Received: 6 January 2022 | Accepted: 13 March 2022

DOI: 10.1111/1346-8138.16374

THE JOURNAL OF DERMATOLOGY

CONCISE COMMUNICATION

Histopathological analysis of skin reactions after coronavirus disease 2019 vaccination: Increment in number of infiltrated plasmacytoid dendritic cell

Hanako Watanabe | Miwa Ashida | Naoyoshi Satomi | Yuta Koike | Sayaka Kuwatsuka | Hiroyuki Murota

Department of Dermatology, Nagasaki University Hospital, Nagasaki, Japan

Correspondence
Hanako Watanabe, Department of Dermatology, Nagasaki University Hospital, 1-7-1, Sakamoto, Nagasaki, Nagasaki, 852-8501, Japan.
Email: hn.061201wt@gmail.com

Abstract

Skin disorders are frequent adverse events after coronavirus disease 2019 (COVID-19) vaccination. However, the pathogenesis of these disorders is not fully understood. Here, we report a case series of cutaneous adverse events following COVID-19 vaccination, and the results of our investigation reveal the underlying mechanism. Case 1: a 47-year-old female developed a wheal, confined to the COVID-19 vaccination site, 2 days after her first injection. She was treated with topical steroids and oral antihistamines. Case 2: a 51-year-old female showed generalized petechial erythema accompanied by fever, genital bleeding, thrombocytopenia, liver dysfunction, and disseminated intravascular coagulation, 2 days after her second injection. She was diagnosed with vaccine-induced macrophage activation syndrome and treated with anti-inflammatory therapy. Immunohistological analysis of the skin eruption, in both these cases, showed infiltration of $CD123^+$ $BDCA2^+$ plasmacytoid dendritic cells (p-DC). Despite the distinctive clinical features in these two cases, this finding suggests that p-DC might be involved in different cutaneous adverse events after COVID-19 vaccination.

KEYWORDS
coronavirus disease 2019 vaccine, cutaneous adverse reactions, histopathology, plasmacytoid dendritic cell, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

According to a report from the Ministry of Health, Labor, and Welfare of Japan, the total number of Japanese patients with coronavirus disease 2019 (COVID-19), up until November 2021, was approximately 1.72 million.[1] As of the end of November 2021, the total number of COVID-19 vaccinations was approximately 197 000.[2] Of these, the estimated number of inoculations with Comirnaty (BNT162b2), in Japan, was 155 454 673 with 14 931 (0.01%) adverse reactions reported. The main adverse systemic reactions reported are headache, general malaise, runny nose, and fever, whereas the main adverse local reactions are redness, swelling, induration, pain, heat, and itching. Adverse reactions are more common in young people and women. The number of reports by symptom was 56 144, of which 7967 cases were related to skin disorders.[3] The mechanism by which adverse reactions occur is still obscure but is thought to mimic the immune response to coronaviruses.[4,5] In this report, two cases with cutaneous adverse events, following BNT162b2 vaccination, were studied histopathologically.

2 | CASE REPORTS

2.1 | Case 1

A 47-year-old female without past medical history received the initial dose of BNT162b2, i.m., in her left deltoid region. Two days after the injection, the same area developed a wheal without any

other complicating symptoms (Figure 1a). She was treated with topical betamethasone butyrate propionate and systemic fexofenadine hydrochloride. The skin disorder disappeared 9 days after the inoculation, and she received the second vaccination dose without experiencing further adverse events.

2.2 | Case 2

A 51-year-old female without past medical history received the initial dose of BNT162b2, i.m., in her deltoid region. Two days after the first injection, she noticed genital bleeding. Two days after the second injection, she again experienced genital bleeding accompanied by a fever of 38.3°C. She was admitted to hospital with thrombocytopenia and petechial erythema (Figure 1b,c). The results of laboratory analyses were as follows: white blood cell count, 3200/μL; platelet count, 8.3×10^4/μL; hemoglobin, 14.0 g/dL; red blood cell count, 4.8×10^3/μL; aspartate aminotransferase, 112 U/L; alanine aminotransferase, 36 U/L; alkaline phosphatase, 57 U/L; γ-glutamyl transpeptidase, 13 U/L; total bilirubin, 0.4 mg/dL; lactate dehydrogenase, 1016 U/L; blood urea nitrogen, 4 mg/dL; creatinine, 0.62 mg/dL; C-reactive protein, 6.21 mg/dL; prothrombin time–international normalized ratio, 1.05; fibrin degradation products, 57.9 μg/mL; D-dimer, 26.1 μg/mL; fibrinogen, 305 mg/dL; ferritin, 11 970 ng/dL; haptoglobin, 209.5 pg/dL; soluble interleukin-2 receptor, 1415 U/mL; antinuclear antibody, 1:80; and rheumatoid factor, 5.0 IU/mL.

