LETTER TO THE EDITOR

Influence of Covid-19 vaccination on immune-mediated skin diseases

To the Editor,

Covid-19 vaccines are either replication-deficient adenoviral vector vaccines or nanoparticle-formulated RNA encoding the SARS-CoV-2 spike protein that produces the vaccine protein by the inoculated cell.[1] The cutaneous adverse events from these vaccines are recorded in large registries. They include local or delayed injection site reactions, urticarial, maculopapular, morbilliform, or papulovesicular rashes and chilblain-, livedo- and vasculitis-like lesions, swelling at the site of cosmetic fillers, varicella-zoster or herpes simplex flares, and pityriasis rosea-like reactions.[2]

Here, we analyse the effect of Covid-19 vaccination on immune-mediated skin diseases (IMSD) based on 10 patients seen in our outpatient clinics (Table 1) and recent publications. The mean age of our cohort was 51.9 years (range 31–81 years), and six patients were female. IMSD developed with a minimal latency of 3 days after the first vaccination and between 5 hours and 2 weeks after the second vaccination. Seven patients showed an exacerbation of a pre-existing IMSD. Four of them had previously been suffering from chronic plaque psoriasis which so far had been well controlled with topical therapy only. Three of them (patients 1, 2 and 3) developed flares of guttate psoriasis (Fig. 1a, patient 2 according to Table 1). In patient 4, plaque psoriasis evolved into severe generalized pustular psoriasis (GPP) that improved upon treatment with an IL-17A antibody (Fig. 1c,d,e). Psoriasis exacerbations occurred predominantly after the second vaccination and could be controlled by systemic therapy. The current literature reports on 45 cases of plaque or guttate psoriasis and GPP in association with Covid-19 vaccination. Ten of these cases (22.2%) had new-onset psoriasis. As in our patients, psoriasis occurred mainly after the second dose (71%, $n = 32$) and less frequently after both doses (9%, $n = 4$), with a mean latency of 14.4 days and a mean PASI of 11.0 ($n = 29$). The mean age at manifestation was 60.3 years, and 25 (55.6%) of the patients were male. Plaque psoriasis was the most common type (60%, $n = 27$), followed by GPP and guttate psoriasis (9%, $n = 4$ each).

In patients 5 (Fig. 1f) and 6, a previously chronic stable hand eczema was aggravated by acute, dyshidrotic episodes. Bullous pemphigoid (BP) flared up in patient 7 (Fig. 1b) after each vaccination, and newly developed after the first vaccination in patient 9 (Fig. 1h), with a severe relapse after the second and third vaccination. We also identified more than 26 cases of vaccination-related BP in the literature.[3,4] Other newly induced skin diseases in our patients were plaque psoriasis (patient 8) and chilblain-like/gloves and socks-like skin lesions (PPGSS, patient 10, Fig. 1i). Cases of dyshidrotic eczema and PPGSS have previously been observed only after Covid-19 infection but not vaccination.[5]

Also, 5 of the 10 patients had undergone booster immunization. Patient 7 received the same vaccine, patient 9 received another mRNA vaccine and both developed a relapse of BP again. Patients 8 and 10 changed vaccines and IMSD did not recur. Patient 6 received the same vaccine as a booster under systemic therapy of alitretinoin and did not suffer an aggravation (Table 1). Patients 4 and 5 refused booster vaccination.

Based on the cases presented here, we conclude that Covid-19 vaccination may either aggravate or newly induce IMSD. Free intracellular RNA may cause a pronounced activation of innate immune mechanisms by binding to intracellular Pattern Recognition Receptors (PRRs) sensing viral RNA.[6] Activation of innate immunity is required for the development of various immune-mediated skin diseases. The effect on immune-mediated skin diseases is therefore likely due to the vaccination-induced innate immune activation in susceptible individuals. Although a direct relationship is hard to prove, the temporal association, the emerging number of reports, and the fact that the aforementioned manifestations have also been associated with SARS-CoV-2 infection, strongly suggest a causal link. Accordingly, patients with a pre-existing IMSD should be informed about a possible disease exacerbation following vaccination. Treatment of induced exacerbation should be chosen in such a way that it does not interfere with the vaccine efficacy and temporarily avoid drugs such as methotrexate or systemic glucocorticoids. Patients who already are under systemic treatment for IMSD should stop the immunobiological or immunosuppressive treatment 2–4 weeks before and restart it again 2–4 weeks after the vaccine. Despite the risk of IMSD exacerbations, patients must not be discouraged to take the vaccination. Heterologous immunization might increase levels of neutralizing antibodies and prevent IMSD from relapsing after booster vaccination.

Acknowledgement

The patients provided their consent to have their cases reported.

