Received: 18 June 2022 | Revised: 5 August 2022 | Accepted: 24 August 2022

DOI: 10.1002/cia2.12279

Journal of Cutaneous Immunology and Allergy

WILEY

CASE STUDY

Neutrophilic dermatosis with necrobiotic changes as an unusual manifestation after the first shot of a COVID-19 mRNA vaccine together with a high fever and liver injury

Shigeruko Iijima MD, PhD[1,2] | Chiaki Enami MD[3] | Mikio Sato MD, PhD[3] | Takahiko Tsunoda MD, PhD[4] | Kazunobu Otoyama MD, PhD[5]

[1]Department of Dermatology, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan

[2]Hanamizuki Clinic, Ushiku, Japan

[3]Department of Gastroenterology and Hepatology, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan

[4]Department of Dermatology, Yamagata City Hospital Saiseikan, Yamagata, Japan

[5]Otoyama Clinic, Yamagata, Japan

Correspondence
Shigeruko Iijima, MD, PhD, Department of Dermatology, Ryugasaki Saiseikai Hospital, 1-1 Nakasato, Ryugasaki, Ibaraki 301-0854, Japan.
Email: imacintosh@poppy.ocn.ne.jp

Abstract

Coronavirus disease 19 (COVID-19) mRNA vaccines sometimes cause various skin rashes. We report an unusual case of erythema nodosum-like nodules with vesicular and pustular papules, which arose after the first shot of a COVID-19 mRNA vaccine. A skin biopsy showed marked neutrophilic infiltration with necrobiotic changes throughout the dermis and subcutis. Immunohistochemically, $CD8^+$ cells were much more common than $CD4^+$ cells in the dense neutrophilic infiltrates. Many $CD68^+$ macrophages were present around the $CD8^+$ cells. No cases of neutrophilic dermatosis with necrobiotic changes have been reported. Thus, our findings should be added to the cutaneous adverse effects of the vaccines.

KEYWORDS
coronavirus disease-19, immunohistochemistry, mRNA vaccine, necrobiotic changes, neutrophilic dermatosis

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially fatal infectious disease, which has caused a global pandemic. However, as there are several effective COVID-19 vaccines, worldwide herd immunity may soon be achieved. COVID-19 mRNA vaccines produce immune responses to the spike glycoprotein that binds to angiotensin-converting enzyme 2 (ACE2), which is required for viral entry. Recently, it has become clear that these vaccines may cause a wide spectrum of skin rashes.[1,2] However, only a few studies have immunohistochemically analyzed these rashes.[3,4] We experienced an unusual case, in which the patient developed impetiginous vesicular or pustular papules on his face and a deep-seated erythema nodosum (EN)-like rash on his lower extremities, together with a high fever and liver injury, after receiving the first dose of a COVID-19 mRNA vaccine. Histologically, the EN-like rash involved dense neutrophilic infiltration and necrobiotic changes to collagen bundles. We report this unique case in detail together with its immunohistochemical findings.

2 | CASE PRESENTATION

A 33-year-old Japanese male with no relevant medical history received his first shot of the Pfizer-BioNTech COVID-19 mRNA vaccine (BNT162b2) intramuscularly in his left deltoid region. The next day (Day 1), he noticed a swollen lymph node on his neck, ipsilateral to the injection site. He developed a headache and nausea with a fever on Day 3 and a facial rash on Day 5. On Day 8, his liver enzyme levels started to increase, and he was admitted to our hospital because of persistent systemic symptoms. On Day 11, he was referred to our department to have his skin rash examined. He

