


REVIEW ARTICLE

Cutaneous findings following COVID-19 vaccination: review of world literature and own experience

T. Gambichler,^{1,2,*}  S. Boms,² L. Susok,¹ H. Dickel,¹ C. Finis,¹ N. Abu Rached,¹ M. Barras,¹ M. Stücker,¹ D. Kasakovski^{3,4}

¹Department of Dermatology, Ruhr-University Bochum, Bochum, Germany

²Department of Dermatology, Christian Hospital Unna, Unna, Germany

³European Center for Angioscience (ECAS), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

⁴Division of Vascular Oncology and Metastasis, German Cancer Research Center Heidelberg (DKFZ-ZMBH Alliance), Heidelberg, Germany

*Correspondence: T. Gambichler. E-mail: t.gambichler@klinikum-bochum.de

Linked Commentary: P. Gisondi *et al.* *J Eur Acad Dermatol Venereol* 2022; **36**: 165–166. <https://doi.org/10.1111/jdv.17854>.

Abstract

There is growing evidence that not only the novel coronavirus disease (COVID-19) but also the COVID-19 vaccines can cause a variety of skin reactions. In this review article, we provide a brief overview on cutaneous findings that have been observed since the emerging mass COVID-19 vaccination campaigns all over the world. Unspecific injection-site reactions very early occurring after the vaccination are most frequent. Type I hypersensitivity reactions (e.g. urticaria, angio-oedema and anaphylaxis) likely due to allergy to ingredients may rarely occur but can be severe. Type IV hypersensitivity reactions may be observed, including delayed large local skin lesions (“COVID arm”), inflammatory reactions in dermal filler or previous radiation sites or even old BCG scars, and more commonly morbilliform and erythema multiforme-like rashes. Autoimmune-mediated skin findings after COVID-19 vaccination include leucocytoclastic vasculitis, lupus erythematosus and immune thrombocytopenia. Functional angiopathies (chilblain-like lesions, erythromelalgia) may also be observed. Pityriasis rosea-like rashes and reactivation of herpes zoster have also been reported after COVID-19 vaccination. In conclusion, there are numerous cutaneous reaction patterns that may occur following COVID-19 vaccination, whereby many of these skin findings are of immunological/autoimmunological nature. Importantly, molecular mimicry exists between SARS-CoV-2 (e.g. the spike-protein sequences used to design the vaccines) and human components and may thus explain some COVID-19 pathologies as well as adverse skin reactions to COVID-19 vaccinations.

Received: 29 June 2021; Accepted: 29 September 2021

Conflict of interest

The authors declare no conflict of interest.

Funding sources

This research received no external funding.

Introduction

In the end of December 2019, a novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China. As a result of the very fast spread of the disease throughout the globe, the World Health Organization (WHO) declared COVID-19 a pandemic on March 2020. Via the SARS-CoV-2 spike protein (SP) at the virus surface, the pathogen is capable to enter human cells by binding to the angiotensin-converting enzyme-2 (ACE-2). Subunits (S1, S2) of the trimeric SP are involved in receptor binding as well as membrane fusion activity. S1 includes the receptor-binding domain finally binding to the ACE-2 receptor. Antibodies particularly binding to the receptor-binding domain

and the N-terminal domain of SP can prevent virus attachment to cells finally resulting in neutralization of the pathogen. Hence, neutralizing antibodies are probably the main players in protection from the virus. Apart from antibody formation, natural infection with SARS-CoV-2 also activates a T helper lymphocyte-1 pronounced immune response with SP-specific CD4+ lymphocytes. A significant variability in the magnitude of adaptive immune responses has been observed in patients with COVID-19. Memory B cell as well as CD4+ lymphocyte responses can be detected in over 90% of patients up to 6 months after infection. However, SARS-CoV-2-specific and neutralizing antibodies decrease over about 8 months, raising concerns for long-term protection and herd immunity post

infection.^{1–5} According to the WHO COVID-19 dashboard accessed on 1 June 2021, there have been more than 170 million confirmed cases of COVID-19, including almost 3.6 million deaths.⁶

Since December 2020, huge vaccination campaigns have been introduced in Europe, using first the mRNA vaccines *Comirnaty*[®] (Pfizer/BioNTech; BNT162b2) and *Moderna*[®] (Moderna; mRNA-1273) and then also the viral vector-based vaccine *Vaxzevira*[®] (AstraZeneca; AZD1222) which all have recently been approved by the European Medicines Agency. Moreover, the vector-based vaccine *Janssen COVID-19 vaccine*[®] (Johnson & Johnson; Ad26.COV2.S) has now also been approved for use in Europe. However, there are other COVID-19 vaccines, including *Convidecia*[®] (CanSino Biologics), *Sputnik V*[®] (Gamaleya Research Institute), *CoronaVac*[®] (Sinovac), which have been approved by at least one country.^{1–5} The vaccine platform of aforementioned vaccines includes mRNA, non-replicating virus vector or inactivated virus material. All these vaccines have to be administered by intramuscular injection. Most vaccines need two doses, except for *Janssen COVID-19 vaccine*[®] and *Convidecia*[®]. End of May 2021, over 1.5 billion vaccine doses have been administered worldwide. Hence, there is also increasing real-world evidence on adverse events associated with the use of the new COVID-19 vaccines.^{1–5} General symptoms that have also frequently been observed after the use of other vaccines include fever, headache, fatigue, chills, muscle pain, diarrhoea and local injection-site reactions. These usually transient AEs are very frequently reported after COVID-19 vaccinations as well. Similar to the natural COVID-19 infection (e.g. chilblain-like lesions, morbilliform rashes and vasculitis) SARS-CoV-2 vaccines appear to have also the potential to induce a broad spectrum of cutaneous adverse events.^{1–5} In this review article,^{7–67} we give a brief overview on cutaneous findings that have been observed since the COVID-19 mass vaccination campaigns have started all over the world and add several case snippets observed in our hospitals.

