Mucocutaneous adverse effects following COVID-19 vaccination: a case series with a comprehensive review of the literature

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Since coronavirus disease 2019 (COVID-19) vaccines were approved without long-term monitoring, tracking their adverse effects appears to be necessary. Mucocutaneous adverse events are of great importance due to their visibility and the potential effect on inducing fear in patients leading to vaccine hesitancy.

We searched PubMed, Google Scholar, and Scopus in this regard, and all of the relevant papers published until June 28, 2021, were included if we could access their full texts. Moreover, we included some of our cases from Iran.

We found various mucocutaneous manifestations after COVID-19 vaccination, including local injection site reactions (acute or delayed), urticarial lesions, pityriasis rosea-like rashes, angioedema, morbilliform rashes, pernio-like lesions, acrocyanosis, petechial/purpuric/ecchymotic lesions, herpes flare-up, herpetiform rashes, oral erosive lesions, acral pustular rashes, erythema multiform, dermographism, herpes zoster, generalized pruritus, contact dermatitis, reaction to dermal fillers and non-specific rashes. We categorized them by their time of initiation (acute or delayed) and site of involvement (local injection site, remote area, or generalized).

Delayed local reactions, local injection site reactions, urticarial lesions, and pityriasis rosea-like and morbilliform rashes were among the most common cutaneous adverse events.

Dermatologists should be aware of these potential reactions to manage them properly, reassure patients, and encourage them to continue their vaccination.

Keywords: COVID-19 vaccine, angioedema, pruritus, pityriasis rosea

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WHAT IS KNOWN?

SARS-COV2 vaccines were approved without long-term monitoring due to the emergent situation. Hence, monitoring their adverse effects appears to be necessary.

Several articles reported vaccine's systemic, neurologic, cardiovascular, hematologic, and renal adverse events, but mucocutaneous adverse events are also important due to their visibility and the potential effect on inducing fear in affected individuals, leading to vaccine hesitancy.

What does this study add?

In contrast to some important systemic adverse

effects of COVID-19 vaccines, mucocutaneous reactions are usually minor and self-limited. We recommend a strict work-up, management, and follow-up of the patients with unusual dermatologic signs like patients with targetoid vesiculobullous, erosive cutaneous or mucosal lesions, or multiple/generalized petechia-purpuric/ecchymotic lesions.

Dermatologists should be aware of these potential reactions to manage them properly, reassure patients, and encourage them to continue their vaccination.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic posed a significant burden on healthcare systems worldwide and made the year 2020 the most challenging year in this regard. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines were approved without long-term monitoring due to the emergent situation. Hence, monitoring their adverse effects appears to be necessary.

Several articles reported vaccine's systemic, neurologic, cardiovascular, hematologic, and renal adverse events [1-4], but mucocutaneous adverse events are also important due to their visibility and the potential effect on inducing fear in affected individuals, leading to vaccine hesitancy.

Here, we present dermatologists with an overview of the mucocutaneous adverse events reported following COVID-19 vaccination to obtain a better insight in this regard. The authors of this study have dealt with various aspects of COVID-19 during the pandemic, especially certain dermatologic concerns and hot topics. In this regard, they tried to collect all necessary and related data of their practice. Now, they believe that mucocutaneous reactions of the COVID-19 vaccine are among the most important dermatologic issues of the pandemic. They present some original pictures of their patients with different dermatologic signs and symptoms probably related to recent vaccinations.

PARTICIPANTS AND METHODS

We presented six patients with mucocutaneous presentations after COVID-19 vaccination from Iran and searched PubMed, Google Scholar, and Scopus in this regard. All of the relevant papers published until June 28, 2021, were included if we could access their full texts. Studies in languages other than English were not be included. The following keywords were used for the search: COVID-19 vaccine, Vaccine, Adverse effects, Side effect, Cutaneous, Mucocutaneous, Mucosal, Dermatology, Moderna, Pfizer, Sputnik, Bharat, AstraZeneca, Sinopharm, delayed-type hypersensitivity, SARS-CoV-2, adverse event, local site reaction, injection site reaction, remote site reaction, acute, late, delayed, pityriasis rosea, urticaria, angioedema, maculopapular rash, morbilliform rash, exanthematous rash, petechia, purpura, ecchymosis, pruritus, erythema multiforme, herpes, zoster, pernio, cyanosis, edema

RESULTS

The reported dermatology-related adverse events of the COVID-19 vaccine are summarized in Table 1. We divided these reactions into localized and generalized, and in each group, we considered < 24 hours as acute and > 24 hours as a delayed reaction. We also present our six patients, whose eruptions are shown in Figures 1-6. These reactions were pityriasis rosea, urticaria, erythema multiform, generalized petechia, purpura, and ecchymosis.