Table 1 Summary of immune-mediated skin diseases in association with SARS-CoV-2 vaccination in 10 patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age, gender	66 y, F	59 y, F	35 y, F	31 y, F	34 y, F	72 y, M	54 y, M	56 y, M	81 y, F	31 y, M
Vaccination- induced IMSD	Guttate psoriasis	Guttate psoriasis	Guttate psoriasis	Generalized pustular psoriasis	Dyshidrotic hand eczema	Dyshidrotic hand eczema	Bullous Pemphigoid	Plaque psoriasis	Bullous Pemphigoid	Chilblain-like/gloves and socks-like skin lesion
Pre-existing SD	Chronic plaque psoriasis	Chronic plaque psoriasis	Chronic plaque psoriasis	Chronic plaque psoriasis	Chronic hand eczema	Chronic hand eczema, atopic dermatitis	Bullous pemphigoid	None	None	None
Duration pre-existing SD	20 y	5 m	17 y	2 m	20 y	67 y	2 m	n/a	n/a	n/a
Treatment of pre-existing SD at presentation	None	TCS	None	None	None	TCS	None	n/a	n/a	n/a
IMSD Related to vaccine dose	1, 2	2	1	1, 2	2	2	1, 2, 3	1	1, 2, 3	2
Latency vaccine-IMSD	3 d	2 w	2 w	1 w, 1 d	2 d	1 w	2 w	2 w	2 w, 5 h, 5 h	3 d
Vaccine (1st, 2nd, 3rd)	1. + 2. BNT162b2 3. n/a	1. + 2. BNT162b2 3. n/a	1. + 2. BNT162b2 3. n/a	1. + 2. BNT162b2 3. n/a (refused)	1. + 2. BNT162b2 3. n/a (refused)	1. ChAdOx1 nCoV-19 2. mRNA-1273 3. BNT162b2	1. + 2. + 3. BNT162b2	1. ChAdOx1 nCoV-19 2. mRNA-1273 3. BNT162b2	1. + 2. BNT162b2 3. ChAdOx1 nCoV-19	1. + 2. mRNA-1273 3. BNT162b2
Clinical presentation	Small, scaly plaques on trunk, PASI 13,5	Small, scaly plaques on trunk and extremities, PASI 16,5	Small, scaly plaques on trunk and extremities, PASI 9,6	Pustules and erythematous plaques PASI 33,0	Small, tense, clear, fluid-filled vesicles	Small, tense, clear, fluid-filled vesicles, fissures	Tense, clear fluid-filled blisters on trunk and extremities	Erythematous scaly plaques on predilection sites, palms and soles; PASI 7,2	(1) one bulla, left knee, (2) widespread blistering eruption, trunk and extremities	Erythematous pruritic patches on hand and feet
Histopathology	Not performed	Not performed	Not performed	Irregular acanthosis, parakeratosis with massive deposition of serum and neutrophils	Not performed	Not performed	Subepidermal blister, dermal oedema, neutro- and eosinophilic infiltrate (DIF: Fig. 1b)	Acanthosis, hypogranulosis, parakeratosis with neutrophilic granulocytes, superficial perivascular lymphocytic and neutrophilic infiltrate	Subepidermal blistering, dermal oedema, eosinophils & neutrophils DIF: Linear C3 and IgG deposition IIF: BP 230: 105.3 U/mL BP 180: 30.02 U/mL*	Perivascular neutrophilic and eosinophilic infiltration in the dermis with leucocytoclasis, interstitial oedema
Treatment/ outcome	TCS, UVB phototherapy, improved with etanercept	TCS, UVB phototherapy, improved with ciclosporin	TCS, UVB phototherapy, improved with dimethyl fumarate	Dimethyl fumarate, Ixekizumab, resolved by week 4	TCS, completely resolved by day 7	TCS, OCS, Topical PUVA, improved with Alitretinoin	Hospitalization, TCS, resolved after 6–8 weeks	Calcipotriol cream, resolved with Ixekizumab	TCS, OCS Improved but ongoing at week 8, persistent severe flare after 3rd dose	TCS, completely resolved by day 7

*F, female; M, male; SD, skin disease; IMSD, immune-mediated skin disease; BP180/230, antibodies against bullous pemphigoid antigen 180/230; DIF/IIF, direct/indirect immunofluorescence analysis; PASI, psoriasis area and severity index; PUVA, psoralen plus UVA treatment; TCS/OCS, topical/oral corticosteroids; d, days; w, weeks; m, months; y, years.

