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COVID-19: Important Updates and Developments
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The clinical and pathologic spectrum of mucocutaneous reactions after COVID-19 vaccinations in three tertiary referral centers of northern Italy

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Abstract Adverse cutaneous reactions after COVID-19 vaccinations have increased, highlighting not only how SARS-CoV-2 infection but also COVID-19 vaccines may induce adverse cutaneous manifestations. We evaluated the clinical and pathologic spectrum of mucocutaneous reactions after COVID-19 vaccinations, observed consecutively within three large tertiary centers of the Metropolitan City of Milan (Lombardy), comparing our results with the currently available literature. We retrospectively reviewed medical records and skin biopsies of patients diagnosed with mucocutaneous adverse events after COVID-19 vaccinations and followed at three Italian tertiary referral centers in the Metropolitan City of Milan. One hundred twelve patients (77 women and 35 men (112 total); median age, 60 years) have been included in the present study; a cutaneous biopsy was performed in 41 cases (36%). The trunk and arms were the most involved anatomic areas. Autoimmune reactions after COVID-19 vaccinations, urticaria, morbilliform eruptions, and eczematous dermatitis have been the most commonly diagnosed disorders. Compared to the currently available literature, we performed many more histologic examinations, allowing us to make more precise diagnoses. Most of the cutaneous reactions were self-healing and/or responded to topical and systemic steroids and systemic antihistamines, thus not discouraging the general population from carrying out vaccinations, which currently have a good safety profile.
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Introduction

During the last several months, adverse cutaneous reactions after COVID-19 vaccinations have increased, highlighting not only how SARS-CoV-2 infection but also COVID-19 vaccines may induce adverse cutaneous manifestations.[1,2] Each of the currently available COVID-19 vaccines can potentially induce systemic and cutaneous adverse manifestations, albeit with different percentages, mainly due to the different mechanisms of action between the various vaccines and the different vaccine components. To date, the currently available vaccines against COVID-19 can be divided into different subclasses: (1) mRNA vaccines, including Pfizer-BioNTech BNT162b2, USA, and Moderna mRNA1273; (2) viral vector DNA vaccines, such as Oxford-AstraZeneca, Sputnik V, and Johnson & Johnson; (3) recombinant protein subunit vaccines; and (4) inactivated and live attenuated vaccines.[1] Most of the cases of mucocutaneous reactions reported in the literature have been related to Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Johnson & Johnson, since they are the most widely used anti–COVID-19 vaccines in daily clinical practice in Europe and the United States.

COVID-19 vaccine reactions, type I hypersensitivity reactions (such as urticaria, angioedema, and anaphylaxis), and type IV hypersensitivity reactions (such as COVID-19 arm, morbilliform, and erythema multiforme-like eruptions) have been described as the most common manifestations after COVID-19 vaccinations.[1,2] Other manifestations reported include pityriasis rosea-like reactions, autoimmune diseases, herpes zoster reactivations, functional angiopathies, cutaneous vasculitis, and lichenoid drug eruptions.[2-5]

Considering that clinicopathologic correlation plays a pivotal role in reaching a correct diagnosis, even in COVID-19 vaccine reactions, to the best of our knowledge, there are few systematic reports examining the clinicopathologic correlations between the various cutaneous adverse events associated with COVID-19 vaccines.[1] Skin biopsy rates compared to the examined population are always relatively low, reaching a maximum of 7% of all evaluated patients.[1] The case series of reactions after COVID-19 vaccinations usually consist mainly of nonspecific fleeting erythematous reactions, which are evaluated mainly by family doctors or primary medical centers and undergo rapid self-resolution or resolve after treatment.

Lombardy has been the epicenter of the first wave (March and April 2020) of COVID-19 in Italy; consequently, the vaccinated population rate is among the highest in Italy. The present study aimed to evaluate the clinical and pathologic spectrum of mucocutaneous reactions after COVID-19 vaccinations, observed consecutively within three large tertiary centers of the Metropolitan City of Milan (Lombardy), comparing our results with the currently available literature. We sought to highlight the importance of the correlation between the clinical picture and the pathologic features for a correct diagnosis and a classification of mucocutaneous reactions related to COVID-19 vaccines.