Early unspecific injection-site reactions

According to data obtained from large clinical trials, local injection-site reactions following minutes to few days after COVID-19 vaccinations include erythema (20%), oedema (15%), induration (25%), pruritus (35%) and pain (88%).⁴³ Hence, these cutaneous adverse events are very frequent and have been associated with prior vaccines as well. Local injection-site reactions are harmless and largely resolve within few days. Notably, these reactions are more commonly observed in individuals younger than 60 years.^{8,10,15,42}

Type I and type IV hypersensitivity reactions

Type I (immediate)

Immunoglobulin E-mediated (type I) allergic reactions to antiviral vaccines are usually not caused by the viral antigen but

by vaccine ingredients, such as egg proteins, gelatine and formaldehyde. In the case of COVID-19 vaccines, polyethylene glycols (PEGs) and cross-reactive polysorbate 80 have been blamed to be the causal factors for immediate hypersensitive/allergic reactions, such as urticaria, angio-oedema and even anaphylaxis.^{14,41} Urticarial lesions may be limited to the injection site or affect the integument in a disseminated or even generalized pattern. *Comirnaty*[®] and *Moderna*[®], for example, have only rarely been associated with anaphylaxis with frequency rates ranging from 2.5 to 11.1 per million.³⁹ As proposed in a recent review article,¹³ the criteria for allergy testing prior to vaccination are severe type I allergies (e.g. urticaria, angio-oedema and anaphylaxis) to the first vaccination dosage and/or to ingredients of the vaccine, and a history for allergies to PEGs and polysorbates. In subjects with positive tests, other non-mRNA vaccines may be used in these cases, if available and not contraindicated for other reasons.¹³

Type IV (delayed)

Delayed large local hypersensitivity reactions – also known as “COVID arm” – may occur after about 1 week and include erythema, induration and pain. These cutaneous reactions are relatively rare and have almost exclusively been reported in patients with mRNA vaccinations. Johnston *et al.*¹⁰ recently demonstrated that the clinical as well as histopathological findings in localized injection-site reactions to the *Moderna*[®] vaccine are consistent with a delayed hypersensitivity reaction, which may reoccur faster after the second vaccine but usually is harmless and self-limited. In contrast to the immediate hypersensitive/allergic reactions, the “COVID arm” should not be a contraindication for subsequent vaccination.^{10,11,16,23,25,31}

Another recently described local skin reaction following *Comirnaty*[®] and *Moderna*[®] vaccination was reported by Lopatynsky-Reyes *et al.*⁹ In two adults, they observed about 1 day after the second vaccination local skin inflammation in sites of previous Bacillus Calmette-Guérin (BCG) vaccination scars. The inflammatory process in the old BCG scars was also accompanied by shortly transient systemic symptoms, such as headache, malaise, myalgia and arthralgia.⁹ One can only speculate that the vaccinations induced a delayed type hypersensitivity reaction in the BCG scars of these patients. Moreover, Soyfer *et al.*¹⁸ reported two cancer patients who experienced a radiation-recall dermatitis in previously irradiated skin sites on the back following *Comirnaty*[®] vaccination. The authors speculated that the enhanced sensitivity of stem cells in the irradiated field may lead to an acute reaction to subsequent agents or idiosyncratic hypersensitivity reactions.¹⁸ Correspondingly, Steber *et al.*⁴³ observed a *Moderna*[®]-induced radiation-recall pneumonitis limited to a previously irradiated upper lung segment.

COVID-19 vaccine-induced delayed-type hypersensitivity reactions (e.g. facial oedema, erythema) have also been observed in individuals who had used dermal fillers for cosmetic purposes.

Even though it is well known that dermal fillers (e.g. hyaluronic acid) rarely cause delayed-type hypersensitivity reactions (<1%), the time setting in these cases was highly suggestive for a COVID-19 vaccine-induced inflammatory complication – a phenomenon that has also been reported after other vaccines, such as influenza. Moreover, inflammatory dermal filler reactions have also been observed in patients with confirmed COVID-19 infection. In the case of COVID-19 vaccine-induced delayed-type hypersensitivity reactions, ACE blockers (e.g. lisinopril 10 mg for 3–5 days) appear to be a highly effective treatment approach and should be preferred over systemic corticosteroids that might affect the vaccine efficacy.^{11,16,17,23,25,28,31}

Recently, McMahon *et al.*²⁸ reported four cases of mRNA vaccine-induced erythema multiforme (EM) which is considered a delayed hypersensitivity reaction most frequently to viral agents, such as herpes simplex virus. Indeed, there are previous reports of EM occurring after the application of other vaccines.^{28,36,45} Similar to several cases of COVID-19 infection, anti-SARS-CoV-2 vaccines may also trigger itchy maculopapular, morbilliform rashes resembling common drug eruption or infection-associated exanthemas.^{35,36} Most rashes were observed a few days after vaccination and cleared within a week. Histological investigation of cases with confirmed COVID-19 infection revealed spongiotic epidermis and slight dermal perivascular lymphocytic infiltrates, indicating an immune-mediated mode of action rather than a direct effect of SARS-CoV-2.⁴² Indeed, type IV systemic allergic contact dermatitis may sporadically occur as vaccine ingredients, such as PEGs and polysorbates, are not only potential type I but also type IV sensitizers.²⁷ The aforementioned postvaccine skin changes are usually harmless and self-limited. However, a case of severe cutaneous drug reaction likely consistent with a diagnosis of acute generalized exanthematous pustulosis following the *Janssen COVID-19 vaccine*[®] was recently reported by Lospinoso *et al.*²²

Autoimmune-mediated reactions

Infections as well as vaccines can occasionally cause new-onset or flare of autoimmune-mediated diseases. The SP of SARS-CoV-2 vaccine shares genetic similarities with human proteins being an important factor that can trigger autoimmune diseases after vaccination due to molecular mimicry. However, autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) is considered a postvaccination phenomenon which may occur after exposure to vaccine adjuvants that are designed to enhance the immune response.^{24,36,51} As recently observed in five patients,^{24,51} SARS-CoV-2 vaccination (*CoronaVac*[®], *Comirnaty*[®]) can lead to subacute thyroiditis or Graves' disease as a phenomenon of ASIA syndrome which frequently includes several autoimmune endocrinopathies. So far, there are very limited data regarding autoimmune skin diseases following SARS-CoV-2 vaccines (Fig. 1), even though other vaccines have previously been reported to be potential triggers for conditions, such as

lupus erythematosus (LE), bullous pemphigoid, leucocytoclastic vasculitis, vitiligo, and alopecia areata.^{36,66,67}