The patient was diagnosed with disseminated intravascular coagulation (DIC) according to genital bleeding, thrombocytopenia, and elevated fibrinogen degradation products. Ferritin was also elevated at 11 970 ng/dL, but adult Still's disease was ruled out because of a lack of spike fever or arthralgia. Antinuclear antibodies and rheumatoid factor were both negative, and there was no genetic mutation in *MEFV*, *NLRP3*, *TNFAIP3*, *MVK*, or *TNFRSF1A*, which are genes responsible for autoinflammatory diseases. Finally, the patient was considered to have macrophage activation syndrome (MAS) in which vaccination triggered excessive cytokine production. Consequently, she was administered both high-dose intravascular immunoglobulin therapy and i.v. administration of methylprednisolone sodium succinate. During the next 3 days, her fever subsided and the skin manifestation disappeared.

Histopathological analysis was performed of a skin sample of the local injection site and erythema of the right dorsal hand, distant from the local injection site, derived from cases 1 and 2, respectively. Therefore, we initially anticipated that the pathological findings of cases 1 and 2 would represent the direct and indirect responses to vaccination, respectively. Both histopathological examinations showed spongiform changes in the epidermis, liquefaction degeneration, and infiltration of mainly lymphocytes in the stroma and perivascular areas of the upper dermis (Figure 2a–d). In both cases, the predominant inflammatory cells were $CD4^+$ T lymphocytes (Figure 2e–j). Notably, the number of infiltrating lymphocytes, which were immunohistochemically positive for CD123 and BDCA2, markers of plasmacytoid dendritic cells (p-DC), was increased in both skin samples.

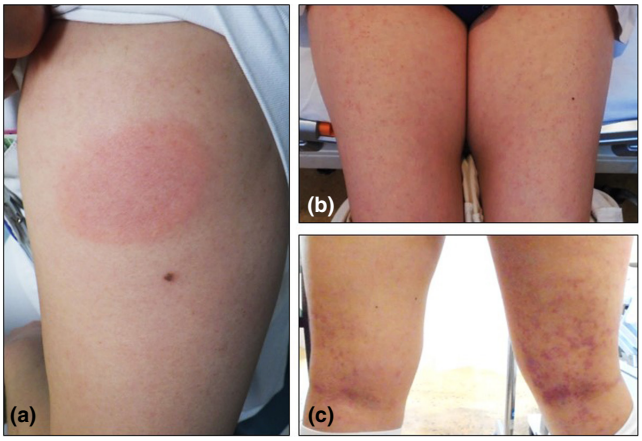

FIGURE 1 (a) Clinical feature of case 1. A 5.0×3.5 cm wheal was observed on the left upper arm. (b, c) Clinical feature of case 2. Petechial erythema was observed on both thighs that, within 4 days, spread to the inguinal regions, the popliteal fossae, and the dorsal hands

