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REVIEW ARTICLE

The pathophysiology and clinical phenotypes of COVID-19 mRNA vaccine-related cutaneous adverse reactions: A narrative review

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ABSTRACT

Cutaneous adverse reactions (CARs) after COVD-19 messenger ribonucleic acid (mRNA) vaccines have been reported worldwide, but the pathophysiology of CARs remains to be elucidated. To understand the pathophysiology, it is essential to know how the innate and adaptive immunity are activated after vaccination. At present, majority of CARs are presumed to be evoked by innate immunity response. Reviewing the previous articles, I propose the clinical classification of CARs; local injection site reaction, generalized eruption, localized eruption and others. Since COVID-19 mutates continuously to overcome the existing vaccines, our steady efforts are indispensable to clarify the pathophysiology of CARs and contribute to the development of novel vaccines with least adverse events and high efficacy.

Keywords: COVID-19; mRNA vaccine; cutaneous adverse reaction; lipid nanoparticle; S protein

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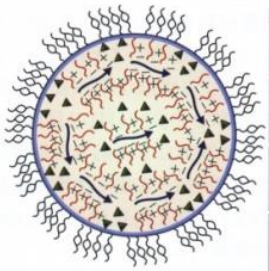
1. Introduction

The World Health Organization (WHO) announced that it completed the declaration of a public health emergency of international concern regarding COVID-19 infection on 5 May 2023. At the same time, it urges further caution that the threat still remains although the state of emergency may be over. A major turning point in the pandemic was the introduction of vaccines. In particular, the rapid introduction of messenger ribonucleic acid (mRNA) vaccines has prevented many people from serious illness and saved lives. Nevertheless, adverse events associated with mRNA vaccination have been reported in several organs although the severe adverse events are rare[1].

The vaccines mainly used in Japan are Pfeizer-Biontec COVID-19 vaccine (BNT162b2) and Moderna COVID-19 vaccine (mRNA-1273), both of which contain full-length mRNA that encodes viral spike (S) protein in lipid nanoparticles (LNPs), which render human cells to produce viral S protein using mRNA as a template (**Figure 1A**)[2]. Most cutaneous adverse reactions (CARs) are mild to moderate and rarely life-threatening, but the precise pathophysiology of CARs remains to be elucidated.

A



LNP component	Predicted Immunogenicity	µg/dose Pfizer-BioNtech	µg/dose Moderna
PEG-lipid	Preexisting Anti-PEG IgM, IgG and/or IgE	50 µg	Total lipid dose is 1,930 µg
Ionizable lipid	Pathogen-associated molecular pattern receptors	430 µg	
neutral lipid (DSPC)	Complement activation	90 µg	
cholesterol		200 µg	
mRNA	Pathogen-associated molecular pattern receptors and Factor XII activation	30 µg	100 µg

B

BNT162b2	mRNA-1273
Nucleoside-modified mRNA encoding the viral spike (S)-glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S)-glycoprotein of SARS-CoV-2
2((polyethylene glycol)-2000)-N, N-ditetradecylacetamide	Polyethylene glycol (PEG) 2000 dimyristoyl glycerol (DMG)
1, 2-distearoyl-sn-glycero-3-phosphocholine	1, 2-distearoyl-sn-glycero-3-phosphocholine
Cholesterol	Cholesterol
((4-hyroxybutyl) azanediyl) bis (hexane-6, 1-diyl) bis (2-hexyl decanoate)	SM-102 (patent from Moderna)
Potassium chloride	Tromethamine
Monobasic potassium phosphate	Tromethamine hydrochloride
Sodium chloride	Acetic acid
Dibasic sodium phosphate-dihydrate	Sodium acetate
Sucrose	Sucrose

Figure 1. Structure **(A)** and components **(B)** of COVID-19 mRNA LNP in Pfeizer-BionTech and Moderna COVID-19 vaccine package inserts.

2. Pathophysiology of CARs

It is assumed that there are two pathways in the pathogenesis of CARs: adaptive immunity against translated S protein and innate immunity against danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) derived from mRNA vaccines. To understand the pathophysiology of CARs, it is essential to know when adaptive immunity is established after vaccination, and whether the mRNA vaccine has immunogenicity as well as the induction of adaptive immunity against S protein.

2.1. When is the adaptive immunity established after the first vaccination?

LNPs internalized into muscle cells by endocytosis are degraded, and mRNA is translated to S protein in ribosomes. Then, S protein is presented as antigen by major histocompatibility complex (MHC) class I molecules to $CD8^+$ T cells that generate cellular immunity. Alternatively, S protein is released outside of muscle cells[3], taken up by antigen-presenting cells such as macrophages, dendritic cells and B cells, and presented to $CD4^+$ T cells by MHC class II molecules to initiate antibody production against S protein. It is, however, unknown whether adaptive immunity is established against LNP components other than S protein. Li et al.[4] demonstrated that mice immunized with BNT162b2 developed potent antibody and antigen-specific T cell response, as well as strikingly enhanced innate responses after secondary immunization, which was concurrent with elevated levels of serum interferon (IFN)-γ. They found that natural killer cells and $CD8^+$ T cells in the draining lymph nodes were the major producers of the circulating IFN-γ. Furthermore, the analysis of knockout mice revealed that induction of antibody and T cell responses against BNT162b2 was not dependent on signaling via Toll-like receptors (TLRs) 2,3,4,5 and 7 nor inflammasome activation, nor the necroptosis cell death pathways. Rather, the $CD8^+$ T cell responses induced by BNT162b2 was dependent on type I INF-dependent melanoma differentiation-associated protein 5 (MDA5) signaling.

Barrios et al.[5] measured IgG antibody levels against S protein before and 10 and 20 days after the 1st BNT162b2 vaccination, and 15 days after the 2nd dose in 28 healthy volunteers. They also performed intradermal skin tests with recombinant S protein 20 days after the 1st dose and 14 days after the 2nd dose. The 2nd dose was administered 21 days after the 1st dose. Six out of 28 subjects were antibody-positive 10

days after the 1st dose and all of them were antibody-positive 20 days after the 1st dose. In addition, the antibody levels further increased 15 days after the 2nd dose in all subjects. Intradermal skin test revealed that 8 of 11 subjects were positive 20 days after the 1st dose and all subjects were positive 14 days after the 2nd dose. This study suggests that humoral and cellular immunity may require at least more than 10 days to be established in most of healthy individuals. In another study in 13 healthy subjects[3], S protein was detected in peripheral blood from the first day of vaccination with mRNA-1273, reached a peak at day 5 and fell below the detection limit on day 14, and not detected until 56 days after the 2nd dose. Anti-S protein antibody reaches positive level in all subject 14 days after the 1st dose. This study indicates that as the level of anti-S protein antibody increased, S protein was promptly cleared from peripheral blood possibly as immune complex of anti-S protein antibody and S protein and/or the binding to S-protein receptor, angiotensin converting enzyme 2 (ACE2), which is present on the surface of certain cells or a soluble form in the peripheral blood.

Given the establishment of adaptive immunity after vaccination, CARs that develop within one week after the 1st dose may be caused by not adaptive immunity but innate immunity. Once adaptive immunity is established, both innate and adaptive immunity should be considered as being responsible for the development of CARs after the subsequent doses.

2.2. mRNA vaccines elicit the innate immune responses

Figure 1B shows the composition of BNT162b2 and mRNA-1273[6]. Although there are some differences in mRNA and lipids contained, the structure of LNP is basically same. The LNP maintains mRNA as a water-soluble form within it. Divalent polyethylene glycol (PEG) 2000 bound to the LNP surface (PEGylated) works as a steric barrier. LNP plays the role of a cargo that transfers mRNA into human cells in a stable state, and also acts as an adjuvant to effectively establish the adaptive immunity against S protein[6].