We recently treated a patient with an EM-like rash occurring after the first *Comirnaty*[®] vaccination.⁴⁷ However, immunological findings included elevated antinuclear autoantibodies (speckled pattern) as well as positive anti-Ro/SSA and anti-La/SSB antibodies. Histology showed a vacuolar interface dermatitis, including lymphocytic infiltrates along the dermo-epidermal junction associated with dyskeratoses of basal keratinocytes. Together, these findings were consistent with a diagnosis of Rowell's syndrome – a very uncommon subtype of LE.⁴⁷ Accordingly, Niebel *et al.*⁴⁶ observed a patient with subacute cutaneous LE in long remission who experienced a flare of her disease timely after her first *Comirnaty*[®] vaccination.

As illustrated in Figures 2 and 3, different clinical presentations of new onset or re-activation of leucocytoclastic vasculitis may also be observed following COVID-19 vaccinations.^{7,31} Cohen *et al.*³¹ reported a female patient with a history of leucocytoclastic vasculitis which was in complete remission for 2 years. Twenty-four hours after her first *Comirnaty*[®] vaccination, she experienced a flare of leucocytoclastic vasculitis on her lower legs. Two days after the second *Comirnaty*[®] vaccination the vasculitis re-exacerbated with disseminated purpuric papules on her legs and lower trunk.³¹ Akinosoglou *et al.*³³ reported a healthcare worker presenting with an annular rash on her elbows 2 days following the first *Comirnaty*[®] vaccination. Skin biopsy showed a small vessel vasculitis. The lesions resolved spontaneously after few days.³³ Even though not always

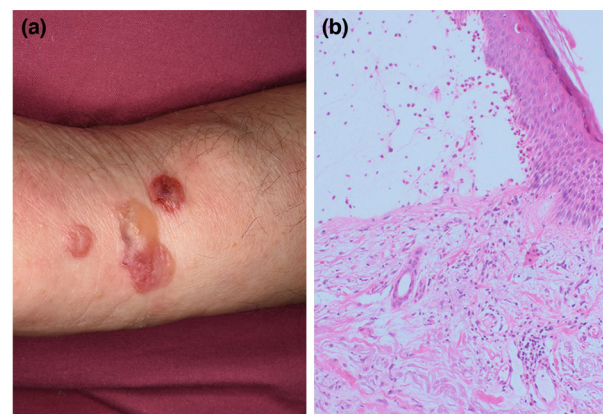


Figure 1 An old man had a history of intense itch and erythematous skin lesions after his first *Comirnaty*[®] vaccination. After the patients' second *Comirnaty*[®] vaccination, erythematous-bullous skin lesions (a) spread over his extremities and back. Serology, routine histopathology (b) as well as direct and indirect immunofluorescence confirmed the diagnosis of bullous pemphigoid that was most likely triggered by the vaccine. Under medium-dose corticosteroids the itch and skin lesions gradually resolved.

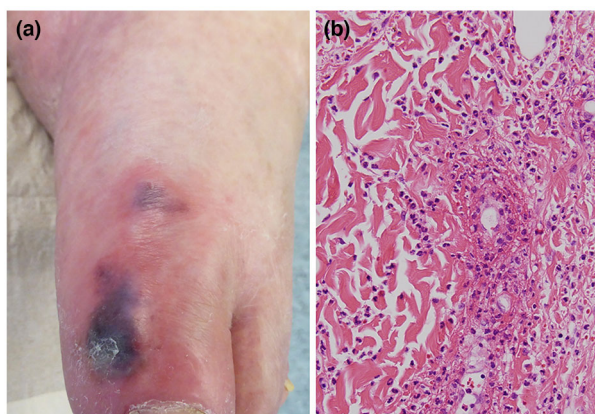


Figure 2 Chilblain-like lesions (a) on the left big toe of a patient who had received his first shot *Comirnaty*[®] about 2 weeks ago. One week ago, the same skin findings were noticed on his right big toe. Histopathology was consistent with a leucocytoclastic vasculitis (b). Complete work-up (e.g. infection serologies, antibody tests, X-ray, ultrasound) did not reveal relevant pathologies. Since there was no evidence for other causes, we made a diagnosis of vaccine-induced leucocytoclastic vasculitis. The skin lesions gradually resolved after tapered systemic corticosteroids.

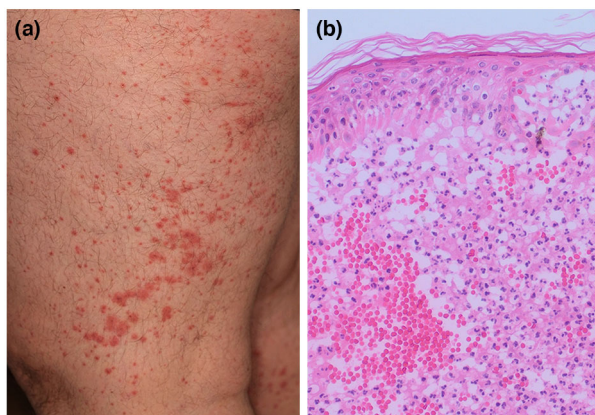


Figure 3 Widespread purpuric rash on the left thigh (a) of an elderly male which had developed a few days after his first *Comirnaty*[®]. He had no history for previous infections or new medication. Histopathology was consistent with a leucocytoclastic vasculitis (b). Complete work-up (e.g. infection serologies, antibody tests, X-ray, ultrasound) did not reveal relevant pathologies. A diagnosis of vaccine-induced leucocytoclastic vasculitis was made. The skin lesions gradually resolved after tapered systemic corticosteroids.

histopathologically confirmed, purpuric/petechial skin rashes after COVID-19 vaccination have also been reported by others as well.^{8,29} However, COVID-19 vaccine-induced purpuric rashes are not always due to leucocytoclastic vasculitis (Fig. 4).