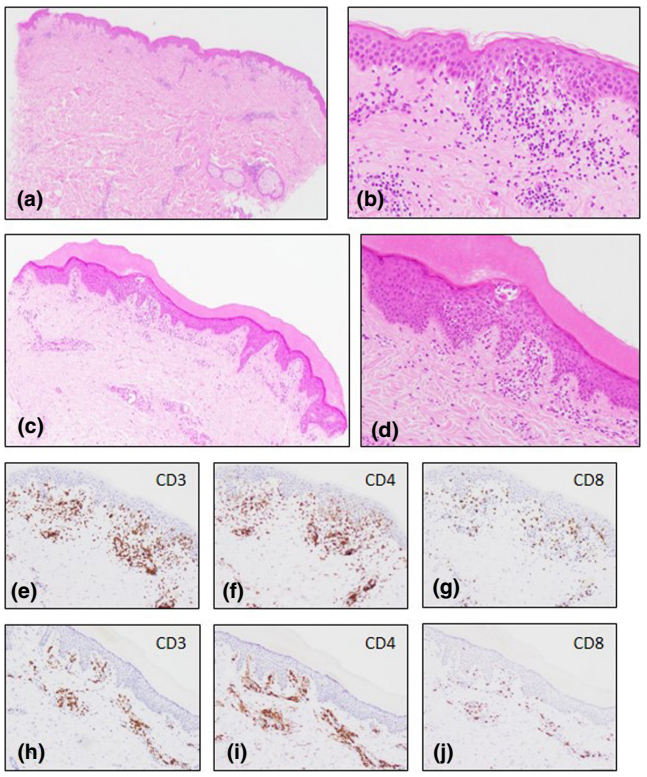

FIGURE 2 (a) Histopathological feature of case 1. Perivascular lymphocytic infiltration was found (hematoxylin–eosin [HE], original magnification ×100). (b) In the epidermis, spongiosis and liquefaction degeneration were observed (HE, ×400). (c) Histopathological feature of case 2. Perivascular lymphocytic infiltration was found (HE, ×100). (d) In the epidermis, spongiosis was observed (HE, ×400). (e–g) Immunohistochemical staining of case 1 for (e) CD3, (f) CD4, and (g) CD8 (×200). (h–j) Immunohistochemical staining of case 2 for (h) CD3, (i) CD4, and (j) CD8 (×200). In both cases, the inflammatory cells were CD4-dominant T lymphocytes

3 | DISCUSSION

The most frequent adverse events reported following mRNA COVID-19 vaccination are delayed diffuse local reactions, local injection site reactions, urticaria, and disseminated maculopapular erythematous-type eruptions.[6] Our cases presented with typical cutaneous reactions. In both cases, pathological findings showed intraepidermal spongiosis, liquefaction degeneration, and dermal infiltration by lymphocyte-dominant inflammatory cells. These manifestations are consistent with the findings of McMahon *et al*.[7]

The pathogenesis of cutaneous adverse events, following COVID-19 vaccination, is caused by an immune response similar to that elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. When the virus enters the body, Toll-like receptors (e.g., TLR3 or 7/8) on the surface of p-DC recognize viral mRNA and produce type I interferon (IFN-I).[8] It has been suggested that excessive production of IFN-I may cause the side-effects of the vaccine, such as fever, headache, myalgia, and general malaise.[9] Indeed, myxovirus-resistance protein 1-exposed skin-derived IFN-I is a cause of skin disorder after COVID-19 vaccination.[10]

In the present cases, we performed staining for CD123 and BDCA-2, markers of p-DC, in the dermis. Cells positive for both markers were considered p-DC. We detected 90 p-DC/field (×300) in case 1 and 32 p-DC/field (×300) in case 2 (Figure 3). The numbers of p-DC in our two cases were elevated based on the numbers of p-DC in HIV-associated psoriasis and psoriasis vulgaris reported by Kuwatsuka *et al*.[11] Nevertheless, direct comparison of our data and these previously reported data should only be regarded as a guide. The clinical features in the two cases reported were clearly distinguishable from each other: case 1 developed only a cutaneous manifestation, whereas case 2 was accompanied by serious systemic symptoms. Although we cannot explain why the systemic manifestation (e.g., MAS) was severe in case 2, the prominent infiltration of p-DC in erythema suggested the possible pathogenic contribution of anomalous activation of p-DC in this case. Furthermore, a pathological study of "COVID-toes" lesions showed that p-DC infiltrate the perivascular and perieccrine sweat gland of the mid-dermis.[12] It can be speculated that cutaneous adverse events following COVID-19 vaccination could be the result of an immune response that mimics the response seen following SARS-CoV-2 infection. We propose that p-DC infiltrate the skin, as a cutaneous response to the COVID-19 vaccine, where they produce IFN-I, which elicits skin disorders.

Recently, COVID-19 vaccination has been widely implemented worldwide; consequently, the number of cases of post-vaccination skin disorders has increased. As there remains the possibility that skin reactions could be due to treatment with systemic, non-steroidal anti-inflammatory agents, we should distinguish the type of skin disorder by its etiology. To our knowledge, this is the first report to examine, histopathologically, p-DC in COVID-19 vaccine-induced skin manifestations. In the future, further investigation of p-DC in drug eruption or viral exanthems may help determine whether rashes are caused by vaccination. Further cases are needed to establish the clinical significance of p-DC.