presented with generalized weakness; a high temperature of 39.3°C; and a generalized skin rash, consisting of impetiginous vesicular or pustular papules on his face, pustules around the injection site and at the blood-drawing site on his right cubital fossa, and deeply infiltrating EN-like nodules with vesicles or pustules on his lower extremities (Figure 1A-E). A histopathological examination of an EN-like lesion with a few pustules revealed dense perivascular and periglandular infiltrates throughout the dermis and subcutis, which were composed of neutrophils, histiocytes, lymphocytes, and a lot of cell debris with marked necrobiotic changes (Figure 2A,B). Some blood vessels showed lymphocytic vasculitis with scattered red blood cell extravasation (Figure 2C). The epidermis showed ballooning changes and vacuolar degeneration in the basal layer together with a subepidermal bulla. Necrobiotic changes were seen below the bulla (Figure 2D). There were no microthrombi in the blood vessels. Immunohistochemically, cytotoxic $CD8^+$ cells were much more common than $CD4^+$ cells in the dense neutrophilic infiltrates. Many $CD68^+$ macrophages were present around the $CD8^+$ cells (Figure 2E-H). Most of the $CD4^+$ cells were thought to be macrophages. No CD79a, CD56, CD30, or Epstein-Barr virus (EBV)-encoded small RNA immunoreactivity was evident.

The following laboratory data were obtained: white blood cell count (WBC): 4430/μl (neutrophils: 85.1%), C-reactive protein (CRP): 11.76 mg/dl, aspartate aminotransferase (AST): 422 U/L, alanine aminotransferase (ALT): 765 U/L, lactate dehydrogenase (LDH): 482 U/L, alkaline phosphatase (ALP): 826 U/L, gamma-glutamyl transpeptidase (γ-GTP): 543 U/L, prothrombin time (PT): 15.9 s, prothrombin time-international normalized ratio (PT-INR): 1.34, activated partial thromboplastin time (ATPP): 27.9 s, fibrinogen: 749 mg/dl, fibrin degradation products (FDP): 8.0 μg/ml, and D-dimer: 5.2 μg/ml. Tests for SARS-CoV-2 (polymerase chain reaction-based); hepatitis A, B, and C; herpes simplex virus; EBV; cytomegalovirus; and human immunodeficiency virus (HIV) were all negative. Tests for anti-nuclear and anti-mitochondrial antibodies and blood cultures were negative. Abdominal computed tomography did not reveal any infection foci.

He was treated with diflucortolone valerate ointment for his extremities and hydrocortisone butyrate ointment for his face. Then, most of the rash resolved within a week. However, it was suspected that the rash had resolved because it had a self-limiting course, rather than due to the treatment. However, the patient's fever, elevated WBC, and increased CRP and liver enzyme levels persisted, and, thus, 200 mg/day oral minocycline was started on Day 19, which was effective within a few days. He was discharged on Day 25 and refused a second vaccine shot because he feared his symptoms would recur. We diagnosed him with COVID-19 vaccine-induced adverse cutaneous effects; however, we did not establish a clear causal relationship between the vaccine and the liver injury.

3 | DISCUSSION

Many cases of cutaneous reactions to COVID-19 vaccinations have been reported, including over 400 reactions from the USA[1] and Spain.[2] These reports described various morphological reaction patterns, including local injection site reactions; delayed large local reactions (COVID arm); urticaria/angioedema; and morbilliform, papulovesicular, pityriasis rosea-like, and purpuric (petechiae) rashes. Histologically, the most common patterns were eczematous dermatitis, interface dermatitis, interstitial granulomatous features, and lymphocytic vasculitis.[4] No cases of severe neutrophilic infiltration with marked necrobiotic changes following the administration of a COVID-19 vaccine have been reported in the English language literature.

