REVIEW ARTICLE

Dermatological Complications of COVID 19 Vaccines: An Updated Review

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ABSTRACT

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the 2019 coronavirus disease (COVID-19) pandemic, have been rapidly developed and authorized. However, recent studies showed that COVID-19 vaccination is associated with a wide range of dermatological reactions. The most prevalent adverse dermatological reaction observed in observational studies was a delayed large local reaction (DLRs), which is characterized by the appearance of an erythematous and edematous patch at the injection site four days or more after vaccination. Most of these reactions are common in females and resolve spontaneously within a few days to a weak. The second dose of the vaccine was associated with a higher incidence of cutaneous reactions compared to the first dose but milder in intensity. It seems that the Moderna vaccine is associated with a higher incidence of these adverse events compared to the Pfizer vaccine. Furthermore, mRNA vaccines had a higher incidence than vector-based and inactivated vaccines. There is a lack of evidence regarding the side events of the Johnson & Janssen vaccine. Further long-term, multicenter studies are required to compare these vaccines and highlight the best practice in managing these reactions.

Keywords: Dermatological reactions, SARS-CoV-2, COVID-19, Vaccine

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INTRODUCTION

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the 2019 coronavirus disease (COVID-19) pandemic, have been rapidly developed and authorized.[1] Using both conventional and innovative vaccine delivery systems, over a hundred companies and academic institutions from across the globe developed vaccine candidates.[2] While protein subunit vaccines may eventually be included in large-scale vaccination programs, this has not yet happened. Even though most of the population in several high-income countries has already been vaccinated, many nations lack access to COVID-19 vaccinations. Several different, highly effective, and less risky COVID-19 vaccines are presently being distributed globally after almost a year. Currently available vaccines are manufactured utilizing vaccination platforms, such as inactivated viruses, viral vector platforms (using multiple adenovirus strains), and messenger ribonucleic acid (mRNA).[1]

Humoral and cellular immune responses potentiate antiviral immunity.[3] In order to properly activate the innate immune system and induce adaptive immunological responses, most vaccination methods, with the exception of those using a live attenuated virus, need several doses and/or adjuvants.[4] Toll-like receptors (TLRs) are one kind of pattern recognition receptor (PRR) that mediates immunogenic effects by recognizing danger-associated molecular patterns (DAMPs), such as nucleic acids (including mRNA).[5] Therefore, adjuvants are unnecessary for the currently available COVID-19 mRNA vaccines.[6] Currently, the most commonly authorized used vaccines are BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), Ad26.COV2.S (Janssen), and Sinovac-CoronaVac vaccine.[7]

SARS-CoV-2 is associated with a wide spectrum of skin manifestations.[8–10] After receiving a vaccination containing the SARS-CoV-2 spike (S) protein, some people may develop dermatological reactions. While vesicular, urticarial, and chilblain-like eruptions are uncommonly induced by SARSCoV2 infection, they may occur in a small percentage of people.[11,12] After an immunogenic challenge with a vaccine of a similar kind, similar pathophysiological reactions may be seen. Vaccine reactions are only one example of the skin manifestation of a potentially life-threatening drug reaction involving several organ systems.[13] Finally, it seems that COVID19 vaccines are associated with a high rate of cutaneous adverse drug reactions (ADRs), such as widespread rashes, pernio-like lesions, itching, swelling, and erythema.[14] Clinical studies rarely represent them correctly from a dermatological perspective, despite the fact that they might be scary for patients and treating clinicians. This review aimed to summarize the current evidence regarding the dermatological reactions of COVID-19 vaccines.

