous oral intake of an antihistamine agent (Figure 1A-C). She discontinued the antihistamine agent 5 days after COVID-19 vaccination without the occurrence of novel skin lesions.

2.2 | Case 2

A 58-year-old female had experienced skin eruption following the second administration of the COVID-19 vaccine, as previously described.\(^2\) She previously recognized erythematous papules on her face and hands, without mucosal eruption. She consulted our department for a third administration of the BioNTech COVID-19 vaccine (Pfizer). She received an antihistamine agent, fexofenadine 120 mg, 3 days before the third vaccination for COVID-19. She experienced a fever of 37.8 °C; however, skin eruptions were not completely observed after COVID-19 vaccination (Figure 2). Discontinuation of the antihistamine agent occurred

FIGURE 1 Clinical manifestation of Case 1. No skin eruption was observed on her trunk (A). Small macules presented on both her arms (B, C)
3 | DISCUSSION

Recent reports have updated COVID-19 vaccine-associated delayed cutaneous adverse reactions. Although there are a limited number of case reports that show severe cutaneous adverse reactions, almost all cases seem to be mild. The delayed hypersensitivity reaction is classified as a Type IV allergy, namely delayed hypersensitivity reaction. Antihistamine agents impair the degree of inflammatory response in contact dermatitis, and patch testing under the administration of antihistamine drugs impairs skin inflammation. A previous clinical study collected data on patients with large local reactions to conventional allergen subcutaneous immunotherapy regimens. The use of oral antihistamines 2 h prior to venom immunotherapy has shown to decrease the rate of large local reactions. During the elicitation phase of the cutaneous delayed hypersensitivity reaction, mast cell deficiency impaired the cutaneous immune response of contact hypersensitivity. External hapten exposure also increases vascular permeability through mast cell-derived histamine, which enhances the infiltration of immune cells into the skin. These findings suggest that antihistamine agents are a possible therapeutic option to impair the inflammatory response mediated by Type IV delayed hypersensitivity reactions.

Oral steroid administration may also be a therapeutic option; however, it may impair the acquired antiviral immune response to the vaccine. Although we could not exclude the possibility that antihistamine agents also suppress antiviral immunity after the administration of the COVID-19 vaccine, the antihistamine agent cimetidine can enhance the antiviral immune response following vaccination, suggesting that pretreatment with antihistamine agents are useful in impairing cutaneous adverse reactions and acquiring antiviral immune responses.

Another possibility in our cases is that cutaneous adverse effects do not always worsen. Based on this finding, there was a possibility that no adverse reactions to the third vaccination were related to the administration of the antihistamine agent. Therefore, our case studies might not determine the direct therapeutic potency to impair cutaneous adverse reactions to the COVID-19 vaccine.

In the mechanism of vaccine-associated cutaneous adverse events, vaccine components may play a role. Polyethylene glycol (PEG) is one of the candidates and is a polymer compound derived from petroleum with many products, from industrial manufacturing to medicine. PEG is used as an excipient in many pharmaceutical products, including both Moderna and PfizerBioNTech vaccines for SARS-CoV-2. Both RNA vaccines consist of messenger RNA (mRNA) encased in a bubble of oily molecules that are coated with a stabilizing molecule of PEG. Consequently, PEG is recognized as an allergic causative agent, similar to various allergic reactions that occur in PEG-containing medications. There are ongoing debates on the mechanism of skin adverse reactions to COVID-19 vaccines and whether the PEG in the vaccine is the cause. In this case, patch testing of a representative additive in this vaccine, such as PEG, using PEG 400 and PEG 1000 yielded negative results, as shown in our previous report. PEG also enhanced histamine release, suggesting a therapeutic efficacy of antihistamine agents, even in the case of PEG-mediated cutaneous adverse reactions. Therefore, antihistamine drugs may also suppress the PEG-induced cutaneous adverse reactions to the COVID-19 vaccine.

Another possible mechanism of skin eruption is that COVID-19-related proteins may trigger cutaneous adverse events. There are several reports regarding skin eruption following COVID-19 infection. The mRNA vaccine drives the production of COVID-19 spike protein and enhances cytotoxic lymphocyte activation, which may play an essential role in the elicitation phase of cutaneous delayed hypersensitivity reaction.

Although we could not completely conclude on the absolute efficacy of pretreatment with antihistamine agents for the prevention of cutaneous adverse reactions to the COVID-19 vaccine, further investigation will provide an alternative method to avoid the administration of the COVID-19 vaccine itself.

DECLARATION SECTION

Approval of the research protocol: No.
Informed Consent: N/A.
Registry and the Registration No: N/A.
Animal Studies: N/A.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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