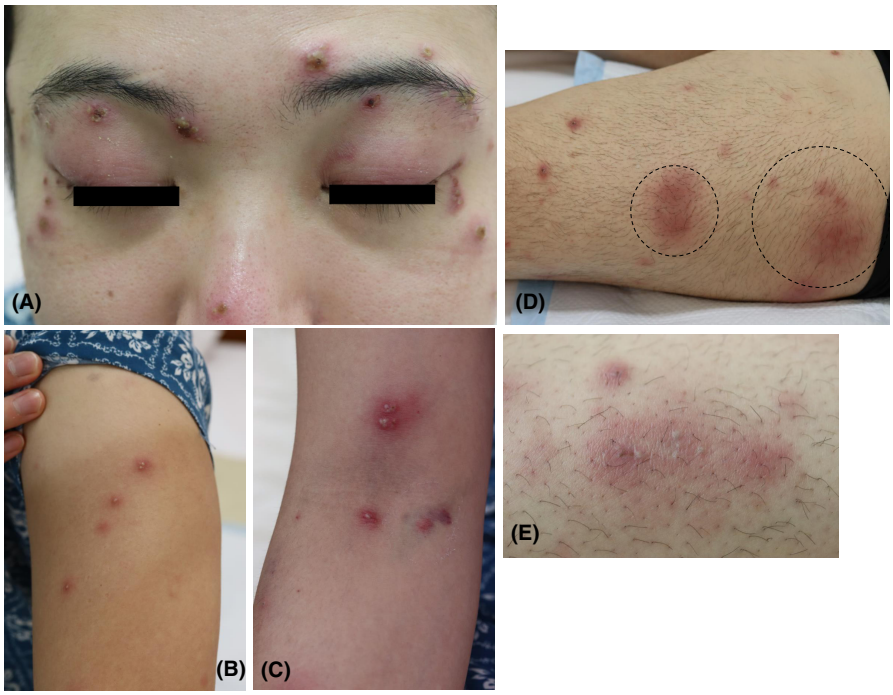

FIGURE 1 Clinical findings of the patient at the initial consultation. The patient showed impetiginous vesicular or pustular papules on his face (A), some pustules around the injection site (B) and at the blood-drawing site on his right cubital fossa (C), and deeply infiltrating EN-like nodules (dotted circles) with some vesicles or pustules on his lower extremities (D, E).