EARLY UNSPECIFIC INJECTION-SITE REACTIONS

Reactions at the injection site are mild and resolve spontaneously in a few days. The most commonly reported local injection-site reactions after COVID-19 vaccinations were pain (88%), pruritus (35%), induration (25%), erythema (20%), and edema (15%).[15] In mRNA and adenoviral vector vaccines, tromethamine, thimerosal, dimyristoyl glycerol, polysorbate, and polyethylene glycol are just a few examples of vaccine components that have the ability to behave as haptens.[16] An influx of different inflammatory cells, including Th2 cells, is rapidly triggered in previously sensitized people upon reactivation of particular memory T cells, resulting in reactions that exceed the spectrum of a "normal" injection-site reaction.[17]

Regarding mRNA-based vaccines, studies showed that patients who received the Pfizer vaccine were associated with mild-to-moderate injection-site reactions; however, those who received the Moderna vaccine had a higher frequency of these reactions. A recent systematic review of 14 studies (n=10,632 participants who received the Pfizer vaccine) revealed that the average incidence of injection-site pain was 77.3%, swelling 33.5%, and pruritus 9.3%.[18] According to McMahon et al., 52% of the patients who received either Moderna or Pfizer vaccine were associated with local injection-site reactions, including pain, erythema, and swelling. Approximately 92% of these reactions were associated with the Moderna vaccine, and 94% were females, with a median age of 44 (21 – 88) years.[19] Similarly, a worldwide review showed that individuals who received the Moderna vaccine were associated with a higher incidence of local injection-site reactions compared to those who received the Pfizer vaccine (79.5% vs. 20.5%), respectively.[20] Furthermore, a Spanish study showed that 61.9% of the participants who received the Moderna vaccine had COVID-arm compared to 14.1% of those who received the Pfizer vaccine[7]. Vector-based vaccines, like AstraZeneca, showed a lower rate of local injection-site reactions than those reported with mRNA-based vaccines.[21] Kroumpouzos et al. showed that among the participants who received the AstraZeneca vaccine, no patients showed local injection-site reactions.[20] However, other studies demonstrated that both AstraZeneca and Pfizer vaccines had comparable rates of injection-site reactions.[7,22,23]

Regarding the CoronaVac vaccine, the incidence of local injection-site reactions was low, according to phase 1/2 clinical studies. Han et al. demonstrated that among 550 healthy children and adolescents, the incidence of pain, swelling, induration, erythema, and pruritus was 13%, 2%, <1%, <1%, and 1%, respectively.[24] In healthy adults aged 60 years and older who received CoronaVac, Wu et al. showed that the incidence of pain at the site of injection was 10%,

while swelling, erythema, and pruritus were reported in only 1% of the participants.[25] On the other hand, another study among healthcare workers who received CoronaVac showed a higher incidence of injection-site pain (41.5%).[26] When compared with the Pfizer vaccine, CoronaVac was associated with a significantly lower incidence of local injection-site reactions.[27,28] There is a lack of knowledge about the cutaneous or systemic adverse effects of CoronaVac since the findings of the phase 3 trials have not been published yet.

Several studies have highlighted that females were associated with a substantially higher incidence of injection-site reactions compared to males.[18,26] Feminine immune systems respond strongly to vaccinations against bacteria and viruses for a variety of biological reasons, including endocrine and sex hormones.[29] Differences in pharmacokinetics and pharmacodynamics have also been identified between the sexes, with women being more likely to experience side effects.[30] It has been hypothesized that this is because women, on average, have a higher body fat percentage than men, which may have implications for the rate and extent to which drugs are metabolized and eliminated from the body.[31]

More severe injection-site responses were recorded following the second dose compared to the first.[18] The US Food and Drug Administration showed that the rate of local side effects was somewhat higher after the second vaccination dose compared to the first.[11] Results from a study by Abu-Hammad et al. showed that adverse effects were more common after the second dose.[23] Around 40% of side effects were more frequent with the second dose, notably in those who had the Pfizer vaccination compared to those who got the Sinovac or AstraZeneca vaccine, as reported by Elnaem et al.[32]

It was reported that almost 8.2% appeared within one hour after vaccination, 69.9% within 24 hours, 18.1% on the second day, and 3.9% within more than 48 hours.[18] Alhazmi et al. showed that 84% of the adverse effects occur within 24 hours, 15% within 48 hours, and 1% within 72 hours.[33] McMahon et al. showed that the majority of these reactions started at 0-1 day following vaccination and resolved at the 4-5 day of vaccination.[19] All vaccine recipients should be monitored for 15 minutes following inoculation, and adrenaline should be nearby in case it's needed, as recommended by the Centers for Disease Control and Prevention (CDC).[34]

