Received: 26 January 2022 | Revised: 21 March 2022 | Accepted: 22 April 2022

DOI: 10.1002/cia2.12248

Journal of Cutaneous Immunology and Allergy

WILEY

CASE STUDY

Prior antihistamine agent successfully impaired cutaneous adverse reactions to COVID-19 vaccine

Hikaru Nanamori MD | Yu Sawada MD, PhD | Sayaka Sato MD | Reiko Hara MD | Yoko Minokawa MD | Hitomi Sugino MD | Natsuko Saito-Sasaki MD, PhD | Kayo Yamamoto MD | Etsuko Okada MD, PhD | Motonobu Nakamura MD, PhD

Department of Dermatology, University of Occupational and Environmental Health, Kitakyushu, Japan

Correspondence
Yu Sawada, 1-1, Iseigaoka, Yahatanishi-Ku, Kitakyushu 807-8555, Japan.
Email: long-ago@med.uoeh-u.ac.jp

Abstract

The coronavirus disease 2019 (COVID-19) vaccine is positively changing the health crises of this pandemic and is currently essential to overcome the COVID-19 pandemic. The vaccine shows high efficacy against the infection and impairs the severity of symptoms. However, this vaccination is associated with concerns, such as vaccine-associated adverse reactions, which are currently highlighted issues for clinicians. We experienced two 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.

KEYWORDS
anti-histamine drug, COVID-19, vaccine

1 | 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).[1] Patients with COVID-19 present symptoms to various degrees, with severe symptoms observed in elderly patients and in patients with certain underlying medical conditions.[2] COVID-19 easily transmits by droplets and small airborne particles containing the virus and can spread globally.[3,4] 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.[5] 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.[6] 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 to the COVID-19 vaccine that was successfully controlled by pretreatment with antihistamine drugs.

2 | 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.[7] She exhibited generalized erythematous

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Journal of Cutaneous Immunology and Allergy* published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society for Cutaneous Immunology and Allergy.

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 vaccine administration (Figure 2). Discontinuation of the antihistamine agent occurred