Sequence and secondary structures formed by mRNA stimulate innate immunity through cellular sensors such as TLRs 3,7, 8, and 9, retinoic acid-inducible gene I (RIG-I) and MDA5. TLRs 3,7,8 and 9 are localized in the endosomal compartment of immune surveillance cells, such as dendritic cells, macrophages and monocytes. TLR3 recognizes double stranded RNA (dsRNA) longer than 40 base pair as well as dsRNA resulting from single stranded RNA (ssRNA) forming secondary structures or derived from viral replication intermediates. TLR7 and 8 are activated by RNAs rich in polyuridines, guanosines and/or uridines[7,8]. TLR7 can bind both dsRNA and ssRNA, whereas TLR8 can bind ssRNA only[9]. TLR activation increases antigen presentation, promotes cytokine secretion and stimulates B cell responses leading to adaptive immunity[10–13]. RIG-I preferentially recognizes ssRNA and dsRNA bearing a 5'phosphate, and induces IFN production[14–17]. MDA5 is another cytosolic RNA sensor that detect long dsRNA generated during RNA virus replication as well as RNA of synthetic origin such as poly I:C[18]. Recognition of dsRNA induces the activation of interferon regulatory factor (IRF) 3 and NF-kB, subsequently leading to increased production of type I INF (mainly α/β)[12,13]. Both type I IFN and type III IFN (λ) act as the primary switch to initiate antiviral immunity[17].

BNT162b2 and mRNA-1273 vaccines use modified RNA, which is designed to minimize immune reaction by sequence optimization and usage of modified nucleoside such as pseudouridine, 5-methylcytidine, cap-1 structure and optimized codon[18–24]. Despite the ingenuity to avoid unnecessary reactions, exogenous mRNA stimulates innate immunity as DAMPs and causes inflammation. The hypersensitivity to exogenous mRNA may be due to robust activation of the innate immunity in predisposed individuals.

S protein translated from mRNA works as antigen and establishes the adaptive immunity. In the skin, immunohistochemical study demonstrated that ACE2, a receptor for S protein, is expressed by basal cell layer of the epidermis extending to the basal cell layer of hair follicle, smooth muscle cells surrounding the sebaceous glands, and eccrine gland cells, as well as vascular endothelial cells in the deep dermis[25]. In particular, eccrine gland cells showed positivity as strong as endothelial cells. Circulating S protein bound to extracellular TLRs and internalized ACE2/S protein complex may trigger the innate immunity response by

skin resident cells before humoral and cellular adaptive immunity is established. A case report by Sano et al.[26] reported the expression of S protein by cutaneous endothelial cells and eccrine glands in the deep dermis of the lesional skin of patients with 3-months' history of generalized exudative erythema after the 2nd dose of BNT162b2. Considering the instability of mRNA, it is of great interest to investigate how long modified mRNA of S protein can survive and be translated to S protein in human skin resident cells in vivo.

PEG-lipid, ionizable lipid and neutral lipid are components of LNP that may have immunogenicity. Ndeupen et al.[27] reported that subcutaneous administration of mRNA-free LNP to mice caused cutaneous erythema and swelling at 24 h, while ionizable lipid-free LNP did not. Flowcytometric analysis of infiltrating cells collected from the inflamed skin revealed that they were mainly neutrophils. The increased expressions of chemokines (CCL-2, 3, 4, 7 and 12) and CXCL1, and IL-1β, granulocyte macrophage colony stimulating factor (GM-CSF) and IL-6, which promote neutrophil and monocyte migration and hyperactivity, were detected by Lumix® assay and RNA-seq analysis. They also demonstrated the increased expression of Il1β and Nlrp3, which reflects inflammasome activation, and the decreased expression of Nlrp10 which suppresses inflammasome activation. Furthermore, gene set enrichment analysis showed the activation of RIG-I, NOD-like and TLRs. Other studies also demonstrated the induction of IL-6[28] and IL-1β[29]. These studies support that ionizable lipid may be a potent inducer of innate immunity[30].

PEG is contained in medicines, foods, cosmetics, etc.[31,32]. It is possible that individuals pre-sensitized to PEG might react with PEG-lipid. Since cholesterol and neutral lipid (1, 2-distearoyl-sn-glycero-3-phosphocholine) contained in LNP is naturally present, they are considered to be neither immunogenic nor reactogenic[33].

2.3. Does the injected vaccine remain at the injection site?

When Wister Han rats intramuscularly administered LNPs radiolabeled with cholesteryl-1,2-^{3}H(N)-cholesteryl hexadecyl ether, more than 80% of radioactivity was detected at the injection site and in other organs such as liver (18%), spleen (<1%), adrenal glands (<0.11%), and ovaries (<0.095%) at 48 h[33]. The radioactivity of plasma reached a peak at 1~4 h after injection. If the similar process was present in human, ionizable lipids and mRNA derived from LNP can stimulate innate immune system in organs including skin via through peripheral blood circulation. In addition, S protein is present in the peripheral blood from 1–14 days after vaccination[3]. Thus, it is probable that S protein bound to ACE2 may triggers the innate immunity response that results in cell damages and/or dysfunction of ACE2 expressing cells of internal organs as well as skin.

3. Cutaneous adverse reactions (CARs)

Since the vaccinated population is unknown in most papers, the exact frequency of each CAR cannot be determined[34]. There have been published 2 systematic reviews and meta-analysis in 2022[35,36]. The pooled incidences of overall CARs were 5% (95% CI, 4% to 6%) in 93,165 participants[35] and 3.8% (95% CI, 2.7% to 5.3%) in 946,366 participants[36]. Washrawirul et al.[36] further found that the incidence of CARs after the 1st and 2nd dose was similar, i.e., 3% (95% CI, 2% to 3%) and the magnitude of incidence of CARs was unchanged independently of vaccine platform and between the general population and healthcare workers.

CARs are more common in women[37–40], but the target population for the 1st and 2nd vaccinations was the elderly and the medical personnel worldwide. Biases have been pointed out that 70%~80% of the medical personnel are female, and that females are more sensitive to adverse reactions than males[34]. Many studies support that women are more responsive than men in terms of both innate and adaptive immunity. For example, TLR7 encoded on X chromosome plays critical role to elicit innate immunity. The expression of TLR7 in women is higher than that in men due to the escape from X chromosome inactivation[41], and enhanced by estrogens[1]. Females have higher levels of INF-α production by peripheral blood mononuclear cells after

stimulation with TLR7 ligands[41]. The increased expression of TLR7 may partly explain a stronger immune response in women.

3.1. Clinical phenotypes of CARs

Robinson et al.[37] reported that the most common cutaneous reaction other than the injection site reaction among 40,640 employees after dose 1 of mRNA vaccine (25% of employees received BNT126b2 and 75% did Moderna-1672) was rash and itching; 1.9% (*n* = 776, 95% CI; 1.8 to 2.1). Then, 741 out of 776 subjects with CARs other than the injection site reaction could complete the dose 2, and 508 (83%) subjects reported no recurrent CARs. This study implies that CARs other than the injection site reactions and recurrence of CARs are rare. A systematic review by Avallone et al.[38] summarized the frequency of COVID-19 vaccine-related CARs among 5941 cases retrieved from 229 articles. Immediate and delayed local injection site reaction (*n* = 2023, 34.1%), rash or unspecified cutaneous reaction (*n* = 1954, 32.9%), urticaria (*n* = 647, 5.4%), angioedema (*n* = 318, 5.4%), herpes zoster (*n* = 160, 2.7%), morbilliform /macropapular/erythematous macular eruption (*n* = 106, 1.8%), pityriasis rosea-like (*n* = 96, 1.6%), vesicular/papulovesicular rash (*n* = 53, 0.9%), chilblains/pernio (*n* = 52, 0.9%), and other CARs less than 50 cases. Local injection-site reaction (34.1%), urticaria (5.4%) and angioedema (5.4%) account for 44.9% of 5941 cases. Therefore, CARs after vaccination can be divided into two groups; common CARs such as local injection site reaction, delayed large local reaction (DLLR) and urticaria/angioedema, and other uncommon CARs. It is of great importance to note that the number of "rash" or "unspecified cutaneous reaction" (*n* = 1954, 32.9%) was in the 2nd place after local injection site reaction.

It is of ease for medical health career to diagnose local injection site reaction, DLLR, urticaria, angioedema, anaphylaxis, and herpes zoster. However, when multiple erythematous macules and papules distribute in the varying patterns, it is difficult to choose the most appropriate description among morbilliform eruption, erythema multiforme, pityriasis rosea/pityriasis rosea-like eruption, or systematic eczematoid reaction, etc. In previous papers, most practitioners who registered patients were medical professionals other than dermatologists and, therefore, it is plausible that cutaneous manifestations might not have been understood accurately[34].

