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REVIEW ARTICLE

Cutaneous and Allergic reactions due to COVID-19 vaccinations: A review

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ABSTRACT

Introduction: The pandemic caused by the novel coronavirus disease 2019 (COVID-19) has had an unprecedented impact on the overall health and the global economy. Vaccination is currently the most dependable strategy to end the pandemic, despite the slower-than-hoped-for rollout, particularly for low-to-middle-income countries, and the uncertain duration of protection afforded by vaccination. The spike protein of the virus (immunodominant antigen of the virus) is the main target of the approved and candidate SARS-CoV-2 vaccines. This protein binds to the ACE2 receptor of the host cell, initiating the entry of the virus into the cell and the chain of subsequent events ending to Acute Respiratory Distress Syndrome. The safety profile of these vaccines needs is closely assessed.

Methods: This comprehensive review includes searching the PubMed, EMBASE, and Web of Science databases using the keywords "coronavirus", "COVID-19", "vaccine", "cutaneous reactions", "allergic reactions", and "SARS-CoV-2". Manual searching of reference lists of included articles augmented the research. The research was updated in June 2021.

Results: In this narrative review, we tried to investigate and discuss the cutaneous and allergic reactions related to SARS-CoV-2 vaccines currently available in the literature. As a result, although COVID-19 vaccines can be reported to develop allergic and anaphylactic reactions, especially after m-RNA vaccines, they remain at a low rate, and it is observed that these reactions may develop more frequently, especially in patients with previous allergies and mast cell disorders. Fortunately, these reactions are generally transient, benign, self-limited.

Conclusion: Although there is still no definitive evidence, as dermatologists, we must be aware of the possibility of cutaneous reactions, newly diagnosed dermatoses, or exacerbation of existing dermatoses that may develop after the COVID-19 vaccinations.

KEYWORDS
allergic reactions, BNT162b2, COVID-19, cutaneous reactions, SARS-CoV-2, vaccination

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1 | INTRODUCTION

The pandemic caused by the novel coronavirus disease 2019 (COVID-19) has had an unprecedented impact on the overall health and the global economy. Rapidly developed public health strategies tried to control the spread of the disease, but were not enough to reduce the impact of the disease.[1] Vaccination is currently the most dependable strategy to end the pandemic, despite the slower-than-hoped-for rollout, particularly for low-to-middle-income countries, and the uncertain duration of protection they afforded. These vaccines are assumed to be more effective in preventing symptomatic disease, severe disease progression, hospitalization, and to reduce mortality rates for the potentially seasonal SARS-CoV-2 infection.[2] Some countries have approved "digital health passes"/"vaccine passports" as a vehicle for "normal life return."[3] The spike protein of the virus (immunodominant antigen of the virus) is the main target of the approved and candidate SARS-CoV-2 vaccines.[4] The spike protein binds to the ACE2 receptor of the host cell, initiating the entry of the virus into the cell and the chain of subsequent events ending to acute respiratory distress syndrome.[5] The vaccines used today include mRNA-based vaccines, which encode for full-length spike (S) protein of SARS-CoV-2 (eg, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna); viral vector vaccines (eg, adenoviruses, adenovirus serotype 26 vector vaccine (Ad26. CoV2.S; Johnson & Johnson), and chimpanzee adenovirus vector vaccine (ChAdOx; AstraZeneca); and virus-related protein-based weakened inactivated SARS-CoV-2 virus vaccines (eg, Sinopharm, Sinovac, and Novavax).[4] Following mass vaccination campaigns related to SARS-CoV-2 vaccines, vaccine-related reactions have been increasingly reported, despite its benign course in general. The significance of these reactions is still to uncover. The safety profile of these vaccines' needs is closely assessed. In this narrative review, we tried to investigate and discuss the cutaneous and allergic reactions related to SARS-CoV-2 vaccines currently available in the literature.

2 | METHODS

This comprehensive review includes searching the PubMed, EMBASE, and Web of Science databases using the keywords "coronavirus," "COVID-19," "vaccine," "cutaneous reactions," "allergic reactions," and "SARS-CoV-2." Manual searching of reference lists of included articles augmented the research. The research was updated in June 2021 (Table 1).