At the end of February 2021, a novel clinical syndrome characterized by cerebral venous sinus thrombosis and/or splanchnic

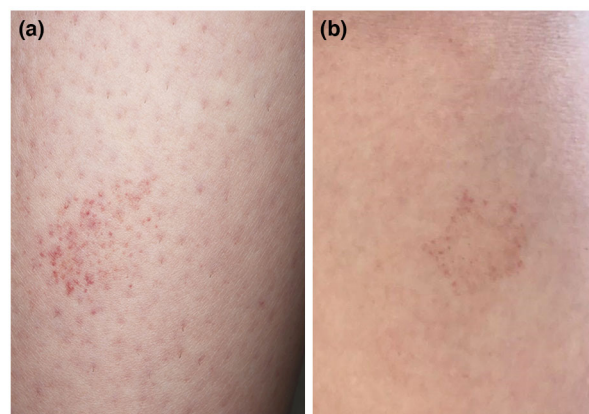


Figure 4 A young healthy female had a history of an asymptomatic petechial rash developing 1 day after her first *Comirnaty*[®] vaccination on her arms and legs. The discrete lesions spontaneously regressed within a few weeks. Six weeks later after her second *Comirnaty*[®] shot she presented with the same petechial macules, in part with bizarre annular configuration (a); histopathology revealed slight perivascular lymphocytic infiltrates, mild vacuolar changes with occasional necrotic keratinocytes and erythrocyte extravasates (b). On laboratory investigations, her thrombocytes and other coagulation parameters were within the normal range. Clinically and histopathologically, a vaccine-induced Majocchi's disease-like rash was diagnosed. Again, her skin lesions slowly resolved without treatment after few weeks.

venous thrombosis combined with thrombocytopenia was observed in several patients following virus vector-based COVID-19 vaccinations. The clinical findings strikingly resembled those of heparin-induced thrombocytopenia (HIT), except for absence of prior heparin exposure and sites of thrombotic manifestations. Hence, the condition was named vaccine-induced thrombotic thrombocytopenia or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) in some European countries. Conversely, in mRNA vaccines, VIPIT has not been observed so far. HIT as well as VIPIT are characterized by high-titre platelet factor 4 (PF4) autoantibodies and predominantly thrombotic events – purpuric skin lesions may be more infrequently observed in cases associated with very severe thrombocytopenia. However, purpura and bleeding events (e.g. nasal, oral, gastrointestinal, genital, central nervous) are much more common in patients with vaccine-induced immune thrombocytopenia (VIIT) or thrombocytopenic purpura (Fig. 5).^{19,32,33,38,54–59,61}

Indeed, VIIT was previously observed in patients with vaccinations against measles-mumps-rubella, hepatitis A and B, and varicella.³⁶ However, multiple cases including fatal ones have also been reported after COVID-19 vaccination.^{26,38,55,61} With respect to the Vaccine Adverse Event Reporting System (VAERS), however, fewer thrombocytopenia cases were reported than expected when considering the background rate of immune

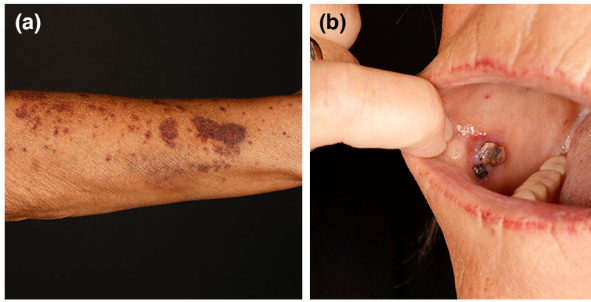


Figure 5 Showing a female patient with a 2-week history of widespread dry purpuric skin lesions on her extremities (a). A few days prior to presentation in our hospital, she had a history for spontaneous gastrointestinal, genital, nasal and oral bleedings (b). Notably, about 2 weeks before the manifestation of purpuric skin lesions she had her first *Vaxzevira*[®] shot. She was otherwise well-being and had no new medications. On presentation, her thrombocytes counted 1000/ μ L (150.000–400.000/ μ L) and the immature thrombocyte fraction was 0.0% (1.1–6.1). A complete work-up did not reveal potential causes for the thrombocytopenic purpura observed, except for her COVID-19 vaccination. A diagnosis of vaccine-induced immune thrombocytopenic purpura was made. Under high-dose corticosteroids her thrombocytopenia gradually recovered.

thrombocytopenia and the number of subjects vaccinated.³⁸ Nevertheless, the temporal context and the fact that the patients reported in the literature were otherwise healthy are suggestive for vaccine-induced thrombopenic complications.³⁸ Moreover, COVID-19 infection is also frequently associated with immune thrombocytopenic purpura. Unlike with VIPIT patients, VIIP has also been observed in patients who received mRNA vaccines. Again, one of the suggested mechanisms by which COVID-19 infection as well as the COVID-19 vaccination may induce autoimmune responses against platelets is the presence of molecular mimicry.^{32,33,36} Another cause for postvaccine cutaneous haemorrhages may also be acquired haemophilia (AHA) also known as an autoimmune-mediated condition. In fact, Radwi and Farsi⁵² reported a patient who developed bruises on his arms and legs shortly after *Comirnaty*[®] vaccination. He had a severely prolonged activated partial thromboplastin time, elevated Willebrand antigen/function, FVIII level at 1% and FVIII inhibitor titre at 80 Bethesda units, which were consistent with the diagnosis of AHA. After 4-week prednisone, his blood parameters normalized and bruises resolved.⁵²

Functional angiopathies

Chilblains-like or perniosis-like lesions (e.g. COVID toes) belong to the very first skin findings that have been observed in COVID-19-infected individuals.^{20,53} In some of COVID-19 confirmed patients, SARS-CoV-2 could also be detected in endothelial cells of chilblains-like lesions.⁶⁰ Due to conflicting evidence,

however, a causal relationship between COVID-19 infection and chilblain-like lesions has not been established.²⁰ Chilblains-like lesions are usually asymptomatic, bluish-reddish acral macules which may worsen after cold exposure. To date, only few COVID-19 vaccine-induced chilblains-like lesions have been reported. Histopathology of these vaccine-induced acral lesions was consistent a diagnosis of chilblains. However, similar to SARS-CoV-2 infection, it remains unclear whether there is a real causal relationship between chilblain-like lesions and the vaccine.^{8,10,15,28,42} Furthermore, McMahon *et al.*²⁸ observed a case of mRNA vaccine-induced erythromelalgia – an uncommon condition that has been noted in response to other vaccines as well, such as those for influenza and hepatitis B.