To clarify the pathophysiology of uncommon CARs, it is essential to classify the CARs accurately by the specialist along with the records of onset time after vaccination and the subsequent clinical course and treatments, etc.

More than 20 systematic reviews have been published but there has been no established classification of CARs. In this review article, I basically follow the classification commonly used[34,37–39] with some modification.

3.1.1. Common CARs

1) Local injection site reaction[39]

This is the most common CAR of mRNA vaccination due to innate immunity, occurring in 96% of recipients. It lasts for 2 to 3 days from the day of vaccination, and accompanies pain (75.7%), redness (9.2%) and swelling (11.4%). Local injection site reaction is more frequent in the young than in the elderly.

2) Delayed large local reaction (DLLR)

The lesions developed 8 days after the 1st dose of mRNA-1273. DLLR on the left upper arm and contact dermatitis type on the right thigh coexisted. Multiple vesicles were present on the erythema. She administered the 2nd dose uneventful.

DLLR is clinically characterized by indurated erythema extending widely from the injection site and accompanies tenderness and itching, and sometimes by vesicles and/or blister[42–44]. It is of note that DLLR

sometimes coexists with generalized or localized eruption apart from injection site (**Figure 2**). DLLR develops around 7 days after vaccination and disappears within 7 days. DLLR occurs after vaccination not only with mRNA-1273 but also does with BNT162b2.

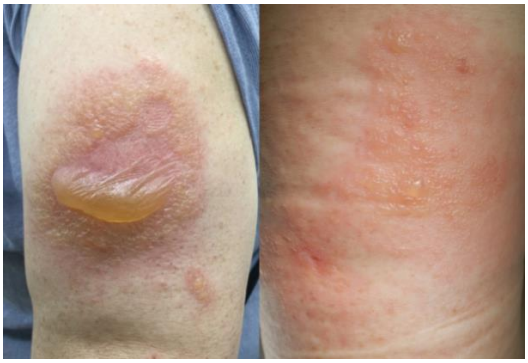


Figure 2. Bullous DLLR and contact dermatitis type (female in her 60s).

In phase III clinical trial of mRNA-1273 (number of recipients: 30,420)[45], the incidence of DLLR was 0.8% at the 1st dose and 0.2% at the 2nd dose. In a cohort study of hospital employees (number of recipients: 1275 females and 675 males)[46], the incidence was 1% (n = 13) at the 1st dose and 0.4% (n = 6) at the 2nd dose in females, but 0% at the 1st and the 2nd dose in males. Five out of 6 females with DLLR after the 1st dose had also developed DLLR after the 2nd dose. Hoff et al.[47] reported that the incidence of DLLR was 0.16% (n = 11) at the 1st dose and 0.0 4% (n = 3) at the 2nd dose in 6821 recipients. Three patients with DLLR at the 2nd dose had also developed it at the 1st dose.

Epidemiological studies in which the population size was determined have been reported from Japan. In a report by Higashino et al.[48], 5893 subjects (3318 men and 2575 women) administered the 1st and 2nd dose of mRNA-1273, and the incidence of DLLR after the 1st dose was 12.7% (747/5893) overall, and 22.4% (577/2575) in women and 5.1% (170/3318) in men, with a significant high incidence in women. Hibino et al.[49] reported that the incidence of DLLR after 1st dose of mRNA-1273 was 12.5% in women (69 out of 551 individuals with average age 68 years) and 1.5% in men (8 out of 547 individuals with average age 70 years). They asked why the incidence of DLLR in Japanese was so high compared to those reported from Europe and the United States.

The histologic changes of DLLR reported so far are almost consistent. The epidermis exhibited mild lymphocytic infiltration and spongiosis, and varying degrees of cellular infiltration consisting of lymphocytes mixed with eosinophils and neutrophils was observed around dilated blood vessels in the upper to middle dermis[38,50–53]. Immunohistochemical studies have rarely demonstrated the deposition of S protein in blood vessels of DLLR lesions[49,50]. It is of interest that strong lesional expression of myxovirus resistance protein 1(MxA), which is induced by the stimulation of type I/III IFNs, was observed[47].

McMahon et al.[34] reported that there was a tendency that DLLR did not recur or the response became weaker when patients with DLLR administered the 2nd dose. According to the previous study by Guerreo et al.[53], among 14 patients with DLLR who administered the 1st and 2nd dose of Moderna-1273 or BNT162b2, 8 patients developed DRLL after both the 1st and 2nd dose, 5 patients only after the 1st and 1 patient only after 2nd dose. Gambichler et al.[54] maintain that cellular adaptive immunity is responsible for DLLR, and many reports agree the hypothesis as the pathogenic mechanism of DLLR. Although it cannot be denied that certain individuals can establish the cellular immunity against S protein very fast, it is less likely that cellular immunity is established around 7 days after the 1st vaccination. In addition, it is difficult to explain why DLLR does not recur or attenuate after the 2nd vaccination in the same person. I consider that DLLR develops in individuals with strong innate immune responses. Inflammation caused by innate immune response may provoke necroptosis of cells, and molecules released from these cells may act as DAMPs or PAMPs, which further

intensify and prolong the inflammation. Additionally, as suggested by Ju et al.[55], molecules that suppress the innate immunity may be induced quickly after the 2nd dose in individuals with DLLR after the 1st dose, which may account for the diminishment or wane of CARs after the 2nd dose and booster doses.

3) Urticaria/Angioedema

According to the definition by the Centers for Disease Control and Prevention (CDC), urticaria due to an immediate hypersensitivity reaction develops within 4 h after vaccination. Anvari et al.[56] reported that among 481 adverse reactions registered by physicians in the COVID-199 Vaccine Allergy Case Registry, urticaria/angioedema accounted for 60 cases; 50 cases (83%) were female, and 31 cases (52%) were with BNT162b2 and 29 cases (48%) with mRNA-1273. The onset time was as follows: 15 cases (25%) were within 1 h, 4 (7%) cases between 1 and 4 h, 13 cases (22%) between 4 and 24 h and 28 cases (47%) after 24 h. Most cases improved with oral antihistamines and corticosteroids, and epinephrine was used in 3 cases. They emphasize that post-vaccination urticaria/angioedema is not IgE-mediated allergic reaction to vaccines or additives, but rather physiological immune-inflammatory responses to the vaccine. The most plausible mechanism is the so-called complement activation-related pseudoallergy (CARPA). CARPA results in mast cell degranulation via complement activation and generation of inflammatory stimulators, such as C1q, C3a, C4, anaphylatoxins, C5a, and complement factor B[1]. As shown in **Figure 1A**, neutral lipid may be one of causative factors[2].

PEG contained in mRNA vaccines has attracted attention as the cause of urticaria, angioedema or anaphylaxis[57]. Wolfson et al.[58] performed skin prick test with vaccine additives, PEG-3350 (Miralax®) and polysorbate 80 (Refresh Tears®), and intradermal test with polysorbate 80 (Refresh Tears®) and methylprednisolone acetate which contains only PEG3350 in 80 cases who were suspected to have an immediate reaction within 4 hours or delayed reaction from 4 h to 72 h after the 1st dose of BNT162b2 or mRNA-1273. They found 5 cases with PEG-positive reaction; one case was skin prick test-positive and 4 cases were intradermal test positive, and 9 cases with polysorbate 80-positive reaction. Thus, 14 out of 80 (17.5%) patients showed positive skin tests. However, 3 of 5 PEG-positive cases and 7 of 9 polysorbate80-positive cases revealed no adverse events after the 2nd dose. This result casts doubt on the clinical usefulness of the skin test of PEG. Furthermore, 8 out of 25 healthy individuals without history of allergies were positive by skin prick test with polysorbate 80 (Refresh Tears®). They concluded that that polysorbate 80 (Refresh Tears®) should not be used for skin test because of the high frequency of transient reactions in healthy individuals.

It is of interest to ask whether patients who had been treated for chronic urticaria before vaccination get worse after vaccination. Grieco et al.[59] reported that worsening of symptoms was observed in 13 out of 160 patients with chronic spontaneous and inducible urticaria.

The frequency of anaphylaxis with urticaria, angioedema and dyspnea that develops within 15 minutes after vaccination has been reported to be 11.1 per million people by BNT162b2 and 2.5 per million by mRNA-1273[60]. However, no death has been reported to date, and all cases have recovered with epinephrine.