DISCUSSION

As seen with other vaccines, the most prevalent dermatologic reactions after COVID-19 vaccination are localized erythema, tenderness, and swelling [5,6].

In an observational cohort study of hospital workers in California, 1.1% of female participants who received the first dose of mRNA-1273 SARS-CoV-2 (Moderna) vaccine developed a delayed-onset pruritic rash at the injection site, and about half of them developed this rash even earlier after receiving the second dose [5]. In that study, none of the employees receiving BNT162b (Pfizer) reported such reactions. Interestingly, this rash was seen only in female cases. Since that study was based on self-reported data, it is possible that many healthcare professionals, especially men, may not consider the rash important enough to report. However, some studies indicate that women are at a greater risk for adverse drug reactions [6], and several hypotheses such as sex-based differences in pharmacodynamics and different body mass indexes

Table 1. Mucocutaneous adverse effects of COVID-19 vaccine

Local lesions
Acute (<24h)
Injection site
McMahon *et al.* [6] (second most common reaction)
Baden *et al.* [43] (most common reaction)
Jęśkowiak *et al.* [1] (most common reaction)
Remote site
Angioedema (lips and acral)
Delayed (>24h)
Injection Site
McMahon *et al.* [6] (most common reaction)
Jacobson *et al.* [5] (most common reaction, seen only in women)
Johnston *et al.* [44] (reported "COVID-19 arm" in 16 patients)
Remote site
Filler
Munavalli *et al.* [15] (DIR to fillers, rapid response to ACEI)
Perniosis, acrocyanosis
Kha *et al.* [45] (reported a case of perniosis two days after vaccination)
Contact dermatitis
Baden *et al.* [43] (third most common reaction)
Others
Erythromelalgia, dermographism, EM, acral pustular rash, herpes flare-up, erosive oral lesions, varicella-zoster
Generalized lesions
Acute (<24h)
Petechial rash
Cebeci *et al.* [46] (an 82-year-old woman with petechial rash on her feet 10 hours after vaccination)
Delayed (>24h)
Urticarial
McMahon *et al.* [6] (third most common reaction)
Baden *et al.* [43] (second most common reaction)
Pityriasis Rosea
McMahon *et al.* [6]
Generalized pruritus
Authors' experience
Morbilliform Rash
McMahon *et al.* [6] (fourth most common reaction)
Non-specific rash
McMahon *et al.* [6] (reported non-specific rashes in infants of breastfeeding women who received vaccine)

Abbreviations: DIR, delayed inflammatory reaction; ACEI, angiotensin-converting enzyme inhibitor; EM: erythema multiforme

have been raised as potential explanations [7,8]. Since this delayed-type hypersensitivity-based reaction was only seen in the Moderna vaccine, one can infer that the Moderna vaccine might have more immunogenic ability than the Pfizer vaccine, but more studies are needed to shed some light on this issue.

Another study recorded 414 cases of mucocutaneous reactions following vaccination with the Moderna and Pfizer COVID-19 vaccines from December 2020 to February 2021. Of those, 83% received Moderna and 17% Pfizer. Delayed local reactions, local injection site reactions, urticaria, and morbilliform rash were the most common dermatologic adverse events in the order stated [6]. Moreover, about half of the patients with mucocutaneous reactions experienced an earlier recurrence following the second dose of the vaccine, consistent with Jacobson *et al.* [5]. Though the exact etiology of this delayed-type reaction (DTR) after the Moderna vaccine is not clear, hypersensitivity to polyethylene glycol used as an excipient in the vaccine is considered a potential etiology [9]. This hypothesis can be tested in future studies by checking the affected individuals regarding their positive history of hypersensitivity to other products