Reactivation of other viral conditions

Several pityriasis rosea (PR) and PR-like eruptions have been reported during COVID-19 infection.²⁰ Drago *et al.*⁴⁹ recently suggested that SARS-CoV-2 may have played a trans-activating role, triggering human herpes virus 6 and 7 reactivation and, consequently, causing cutaneous PR manifestations. Indeed, immune dysregulation may be induced by vaccine-specific infectious particles resulting in human herpes virus reactivation and typical PR rash, akin to recently observed herpes zoster virus reactivations following COVID-19 vaccinations.^{27,63,64} Alternatively, vaccines may result in a delayed hypersensitivity response, similar to medication-induced PR-like rashes.²⁷

Herpes zoster following COVID-19 vaccination has been reported not only in case series but also documented in the VAERS of the Center of Disease Control. Over 1000 patients with mRNA vaccine-induced herpes zoster have been documented in VAERS, whereby most patients were over the age of 60 years.^{8,10,15,21,39,42,62–65} However, we have to be aware that the aforementioned associations could be coincidental, since herpes zoster, in particular in the elderly, is a very frequent condition. Many of the reported patients also had other possible reasons for herpes zoster exacerbation, including malignancies or immunosuppressive treatments.

Conclusions

In this brief review article, we demonstrated that unspecific injection-site reactions are most frequent following COVID-19 vaccination. Moreover, different type I and type hypersensitivity reactions, autoimmune-mediated skin findings, functional angiopathies and (re)activation of viral conditions may be associated with COVID-19 vaccination. Hence, there are numerous cutaneous reaction patterns that may occur following COVID-19 vaccination, whereby many of these skin findings are of immunological/autoimmunological nature (Fig. 6).^{7–67} It has been demonstrated that molecular mimicry exists between SARS-CoV-2 and human components (e.g. the spike-protein sequences used to design the vaccines) and may thus explain some COVID-19 pathologies as well adverse reactions to