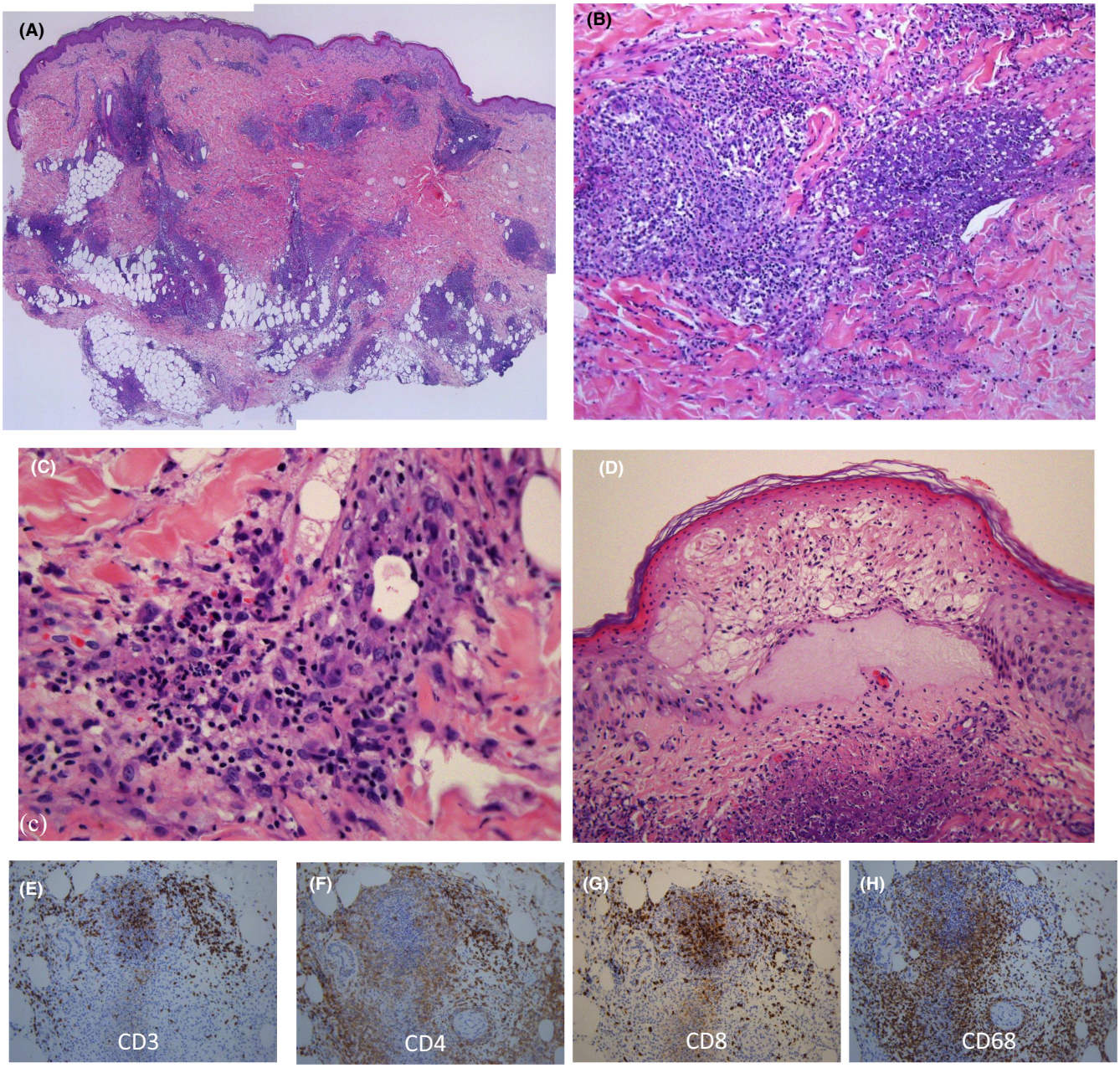

FIGURE 2 Histopathological and immunohistochemical findings of an EN-like nodule with some pustules on the patient's thigh. Histopathology showed dense perivascular and periglandular infiltrates throughout the dermis and subcutis (A; hematoxylin-eosin [HE], ×10), which were composed of neutrophils, histiocytes, lymphocytes, and a lot of cell debris with marked necrobiotic changes (B; HE, ×100). Some blood vessels showed lymphocytic vasculitis with scattered extravasation of red blood cells (C; HE, ×400). The epidermis showed ballooning changes and vacuolar degeneration in the basal layer, together with a subepidermal bulla, and necrobiotic changes were seen below the bulla (D; HE, ×200). Immunohistochemical studies involving CD3 (E), CD4 (F), CD8 (G), and CD68 (H) staining showed that cytotoxic $CD8^+$ cells were much more common than $CD4^+$ cells in the dense neutrophilic infiltrates. Many $CD68^+$ cells were present around the $CD8^+$ cells. Most of the $CD4^+$ cells were thought to be macrophages.

In a study of 22 patients with COVID-19 vaccine-induced skin rashes, Magro et al.[4] described a case of necrotizing neutrophilic and granulomatous folliculitis that arose after the administration of the Pfizer vaccine and involved very striking vesicular pustular eruptions. It was not possible to obtain further detailed information about this case; however, it may be similar to ours because the rashes that appeared on the patient's face and upper extremities involved impetiginous vesicular or pustular papules. Conversely, our patient did not show perifollicular neutrophilic infiltration, and the correct diagnostic label for his condition remains to be established.

Behçet's disease may be one of the diseases we should differentiate. A woman in late her 20s was recently reported, who was diagnosed as new-onset Behçet's disease or Behçet's disease-like adverse event following the second shot of mRNA Moderna vaccine.[5]

TABLE 1 Reported cases and our case of neutrophilic skin disorder associated with COVID-19 vaccination