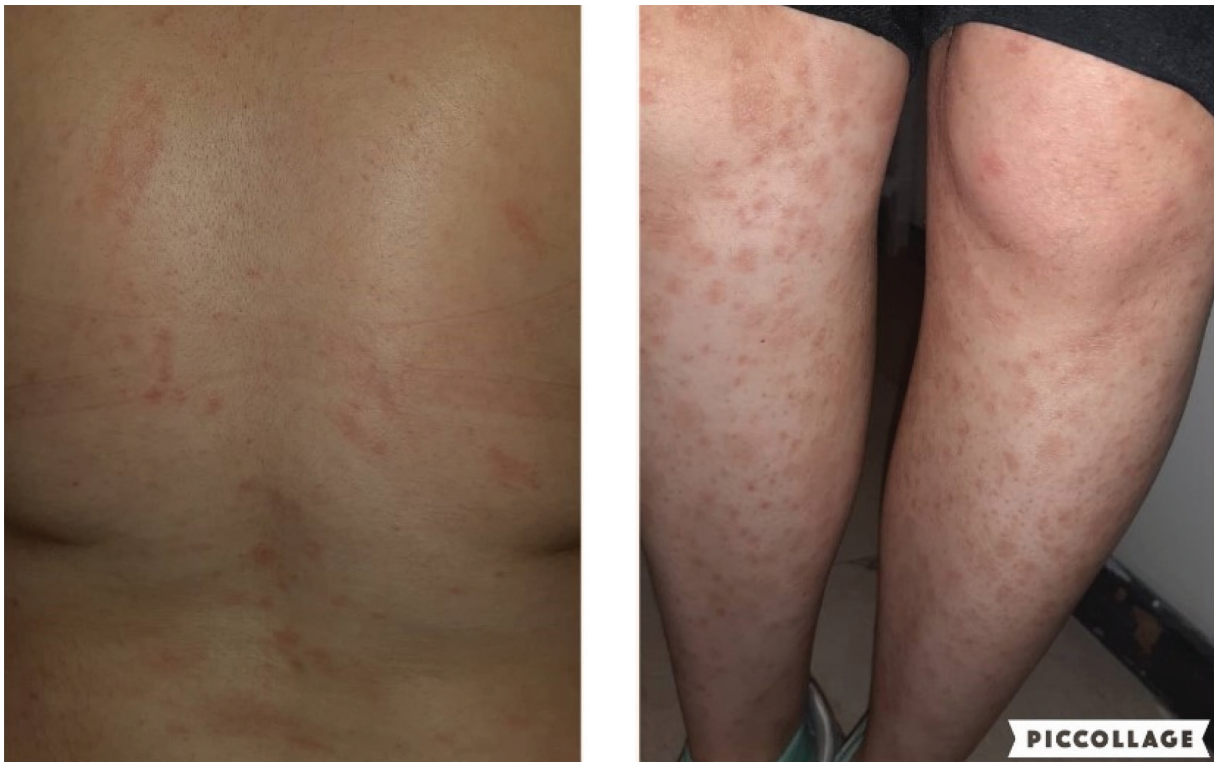

Figure 1. Generalized pityriasis rosea 3-4 weeks after vaccination in two young women