Type IV (delayed) Large Local Reactions

The most prevalent adverse dermatological reaction observed in observational studies was a delayed large local reaction (DLRs), which is characterized by the appearance of an erythematous and edematous patch at the injection site four days or more after vaccination.[19] In general, studies reported that DLRs were transient and mild, with limited recurrences. After 11 days, DLRs mentioned in the observational studies had subsided. Only 11 people in the McMahon et al. study4 had DLRs after both doses. These people had all received the Moderna vaccine, and the reactions after the second dosage were often milder and appeared sooner. After a median of two days, 6 of the 12 patients who got the Moderna vaccination in the study by Blumenthal and colleagues had a recurrent DLRs, but this time it was milder than the first reaction.[35] Similar DLRs occurred in 4 of 11 patients who got the Moderna vaccination in Ramos and Kelso after the second dosage, beginning 2 to 3 days after injection.

Observational studies of DLRs tend to focus on the Moderna vaccine, although similar results have been seen with the Pfizer vaccine as well. The recurrence of DLRs that previously appeared after the first dose was reported in 50% of the individuals who received the second dose of Pfizer vaccine in the study of Fernandez-Nieto and colleagues.[36] These DLRs had a variety of morphologies, including large plaques and erythematous targetoid patches.[36] Lesion sizes in two investigations of people who received the Moderna vaccination varied from 6 to 20 cm, with about half of the lesions being classified as grade 3 plaques.[35,37] These skin lesions were confirmed to be "a delayed T-cell-mediated hypersensitivity response" after histological examination showed perivascular lymphocytic infiltrates with few eosinophils and scattered mast cells.[35,36,38] To far, no reports of similar results with other non-mRNA COVID-19 vaccinations have emerged, and the underlying cause remains unclear. Both the Pfizer and Moderna vaccines include the active ingredients polyethylene glycol, which may explain these reactions.[37] Most of these reactions were minimal and subsided spontaneously, so no treatment was required. However, some patients received glucocorticoids, pain relievers, or antihistamines.[19,27,35,36,38,39] Moreover, many patients were given unneeded antibiotics due to fears of cellulitis or other infections, which emphasize the importance of improving the awareness of the physicians that there is no need to postpone the second dose of the vaccine due to the benign DLRs. Regarding the AstraZeneca vaccine, there are only very few scattered case reports documenting the presence of DLRs following the vaccine.[39,40]

Moreover, when compared with Pfizer and Moderna vaccines, the AstraZeneca vaccine showed a significantly lower rate of DLRs (3.5% vs. 24.5% and 72%), respectively.[20] In the interim primary efficacy analysis of four phase 3 randomized controlled trials of the AstraZeneca vaccine, no case with delayed cutaneous reaction was reported.[41] In terms of the CoronaVac vaccine, Kahraman et al. showed that participants who received the CoronaVac vaccine were associated with a significantly lower incidence of DLRs compared to the Pfizer vaccine (0.05% vs. 3.8%; $p<0.001$) after the first dose, and comparable rates

after the second dose (0.05% vs. 0.05%).[28] The majority of the previously reported studies showed that the incidence of DLRs was higher in females compared to males. Considering that early vaccination programs primarily targeted healthcare providers and that women may be more likely to see a physician, the finding may simply reflect a reporting bias. Nevertheless, there are undoubtedly several factors at play, and biology is one of them. Even while women show a larger immunological response to vaccinations than men do, they also have more adverse outcomes.[42–45]

Morbilliform Rashes

There have been 43 people reported with morbilliform and maculopapular exanthems from 3 different observational studies; 49% of the participants who received the Pfizer vaccination and 51% of those who received the Moderna vaccine. The CDC classified 11 of these instances as anaphylactic reactions after they were reported via the Vaccine Adverse Event Reporting System (VAERS).[46] Most incidences of skin rash that weren't anaphylactic developed during the first few days after injection and resolved within a week. After receiving the Pfizer vaccination, one person had pruritic, maculopapular exanthem that lasted for more than a month. An erythematous rash covered 30% of this patient's body, excluding the oral and genital mucosa but included his face, torso, upper limbs, and thighs.[47] Maculopapular toxidermia was supported by findings of lymphocytic perivascular infiltrates on histology.[47] The patient had no additional systemic symptoms, although he developed simultaneous liver damage with modestly increased gamma-glutamyl transferase and aspartate transaminase enzymes.[47] With this exanthem still present, the doctor recommended against giving the patient a second dosage, and corticosteroids helped the patient's rash and raised liver enzymes over time.[47] A pruritic morbilliform rash appeared on the lower back of another Pfizer vaccine recipient two days after injection from Pfizer; the rash resolved one day later.[48]