3.1.2. Uncommon CARs

1) Herpes zoster

Since the first case report of herpes zoster (HZ) after mRNA vaccination by Eid et al.[61], a lot of case report and case series have been published, and more than 1000 cases have been registered in the U.S. Vaccine Adverse Event Reporting System. The clinical characteristics of HZ after COVID-19 vaccination or infection were summarized by the systematic review by Martinez-Reviejo et al.[62] In the vaccinated patients, median age was 56.5 (42–70) years, and 56.8% were female. The median latency time after vaccination was 6 (3–10) days, and 84.4% received mRNA vaccines. HZ occurred after the 1st dose (68.2%), the 2nd dose (12.8%) or booster doses (0.6%). The most common manifestation was dermatome HZ, which accounted for 86.4% of

events in vaccinated subjects. Serious events were documented in 20 patients (11.3%), with herpes zoster ophthalmicus (5.6%) and post-herpetic neuralgia (3.4%), but no varicella zoster virus pneumonia or deaths were recorded. Clinical courses of HZ in vaccinated patients were not different from those of unvaccinated patients.

Several hypotheses have been proposed to explain the reactivation of varicella zoster virus (VZV) after vaccination. It is plausible that the massive production of $CD8^+$ and $CD4^+$ T cells may shift naïve $CD8^+$ T cells from producing VZV-specific $CD8^+$ T cells and consequently result in the shortage of effective T cells to control the dormant VZV[63]. IFN have a central role in viral infection control, proliferation, and antibody production. IFN is essential to stop VZV replication via through the arrest of host's cell cycle. It was pointed out that mRNA vaccines interfered with IFN-1 receptor signaling in $CD8^+$ T cells, which lead to the impaired production of effector and memory T cells[30].

Recently, large-scale cohort studies have been published to examine the causal relationship between HZ and COVID-19 vaccines, but the results are controversial[64–70]. Barda et al.[64] reported that the risk ratio of HZ within 21 days after the 1st and 2nd vaccination was 1.43 (95% CI, 1.20 to 1.73) between BNT162b2-vaccinated group and unvaccinated group (n = 888,647 in each group) using the database of Clalit Health Service in Israel. Hertel et al.[65] reported that the risk ratio of HZ within 60 days after the 1st and 2nd vaccination with mRNA vaccines (98.49%) or Ad26.COV2.S (1.51%) was 1.802 (95% CI, 1.680 to 1.932) between vaccinated group and unvaccinated group (n = 1,095,086 in each group), in which data were retrieved from the TriNetX database from 120 healthcare organizations across 19 countries. Florea et al.[66] conducted a cohort study including recipients of the 1st and 2nd doses of mRNA-1273 (n = 1,052,362), BNT162b2 (n = 1,055,461) and unvaccinated individuals (n = 1,020,334). Adjusted hazard ratio for HZ up to 90 days after the 2nd dose of mRNA-1273 and BNT162b2 was 1.14 (95% CI, 1.05 to 1.24) and 1.12 (95%CI, 1.03 to 1.22), respectively. They pointed out the potential increased risk of HZ after the 2nd dose of mRNA vaccines. On the other hand, Shasha et al.[67] reported that the risk ratio of HZ after the 1st and 2nd dose of BNT162b2 was 1.07 (95% CI, 0.85 to 1.35) between BNT162b2-vaccinated group and unvaccinated group (n = 364,192 in each group), referring the Meuhedet Health Maintenance Organization database in Israel. In this study, the follow-up period for herpes zoster after vaccination was not stipulated. Akpandak et al.[68] conducted the cohort study of 2,039,854 cases who received COVID-19 vaccine recorded in a health care claims database of U.S.A.. A self-controlled risk interval analysis revealed that the incidence rate ratio of HZ after COVID-19 vaccination was 0.91 (95% CI, 0.82 to 1.01; P = 0.08), comparing the risk of HZ during the risk interval (30 days) after vaccination with that of the control interval (30–60 days after the end of the last interval). A cohort study by Birabaharan et al.[69] using TriNetX reported that there was no difference in the incidence of HZ within 28 days among persons receiving the mRNA COVID-19 vaccine compared to both the historical cohort (relative risk, 0.91; 95% CI, 0.82 to 1.01, n = 555,256) and the contemporary cohort (relative risk, 0.98; 95% CI, 0.87–1.11, n = 359,789). Patil et al.[70] carried out a cohort study using the Epic electronic health data of 596,111 patients who received at least one COVID-19 vaccination at NYU Langone Health from 12 January 2020 to 30 September 2021. They found that 716 patients were diagnosed with HZ within 3 months prior to vaccination and 781 patients diagnosed with HZ within 3 months afterwards. Using the chi-square test for independence of proportions, there was not statistically significant difference in frequency of HZ before (proportions, 0.0013, 95%CI, 0.0011 to 0.0013) vs. after vaccination (proportions, 0.0012, 95%CI, 0.0012 to 0.0014). Multiregional population-based cohort study[71] reported from Japan denied an increased risk of HZ; the adjusted incidence rate ratios of the 1st and 2nd BNT162b2 vaccinations were 1.05 (95% CI, 0.84–1.32) and 1.09 (95% CI, 0.90 to 1.32), respectively, and no case of HZ were observed after mRNA-1273 vaccination.

Three systematic reviews were published in 2022 and 2023[72–74]. In 2022, Chu et al.[72] include 4 cohort studies and reported that there was no increased incidence of HZ between COVID-19 vaccination group and the placebo group (risk ratio: 1.06; 95% CI, 0.91 to 1.24). In 2023, Shafiee et al.[73] conducted proportion meta-

analysis including 11 studies, showing the rate of VZV reactivation was 14 persons per 1000 vaccinations (95% CI, 2.97 to 32.80). However, among 11 studies included, 7 studies[41,75–80] lacked a control group and 3 of them targeted only patients with rheumatic disease[78–80]. Chen and Chiu[74] also performed meta-analysis using a random-effects model to calculate the pooled odds ratios (ORs) and 95% CIs. They included 9 studies[64,65,67–70,76,81,82] and pointed out that COVID-19 vaccination was associated with a significant increased risk of HZ (OR, 1.32; 95% CI, 1.09 to 1.62, $P = 0.006$). Among them, the study by Wan et al.[82] reported the high adjusted incidence rate ratios (aIRR) in comparison to other studies. They conducted self-controlled case series (SCCS) and nested case-control analyses between 91 hospitalized patients with HZ within 28 days after vaccination with CoronaVac ($n = 44$) and BNT162b2 ($n = 47$) and 454 hospitalized unvaccinated patients as a control. In SCCS analysis, CoronaVac vaccination was associated with significantly higher risk of HZ within 14 days after the 1st dose ([aIRR] = 2.67, 95% CI, 1.08 to 6.59) but not in other periods afterwards compared to the baseline period. Regarding BNT162b2 vaccination, a significantly increased risk was observed after the 1st dose up to 14 days after the 2nd dose; 0–13 days after the 1st dose: aIRR = 5.23, 95% CI, 1.61–17.03); 14–27 days after the 1st dose: aIRR = 5.82, 95% CI, 1.62 to 20.91; 0–13 days after the 2nd dose: aIRR = 5.14, 95% CI, 1.29–20.47). I deduce that there might have been strong anxiety against novel vaccines among vaccinated patients as well as physicians, which may partly account for the high incidence of hospitalized vaccinated patients with HZ.

Collectively, the link between mRNA vaccines and herpes zoster is a matter of debate, and further studies are warranted.

2) Generalized eruption

This condition is characterized by multiple erythematous macules and/or papules on body sites distant from the injection site, and includes morbilliform/maculopapular type, erythema multiforme type and pityriasis rosea-like type. Reviewing the previous histological findings of morbilliform/maculopapular type[83–88], pityriasis rosea-like type[87] and erythema multiforme type[88–91], the histological features can be summarized as follows: 1) lymphocytic infiltration into the epidermis, sometimes accompanied by individual keratinocyte necrosis (dyskeratotic cell), 2) varying degrees of epidermal spongiosis, sometimes evolving into the intraepidermal vesicle, 3) lymphocytic infiltration at the epidermal-dermal junction, sometimes resulting in vacuolar degeneration of basal cells and subepidermal blister, and 4) perivascular lymphocytic infiltration in the upper to middle dermis with varying degrees of eosinophil, histiocyte and neutrophil infiltration, and occasional extravasation of red blood cells. The clinical phenotype of exanthema may be determined by the dominant histological changes. To date, S protein has been scarcely proved in the lesional skin of CARs.

i) Morbilliform/Maculopapular type

Morbilliform/maculopapular type is characterized by multiple small erythematous macules (usually < 1 cm) and papules distributing in the trunk and extremities with or without facial involvement (**Figure 3**).