3 | ALLERGIC REACTIONS

The quick improvement of SARS-CoV-2 vaccines and the report of anaphylactic reactions during the early stage of worldwide mass vaccination, especially among those with a history of allergy, has raised safety concerns. Acute allergic reaction symptoms

TABLE 1 Allergic and cutaneous reactions related to COVID-19 vaccines

The type of COVID–19 vaccine	Allergic reactions (% incidence if detected)	Cutaneous reactions (% incidence if detected)
mRNA vaccines • BNT162b2 (Pfizer-BioNTech) • mRNA-1273 (Moderna)	• mRNA-1273 (Moderna) • Anaphylaxis (0.0002–0.0005%)[14,18]	• COVID arm (0.2–0.8%)[7] • Pityriasis rosea (0.4%)[35] • Urticaria (0.2%)7 • Chilblain-like lesions (<0.1%)[7] • Vasculitis • Erythema multiforme • Rowell's syndrome • Herpes zoster • Herpes labialis • Lichen planus • Immune thrombocytopenia with secondary cutaneous petechial lesions
Vector vaccines • Adenovirus serotype 26 vector vaccine (Ad26. CoV2.S; Johnson & Johnson) • Chimpanzee adenovirus vector vaccine (ChAdOx; AstraZeneca)	• No allergic reaction has been reported yet	• Morbilliform rash (<0.1%)[15]Petechial skin rash (<0.1%)[15]
Inactive SARS-CoV-2 vaccines • Sinopharm • Sinovac • Novavax	• No allergic reaction has been reported yet	• COVID arm (0.2–0.6%)[26] • Pityriasis rosea (<0.1%)[26] • Herpes zoster (<0.1%)[26] • Chilblain-like lesions • Herpes labialis • Petechial skin rash

mostly include itching, rash, hives, swelling, and/or respiratory symptoms. The first vaccines to be approved for emergency use in humans were the *BNT162b2 Pfizer-BioNTech* and mRNA-1273 *Moderna* mRNA vaccines. In mRNA vaccines, the synthetic SARS-CoV-2 spike (S) glycoprotein encoding mRNA is transported to the cells where the mRNA is translated into viral S glycoprotein via an envelope containing polyethylene glycol (PEG), and neutralizing antibodies are produced against it.[6,7] So far, numerous allergic reactions have been reported due to COVID-19 vaccines, especially mRNA vaccines.[8-13] Blumenthal et al. studied 64 900 healthcare workers after the first dose of mRNA COVID-19 vaccine, 40% received Pfizer-BioNTech vaccine, and 60% received Moderna vaccine. Approximately 98% of individuals have not developed any allergic reaction symptoms after receiving the mRNA COVID-19 vaccine. The remaining 2% reported some degree of allergic symptoms that were more frequent with the Moderna vaccine compared with Pfizer-BioNTech. Anaphylaxis was confirmed in 16 employees: 7 cases from the Pfizer-BioNTech vaccine, and 9 cases from the Moderna vaccine; 10 (63%) had history of allergy, and 5 (31%) had history of anaphylaxis. Female healthcare workers represented the majority of them (94%). All of them recovered without shock or endotracheal intubation.[14]

Case reports suggested a cutaneous adverse reaction related to COVID-10 vaccination. The proposed mechanism is a delayed inflammatory reactions (DIR) to hyaluronic acid (HA). DIR has been observed without any exposure to vaccines for decades. The cause remains unresolved, but infections may trigger the process.[15] A 39-year-old woman developed swelling after vaccination in the tear trough area for someday, that was previously been treated with HA filler. A 61-year-old woman reported intermittent facial swelling of previously treated areas. She also got HA soft tissue filler. Both women received RNA Pfizer-BioNTech COVID-19 vaccine.[16] A 51-year-old healthy woman who received HA fillers in various part of the face over the course of 18 months got the first shot of mRNA-1273 vaccine (Moderna) 5 weeks after the last HA injection. Eight days later, she presented with facial edema, erythema, and tenderness, which deteriorated in the following days. Further on, she developed painful indurated plaques and nodules for about 4 weeks. A head CT scan which demonstrated soft tissue swelling without drainable fluid collection. A healthy 36-year-old woman with repeated injections of HA soft tissue fillers experienced a bilateral infraorbital perioral edema after the first shot of the Moderna COVID-19 vaccine and almost 6 months after the last filler injection. A 43-year-old woman with HA filler correction of tear troughs more than 2.5 years ago developed a mild tenderness underneath followed by swelling under the eyes 24 hours after the second shot of them RNA vaccine from Pfizer/BioNTech.[17] All the patients were treated with a combination of hyaluronidase, antibiotics, and corticosteroids, depending on severity and area of adverse events. Oral antihistamines were not of benefit for treatment or prevention of DIR due to HA fillers. A new approach was introduced by Munavalli et al.[18] They used oral angiotensin-converting enzyme (ACE) inhibitor (lisinopril 5 to 10 mg/day) in 4 female patients aged between 31 and 76 years. All of these 4 patients had their last HA filler injection at least one year ago. They proposed that the ACE inhibitor would reduce the angiotensin II-induced pro-inflammatory pathway. In a survey from patients of 18 countries who received soft tissue filler injections prior to at least one shot of vaccination, 5.1% reported pain that lasted longer than 2 days. From the current knowledge, adverse events following immunization with HA do not seem to have a causal relationship to the vaccination itself.[19] Interestingly in a prospective study on more than 1000 patients who had facial hyaluronic acid injections during the COVID-19 pandemic and followed up at 1 and 3 months, no unexpected side effects were noted apart from erythema, edema, and local injection site discomfort. However, within 3 months of HA injection, five patients were diagnosed with an active COVID-19 infection.[20]