After the second dosage, he had a more severe and persistent morbilliform eruption that spread to his lower back, upper back, proximal extremities, and flanks.[48] In the absence of medical care, this rash resolved within the same period of time. Some incidences of COVID-19 infection in children and adults have been accompanied by distinctive morbilliform rashes.[49,50] Spongiosis and minor cutaneous perivascular lymphocytic infiltrates have been seen in histologic investigations of such instances, indicating immune-mediated pathogenesis rather than a direct viral action.[51] Therefore, it is likely that the morbilliform rashes generated by the COVID-19 vaccination are similarly the consequence of immune activation, although the precise mechanism by which this occurs is yet unclear.

Urticaria

Urticaria is a condition characterized by wheals (hives) that resolve within 24 hours.[52] Among six observational reports, urticaria was reported in 55 participants.[52,53] About 30 (55%) of them got the Pfizer vaccination, whereas 25 (45%) got the Moderna vaccine. The CDC classified 11 of these incidents as anaphylactic reactions after they were reported to the VAERS.[46] In contrast, no acute hypersensitivity rashes were seen among the 40 urticaria events in the study of 414 patients from the COVID-19 dermatological registry (17 related with Pfizer vaccine, 23 associated with Moderna).[19] Within three minutes of receiving the Pfizer vaccination, one female patient in the study by Park and colleagues had pruritic urticaria on her limbs and face.

However, the patient's history and tests indicated underlying cholinergic urticaria that had not been identified before.[53] The anaphylaxis was probably caused by heat-induced cholinergic urticaria rather than vaccine-induced urticaria, given that she felt hot while waiting in line for the dosage. As a result, she was able to get the second dosage in a temperature-controlled environment without any complications.[53]

Dermal Hyaluronic Acid Fillers and the Risk of Delayed Inflammatory Reactions

The longevity and the increased frequency of DIRs to hyaluronic acid fillers are the results of their increased resistance to biodegradation. Flu vaccinations, dental operations, low-quality products, viruses, and, most recently, COVID-19 vaccinations have all been linked to the development of DIRs to fillers. Viruses, low-quality products, dental operations, flu vaccinations, and, most recently, COVID-19 vaccinations have all been linked to the development of DIRs to fillers.[54,55] Three observational studies have recorded 15 occurrences of DIRs. Eleven (73%) of the reports are linked to the Moderna vaccination, while four (or 27%) are linked to the Pfizer vaccine. DIRs were developed in fillers that had been administered more than a year or two before the introduction of the COVID-19 vaccine.[55] Rapid onset of symptoms, often within 24 to 48 hours, manifested as localized edema and inflammation at the injection sites.[54,55]

The majority of the cases were resistant to treatment with acetaminophen, hyaluronidase, and antihistamines.[54,55] On the other hand, recent research has provided a new mechanism for these events, opening the door to therapies based on their underlying aetiology. Previous studies have shown that adipose tissue, where most fillers are injected, has a high expression of angiotensin-converting enzyme (ACE) 2 receptors.[55] DIRs to hyaluronic acid fillers may be detected in COVID infection because the SARS-CoV-2 spike protein targets these receptors, and the subse-

quent engagement in the skin triggers a proinflammatory cascade.[56] Inhibitors of ACE (ACEIs) stimulate an anti-inflammatory response by preventing the formation of angiotensin II and lowering the substrate for ACE2.[54,57] All DIRs disappeared entirely within 24 and 72 hours after starting oral lisinopril.[54] There has been promising effectiveness in using ACE-Is to treat DIRs, but further studies are needed to confirm the suggested mechanism of action. Laboratory testing to screen for metabolic changes is essential when treating these reactions with ACEIs, particularly if the patient is taking drugs that potentially interact with ACEIs.[55]

Short-term discontinuation of concomitant medications may be sufficient for the treatment of DIRs to hyaluronic acid fillers since a lengthy course of ACEIs is not necessary.