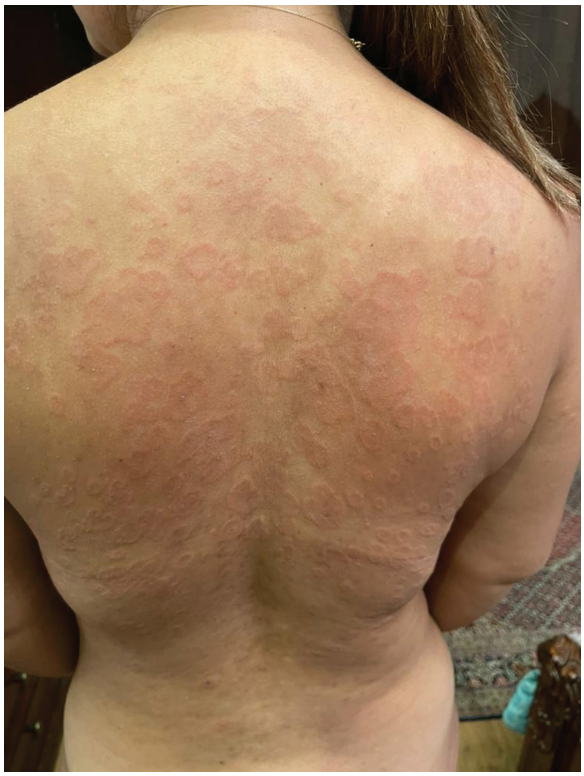

Figure 2. Generalized urticaria after the second dose of vaccine

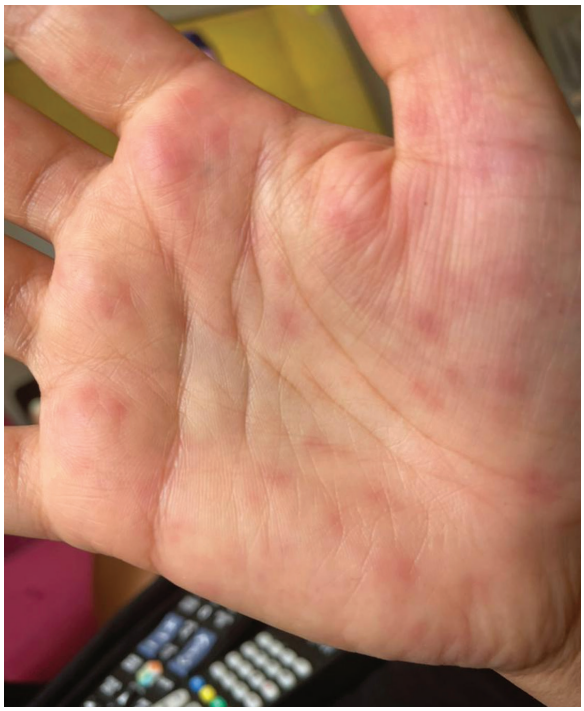

Figure 3. Erythema multiform-like lesions a few weeks after vaccination in a young woman vaccinated in another country before traveling to Iran. The patient simultaneously had extensive erosive mucosal lesions

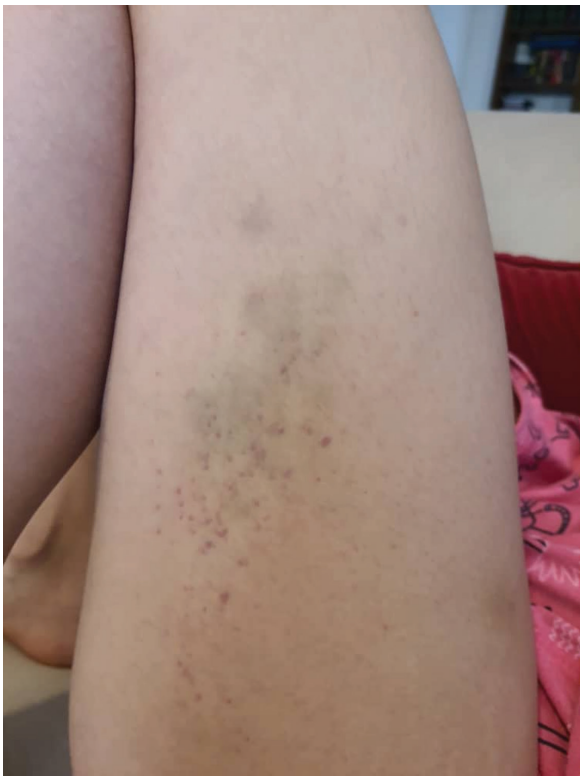

Figure 4. Multiple ecchymotic and purpuric lesions in association with generalized pruritus in a young woman without any history of trauma that had a resolving course within 1-2 weeks without any treatment