The US Centers for Disease Control and Prevention (CDC) reported 157 reactions in approximately 6 million doses of mRNA vaccine, and only 1 out of 5 reactions were anaphylaxis. Therefore, the incidence of anaphylaxis due to COVID-19 vaccine is very low (5 out of 1 000 000 doses) but at least 5 times higher than reported for other vaccines.[21] In fact, since these mRNA vaccines are the first mRNA vaccines approved for human use, there is limited knowledge about the mechanisms underlying anaphylactic reactions associated with their administration. It has been suggested that the underlying mechanism for anaphylaxis caused by these mRNA vaccines may be related to an IgE-mediated hypersensitivity to polyethylene glycol (PEG), a commonly used additive, which is a rare but increasing cause for anaphylaxis.[22] PEG is an ethylene oxide polymer and can be found in a wide variety of medicines, cosmetics, and food additives. In addition, PEG can cross-react with polysorbate, a nonionic surfactant that can also be found in other vaccines.[23] According to the European Anaphylaxis Registry, only 0.3% of all drug-induced anaphylaxis cases are related to PEG and the cross-reacted allergen polysorbate.[24] In addition to PEG, the mRNA-1273 vaccine also contains tromethamine, which can cause an allergic reaction to gadolinium-based contrast material. Tromethamine can also available in certain healthcare and cosmetic products.[22] On the contrary, serious systemic reactions were not reported in clinical studies of these vaccines, but it should be noted that patients with a previous history of allergic reactions were excluded from trial.[6,7,25] The AstraZeneca (ChAdOx1-S [recombinant]) vaccine is based on a chimpanzee adenovirus vector encoding the SARS-CoV-2 S glycoprotein produced in genetically modified human embryonic kidney (HEK) 293 cells. This vaccine contains polysorbate 80, which may principally be responsible for allergic reactions, but yet no reports of allergic reactions have been reported so far, apart from a case of anaphylaxis in a single study.[26] On the contrary, concerns remain that the AstraZeneca (ChAdOx1-S [recombinant]) vaccine increases thromboembolic events.[27]

Inactive SARS-CoV-2 vaccine is a vaccine prepared via inactivation of the SARS-Cov-2 virus in cell culture (such as the Sinovac / Coronavac vaccine). Since it contains a complete virus, it is

possible to obtain immunity from other structures of the virus together with the S protein, as in those who have had the disease. However, the immune response is lower than other SARS-CoV-2 vaccines. Till now, no anaphylactic reaction due to inactivated SARS-CoV-2 vaccine has been found.[28] Throughout the vaccine history, inactive vaccines have been safer in terms of possible allergic reactions.[29]

It should be noted that patients with allergic skin diseases, such as atopic dermatitis and urticaria, are to be actively treated with no need to delay their vaccination dates. Furthermore, atopic dermatitis per se is not a risk factor to develop anaphylactic reactions to any of COVID-19 vaccines. The drug allergy test prior to COVID-19 vaccination should be considered for patients with history of anaphylaxis to any drug, including mast cell tryptase determination, and vaccinations in patients with systemic mastocytosis or idiopathic anaphylaxis.[30] Currently, the only absolute contraindication to COVID-19 vaccination is a known severe allergic reaction to any of the ingredients of the vaccines. Patients with anaphylaxis should be evaluated by an allergist and an immunologist for directed care and not be categorically denied the COVID-19 vaccine.[31] Experts recommended only combined H1 and H2 receptor antagonists plus oral glucocorticoids prior to vaccination, and intramuscular epinephrine as a main acute pharmacotherapy in case of anaphylaxis.[30] Currently, no data to suggest that antihistamines could reduce immunogenicity of SARS-COV-2 vaccination. Finally, Bermingham et al.[32] reported that chronic spontaneous urticarial/angioedema patients may have a lower risk to develop an IgE-mediated reaction to SARS-CoV-2 vaccination.