Case	Age, sex	Type of vaccine	Dose	Onset time of skin rash after vaccination	Location of skin rash	Other systemic symptoms	Laboratory data	Histology	Diagnosis	Effective treatment	Second inoculation	Reference no.
1	45, F	mRNA (Pfizer-BioNTech)	First	1 day	Trunk, extremities	None	Neutrophilia AST: 67 U/L ALT: 116 U/L	Dense infiltrates of neutrophils, eosinophils, and lymphocytes throughout the dermis	Sweet syndrome	Oral PSL (0.5 mg/kg/day), 5 days	Refused by patient	10
2	65, F	Viral vector (Oxford-AstraZeneca)	First	7 days	Hands, feet	Fever	WBC: 14,000/μl (neut.: 82%) CRP: highly positive	Dense infiltrates of neutrophils in the dermis	Sweet syndrome	Intravenous dexamethasone, 1 week	N.S.	11
3	77, M	mRNA (Moderna)	First	3 days	Trunk, extremities	Acute encephalitis (headache, dizziness, double vision) Myoclonus, fever	WBC: 18,500/μl (neut.: 83.8%) AST: 67 U/L ALT: 93 U/L	A band-like infiltrate of neutrophils and histiocytes with nuclear debris in the superficial dermis Intracorneal microabscess	Sweet syndrome	Methylprednisolone (1 g/day, 4 days) →PSL 60 mg/day	N.S.	12
4	27, F	mRNA (Pfizer-BioNTech)	First	2 weeks	Chest	Joint pain History of MCTD	N.S.	Extensive infiltration of the outer root sheath epithelium by mixed inflammatory cell infiltrates	Necrotizing neutrophilic and granulomatous folliculitis	N.S.	N.S.	4
Ours	33, M	mRNA (Pfizer-BioNTech)	First	5 days	Face, extremities (lower > upper)	Fever, headache, nausea	WBC: 4430/μl (neut.: 85.1%) CRP: 11.76 mg/dl AST: 422 U/L ALT: 765 U/L	Dense infiltrates of neutrophils, histiocytes, and lymphocytes throughout the dermis with cell debris and severe necrobiotic changes Ballooning epidermal changes	Neutrophilic dermatosis with necrobiotic changes	The skin rash was self-limiting Minocycline for systemic symptoms	Refused by patient	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; MCTD, mixed connective tissue disease; N.S., not stated; neut., neutrophils; PSL, prednisolone; WBC, white blood cell count.

Panuveitis was also reported in a case of new-onset Behçet's disease after the vaccine.[6] Our patient had EN-like nodules on his lower extremities, pustules on his face, and a positive pathergy reaction on the injection site; however, in his whole clinical course, neither recurrent oral and genital ulcers nor ocular lesions were observed. These symptoms of our patient did not meet the international criteria of Behçet's disease.[7]

Furthermore, our case had to be differentiated from palisading neutrophilic granulomatous dermatitis (PNGD),[8] which is related to connective tissue diseases, mostly rheumatoid arthritis. However, we ruled out PNGD clinically because the cutaneous eruptions caused by PNGD are most commonly found on the extensor surfaces of the extremities, and our patient was a healthy individual without any underlying diseases, and his histopathology did not show a palisading appearance. On the contrary, necrobiotic changes at the injection site have been reported after a shot of hepatitis B vaccine in two cases, and these changes were diagnosed as necrobiotic palisading granuloma.[9]

There have been three cases of neutrophilic dermatosis without necrobiotic changes, which were diagnosed as Sweet syndrome.[10–12] Those cases (cases 1-3), Magro's case (case 4),[4] and our case are summarized in Table 1. All of the patients developed a skin rash within 2 weeks of receiving the first shot of a COVID-19 vaccine, four of which were mRNA-type vaccines (Pfizer in 3 cases, Moderna in one case), and the remaining one was a viral vector-type vaccine (Oxford-AstraZeneca). Marked necrobiotic changes were detected in collagen bundles after the vaccination in our case, but not any of the others.

Immunohistochemically, the perivascular and intraepidermal lymphocytes found in a previous case of a morbilliform rash caused by a COVID-19 mRNA vaccine were reported to be predominantly composed of $CD8^+$ cells rather than $CD4^+$ cells.[3] Our patient showed the same immunohistochemical findings. Furthermore, cytotoxic T cells ($CD8^+$) were characteristically seen in the neutrophilic infiltrates, which may have attacked neutrophils, leading to necrobiotic changes in collagen bundles. Furthermore, there were many $CD68^+$ cells surrounding the $CD8^+$ cells, which may have phagocytized the necrobiotic material.