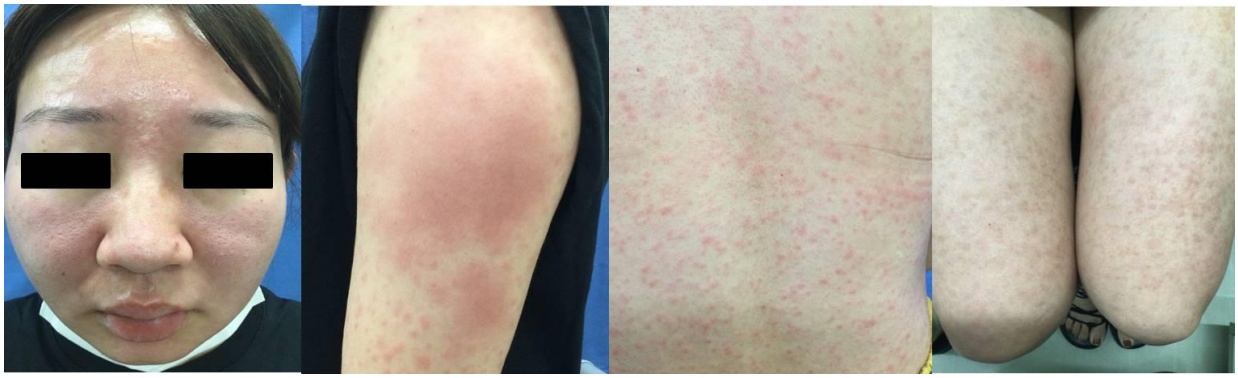


Figure 3. Morbilliform type with DLLR (female in her 20s).

The eruption appeared 2 days after the 2nd dose of mRNA-1273. Small erythematous macules were disseminated in the entire body with DLLR. The 1st dose had been administered uneventful.

This type of generalized eruption usually lacks systemic manifestation such as fever, malaise or fatigue. Although the distinction between "morbilliform" and "maculopapular" is not present, the choice of "morbilliform" or "maculopapular" seems to depend on the authors' knowledge and experience. After reviewing many photographs of reported cases, I opine that "morbilliform" is characterized by disseminated erythematous macules involving almost entire body, and "maculopapular" is characterized by scattered erythematous macules and/or papules involving some body sites.

According to the review article by Mahmood et al.[40], the skin rash occurred around 3–28 days after the 1st dose of Moderna-1273, lasting 4–10 days, and around 1–2 days after the 2nd dose, lasting from 2.5–35 days. Also, it occurred around 1–7.5 days after the 1st dose of BNT162b2, lasting around 4–12 days, and around 4 h to 2 days after the 2nd dose, lasting around 2.5 days. There is a tendency that skin rash after 2nd dose disappeared faster compared to that after the 1st dose. In the study by Guerrero et al.[53], among 7 patients with maculopapular rash after BNT162b2 (n = 5) and Moderna 1273 (n = 2), 5 patients developed maculopapular rash only after 1st dose of BNT162b2 (n = 3) and Moderna-1273 (n = 2), 1 patient only after 2nd dose of BNT126b2 dose and 1 patient after 1st and 2nd doses of BNT162b2. These facts support that morbilliform/maculopapular type is not elicited by adaptive immunity.

ii) Pityriasis rosea (PR)/Pityriasis rosea-like (PR-like) type

Classic pityriasis rosea frequently starts with a herald patch. Multiple oval salmon-colored macules with collarette scales distribute following the lines of cleavage on the trunk (Christmas tree appearance). Eruptions last from 4 to 7 weeks without systemic manifestation. The histologic changes include mononuclear cell infiltrate in the upper dermis with a few eosinophils and histiocytes. Spongiosis, spongiotic vesicles and intracellular edema occur at the site of mononuclear cell infiltrate. Mild acanthosis and focal parakeratosis are also present. The peculiar features are dyskeratotic cells in the epidermis and extravasated erythrocytes in dermal papillae.

Several case report and case series have been published. Khan et al.[87] analyzed 111 patients' data retrieved from 31 studies published from 1 December 2019 to 28 February 2022. In 111 patients with PR or PR-like eruption, 36 (55.4%) patients were female, the average age was 44.9 years, and 63 (62.4%) patients developed eruption after the 1st dose and 38 (35.5%) patients after the 2nd dose. Vaccines administered were BNT162b2 (n = 38, 35.5%), mRNA-1273 (n = 27, 25.2%), CoronaVac (n = 23, 21.5%), AZD1222 (n = 11, 10.3%), BBV152 (n = 3, 2.8%), BBIBP-CorV (n = 2, 1.9%) and Ad26.COV2.S (n = 1, 0.9%). The mean latency time recorded in 92 patients was 8.5 days, and the mean recovery time in 42 patients was 6.44 weeks. When 39 patients without morphological description were excluded, 34 (37.2%) out of 72 patients presented a typical "herald patch", and 36 (50%) patients showed a typical "Christmas tree appearance". The result of skin manifestation analysis suggests that the number of patients with PR-like eruption, not classic PR, was not a few.

Two case series of PR after vaccination[92,93] have been published. Temiz et al.[92] reviewed clinical data of 31 patients with PR in 3 dermatology centers in Turky. Of 31 cases, 14 cases (45.2%) received BNT162b2 and 17 cases (54.8%) received CoronaVac. The mean age was 44.9 years and 18 cases (58%) were female. Nineteen cases (61.35%) developed PR after the 1st dose. The average time of onset was 12.7 days post-vaccination. Twenty-six cases (84%) were typical PR with herald patch followed by Christmas-tree pattern of the patches, and 5 cases (16%) were atypical with pruritus and vesicles. Herald patch was noted in 24/26 of typical PR cases and 2/5 of atypical PR cases. No patient who had developed PR after the 1st dose experienced recurrence after the 2nd dose. Ramot et al.[93] reported the clinical data of 6 patients with typical PR after BNT162b2 vaccination in their dermatology department. All 6 patients presented a typical herald patch

followed by Christmas-tree pattern of the patches with collarette scale. The rash appeared 4.2 ± 3.1 days after the 1st dose in 3 patients, and the 2nd dose in 3 patients. There was neither systemic symptom nor gastrointestinal symptoms. The rash resolved within 4–6 weeks in all patients.

The distinction between classic PR and PR-like eruption is important to understand the pathogenesis of two conditions. Drago et al.[94] and Broccolo et al.[95] have published many works to elucidate the causal relationship between PR and human herpesvirus (HHV)-6/7, and proposed that classic PR is caused by reactivation of HHV-6/7. They emphasize that PR-like eruption has a pathogenesis completely different from PR: it is not associated HHV-6/7 systemic reactivation but it is rather a vaccine-induced exanthema with clinical features resembling classic PR. They also pointed out that herald patch is usually absent, and the skin lesion is itchier, diffuse and confluent in PR-like eruption. They proposed the clinical, histopathologic and virologic criteria to distinguish PR and PR-like eruption[96]. However, it is not always easy to differentiate PR from PR-like eruption only by clinical history and physical findings. I understand that virologic study of blood (HHV 6/7 DNA plasma and IgM antibodies against HHV 6/7 in serum) and histologic study of the skin lesion (HHV 6/7 antigens) are necessary to accurately diagnose a patient with classic PR. In the previous study[95], however, HHV-6 and HHV-7 were detected in 17% and 39% of plasma of PR patients, respectively, and HHV-6 or HHV-7 antigens were found in 17% and 67% of PR skin samples analyzed respectively. Thus, HHV-6 and HHV-7 are not always proved in blood and skin samples of PR patients. Negative results of virologic study can't exclude the diagnosis "classic PR". At present, it is reasonable that patients with all 3 characteristics, herald patch, Christmas tree appearance and patches with collarette scales, should be reported as classic PR. The result of histological examination and virologic study could be added if the virologic and histologic studies are available in the medical setting.

iii) Erythema multiforme type

As the name of erythema multiforme (EM) implies, the lesion is multiform, showing macules, papules, vesicles and bullae (**Figure 4**). The erythema characteristic to EM is called as "target or iris lesion". It is classified into two groups of EM major and EM minor. In EM minor, cutaneous lesion occupies less than 10% of body surface, preferentially affects the acral extensor surface with minimal or no mucosal involvement. EM major has a cutaneous pattern similar to that of EM minor but with greater extension and mucosal involvement. A few cases only with oral lesions have been reported as oral EM[97]. The histological findings vary depending on the timing of biopsy[88–91].