Materials and methods

We retrospectively reviewed the medical records and skin biopsies of patients diagnosed with mucocutaneous adverse events after COVID-19 vaccinations at three Italian tertiary referral centers in the City of Milan (Ospedale San Raffaele, Ospedale Metropolitano Niguarda, and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico) between December 2020 and February 2022. All patients had previously consulted general practitioners and/or dermatologists in primary and secondary care settings. Only patients with persistent, difficult-to-diagnose, or diffuse cutaneous manifestations with nonregressive symptoms have been re-evaluated for a better diagnostic and therapeutic framework at our tertiary centers.

For each patient, clinical data have been collected: age, sex, personal medical history, comorbidities, type of COVID-19 vaccine performed, total number of vaccine doses received, type of cutaneous manifestations, anatomic area involved (eg, head/neck, trunk, arms, genitals, legs), presence/absence of systemic symptoms, and any topical and/or systemic treatment performed for the mucocutaneous reactions. Three dermatopathologists (V.C., E.B., F.R.) reviewed the available histopathologic slides. A specific diagnosis was made when it was consistent with only clinical or clinical and histopathologic criteria.

Local site reactions have been defined as occurring within 3 days after the first-dose vaccination, whereas delayed significant local reactions have been defined as occurring 4 or more days after the first vaccination.[1] A wheal at the vaccine site has been considered an immediate or delayed sizeable local reaction, depending on timing. Conversely, urticarial reactions have been defined as wheals appearing beyond the injection site.[1] Patients with insufficient data were excluded from the analysis.

Results

A total of 112 patients were enrolled, and the main clinic-pathologic features of our cohort are summarized in Table 1. The mean latency between the first vaccine dose and the onset of the mucocutaneous reactions was 11 days (ranging from 30 minutes to 28 days); also, for the occurrence of mucocutaneous reactions after the second vaccine dose, the mean was 11 days (ranging between 5 and 13 days), whereas for the third dose the mean was 13.5, ranging between 7.5 days and 17 days. The observed mucocutaneous manifestations were mainly autoimmune diseases (24%), allergic diseases (22.2%), inflammatory diseases (48.2%), and

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Table 1 Results of the clinicopathologic analysis of this case series including 112 patients.

	N	%											
Gender													
Female	77	69											
Male	35	31											
Median age	60 (22-93)												
Autoimmune history													
Negative	104	92.9											
Positive	8	7.1											
Allergy history													
Negative	89	79.5											
Positive	23	20.5											
Anatomic area[≠]													
Trunk	102	91											
Limbs	90	80											
Head/Neck	4	3.5											
Genitals	1	1											
Symptoms													
Itching	33	83											
Burning-skin	5	13											
Others[*]	2	6											
Vaccine													
Pfizer®	48	42											
Moderna ®	22	20											
Astrazeneca®	5	5											
Missing	37	33											
Biopsy													
No	71	64											
Yes	41	36											
Cutaneous reactions			T1	T2	T3	FU	Trunk	Limbs	Head/Neck	Mucosal[***]	AH	AIH	TV
• ***Allergic diseases***													
Urticaria	24	21.5	34 hr	NA	7.5d		23	24	0	17	8	2	8Pfizer;1 Moderna
Anaphylactic shock	1	0.9	72 hr	NA	NA		0	0	1	1	1	0	Pfizer
•***Autoimmune diseases***													
Bullous pemphigoid	17	15	25d	13d	NA	3months	17	17	0	0	0	2	11 Pfizer;2 Astrazeneca;2Moderna
Morphea	4	3.5	15d	16d	NA	10 months	4	4	0	0	0	1	3 Moderna; 1 Astrazeneca
Pemphigus foliaceus	2	1.8	28d	NA	17d	6 months	1	0	0	0	0	0	1 Pfizer
Pemphigus vulgaris	2	1.8	NA	NA	15.5d	6 months	1	1	0	2	0	1	1 Pfizer
Urticaria vasculitis	1	0.9	10d	NA	NA		1	1	0	0	0	0	1 Moderna
Small vessel vasculitis	1	0.9	28d	NA	NA		1	1	0	0	0	0	1 Astrazeneca