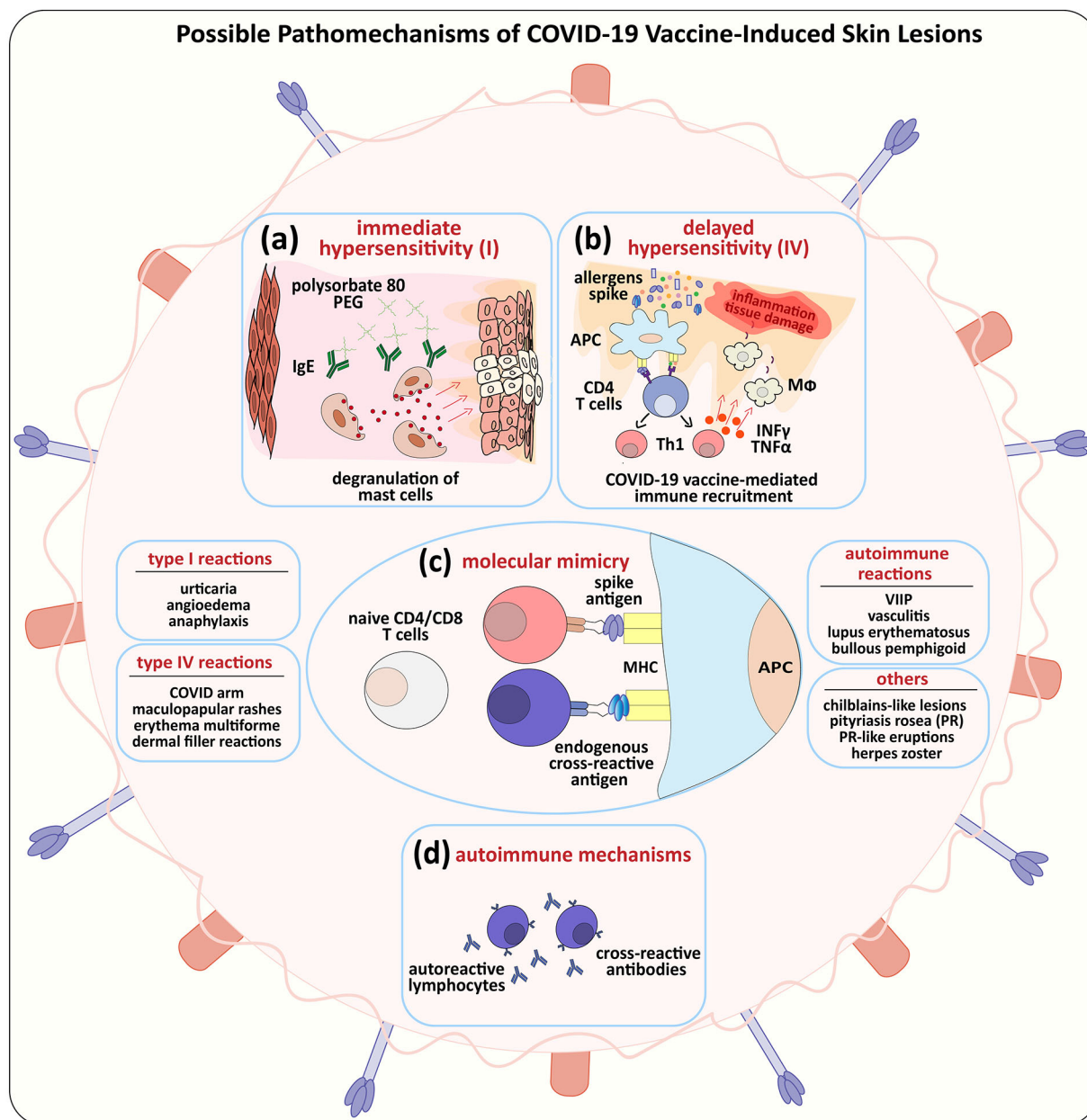


Figure 6 Illustrating possible pathomechanisms of cutaneous findings following COVID-19 vaccination. (a) Immediate (type I) allergic reactions to COVID-19-vaccine components, polyethylene glycols (PEG) and cross-reactive polysorbate 80, can lead to mast cell degranulation causing urticaria, angio-oedema and anaphylaxis. (b) In presence of secondary allergens, increased COVID-19 vaccine-mediated immune recruitment may manifest as delayed (type IV) allergic reactions, such as “COVID arm”, maculopapular rashes, erythema multiforme and dermal filler reactions. (c) Mechanism of molecular mimicry caused by genetic similarities of SARS-COV-2 spike protein components to endogenous cross-reactive human antigens. (d) Generation of autoreactive lymphocytes and cross-reactive antibodies due to molecular mimicry leading to autoimmune reactions, such as vaccine-induced immune thrombocytopenia (VITP) lupus erythematosus, vasculitis and bullous pemphigoid. Other COVID-19 vaccine-related observations include functional angiopathies such as chilblains-like lesions and re-activation of viral conditions such as pityriasis rosea (PR), PR-like eruptions and herpes zoster [IgE = immunoglobulin E, APC = antigen-presenting cells, INF γ = interferon γ , TNF α = tumour necrosis factor α , Th1 = type 1 T helper cells, MΦ = macrophages, MHC = major histocompatibility complex].

COVID-19 vaccinations.⁶⁸ However, there are also uncertainties with regard to the question whether some of the previously reported skin complications after COVID-19 vaccination were really true or just coincident without causality. Even though the temporal relationship as well as experience with other vaccines may be suggestive for causality, the high prevalence of some conditions (e.g. herpes zoster) and the very large number of cases receiving COVID-19 vaccinations during the last months may result in bias including many cases in which the skin manifestations were not caused by the COVID-19 vaccination but developed spontaneously despite the temporal relationship. Moreover, Tan *et al.*⁶⁹ recently demonstrated a significant discordance between morphological descriptions of cutaneous findings among countries. In line with Kantor,⁷⁰ we are afraid that essentially all reports on cutaneous manifestations associated with COVID-19 may be biased, also including data obtained from large registries (e.g. VAERS) in which not only dermatologists report their patients' skin findings.

Together, the skin findings observed after COVID-19 vaccination are widely self-limited and most frequently included common local injection-site reactions which have also been observed in the clinical trials of COVID-19 vaccines as well as after the application of other virus vaccines. Similar to other vaccines, more severe but very rare reactions such as anaphylaxis have been reported but must be ascribed to common ingredients and not the vaccine itself. Since the COVID-19 mass vaccination campaigns have started all over the world, great attention was paid to safety concerns, particularly because of the rashly introduction of novel vaccines, including the mRNA method. Even though further research is necessary to better assess the true prevalence and preventive measures for the above-discussed COVID-19 vaccination reactions, we and other authors want to reassure our patients of the overall compelling safety profiles of the novel COVID-19 vaccines not only perceived from the dermatology viewpoint.³⁹

Acknowledgement

The patients in this manuscript have given written informed consent to the publication of their case details. Open access funding enabled and organized by ProjektDEAL.

Author contributions

T.G. conceived, designed and wrote this review with input (e.g. case snippets, intellectual input, artwork, expertise) from all other authors who contributed to this manuscript. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Derived data supporting the findings of this study are available from the corresponding author on reasonable request.

References

- 1 Kurup D, Schnell MJ. SARS-CoV-2 vaccines - the biggest medical research project of the 21st century. *Curr Opin Virol* 2021; **49**: 52–57.
- 2 Carneiro DC, Sousa JD, Monteiro-Cunha JP. The COVID-19 vaccine development: a pandemic paradigm. *Virus Res* 2021; **17**: 198454.
- 3 Vasireddy D, Atluri P, Malayala SV, Vanaparthi R, Mohan G. Review of COVID-19 Vaccines Approved in the United States of America for Emergency Use. *J Clin Med Res* 2021; **13**: 204–213.
- 4 Li Y, Tenchov R, Smoot J, Liu C, Watkins S, Zhou Q. A comprehensive review of the global efforts on COVID-19 vaccine development. *ACS Central Sci* 2021; **7**: 512–533.
- 5 Blumental S, Debré P. Challenges and issues of anti-SARS-CoV-2 vaccines. *Front Med (Lausanne)* 2021; **8**: 664179.
- 6 World Health Organization Coronavirus Disease (COVID-19) Dashboard. 2021. <https://covid19.who.int/>. [Accessed on 1 June 2021] [Google Scholar] This is the link to the newest information of the WHO on the current cases of Covid-19 and vaccine information.
- 7 Mazzatenta C, Piccolo V, Pace G, Romano I, Argenziano G, Bassi A. Purpuric lesions on the eyelids developed after BNT162b2 mRNA COVID-19 vaccine: another piece of SARS-CoV-2 skin puzzle? *J Eur Acad Dermatol Venereol* 2021; **35**: e543–e545.
- 8 Cebeci F, Kartal İ. Petechial skin rash associated with CoronaVac vaccination: first cutaneous side effect report before phase 3 results. *Eur J Hosp Pharm* 2021; **24**: 2021–002794.
- 9 Lopatynsky-Reyes EZ, Acosta-Lazo H, Ulloa-Gutierrez R, Ávila-Aguero ML, Chacon-Cruz E. BCG scar local skin inflammation as a novel reaction following mRNA COVID-19 vaccines in Two International Healthcare Workers. *Cureus* 2021; **13**: e14453.
- 10 Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the moderna COVID-19 vaccine: a case series. *JAMA Dermatol* 2021; **12**: e211214.
- 11 Tammaro A, Adebajo GAR, Magri F, Parisella FR, Chello C, De Marco G. Local skin reaction to the AZD1222 vaccine in a patient who survived COVID-19. *J Cosmet Dermatol* 2021; **20**: 1965–1966.
- 12 Ferretti F, Cannatelli R, Benucci M *et al.* How to manage COVID-19 vaccination in immune-mediated inflammatory diseases: an expert opinion by IMIDs Study Group. *Front Immunol* 2021; **15**: 656362.
- 13 Erdeljc TV. Anaphylaxis associated with the mRNA COVID-19 vaccines: Approach to allergy investigation. *Clin Immunol* 2021; **227**: 108748.
- 14 Risma KA, Edwards KM, Hummell DS *et al.* Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. *J Allergy Clin Immunol* 2021; **147**: 2075–2082.
- 15 Alpalhão M, Maia-Silva J, Filipe P. Severe acute respiratory syndrome coronavirus 2 vaccines and cutaneous adverse reactions: a review. *Dermatitis* 2021; **32**: 133–139.
- 16 Fernandez-Nieto D, Hammerle J, Fernandez-Escribano M, *et al.* Skin manifestations of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers. 'COVID-arm': a clinical and histological characterization. *J Eur Acad Dermatol Venereol* 2021; **357**: e425.
- 17 Munavalli GG, Knutsen-Larson S, Lupo MP, Geronemus RG. Oral angiotensin-converting enzyme inhibitors for treatment of delayed inflammatory reaction to dermal hyaluronic acid fillers following COVID-19 vaccination—a model for inhibition of angiotensin II-induced cutaneous inflammation. *JAAD Case Rep* 2021; **10**: 63–68.
- 18 Soyfer V, Gutfeld O, Shamai S, Schlocker A, Merimsky O. COVID-19 vaccine-induced radiation recall phenomenon. *Int J Radiat Oncol Biol Phys* 2021; **110**: 957–961.
- 19 Pamukçu B. Inflammation and thrombosis in patients with COVID-19: A prothrombotic and inflammatory disease caused by SARS coronavirus-2. *Anatol J Cardiol* 2020; **24**: 224–234.
- 20 Herman A, Peeters C, Verroken A *et al.* Evaluation of chilblains as a manifestation of the COVID-19 pandemic. *JAMA Dermatol* 2020; **156**: 998–1003.