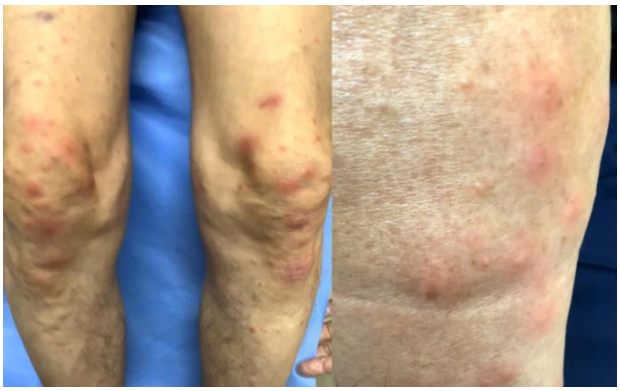


Figure 4. Erythema multiforme type with vesicles (male in his 70s).

The eruption developed 3 days after the 4th dose of BNT162b2. Exudative erythema distributed mainly on the extensor surface of extremities. Some of erythema were accompanied with vesicles. He had administered the previous 3 doses uneventful.

The causes of classical EM are infections of herpes virus or *mycoplasma pneumonia*e in children and adolescent, and drugs in adult, in which the causative agent drives cellular adaptive immunity. Su et al.[98]

analyzed post-vaccination surveillance data collected from 1999 to 2017 for EM, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Of 466,027 cases, EM accounted for 0.2%. The median time from vaccination to the onset of EM was 6 days, mostly within 14 days after vaccination. Vaccine-induced EM has been reported to be caused by measles-mumps-rubella (MMR), influenza, diphtheria-pertussis-tetanus (DPT) and hepatitis B vaccines. Yousefian and Khadivi[99] collected 90 cases with EM after COVID-19 vaccination from 31 articles published by April 2022. They reported that the mean age was 51 years, the prevalence in females was twice than that in males, EM appeared after the 1st dose (44%) and 2nd dose (30%), respectively, in which Moderna-1273 (32%) and BNT126b2 (47%) were used. As for the mucocutaneous involvement, 37% had oral involvement, 93% had cutaneous involvement, and 31% had both oral and cutaneous involvement. In 2 case reports[93,100], 4 patients with EM after the 1st dose did not develop CARs after the 2nd dose. Nevertheless, EM has the risk to evolve into the life-threatening form of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[101]. Therefore, patients with EM after 1st vaccination should be carefully monitored after the subsequent dose.

iv) Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)

SJS and TEN in COVID-19 vaccines administered patients are very rare compared to EM/. SJS, TEN and EM share the common histologic features such as necrosis of keratinocytes, dermal lymphocyte infiltration and detachment of the epidermis from the dermis, while the dermal infiltration is more pronounced in EM. The pronounced epidermal necrosis, a histological hallmark, is observed in SJS/TEN. The distinction of between SJS and TEN is clinically based on the involved total body surface area: SJS is <10% and TEN is >30%[102]. Zou and Daveluy[103] collected 12 cases with TEN/SJS after COVID-19 vaccinations[83,102,104–113] along with 22 cases with TEN/SJS after COVID-19 infection, which had been reported until August 2022. Seven additional case reports (7 patients) of vaccine-related SJS/TEN were found at the time of manuscript writing in Oct 2023[114–120]. Vaccines used in 19 patients were Moderna-1273 (n = 6), BNT162b2 (n = 4), ChAdOx1 nCoV-19 (n = 4) and BBIBB-CorV (n = 5). SJS/TEN developed after 1st, 2nd or 3rd dose and latency time was 1–20 days (mean; 9.6 days). All patients received intensive treatments with special attention to avoid further drug adverse events and recovered well except one lethal case[111].

v) Drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DiHS)

DRESS and DiHS are characterized by widespread erythematous macules, peripheral blood eosinophilia, fever, lymphadenopathy and involvement of one or more internal organs, and usually develop 2 to 8 weeks after exposure to the culprit drugs such as anticonvulsants, antibiotics, antiretrovirals and allopurinol. Reactivation of herpesviruses such as human herpesvirus 6 and 7, Epstein-Barr virus and cytomegalovirus, results in symptom flare-up and organ damages.

Since DRESS/DiHS are sometimes lethal, prompt diagnosis is required. The diagnosis of DRESS can be made using three different sets of criteria: European registry of severe cutaneous adverse reactions to drugs and collection of biological samples (RegjSCAR) criteria[121], Bocquet's criteria[122], and Japanese consensus group to diagnose DIHS/DRESS syndrome[123]. RegiSCAR criteria has been commonly used, which comprise at least 3 of the following 7 characteristics: (1) fever >38 ℃; (2) skin eruption; (3) lymphadenopathy involving at least two sites; (4) involvement of at least one internal organ; (5) lymphocytosis (>4000/mm^3) or lymphocytopenia (<1500/mm^3); (6) blood eosinophilia (>10% or 700/mm^3); thrombocytopenia (<120,000/mm^3). Japanese consensus group further included "reactivation of herpes viruses". It is of interest to examine whether herpes virus reactivation occurs in patients with DRESS associated with vaccination.

To date, 7 patients with DRESS/DiSH associated with COVID-19 vaccines have been reported[124–130]; BNT162b2 (n = 3), Ad26 COV2.S COVID-19 (n = 2), Moderna1273 (n = 1) and ChAdOx1 nCoV-19 (n = 1).

Latency periods after vaccination were 1–7 days (n = 4), 37 days (n = 1) and 6–7 weeks (n = 2). All patients recovered with appropriate treatments.

vi) Vesiculobullous type

Histologically, vesicle and blister are the consequence of epidermal spongiosis and/or dermo-epidermal cleavage. In the clinical practice, the most important issue is to differentiate autoimmune bullous diseases (AIBDs) from non-AIBD condition. Tomayko et al.[131] analyzed 12 patients (6 women and 6 men with mean, age; 42–97) who developed blisters after vaccination. The histological examination revealed subepidermal blisters and lymphocytic infiltration with eosinophils in all cases. Seven patients were diagnosed with bullous pemphigoid based on the results of direct immunofluorescence study and serum anti-BP180 antibody, and the remaining 5 cases were termed as vaccine-triggered benign BP-like condition. Since clinical photographs of each patient were not shown, it is difficult to comment the clinical diagnosis of patients with vaccine-triggered benign BP-like condition. From the histological point of view, EM major or fixed drug eruption must be differentiated.

vii) Autoimmune bullous diseases

An association between COVID-19 vaccination and autoimmune bullous diseases (AIBDs) has been suspected and previously proposed mechanisms include nonspecific bystander immune activation, molecular mimicry and a novel consequence of mRNA vaccine technology[132–134]. Calabria et al.[135] collected 35 definite cases of AIBDs from 20 articles and found 26 cases of bullous pemphigoid (74.3%), 6 cases of pemphigus vulgaris (17.1%), 2 cases of linear IgA bullous dermatosis (5.7%) and 1 case of pemphigus foliaceus.