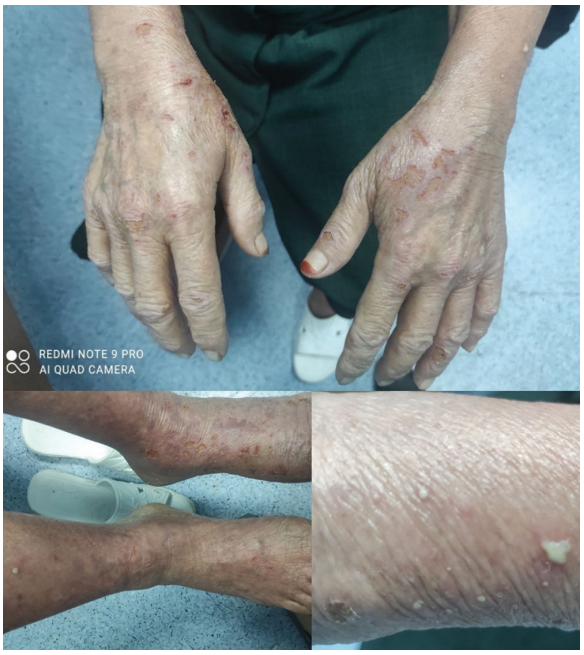

Figure 5. Acral pustular lesions in a 72-year-old woman appearing two weeks after vaccination

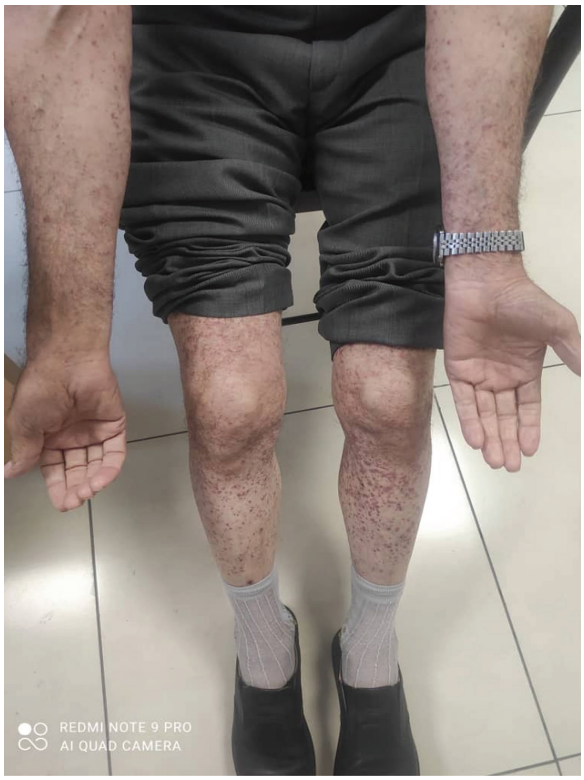

Figure 6. Palpable purpura with a histologic diagnosis of vasculitis in a 69-year-old man with pemphigus vulgaris appearing one week after vaccination

containing polyethylene glycol such as penicillin, injected corticosteroids, laxatives, antacids, and some chemotherapy medications [10,11] or simply by implementing a patch test.

This delayed inflammatory reaction was also seen in a few patients with a history of filler injection [12-16]. Munavalli *et al.* reported 4 cases with DTR to hyaluronic acid filler occurring rapidly within 24 to 48 hours following the first or second dose of COVID-19 vaccines [15]. Since all of these reported cases received their fillers more than eight months before, it is hypothesized that the breakdown of residual filler, which occurs within 3-5 months [14], generates short-chain hyaluronic acid molecules that might be responsible for this reaction [15]. This low-molecular-weight hyaluronic acid, perhaps with biofilms [12,13], might play an important role in developing pre-granuloma milieu and a CD_8+ immune response [12]. Furthermore, the FDA brief on the SARS-CoV-2 Moderna vaccine reported three cases with reaction to dermal fillers, out of which one had filler injection only two weeks

before vaccination [16]. Accordingly, it is impossible to consider filler breakdown as the only mechanism responsible for the reaction to fillers triggered by the vaccine. Genetic susceptibility, HLA subtypes B*08 and DRB1*03, abnormalities in fibrinogen, C-reactive protein, and low complement levels might play a role in this reaction [17-19].