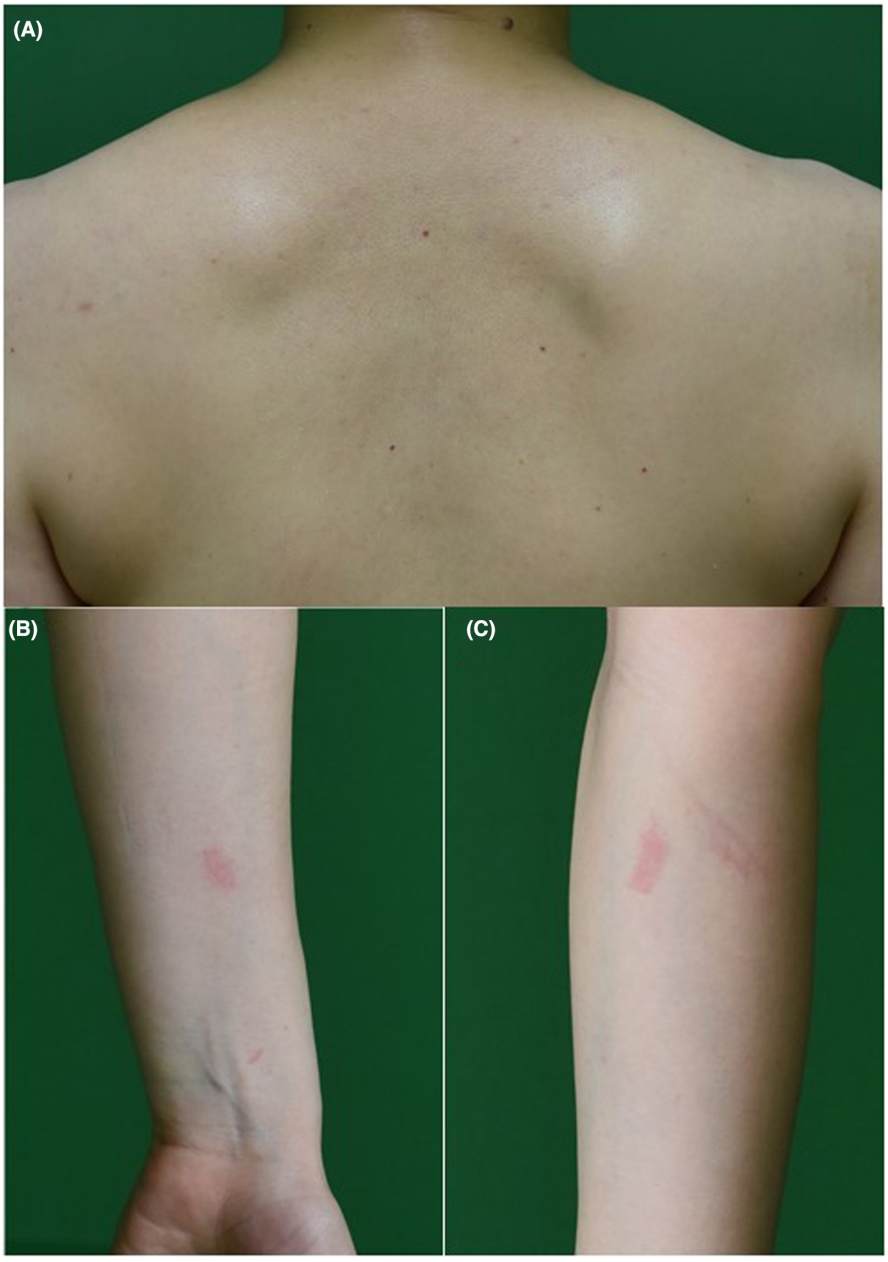

FIGURE 1 Clinical manifestation of Case 1. No skin eruption was observed on her trunk (A). Small macules presented on both her arms (B, C)

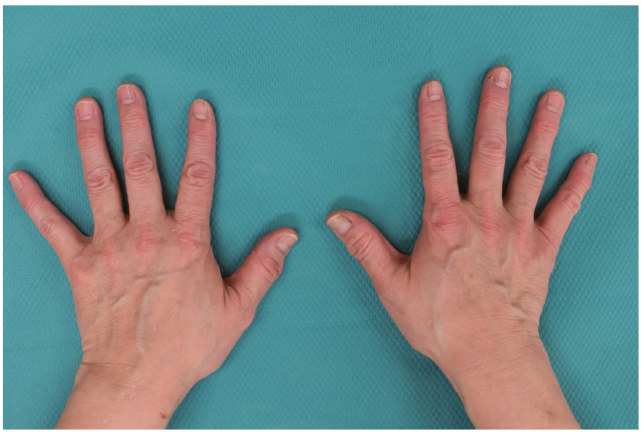

FIGURE 2 Clinical manifestation of Case 2. No skin eruption was observed on the hands

5 days after the COVID-19 vaccination without any occurrence of cutaneous adverse eruptions.

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[8,9] almost all cases seem to be mild.[10] 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,[11] and patch testing under the administration of antihistamine drugs impairs skin inflammation.[12] A previous clinical study collected data on patients with large local reactions to conventional aeroallergen subcutaneous immunotherapy regimens. The use of oral antihistamines 2 h prior to venom immunotherapy has shown to decrease the rate of large local reactions.[13] During the elicitation phase of the cutaneous delayed hypersensitivity reaction, mast cell deficiency impaired the cutaneous immune response of contact hypersensitivity.[14] External hapten exposure also increases vascular permeability through mast cell–derived histamine,[14] which enhances the infiltration of immune cells into the skin.[15] 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,[16] 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.[10] 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 polyether compound derived from petroleum with many products, from industrial manufacturing to medicine.[17] 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.[18] 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,[19] 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.[20] The mRNA vaccine drives the production of COVID-19 spike protein[21] and enhances cytotoxic lymphocyte activation,[22] 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.