In vitro experiments by Vojdani et al.[136], human monoclonal anti-SARS-CoV-2 spike protein antibody was demonstrated to react with 26 out of 55 human tissue antigens; strong reactivity (3+): mitochondrial antigen (M2), neurofilament protein, moderate reactivity (2+): thyroid peroxidase, nuclear antigens, etc. weak reactivity (+): tissue transglutaminase 2/3/6, type V collagen, etc.). They emphasized the possibility that anti-SARS-CoV-2 spike protein antibody can cross-react with multiple human organs resulting in autoimmune diseases. In contrast, Gambichler et al.[134] did not find immunoreactivity in the subepidermal compartment by immunofluorescence confocal scanning microscopy using the antibody against SARS-CoV/SARS-Co-V-2 spike protein S2. Kasperkiewicz et al.[137] confirmed that circulating antibodies in serum from healthy individuals who received two doses of BNT162b2 vaccine did not cross-react pemphigus or pemphigoid autoantigens including desmoglein 1/3, envoplakin, BP180/230 and type VII collagen, using a multi-variant Dermatology Profile ELISA (Euroimmune®, Germany). These studies may deny the relevance of molecular mimicry hypothesis in the pathogenesis of AIBDs.

Many case reports and case series have been accumulated, whereas evidence-based data from large cohorts of patients with AIBDs were lacking until the study by Birabaharan et al.[138] was published. They, for the first time, determined the risk of bullous pemphigoid (BP) in a large federated health research networking (TriNetX) involving 1.5 million people with mRNA vaccination of BNT162b2 or Moderna-1273. They observed no difference in the risk of new-onset BP among participants receiving mRNA COVID-19 vaccine within 24 weeks compared to either the control cohort (RR 0.77, 95%CI; 0.37 to 1.57) or the historical cohort (RR 0.55, 95% CI; 0.30 to 1.20). Further large cohort studies are warranted to clarify the causal relationship between COVID-19 vaccines and AIBDs.

3) Localized eruption

i) Chilblains-like type

Chilblains/pernio is an inflammatory condition, histologically characterized by dermal edema with perivascular lymphocytic infiltrates, and caused by exposure to non-freezing cold conditions. It is clinically characterized by infiltrated purplish erythematous macules on acral surfaces. The similar skin change,

chilblains-like lesion, has been noted among patients with COVID-19 infection and is well recognized to be not rare. Freeman et al.[139] reported that chilblains-like lesion was common, and 18% of 171 patients with laboratory-confirmed COVID-19 had chilblains-like lesions and found to be correlated with milder disease. After the worldwide introduction of commercially available COVID-19 vaccines, it has been noticed that chilblains-like lesion also develops in vaccinated individuals.

In the article by McMahon et al.[34], chilblains-like type was found in 3 (1.1%) out of 267 cases after the 1st dose of mRNA-1273, 0 (0%) out of 102 cases after the 2nd dose of mRNA-1273, 3 (8.8%) out of 34 cases after the 1st dose of BNT126b2 and 2 (5.0%) out of 40 cases after the 2nd dose of BNT126b2. Not only mRNA vaccines but also inactivated whole-virus vaccine, CoronaVac, have been reported to elicit chilblains-like eruption[140]. I experienced 6 cases with chilblains-like lesions after COVID-19 vaccination (**Figure 5**). The characteristics of 6 cases are as follows: (1) All 6 cases (3 females and 3 males) administered mRNA-1273, of whom 5 patients developed chilblains-like lesions after the 1st dose and 1 patient after the 2nd dose, (2) they were young, 5 patients in their 20s and one patient in her early 30s, (3) the onset of symptoms was between 6 to 10 days after vaccination and (4) only 1 out of 5 patients had the same reaction after the 2nd dose. They all had no history of COVID-19 infection and received vaccination in mid-summer of central Japan (daily temperature >25 ℃). Therefore, cold temperature cannot be considered as a causative factor, and adaptive immunity is not responsible for the development of chilblains-like lesions because only 1 out of 5 patients revealed recurrence of chilblains-like lesions after the 2nd dose.

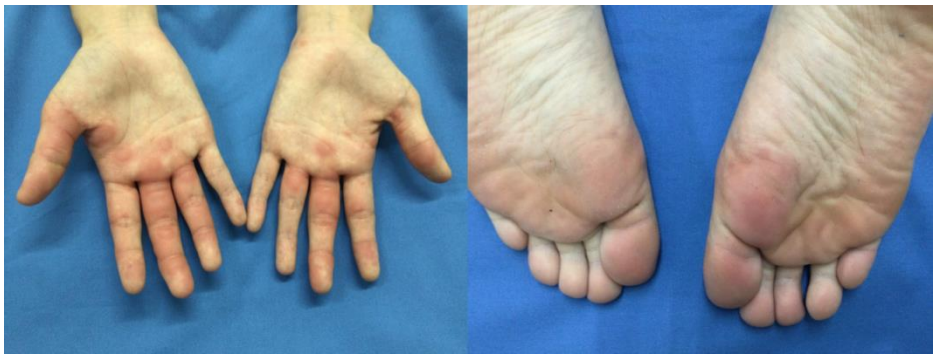


Figure 5. Chilblains-like type (female in her 20s).

The eruption appeared 8 days after the 1st dose of mRNA-1273. Indurated erythema distributed exclusively on the hands and feet with slight pain. Chilblains-like eruption recurred after the 2nd dose.

Reviewing the histological findings of 5 detailed reports[141–145], the common histological changes are dense lymphocytic infiltrates around dermal vessels and eccrine glands, usually without vacuolar degeneration, vasculitis and intravascular thrombi. These histological findings are not different from those of idiopathic chilblains.

Shaikh et al.[146] proposed the etiology of chilblains-like lesions that S protein bound to ACE2 leads to the accumulation of angiotensin II (AngII) by inhibiting the action of ACE2, which results in endothelial damage and dysfunction. Prolonged loss or reduced ACE2 activity by S protein may induce extensive destabilization of the renin-angiotensin system which then triggers vasoconstriction, enhanced inflammation, and/or thrombosis due to unopposed ACE and AngII-mediated effects[147]. Another proposed mechanism is “interferonopathy” that type I INFs induced by vaccine mRNA via through TLR, RIG-I receptors and MDA5 receptors elicit robust immune response and thus can predispose an individual to develop chilblains-like lesions. A case report by Qiao et al.[148] supports the hypothesis ‘interferonopathy’. The patient experienced worsening of chilblains-like lesions after rituximab infusion for seronegative rheumatoid arthritis and Sjögren syndrome because rituximab can activate type I IFN system in individuals with low baseline IFN-response activity[149].

ii) Intertriginous erythema type/Contact dermatitis type

Large erythema distributes in the intertriginous areas such as the neck, axilla, and groin and usually surrounded by multiple small erythematous macules (**Figure 6**).

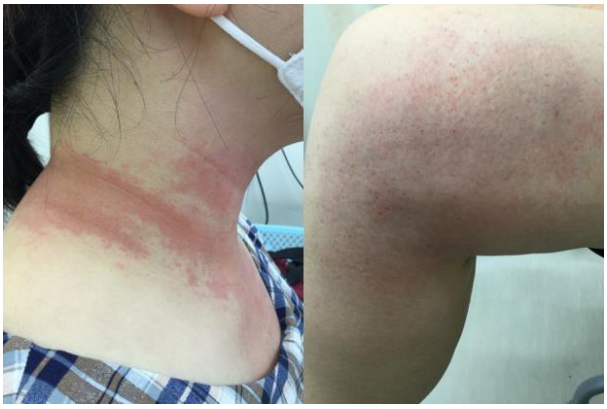


Figure 6. Intertriginous erythema type and contact dermatitis type (female in her 40s).

The eruption appeared 2 days after the 1st dose of mRNA -1273. Diffuse erythema around the neck and on the inner side of knee and thigh. The erythema on the right knee was accompanied with pinhead sized purpura. She administered the 2nd dose uneventful.

Although intertriginous erythema type does not always show symmetrical distribution, this type may correspond to symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)[42,150]. Similar large erythema may be also observed in areas other than intertriginous areas, which may correspond to contact dermatitis type[34]. Both types reveal the histologic changes similar to EM minor (**Figure 7**). External mechanical stimuli such as friction may be one of triggering factors in these conditions.