4 | CUTANEOUS REACTIONS

The COVID-19 has been associated with certain clinical spectrum of cutaneous signs, including urticarial, maculopapular, vesicular, chilblain-like, livedoid, and vasculitic lesions. The pathophysiology and significance of these signs remain uncertain, despite relatively common. Viral hypersensitivity reactions, over-expression of type I interferon, COVID-19 induced coagulopathy, thrombotic microangiopathy, and direct viral endothelial damage are among the proposed theories.[33] Kutlu et al.[34] speculated that itching, even if mild, in COVID-19 patients might be a marker for the severity of the disease, for example, lung involvement. García-Irigoyenetal.[35] studied 97 non-critical hospitalized COVID-19 patients for dermatological signs and relation to inflammatory biomarkers and duration of hospital stay. They noted that these signs are good prognostic markers, as most of the patients discharged shortly after the onset of dermatological signs than those without dermatological signs.

Cutaneous manifestations are increasingly reported following SARS-CoV-2 vaccinations mass campaigns. Most of these cutaneous side effects are mild and transient manifestations of uncertain clinical significance. In addition, the importance of whether a cutaneous reaction develops in terms of vaccine immunization is not yet clear. The following cutaneous reactions were reported in the current literature.

4.1 | Chilblain-like lesions

Pileri et al.[36] reported a 42-year-old man who developed non-painful erythematous-to-purplish patches on his distal phalanges and nail beds with acrocyanosis and chilblain-like lesions (CCL), 12 days after the first dose of Pfizer-BioNTech COVID-19, BNT162b2. No worsening or recurrence of the lesion was noted following the second dose, which is performed 21 days from the first dose. Lopez et al.[37] reported a 64-year-old man with painless, dark erythematous-to-violaceous discoloration of bilateral toes for 10 days. The lesions developed gradually 3 days after the second dose of Pfizer-BioNTech COVID-19, BNT162b2. Two weeks after topical corticosteroid, the discoloration remained unchanged, but improved on rewarming and leg enervation. Piccolo et al.[38] noted a 41-year-old woman with severely painful CLL located on the volar aspects of the second and the third fingertip of right hand only 24 hours after the second dose of Pfizer BNT162b2 mRNA COVID-19 vaccine. Davido et al.[39] reported a 41-year-old woman who developed "blue toes" 4 days after the first dose of Pfizer-BioNTech COVID-19, BNT162b2. As the lesions remained even after 4 weeks of vaccination, the authors contraindicated the second dose of the vaccine to avoid further possibly serious, vascular symptoms. McMahon et al.[40] have reported 8 out of 414 cases with CLL after vaccination; 5 with Pfizer/ BioNTech, BNT162b2; and 3 with Moderna, mRNA-1273 vaccines. Recently, we have reported two male patients, 44 and 53 years old, presented with seven-day history of CLL, mildly pruritic erythematous-to-violaceous patches, and plaques, on dorsal aspects of both hands after the first dose of the inactivated COVID-19 vaccine (CoronaVac) (Figure 1A). Topical corticosteroids and antihistamines were sufficient to control the lesions within three weeks later. These two cases of CLL were the first to report following inactivated SARS-CoV-2 vaccine against COVID-19.[41]

COVID-19 vaccines may increase an immunological reaction leading to CCL. CLL is mostly seen in young symptomatic to asymptomatic patients as a late manifestation of SARS-CoV-2 infection. Despite the contradictory reports, an association between CLL and immune response against SARS-CoV-2 through virus-induced interferonopathy or viral collateral effect in patients with active innate immune system has been considered. Post-vaccine CLL may reinforce this immunological connection to SARS-CoV-2 infection. Of note, reactivation of CLL during the second COVID-19 wave in patients who had history of CLL to be considered.[42]