(*continued on next page*)

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Table 1 (*continued*)

	N	%										
• ***Inflammatory diseases***												
Eczematous dermatitis	20	17.8	22hr	NA	15d	20	20	1	0	8	1	10 Pfizer; 10 Moderna
Morbilliform rashes[∞]	15	13.4	20hr	NA	NA	15	2	0	0	2	0	10 Pfizer; 2 Moderna
Lichenoid drug eruption	9	8	NA	NA	NA	6 months	7	9	0	0	3	1	4Pfizer; 2 Moderna
Pityriasi rosea-like	5	4.5	14d	NA	NA	2 months	5	2	0	0	0	0	3 Pfizer, 2 Moderna
Covid-arm	2	4.5	9d	NA	NA	0	2	0	0	0	0	2 Moderna
Erythema multiforme	1	0.9	NA	NA	NA	1	1	0	0	0	0	1 Moderna
Erythroderma	1	0.9	5d	5d	NA	1	1	0	0	0	0	1 Pfizer
Psoriasis	1	0.9	NA	NA	NA	1	1	0	0	1	0	1 Pfizer
• ***Others***												
Grover-like eruptions	3	2.6	7d	NA	NA	3	1	0	0	0	0	1 Astrazeneca
Herpes reactivation	3	2.6	15d	NA	NA	1	0	2	0	0	0	3 Pfizer

* others included diarrhea/ headache/difficulty in breath;
≠ including different anatomic areas in the same patients;
*** including more mucosal manifestations in the same patients (1 genital, 9 oedema lips, 1eyelids, 2 throat, 7 tung)
∞ morbilliform rashes include erythema and generalized maculo-papular rash.T1 Mean time from the first dose
T2 Mean time from the second dose
T3 Mean time from the third dose
β including 9 oedema lips, 1eyelids, 2 throat, 7 tung
NA means not available
BA means body area; FU means follow-up;
AH means personal history positive for allergy (urticaria: 6 allergy; 2 allergy to nichel including 1 case of allergy to profillins and 3 cases of chronic urticaria; eczematous dermatitis: 7 allergy to pollens and 1 to Nichel; morbilliform rashes: 2 allergy to pollens; lichenoid drug eruption: 2 allergy to pollens, 1 allergy to nichel;);
AIH means personal history positive for autoimmune diseases (urticaria: 2 autoimmune thyroiditis; bullous pemphigoid: 2 autoimmune thyroidits; morphea: 1 eosinophilic fasciitis; pemphigus vulgaris: 1 eosinophilic fasciitis; eczematous dermatitis: 1 autoimmune thyroidits; lichenoid drug eruption: 1 autoimmune thyroidits; psoriasis: 1 systemic lupus erythematosus; TV means type of vaccination