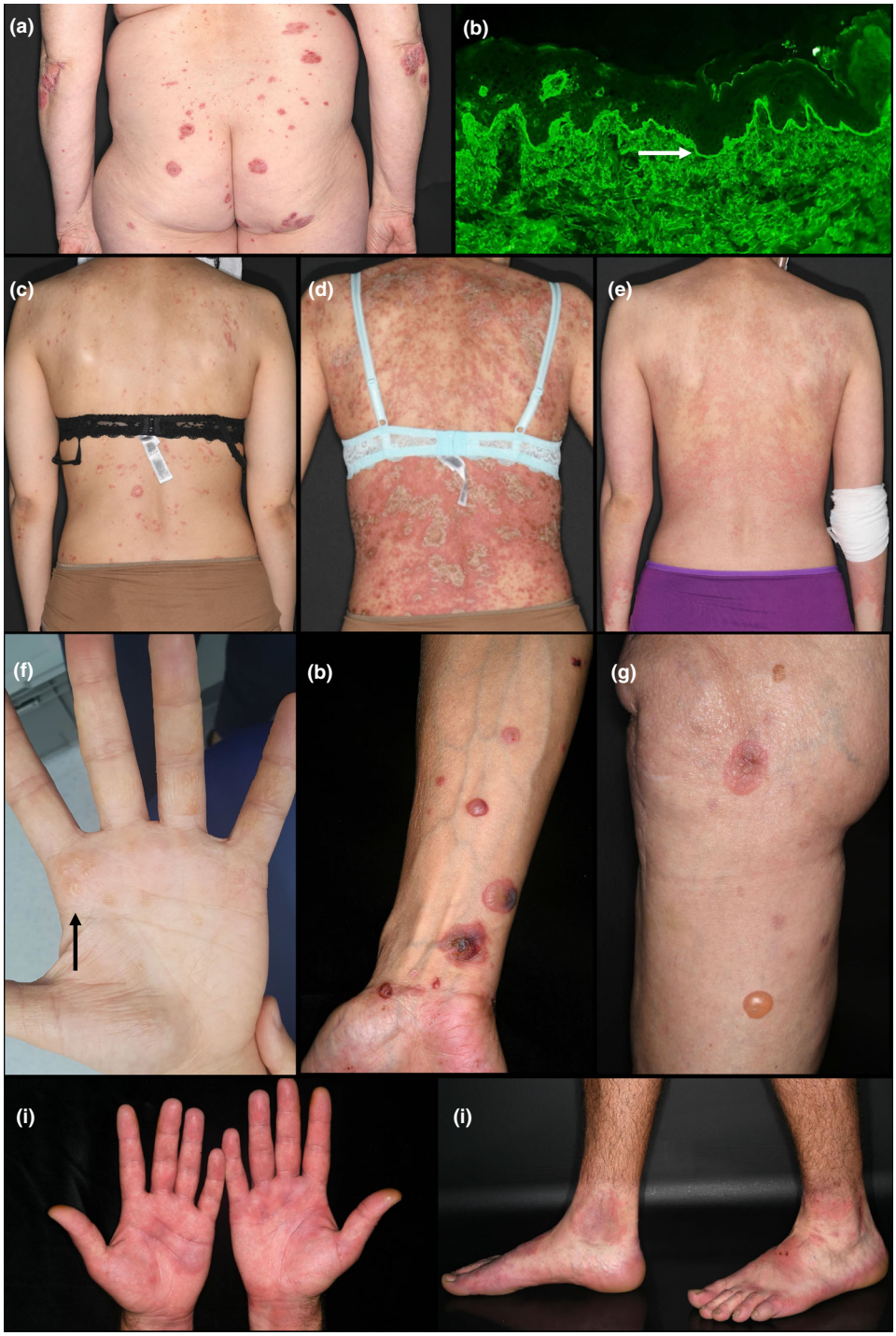

Figure 1 Representation of individual patients from Table 1. (a) Patient 2 with typical manifestation of plaque psoriasis. (b) In Patient 7, BP was confirmed by linear deposition of IgG and C3 along the basal membrane zone in immunohistology and BP180 or BP230 antibody titres of 130.7 U/mL or 1.4 U/mL. (c–e) Patient 4 had chronic plaque psoriasis (c) that developed into a first GPP episode 5 d after the first vaccination (d) followed by severe aggravation 7 d after the second dose of BNT162b2 which was finally resolved by treatment with an IL-17A antibody (ixekizumab) (e). (f) Patient 5 developed a pruritic eruption of small vesicles (arrow) on both palms. (h) Patient 9 presented with tense blisters (arrow) on the trunk and extremities diagnosed as de-novo BP. (i) In Patient 10, examination revealed erythematous pruritic plaques on both hands and feet resembling purpuric gloves and socks syndrome.

Conflicts of interest

None declared.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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