4.2 | Vasculitis

Cohen et al.[43] reported a 46-year-old woman with history of psoriasis, psoriatic arthritis, irritable bowel syndrome, and leukocytoclastic vasculitis. Within 2 days following Pfizer-BioNTech COVID-19, a mild exacerbation of vasculitis limited to the lower limbs occurred. In the same report, it was stated that 2 days after administration of the second dose of the same vaccine, the vasculitic lesions occurred again with increasing pain and anatomical distribution. The patient

FIGURE 1 (A) CLL on the dorsal hands of a male patient. (B) Vaculitis on the extensors of both lower limb. (C) PR lesions on the trunk. (D) HZ on the hemi-buttock of an elderly woman

improved after initiation of both topical and systemic corticosteroids, with no exacerbation of psoriasis. The SARS-CoV-2 virus may induce immune system dysregulation secondary to cross-reactivity and molecular mimicry between the virus and self-antigens, triggering autoimmune disorders such as vasculitis (Figure 1B) and systemic lupus erythematosus.[44,45] COVID-19 vaccine may provoke the same scenario in genetically predisposed individuals. Of note, the use of the SARS-CoV-2 vaccine for psoriatic patients, even for those on immunosuppressive and/or biological therapy, is recommended without treatment discontinuation.[46] However, flare up of psoriasis "psoriasis vaccinalis" should be taken into consideration.[47]

4.3 | Pityriasis Rosea

Akdaş et al.[48] reported a histopathological-confirmed pityriasis rosea (PR) in a 45-year-old female healthcare worker that had developed four days after the first dose of CoronaVac COVID-19 vaccine, and the lesions that exactly at the same sites of the previous one recurred four days after the second dose of the vaccine. The patient reported no "recent" history of any infection. Akdaş et al.[48] had not detected any evidence of SARS-CoV-2 particles in their patient's lesions by polymerase chain reaction (PCR). Both lesions faded within few weeks without symptomatic therapy. Busto-Leis et al.[49] reported two patients with PR developed a day and 7 days after the second dose of the Pfizer-BioNTech vaccine, respectively. Both patients had negative nasopharyngeal PCR test, lack of systemic symptoms, while they demonstrated positive SARS-CoV-2 IgG antibodies and HHV-6 serology. Cyrenne et al.[50] reported 2 cases with PR developed after the first dose with exacerbation after the second dose of Pfizer-BioNTech vaccine in one who had alopecia areata, and one developed the lesion 3 weeks of the second dose of the same vaccine. SARS-CoV-2 vaccines may trigger a chain of collateral endogenous latent viral reactivation, such as HHV-6/7. In an immunohistochemical study, Welsh et al.[51] detected SARS-CoV-2 viral particles in the skin biopsies of PR-like dermatosis and urticarial rash of two COVID-19 patients following 6 weeks of the initial diagnosis. It should be addressed whether SARS-CoV-2 infection plays a role in PR development after COVID-19 vaccination (Figure 1C).

4.4 | Maculopapular rash with systemic associations

Jedlowski et al.[52] first reported a 30-year-old male healthcare worker presented with recurrent pruritic maculopapular rash, though not exactly at the same sites, 48 hours after administration of the first and second doses of Pfizer-BioNTech vaccine, respectively. The rash in both situations was self-limiting within the next 24 hours with no systemic sequels. Later, Ackerman et al.[53] reported a 55-year-old male healthcare worker presented with a 3-week history of pruritic maculopapular rash affecting 30% of body surface area following the first dose of the Pfizer-BioNTech COVID-19 vaccine. Extensive workup showed only slight hepatic cytolysis. Weeks later, the

authors noted gradual improvement of the rash compatible with the improvement of liver enzymes. We think this case might be an example of "hypersensitivity drug reaction with hepatic involvement." The physician should be vigilant to persistent post-vaccination rash, particularly if increasing, to rule out possible systemic associations. Those with ongoing deterioration of liver function should be managed in a multidisciplinary approach.