ORCID

Yu Sawada https://orcid.org/0000-0001-8793-708X

REFERENCES

1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. Lancet. 2020;395(10229):1015–8.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
3. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514–23.
4. Chowell G, Mizumoto K. The COVID-19 pandemic in the USA: what might we expect? Lancet. 2020;395(10230):1093–4.
5. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Final analysis of efficacy and safety of single-dose Ad26. COV2.S. N Engl J Med. 2022;386(9):847–60.
6. Sawada Y, Nakamura M, Tokura Y. Generalized fixed drug eruption caused by pazufloxacin. Acta Dermato-venereol. 2011;91(5):600–1.
7. Nanamori H, Sawada Y, Sato S, Minokawa Y, Sugino H, Saito-Sasaki N, et al. Two cases of mild systemic adverse skin eruption after coronavirus disease 2019 vaccination. J Dermatol 2021;48(11):e547–8.
8. Dash S, Sirka CS, Mishra S, Viswan P. COVID-19 vaccine-induced Stevens-Johnson syndrome. Clin Exp Dermatol. 2021;46(8):1615–7.
9. Elboraey MO, Essa E. Stevens-Johnson syndrome post second dose of Pfizer COVID-19 vaccine: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;132(4):e139–42.
10. 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.
11. Katagiri K, Arakawa S, Hatano Y, Fujiwara S. Fexofenadine, an H1-receptor antagonist, partially but rapidly inhibits the itch of contact dermatitis induced by diphenylcyclopropenone in patients with alopecia areata. J Dermatol. 2006;33(2):75–9.
12. Grob JJ, Castelain M, Richard MA, Bonniol JP, Béraud V, Adhoute H, et al. Anti-inflammatory properties of cetirizine in a human contact dermatitis model. Clinical evaluation of patch tests is not hampered by antihistamines. Acta Derm Venereol. 1998;78(3):194–7.
13. Golubski S, Gobel T, Gutta R, Pien L. Role of preventive antihistamine medications for local reactions with conventional aeroallergen subcutaneous immunotherapy (SCIT). J Allergy Clin Immunol. 2012;129(2):AB57.
14. Dudeck A, Dudeck J, Scholten J, Petzold A, Surianarayanan S, Köhler A, et al. Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. Immunity. 2011;34(6):973–84.
15. Honda T, Egawa G, Grabbe S, Kabashima K. Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. J Invest Dermatol. 2013;133(2):303–15.
16. Wang J, Su B, Ding Z, Du X, Wang B. Cimetidine enhances immune response of HBV DNA vaccination via impairment of the regulatory function of regulatory T cells. Biochem Biophys Res Commun. 2008;372(3):491–6.
17. Garvey LH, Nasser S. Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? Br J Anaesth. 2021;126(3):e106–8.
18. Nanomedicine and the COVID-19 vaccines. Nat Nanotechnol. 2020;15(12):963.
19. Wenande EC, Skov PS, Mosbech H, Poulsen LK, Garvey LH. Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: a case of probable polyethylene glycol allergy. J Allergy Clin Immunol. 2013;131(5):1425–7.
20. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. J Am Acad Dermatol. 2020;82(5):e177.
21. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. N Engl J Med. 2020;383(20):1920–31.
22. Rijkers GT, Weterings N, Obregon-Henao A, Lepolder M, Dutt TS, van Overveld FJ, et al. Antigen presentation of mRNA-based and virus-vectored SARS-CoV-2 vaccines. Vaccines. 2021;9(8):848.

How to cite this article: Nanamori H, Sawada Y, Sato S, Hara R, Minokawa Y, Sugino H, Prior antihistamine agent successfully impaired cutaneous adverse reactions to COVID-19 vaccine. J Cutan Immunol Allergy. 2022;5:170–173. doi:10.1002/cia2.12248