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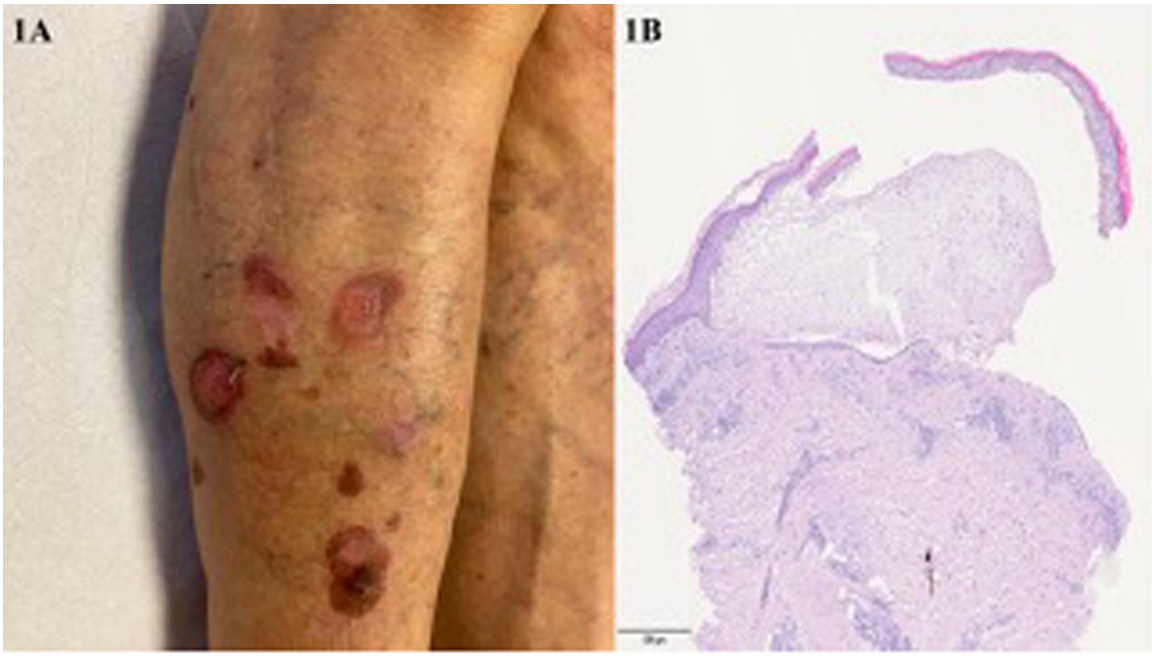

Fig. 1 (A) Bullous pemphigoid after Moderna anti–COVID-19 vaccine. (B) Subepidermal blister, with underlying inflammation and infiltrates with eosinophils (hematoxylin and eosin, × 4).

other mucocutaneous manifestations (5.3%). Specifically, after the first dose, autoimmune diseases rose with a mean of 21.5 days from the doses of the anti–COVID-19 vaccine (ranging between 10 and 28 days), inflammatory diseases with a mean of 6 days (ranging between 22 hours and 14 days), and allergic diseases with a mean of 53 hours (ranging between 0.3 hours and 72 hours). Table 1 summarizes the anatomic distribution of the cutaneous manifestations after COVID-19 vaccinations, with the relative past medical histories of the patients and type of vaccines (Table 1).

For treatment of the cutaneous reactions, 52 patients (29%) received systemic steroids, that is, betamethasone (n = 15) and prednisone (n = 37), while clobetasol was the most widely used topical steroid. Thirty (n = 30; 26.7%) patients received antihistamines, mainly second-generation, such as cetirizine and ebastine. Intravenous chlorpheniramine (first-generation antihistamine) was given only during the acute phase in the more severe cases. A 55-year-old man with angioedema received intramuscular adrenaline with the resolution of signs and symptoms, while a 61-year-old White woman with generalized morphea required a different therapeutic regimen. She received methotrexate with 7.5 mg/wk administration, but after discontinuation due to hepatotoxicity, she was given mycophenolate mofetil and clobetasol 0.5% cream.[3] The remaining patients had spontaneous resolution of the cutaneous manifestations without any intervention.

The patients listed in Table 1 improved after treatment or experienced spontaneous resolution. The mean followup of the patients was 6 months. The diagnosis of the patients with pemphigoid (n = 17), pemphigus (n = 4), and urticarial vasculitis (n = 1) were confirmed by histopathology, direct and indirect immunofluorescence studies, and circulating auto-antibodies detection. In contrast, patients with morphea (n = 4), lichenoid drug eruption (n = 9), erythroderma (n = 1), small-vessel vasculitis (n = 1), Grover-like eruption (n = 3), and eczematous spongiotic dermatitis (n = 1) were confirmed by histopathology. We noted the latency between the vaccine dose administration and the onset of cutaneous manifestation.