4.5 | COVID arm

López-Valle et al.[54] reported a 27-year-old female ophthalmologist of COVID arm, a poorly defined erythematous-edematous plaque, at site of injection of BNT162b2 mRNA vaccination with the first and second doses, 7 days and 6 hours, respectively. COVID-arm lesion and associated constitutional symptoms in both situations were resolved within 2 days of symptomatic therapy. The authors referred this reaction as a nonspecific inflammatory response. In a retrospective Spanish study on 4775 individuals, it has been reported that following BNT162b2 mRNA vaccination, 864 of the individuals (18.1%) had vaccine-related side effects that were predominant in female patients (83.4%). Cutaneous reactions showed mainly to itching (68.0%).[55] However, in few cases, localized COVID arm as an erythematous targetoid patch that developed at the injection site of the vaccine, disseminated lesions, and urticarial have been observed. Half of the patients reported recurrence of similar reactions after the second dose. Overall, these reactions onset within a median 8 days, and resolved within a median 6 days. Wei et al. reported 4 women with COVID arm several days following the first dose of the Moderna COVID-19 vaccine; 2 resolved spontaneously; and 2 improved on topical steroids and oral antihistamines.[56] Johnston et al.[57] studied COVID arm at a histopathological level in patients who received Moderna COVID-19 vaccine. The authors stated that COVID-19 arm is a delayed-type hypersensitivity reactions to either vaccine excipient, lipid nanoparticle, or mRNA component that developed at injection site, and presented with erythema, pruritus, induration, and tenderness in a median 7 days after the first dose and for a median 5 days. Recurrence of COVID arm after the second dose of Moderna COVID-19 vaccine with the same to lesser severity of the first dose has been noted, despite with a median onset of 2 days.[58] Recurrent COVID arm may develop due to faulty subcutaneous injection of the Pfizer-BioNTech vaccine instead of intramuscular injection to the deltoid muscle as recently noted.[59]

4.6 | Erythema multiforme (EM)

Nawimana et al.[60] reported a 58-year-old woman with multi-systemic diseases, rheumatoid arthritis, endometriosis, and a multinodular thyroid goiter, who presented with recurrence of her erythema multiforme (EM) lesions after 12 hours of the first dose of BNT162b2 vaccine. It has been reported that lesions improved with topical corticosteroids. One of the explanations of the EM-like eruption after COVID-19 vaccines may be due to a T-lymphocyte immune response against epidermal cells harboring, yet an unknown, antigen present in the vaccine eventually leads to cell death and dermal-epidermal junction detachment.[60]

4.7 | Lichen planus

Lichen planus has been reported to be triggered by SARS-CoV-2 infection.[61,62] Hiltun et al.[63] reported a 56-year-old female, with history of treated lichen planus 7 years earlier, presented with well-defined polygonal, erythematous papules affecting the ankles, periumbilical area, flexural wrist, forearms, and both mammary and axillary folds 48 h after the second dose of Pfizer-BioNTech vaccine. Skin biopsy confirmed the diagnosis of lichen planus. Burlando et al.[64] reported flared up and spread to the trunk of the previous lichen planus lesions of a 47-year-old healthcare worker, one day after BNT162b2 mRNA COVID-19 vaccination. The lesions had improved within 10 days undertopical steroid. Certain vaccines may trigger or exacerbate lichen planus with uncertain mechanisms. The hypothesis on how COVID-19 vaccines may induce lichen planus is related to vaccine-induced increased Th1 immune response that leads to increased serum level of inflammatory cascades, such as IL-2, TNFα, and IFNγ, eventually leading to basal keratinocyte apoptosis.[63]

4.8 | Rowell's syndrome

Gambichler et al.[65] reported a case of a 74-year-old woman who developed an erythema multiforme (EM)-like lesions with immunologic findings of Rowell's syndrome one day after BNT162b2 mRNA COVID-19 vaccination; the speckled pattern of ANA, positive anti-Ro/SSA, or anti-La/SSB.

4.9 | Herpes zoster

Burlando et al.[64] reported a 42-year-old healthcare worker with typical unilateral dermatomal papulovesicular lesion of herpes zoster (HZ) on right hemithorax 2 days after the first dose of Pfizer-BioNTech vaccine. Complete resolution with systemic acyclovir was noted within 7 days. Vaccine-induced cell-mediated immune system dysregulation may be related to this reaction. Bostan et al.[66] reported a 78-year-old man presented with eruptive erythematous, painful, and pruritic lesions on his chest throughout T3-T4 dermatomes compatible with HZ that developed five days after administration of inactivated COVID-19 vaccine. The lesion improved on systemic antiviral treatment over 7 days. Eid et al.[67] reported a 79-year-old man with stable antineutrophilic cytoplasmic antibody-related glomerulonephritis and not on immunosuppressive therapies presented HZ on the right thigh 7 days of mRNA COVID vaccine that was resolved with systemic antiviral. In an observational study monitoring the post-vaccination adverse effects in patients with autoimmune