Some resident cutaneous cells such as fibroblasts and lymphocytes have angiotensin-converting enzyme receptors (ACE2), the target ligand for the SARS-CoV-2 spike protein [20]. This might explain the capability of ACE inhibitors in providing rapid clinical resolution seen in DTR [15]. Other therapeutic options include a short course of oral steroids (less than two weeks; does not appear to negatively impact vaccine efficacy), oral antihistamines, and even hyaluronidase for prolonged reactions [14,21,22]. ACE inhibitors might be initiated prophylactically before vaccination to prevent DTR in concerned people with a history of long-lasting dermal fillers or before the second dose of vaccine in those with a history of DTR after the first dose [15]. Another prophylactic measure might be the dilution of hyaluronic acid with lidocaine, saline, or sterile water to reduce the risk of DTR [23,24].

Some less common mucocutaneous adverse effects reported following COVID-19 vaccination include erythromelalgia, pernio/chilblain, pityriasis rosea-like exanthema, herpes simplex flares, varicella-zoster, and non-specific rashes in infants of breastfeeding women [6,25]. Some of them have also been reported following the SARS-CoV-2 infection itself [26,27], reflecting the role of the immune system in presenting these manifestations rather than a direct effect of the virus [28].

A summary of the findings of the studies mentioned above is presented in Table 1.

Since vaccination for COVID-19 began in Iran, the authors of this study have encountered some non-critical and self-limited mucocutaneous reactions, most of which were related to a vaccination history of COVID-19 a few weeks before dermatologic presentations. These eruptions included exanthematous morbilliform maculopapular rashes, symptomatic dermographism, urticaria and angioedema, pityriasis rosea, multiple petechial/purpuric and ecchymotic lesions, generalized pruritus, erythema multiforme, erosive herpetiform oral mucosal lesions or herpetic or herpetiform skin lesions, non-specific papular eruptions, pernio-like lesions, mild acral cyanosis, acral pustular eruptions and acute acral edema observed in our outpatient clinic. Six patients are presented here, and their eruptions are shown in Figures 1-6.

In our short experience with probable COVID-19 vaccine-associated mucocutaneous presentations, most of the reactions were typical rosea-like lesions and even a few atypical forms, symptomatic dermographism, generalized urticaria, non-critical angioedema, and non-specific maculopapular exanthems. Other mentioned signs and symptoms were observed with a lower prevalence. We experienced that almost all of these dermatologic presentations were non-critical and self-limited, but it appears necessary to discuss possible less common and rare critical or potentially life-threatening reactions to increase the body of knowledge in this field, and to publish more reports of vaccine-associated side effects. It was surprising that most of our observations about mucocutaneous eruptions of the COVID-19 vaccine occurred in women, especially young women.

The authors of this study have focused on hot topics of COVID-19 research during the pandemic [27,29-42] and now turned their focus on mucocutaneous eruptions associated with the COVID-19 vaccine as an issue of great importance discussed in this paper. Some of these presentations occurred within one to six weeks after vaccination with various types of COVID-19 vaccines. Most of these mucocutaneous presentations emerged about three to four weeks after vaccination. These patients did not have any other recent medical history that could be related to these dermatologic signs and symptoms other than the COVID-19 vaccination history.

CONCLUSION

In conclusion, in contrast to some important systemic adverse effects of COVID-19 vaccines, mucocutaneous reactions are usually minor and self-limited. Dermatologists should be aware of these potential reactions to properly manage them, reassure patients, and encourage them to continue their vaccination. It is needed to know more about COVID-19 vaccines-associated dermatologic reactions during a time, especially considering the high rate of these types of reactions worldwide. Logically among them, we

may encounter some rare but important and even life-threatening reactions that should be better studied and managed. We recommend a strict work-up, management, and follow-up of patients with rare and unusual dermatologic signs like patients with targetoid vesiculobullous lesions, erosive cutaneous or mucosal lesions, or multiple/generalized petechia-purpuric/ecchymotic lesions. In the feature perspective of COVID-19 adverse effects in the field of dermatology, it is of great value to systematically review these eruptions, especially to distinguish non-critical from critical reactions, risk factors of critical reactions, the impact of immune system status on probable vaccine adverse effects like any severity changes of reactions in immunocompromised patients or patients with certain dermatologic disorders under treatment with immunomodulator medications.

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Conflict of Interests: None declared.

Study approval

Any aspect of the work that has involved human patients was conducted after obtaining the ethical approval of all relevant bodies.

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