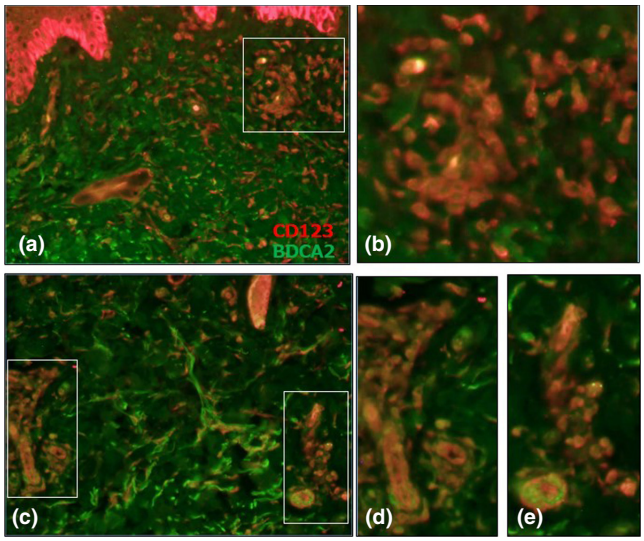

FIGURE 3 Merged immunofluorescence staining view of CD123 (red) and BDCA2 (green). CD123 and BDCA2 double-positive cells in the dermis reflect dermal plasmacytoid dendritic cells (p-DC). (a) Case 1 showed 56 p-DC/field (×300). (b) Case 1, enlarged view of the square in (a). (c) Case 2 showed 23 p-DC/field (×300). (d,e) Case 2, enlarged view of the square in (c). Three, random, ×300 microscopic fields were examined

ORCID

Hanako Watanabe https://orcid.org/0000-0003-2090-072X
Miwa Ashida https://orcid.org/0000-0002-4215-680X
Yuta Koike https://orcid.org/0000-0002-7921-8840
Hiroyuki Murota https://orcid.org/0000-0002-0450-1377

REFERENCES

1. Domestic situation, Ministry of Health, Labor and Welfare of Japan. 2021 November [cited 2021 Des 1]. Available from https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html
2. Ongoing Topics, Novel Coronavirus Vaccines, Prime Minister of Japan and His Cabinet. 2021 November [cited 2021 Des 1]. Available from https://japan.kantei.go.jp/ongoingtopics/vaccine.html
3. Health sciences council (vaccination and vaccine subcommittee meeting Associate reaction consideration section), Ministry of Health, Labor and Welfare of Japan. 2021 November [cited 2021 Des 1]. Available from https://www.mhlw.go.jp/content/10601000/000853741.pdf
4. Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultraestructural study of 7 paediatric cases. *Br J Dermatol*. 2020;183:729–37.
5. Welsh E, Cardenas-de la Garza JA, Cuellar-Barboza A, Franco-Marquez R, Arvizu-Rivera RI. SARS-CoV-2 spike protein positivity in pityriasis rosea-like and urticaria-like rashes of COVID-19. *Br J Dermatol*. 2021;184:1194–5.
6. 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;85:46–55.

7. McMahon DE, Kovarik CL, Damsky W, Rosenbach M, Lipoff JB, Tyagi A, et al. Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: a registry based study. *J Am Acad Dermatol*. 2021;85:46–55.
8. Cagigi A, Loré K. Immune responses induced by mRNA vaccination in mice, monkeys and humans. *Vaccines (Basal)*. 2021;9:61.
9. Sprent J, King C. COVID-19 vaccine side effects: the positives about feeling bad. *Sci Immunol*. 2021;6:eabj9256.
10. Ohsawa R, Sano H, Ikeda M, Sano S. Clinical and histopathological views of morbilliform rash after COVID-19 mRNA vaccination mimic those in SARS-CoV-2 virus infection-associated cutaneous manifestations. *J Dermatol Sci*. 2021;103:124–7.
11. Kuwatsuka S, Koike Y, Asai M, Sato Y, Murota H. Numerous plasmacytoid dendritic cell infiltration in HIV-associated psoriasis relieved only with antiretroviral therapy. *J Dermatol*. 2018;45:1126–9.
12. Kanitakis J, Lesort C, Danset M, Jullien D. Chilblain-like acral lesions during the COVID-19 pandemic ("COVID toes"): histologic, immunofluorescence, and immunohistochemical study of 17 cases. *J Am Acad Dermatol*. 2020;83:870–5.

How to cite this article: Watanabe, H., Ashida, M., Satomi, N., Koike, Y., Kuwatsuka, S. & Murota, H. (2022) Histopathological analysis of skin reactions after coronavirus disease 2019 vaccination: Increment in number of infiltrated plasmacytoid dendritic cell. *The Journal of Dermatology*, 49, 732–735. Available from: https://doi.org/10.1111/1346-8138.16374