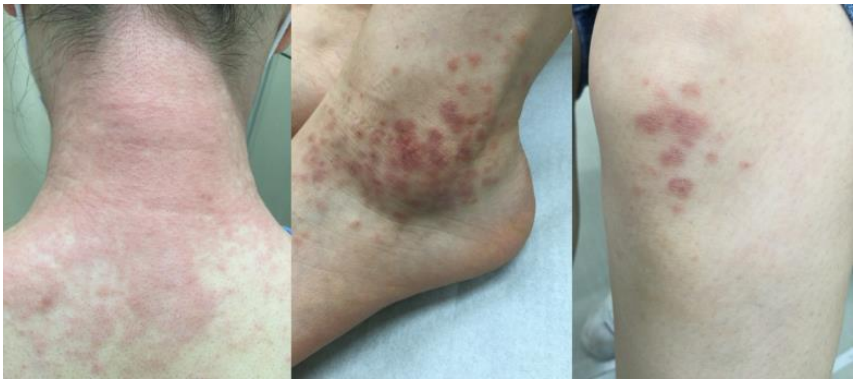


Figure 7. Contact dermatitis type and erythema multiforme type (female in her 20s).

The eruption appeared 21 days after the 1st dose of mRNA -1273. Large erythema was localized on the nape and upper back, and exudative erythema distributed both on the knees and ankles. She administered the 2nd dose uneventful.

iii) Filler reactions

Erythema, painful induration, tissue hardening, and edema develop at the site of hyaluronic acid injection. According to a review article by Tan et al.[39], the average time of onset was 1 day after vaccination, and in 50% of cases it occurred after the 1st vaccination and in 50% after the 2nd vaccination. Similar to other CARs, suspected pathogenic mechanisms include an inflammatory response induced by vaccine-derived S protein, or immune response mediated by overproduction of type I interferon. Another hypothesis is the functional disturbance of ACE2 by S protein[30,147]. Certain types of skin resident cells are replete with ACE2[25]. Membrane-bound and soluble ACE2 catalyzes conversion of proinflammatory AngII to angiotensin 1–7,

which serves a protective function. S protein irreversibly binds to membrane-bound ACE2, initiates membrane fusion and enter the cell, and effectively down-regulates the function of ACE2[147]. AngII up-regulates the expression of monocyte chemoattractant protein type 1, tumor necrosis factor α, interleukin 6, and interleukin 8[151], which act as an initiator of subsequent inflammation. Furthermore, AngII up-regulates the expression of CD44 on the cell surface of lymphocytes, macrophages, fibroblasts and keratinocytes. CD44 is a receptor of low molecular weight hyaluronic acid[152]. The increased expression of CD44 may enhance the infiltration of lymphocytes and macrophage. Munavalli et al.[153] obtained an excellent outcome in patients with filler reaction who administered an angiotensin converting enzyme inhibitor.

The number of individuals receiving hyaluronic acid injections for cosmetic purposes is increasing. From the clinical point of view, we must differentiate filler reactions from erysipelas and cellulitis.

4) Onset of new cutaneous autoimmune diseases and flare-up of pre-existing cutaneous diseases.

The causal relationship between vaccination and the onset of new cutaneous autoimmune diseases and the flare-up of pre-existing cutaneous diseases is ambiguous. According to the review article by Mahmood et al.[40], cutaneous autoimmune diseases include cutaneous small vessel vasculitis, vitiligo, morphea, lichen planus, alopecia areata, and cutaneous lupus erythematosus, and new cutaneous non-autoimmune diseases are Sweet's syndrome, psoriasis, pityriasis lichenoides et varioriformis acuta and radiation recall phenomenon. Flare-up of pre-existing cutaneous diseases include AIBDs[154], psoriasis[155–157], mucosal lichen planus[158], Darier's disease[159], Hailey-Hailey Disease[160], Behçet syndrome[161] and dermatomyositis[162]. Since only a few case reports of each disease except for psoriasis have been reported, the accumulation of cases is essential to clarify the true causal relationship.

4. Relationship between pathophysiology and clinical phenotype

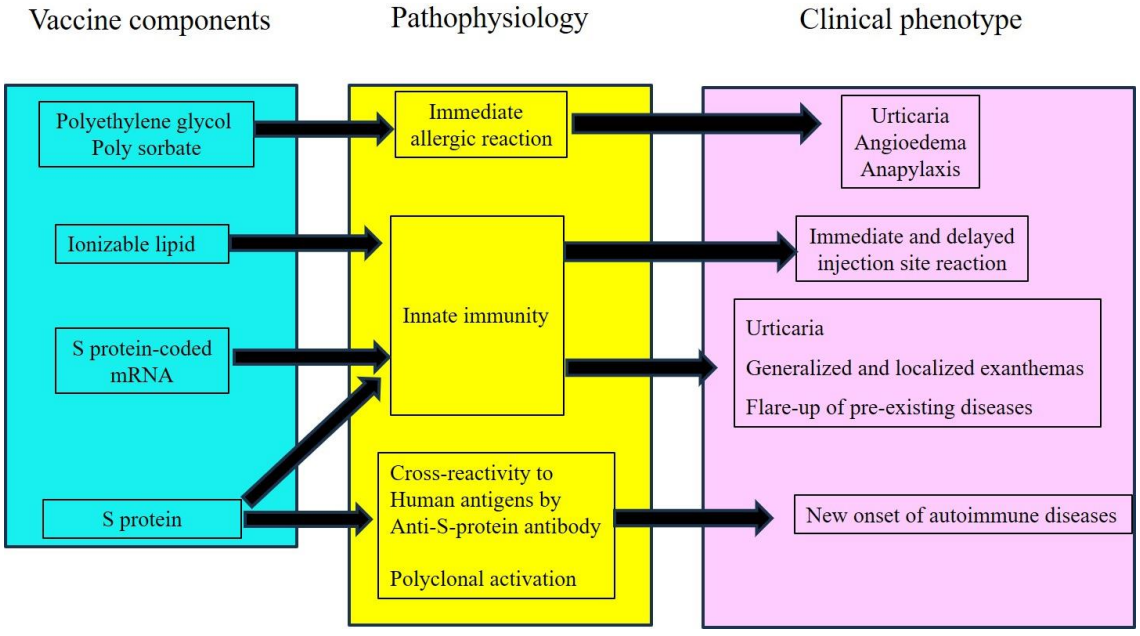


Figure 8. Relationship of vaccine components to pathophysiology and clinical phenotype.

The pathogenesis of CARs cannot be explained by adaptive immunity in patients with the latency period less than 7 days after the 1st dose or no recurrence of the same reaction after the 2nd dose. Therefore, the innate immune system may play a central role in the majority of CARs. Prior to the establishment of adaptive immunity, LNPs are degraded inside and outside of the cells and degraded components act as PAMPs and DAMPs that trigger the innate immune responses. In particular, mRNA and ionizable lipids as DAMPs and S protein as PAMPs are the suspected culprits (**Figure 8**). The clinical phenotype may reflect the intensity of

individual's innate immune response. In addition, the dysregulation of ACE2 by S protein originated from mRNA vaccines might be involved in the development of CARs via through the damage of endothelial cells and other cells due to the accumulation of AngII.

5. Proposed clinical classification of CARs

Reviewing the previous articles, I propose the following classification of CARs.

I. Local injection site reaction and delayed large local reaction

DLLR is sometimes coexistent with II or III.

II. Generalized eruption

morbilliform type, maculopapular type, pityriasis rosea/pityriasis rosea-like type, erythema multiforme type, Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DiSH).

III. Localized eruption distant from injection site

chilblains-like type, intertriginous erythema type, contact dermatitis type, filler reaction.

IV. Others

herpes zoster, autoimmune bullous diseases, vasculitis, onset of a new cutaneous disease, flare-up of a preexisting disease.

6. Conclusion

A prompt introduction of mRNA vaccines has contributed the prevention of severe illness and, at the same time, varying adverse events have been reported including CARs. As the local injection site reactions have been widely recognized by general population, people with local injection site reactions will not visit a hospital anymore. Although the frequency of other CARs is low, patients with rare CARs will visit medical institutions to consult whether or not the eruption is vaccine-related CARs. In order to prepare for the future issues, we should record and accumulate cases with CARs including probable and possible cases and classify them by the clinical phenotype of CARs, the onset time after vaccination, the number of vaccine doses and clinical outcome.

COVID-19 mutates continuously to overcome the existing vaccines. Our steady efforts are indispensable to understand the pathophysiology of CARs and will contribute to the development of novel vaccines with least adverse events and high efficacy.

Ethics approval

The study adhered to the principles outlined in the World Medical Assembly Declaration of Helsinki, as well as national and institutional guidelines, and strictly ensured informed consent from participants.

Conflict of interest

The author declares no conflicts of interest.

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