- 21 Tessa I, Kluger N. Ipsilateral Herpes Zoster after the first dose of BNT162b2 mRNA COVID-19 vaccine. *J Eur Acad Dermatol Venereol* 2021; **35**: e620–e622.
- 22 Lospinoso K, Nichols CS, Malachowski SJ, Mochel MC, Nutan F. A case of severe cutaneous adverse reaction following administration of the Janssen Ad26.COV2.S COVID-19 vaccine. *JAAD Case Rep* 2021; **13**: 134–137.
- 23 Farinazzo E, Ponis G, Zelin E *et al.* Cutaneous adverse reactions after mRNA COVID-19 vaccine: early reports from North-East Italy. *J Eur Acad Dermatol Venereol* 2021; **35**: e548–e551.
- 24 FormularbeginnFormularendeVera-Lastra O, Ordinola Navarro A, Cruz Domiguez MP, Medina G, Sánchez Valadez TI, Jara LJ. Two cases of graves' disease following SARS-CoV-2 vaccination: an autoimmune/inflammatory syndrome induced by adjuvants. *Thyroid* 2021; **31**: 1436–1439.
- 25 Stingeni L, Bianchi L, Zalaudek I *et al.* Board Members of SIDeMaST. Adverse cutaneous and mucous reactions from anti SARS-CoV-2 vaccines: recommendations from the Italian Society of Dermatology (SIDeMaST). *Ital J Dermatol Venereol* 2021; **156**: 115–117.
- 26 Helms JM, Ansteatt KT, Roberts JC *et al.* Severe, refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccine. *J Blood Med* 2021; **6**: 221–224.
- 27 Abdullah L, Hasbani D, Kurban M, Abbas O. Pityriasis rosea after mRNA COVID-19 vaccination. *Int J Dermatol* 2021; **60**: 1150–1151.
- 28 McMahon DE, Amerson E, Rosenbach M *et al.* Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol* 2021; **85**: 46–55.
- 29 Lam M, Egail M, Bedlow AJ, Tso S. Ribonucleic acid COVID-19 vaccine-associated cutaneous adverse drug events: a case series of two patients. *Clin Exp Dermatol* 2021; **46**: 1131–1134.
- 30 Corbeddu M, Diociaiuti A, Vinci MR, Santoro A, Camisa V, Zaffina S, El Hachem M. Transient cutaneous manifestations after administration of Pfizer-BioNTech COVID-19 Vaccine: an Italian single-centre case series. *J Eur Acad Dermatol Venereol* 2021; **35**: e483–e485.
- 31 Cohen SR, Prussick L, Kahn JS, Gao DX, Radfar A, Rosmarin D. Leukocytoclastic vasculitis flare following the COVID-19 vaccine. *Int J Dermatol* 2021; **60**: 1032–1033.
- 32 McGonagle D, De Marco G, Bridgewood C. Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. *J Autoimmun* 2021; **19**: 102662.
- 33 Akinosoglou K, Tzivaki I, Marangos M. Covid-19 vaccine and autoimmunity: awakening the sleeping dragon. *Clin Immunol* 2021; **226**: 108721.
- 34 Ackerman M, Henry D, Finon A, Binois R, Esteve E. Persistent maculopapular rash after the first dose of Pfizer-BioNTech COVID-19 vaccine. *J Eur Acad Dermatol Venereol* 2021; **35**: e423–e425.
- 35 Jedlowski PM, Jedlowski MF. Morbilliform rash after administration of Pfizer-BioNTech COVID-19 mRNA vaccine. *Dermatol Online J* 2021; **27**: 13030/qt4xs486zg.
- 36 Guimarães LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. *Pharmacol Res* 2015; **100**: 190–209.
- 37 Helms JM, Ansteatt KT, Roberts JC *et al.* Severe, refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccine. *J Blood Med* 2021; **12**: 221–224.
- 38 Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2021; **39**: 3329–3332.
- 39 Gronbeck C, Grant-Kels JM. Attention all anti-vaccinators: the cutaneous adverse events from the mRNA COVID-19 vaccines are not an excuse to avoid them! [published online ahead of print, 2021 May 21]. *Clin Dermatol* 2021. doi: 10.1016/j.clindermatol.2021.05.027
- 40 Pormohammad A, Zarei M, Ghorbani S *et al.* Efficacy and safety of COVID-19 vaccines: a systematic review and meta-analysis of randomized clinical trials. *Vaccines (Basel)* 2021; **9**: 467.
- 41 Bogdanov G, Bogdanov I, Kazandjieva J, Tsankov N. Cutaneous adverse effects of the available COVID-19 vaccines. *Clin Dermatol* 2021; **39**: 523–531.
- 42 Sun Q, Fathy R, McMohan D, Freeman E. COVID-19 vaccines and the skin. *Dermatol Clin* 2021; **39**: 653–673.
- 43 Steber CR, Ponnatapura J, Hughes RT, Farris MK. Rapid development of clinically symptomatic radiation recall pneumonitis immediately following COVID-19 vaccination. *Cureus* 2021; **13**: e14303.
- 44 Kha C, Itkin A. New-onset chilblains in close temporal association to mRNA-1273 vaccination. *JAAD Case Rep* 2021; **12**: 12–14.
- 45 Lavery MJ, Nawimana S, Parslew R, Stewart L. A flare of pre-existing erythema multiforme following BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine. *Clin Exp Dermatol* 2021; **46**: 1325–1327.
- 46 Niebel D, Ralser-Isselstein V, Jaschke K, Braegelmann C, Bieber T, Wenzel J. Exacerbation of subacute cutaneous lupus erythematosus following vaccination with BNT162b2 mRNA vaccine. *Dermatol Ther* 2021.
- 47 Gambichler T, Scholl L, Dickel H, Ocker L, Stranzenbach R. Prompt onset of Rowell's syndrome following the first BNT162b2 SARS-CoV-2 vaccination. *J Eur Acad Dermatol Venereol* 2021; **35**: e415–e416.
- 48 Merhy R, Sarkis AS, Stephan F. Pityriasis rosea as a leading manifestation of COVID-19 infection. *J Eur Acad Dermatol Venereol* 2021; **35**: e246–e247.
- 49 Drago F, Ciccarese G, Rebora A, Parodi A. Human herpesvirus-6, -7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol* 2021; **93**: 1850–1851.
- 50 An QJ, Qin DA, Pei JX. Reactive arthritis after COVID-19 vaccination. *Hum Vaccin Immunother* 2021; **25**: 1–3.
- 51 İremli BG, Şendur SN, Ünlütürk U. Three cases of subacute thyroiditis following SARS-CoV-2 vaccine: post-vaccination ASIA syndrome. *J Clin Endocrinol Metab* 2021; **106**: 2600–2605.
- 52 Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost* 2021; **19**: 1515–1518.
- 53 Wollina U, Karadağ AS, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: a review. *Dermatol Ther* 2020; **33**: e13549.
- 54 Aleem A, Nadeem AJ. Coronavirus (COVID-19) vaccine-induced immune thrombotic thrombocytopenia (VITT). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. PMID: 34033367.
- 55 Krajewski PK, Szepietowski JC. Immune thrombocytopenic purpura associated with COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccine. *J Eur Acad Dermatol Venereol* 2021; **35**: e626–e627.
- 56 Candelli M, Rossi E, Valletta F, De Stefano V, Franceschi F. Immune thrombocytopenic purpura after SARS-CoV-2 vaccine. *Br J Haematol* 2021; **194**: 547–549.
- 57 Taherifard E, Taherifard E, Movahed H, Mousavi MR. Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases. *Hematology* 2021; **26**: 225–239.
- 58 Lee EJ, Cines DB, Gernsheimer T *et al.* Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol* 2021; **96**: 534–537.
- 59 Tarawneh O, Tarawneh H. Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine. *Am J Hematol* 2021; **96**: E133–E134.
- 60 Gambichler T, Reuther J, Stücker M *et al.* SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion. *J Eur Acad Dermatol Venereol* 2021; **35**: e187–e189.
- 61 Julian JA, Mathern DR, Fernando D. Idiopathic thrombocytopenic purpura and the moderna Covid-19 vaccine. *Ann Emerg Med* 2021; **77**: 654–656.
- 62 Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. *Rheumatology (Oxford)* 2021; **60**: S190–S195.
- 63 Rodríguez-Jiménez P, Chicharro P, Cabrera LM *et al.* Varicella-zoster virus reactivation after SARS-CoV-2 BNT162b2 mRNA vaccination: report of 5 cases. *JAAD Case Rep* 2021; **12**: 58–59.