inflammatory rheumatic diseases (AIIRD), the authors observed six relatively young female patients with mild-to-stable AIIRD who developed HZ, with no dissemination or post-herpetic neuralgia, for the first time shortly (maximum 10 days) after vaccination with the BNT162b2 mRNA vaccine, and 5 of them developed HZ after the first dose of the vaccine.[68] Interestingly, there was a patient who had been vaccinated against HZ before the COVID-19 vaccination. This condition may point out the role of the current COVID-19 vaccination as a possible trigger for HZ. There was another patient who was immunocompromised. The vaccine may trigger T and B immune responses through stimulation of potent inflammatory cytokines but has a negative effect on the degree of antigen expression potentially contributing to HZ reactivation.[68] (Figure 1D). Interestingly, Nanova et al. reported a case of recurrent varicella infection in an immunocompetent patient after Pfizer-BioNTech mRNA vaccine.[69] The authors speculated that this may be due to the unknown immune effects of mRNA vaccines and the ability of viral particles to trigger herpes infections.[69]

4.10 | Miscellaneous

Immune thrombocytopenia (ITP) cases with secondary cutaneous petechial lesions have been reported especially after mRNA vaccines.[70,71] Although the pathogenesis of vaccine-related ITP is unclear, it has been suggested that peptides in vaccines may show similar properties to platelet antigens, leading to ITP through activation of autoreactive B or T cells.[72] In the literature, Cebeci et al.[73] also reported a case of petechial skin rash without vasculitis and immune thrombocytopenia after inactivated COVID-19 vaccine. The authors interpreted this situation as a vaccine-associated hypersensitivity reaction. Soyfer et al.[74] reported 2 cases of radiation recall phenomenon in patients with metastatic soft tissue sarcoma after 5 and 21 days of the second dose of BNT162b2 mRNA COVID-19 vaccination respectively. Both were improved on topical steroids and analgesics within few days. Flare of existing dermatologic condition (eg, herpes simplex virus, atopic dermatitis, psoriasis, urticarial vasculitis, and unspecified eczema), onset of new dermatologic conditions (eg, lichen planus), others (eg, Sweet's-like fixed urticarial plaque and eczematous pigmented purpura), even systemic reactions (eg, vomiting, nasal congestion, dizziness, and hematuria) following mRNA vaccines COVID-19 vaccines have been reported.[40]

5 | CONCLUSION

Although COVID-19 vaccines can be reported to develop allergic and anaphylactic reactions, especially after mRNA vaccines, they remain at a low rate. It was reported COVID-19-related reactions may be seen more commonly in patients with previous allergic and mast cell disorders. Even in patients who may be at risk for these allergic reactions, continued vaccination is recommended provided that emergency conditions are met. However, of course, it is a definite contraindication to administer these vaccines in individuals with previous anaphylaxis against any of the vaccine components. Given the experience with different vaccines and the mechanisms of action of the new COVID-19 vaccines, it is plausible that post-vaccination cutaneous reactions may develop and be responsible for certain exacerbations of dermatoses.[75] However, we still do not know enough about the cutaneous reactions associated with COVID-19 vaccines. This review was important due to it is the first review in the literature, to the best of our knowledge, dealing with the allergic and cutaneous effects of these vaccines, which have been used for about six months. In a nutshell, these cutaneous reactions are generally transient, benign, self-limited, and usually not a contraindication to further doses of the vaccine. The number and profiles of cutaneous side effects in different vaccine groups may be related to the frequency of administration of vaccination. In the near future, the exact cutaneous side effects' profiles of the different vaccines will be more illuminated. Although there is still no definitive evidence, as dermatologists, we must be aware of the possibility of cutaneous reactions, newly diagnosed dermatoses, or exacerbation of existing dermatoses that may develop after the COVID-19 vaccinations.

AUTHOR CONTRIBUTION

Selami Aykut Temiz put the manuscript conception. Omer Kutlu, Recep Dursun, Anant Patil, Michelangelo Vestita, and Mohamad Goldust worked equally in literature review and editing the initial draft. Uwe Wollina wrote "cosmetic fillers and vaccine" section. Torello Lotti revised the final draft. Ayman Abdelmaksoud worked in literature review and editing the final draft, and was corresponded to submit the final draft of the manuscript. All the authors approved the final draft submission.

ETHICAL APPROVAL

The authors confirmed that ethical policies of the journal have been adherent to.

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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