Pernio and Chilblains

"Painless, erythematous, and violaceous papules and macules" on the hands and feet are common symptoms of a condition called pernio, which may be made worse by cold.[58,59] Since the start of the pandemic, patients infected with COVID-19 have shown signs of lesions resembling pernio.[57,60] They have just lately been linked to COVID-19 vaccinations. Out of the 10 cases reported across the 3 observational studies, 6 were linked to the Pfizer vaccination (60%), while the other 4 were linked to the Moderna vaccine (40%). Pernio is confirmed by the presence of "thick, perivascular lymphocytic infiltrates in the superficial to the deep dermis" in vaccine-associated lesions.[58,59] This kind of lesion usually resolves in a week to a month if treated with topical corticosteroids.[58,59] Pernio lesions are not only seen during COVID-19 infection but also after immunization, which may indicate that the infection and vaccines stimulate the same immune action. According to these data, a direct link between the pernio lesions seen in COVID-19 infection and after vaccination and the effects of the virus may be less likely than previously thought.

Lesions resembling chilblains (such as COVID toes) are among the first cutaneous manifestations seen in people infected with COVID-19.[61,62] SARS-CoV-2 was found in the endothelial cells of chilblains-like lesions in several individuals who had COVID-19.[63] A causal link between chilblain-like lesions and COVID-19 infection has not been proven because of contradictory findings.[62] Chilblains-like lesions are mostly asymptomatic, bluish-reddish acral macules that may deteriorate in response to exposure to cold temperatures. There have been very few reports of chilblain-like lesions caused by the COVID-19 vaccination. These vaccine-induced acral lesions histopathologicaly matched the diagnostic criteria for chilblains; however, there was no clear association between COVID-19 vaccination and chilblain-like lesions.[19]

Other Reactions

Purpuric rash, petechial rash, pityriasis rosea-like reactions, herpes simplex reactivation, varicella zoster, lichen planus, erythema multiforme, erythromelalgia, and early-onset local injection site reactions have been reported as other cutaneous reactions of COVID-19 vaccines. Erythromelalgia, pityriasis rosea, and erythema multiforme are examples of responses that resemble well-known skin symptoms of COVID-19 infection. A total of 14 cases of erythromelalgia were reported; 11 of these (79%) were linked to the Moderna vaccination.[19] Three of the four reported cases of erythema multiforme were linked to the Moderna vaccination, while five of the six reported cases of pityriasis rosea were linked to the Pfizer vaccine.[55,64] Similarly, incidents of COVID-19 infection and herpes simplex reactivations following immunization against COVID-19 have also been recorded. Petechial and purpuric rash, which has been linked to thrombocytopenia following the Moderna vaccination, and flares of previously well-controlled lichen planus are three of the rarer reactions.[65]

Conclusion

The current evidence shows that COVID-19 vaccination is associated with a wide range of dermatological reactions, including local injection-site reaction, pernio- and chilblains-like lesions, delayed inflammatory reactions to dermal hyaluronic acid fillers, urticaria, morbilliform rashes, delayed large local reaction, and other reactions such as purpuric rash, petechial rash, pityriasis rosea-like reactions, herpes simplex reactivation, varicella zoster, lichen planus, erythema multiforme, and erythromelalgia. The majority of these reactions are common in females and resolve spontaneously within a few days to a weak. The second dose of the vaccine was associated with a higher incidence of cutaneous reactions compared to the first dose but milder in intensity. It seems that the Moderna vaccine is associated with a higher incidence of these adverse events compared to the Pfizer vaccine. Furthermore, mRNA vaccines had a higher incidence compared to vector-based and inactivated vaccines. There is a lack of evidence regarding the side events of the Johnson& Janssen vaccine. Further long-term, multicenter studies are required to compare between these vaccines and highlight the best practice in managing these reactions.

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