- 64 Bostan E, Yalici-Armagan B. Herpes zoster following inactivated COVID-19 vaccine: a coexistence or coincidence? *J Cosmet Dermatol* 2021; **20**: 1566–1567.
- 65 Arora P, Sardana K, Mathachan SR, Malhotra P. Herpes zoster after inactivated COVID-19 vaccine: a cutaneous adverse effect of the vaccine. *J Cosmet Dermatol* 2021. doi: 10.1111/jocd.14268
- 66 Damiani G, Network YDI, Pacifico A, Pelloni F, Iorizzo M. The first dose of COVID-19 vaccine may trigger pemphigus and bullous pemphigoid flares: is the second dose therefore contraindicated? *J Eur Acad Dermatol Venereol* 2021; **35**: e645–e647.
- 67 Pérez-López I, Moyano-Bueno D, Ruiz-Villaverde R. Bullous pemphigoid and COVID-19 vaccine. *Med Clin (Barc)* 2021; S0025–7753(21): 00293–301.
- 68 Conforti C, Dianzani C, Agozzino M *et al.* Cutaneous manifestations in confirmed COVID-19 patients: a systematic review. *Biology (Basel)* 2020; **9**: 449.
- 69 Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a world-wide review. *JAAD Int* 2021; **2**: 119–133.
- 70 Kantor J. May 2021: heterogeneity in reported skin manifestations of COVID-19 and vaccines. *J Am Acad Dermatol* 2021; **84**: 1251.