It should be noted that we were not able to diagnose the patient's liver injury with the elevated WBC count and CRP level and fever. The possible diagnoses included a drug-induced liver injury, a complication of a Rickettsial disease, or a COVID-19 vaccine-induced liver injury.[13] As for the former possibility, a drug-induced lymphocyte stimulation test for moxifloxacin (Avelox®; Bayer Yakuhin, Ltd.), which he had taken orally only a day before admission, was positive (stimulation index: 228%); however, this would not have been sufficient to cause sensitization. Shroff et al.[13] reported 16 patients with liver injury following mRNA COVID-19 vaccination. According to their report, a half of them had some underlining liver diseases. Ten of 16 patients required treatment; 2 of 10 received *N*-acetylcysteine infusion, and 8 received oral or intravenous steroids. None received minocycline. However, we tried to administer minocycline to our patient, because we suspected he might have Rickettsial diseases. The medicine was markedly effective, but a test for antibodies against Tsutsugamushi disease was negative. Minocycline has a wide variety of effects against many organ diseases other than its antimicrobial activity.[14] We suggest that the patient's abnormal laboratory data and fever may have resolved due to the anti-inflammatory and immunomodulatory effects of the drug.

DECLARATION SECTION

Approval of the research protocol: No human participant was involved in this study.

Informed Consent: Written informed consent for publication was obtained from the patient.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Shigeruko Iijima https://orcid.org/0000-0002-9945-7064
Mikio Sato https://orcid.org/0000-0001-6088-8089

REFERENCES

1. 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.
2. Català A, Muñoz-Santos C, Galván-Casas C, Roncero Riesco M, Revilla Nebreda D, Solá-Truyols A, et al. Cutaneous reactions after SARS-COV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases. Br J Dermatol. 2022;186(1):142–51.
3. 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(3):124–7.
4. Magro C, Crowson AN, Franks L, Schaffer PR, Whelan P, Nuovo G. The histologic and molecular correlates of COVID-19 vaccine-induced changes in the skin. Clin Dermatol. 2021;39(6):966–84.
5. Tagini F, Carrel L, Fallet B, Gachoud D, Ribi C, Monti M. Behçet's-like adverse event or inaugural Behçet's disease after SARS-CoV-2 mRNA-1273 vaccination? Rheumatology. 2022;61(5):e112–3.
6. Bolletta E, Iannetta D, Mastrofilippo V, De Simone L, Gozzi F, Croci S, et al. Uveitis and other ocular complications following COVID-19 vaccination. J Clin Med. 2021;10(24):5960.
7. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28(3):338–47.
8. Kawakami T, Obara W, Soma Y, Mizoguchi M. Palisading neutrophilic granulomatous dermatitis in a Japanese patient with Wegener's granulomatosis. J Dermatol. 2005;32(6):487–92.
9. Ajithkumar K, Anand U, Pulimood S, Chandi SM, George S, Jacob CK, et al. Vaccine-induced necrobiotic granuloma. Clin Exp Dermatol. 1998;23(5):222–4.
10. Darrigade AS, Théophile H, Sanchez-Pena P, Milpied B, Colbert M, Pedeboscq S, et al. Sweet syndrome induced by SARS-CoV-2 Pfizer-BioNTech mRNA vaccine. Allergy. 2021;76(10):3194–6.

11. Majid I, Mearaj S. Sweet syndrome after Oxford-AstraZeneca COVID-19 vaccine (AZD1222) in an elderly female. Dermatol Ther. 2021;34(6):e15146.
12. Torralba-Acosta G, Martin JC, Huttenbach Y, Garcia CR, Sohail MR, Agarwal SK, et al. Acute encephalitis, myoclonus and Sweet syndrome after mRNA-1273 vaccine. BMI Case Rep. 2021;14(7):e243173.
13. Shroff H, Satapathy SK, Crawford JM, Todd NJ, VanWagner LB. Liver injury following SARS-CoV-2 vaccination: a multicenter case series. J Hepatol. 2022;76(1):211–4.
14. Garrido-Mesa N, Zarzuelo A, Géálvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169(2):337–52.

How to cite this article: Iijima S, Enami C, Sato M, Tsunoda T, Otoyama K. Neutrophilic dermatosis with necrobiotic changes as an unusual manifestation after the first shot of a COVID-19 mRNA vaccine together with a high fever and liver injury. J Cutan Immunol Allergy. 2022;00:1–6. https://doi.org/10.1002/cia2.12279