Discussion

As reported in the currently available literature and our study, there is strong evidence that not only the SARS-CoV-2 virus but also the COVID-19 vaccines could induce mucocutaneous reactions (Figures 1-3). Molecular mimicry exists between SARS-CoV-2 and human components (eg, the spike protein sequences used to design the vaccines), activating autoreactive T or B cells, thus explaining some COVID-19-related diseases as well as adverse reactions to COVID-19 vaccinations.[2]

In this study, we enrolled patients who developed mucocutaneous manifestations after administering three COVID-19 vaccine doses; specifically, we included only patients with persistent cutaneous manifestations who were challenging to diagnose. There was also a certain degree of complexity that could not be managed in the setting of primary and secondary care and consequently required the services of our tertiary referral centers.

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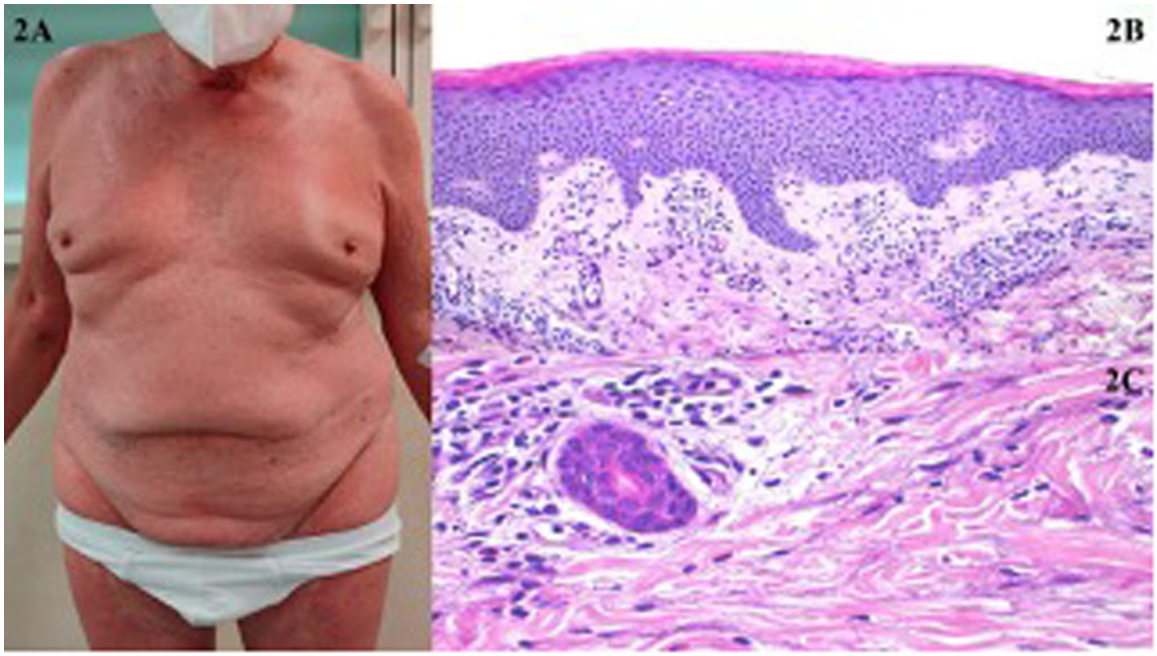

Fig. 2 (A) Erythroderma in an 81-year-old man occurring 5 days after the Pfizer-BioNTech COVID-19 vaccine. (B) Hyperkeratosis, acanthosis, focal spongiosis with exocytosis, slight perivascular lymphocytic infiltrate with some eosinophils, and occasional apoptotic keratinocytes (hematoxylin and eosin, × 20). (C) Scattered eosinophils are present in the inflammatory infiltrate (hematoxylin and eosin, × 30).

Our findings are in accordance with the literature, and they show a high prevalence of type I reactions (urticarial-type/angioedema) in 47% of cases[1,2,6-13]; among them, 12 patients had a positive history of allergy and/or urticarial-like reactions, and the remaining patients had reactions that were *de novo*. As recently reported, most vaccine reactions are "nonallergic" per se but due to an autoimmune/inflammatory syndrome induced by adjuvants.[8] The onset of these eruptions is mainly associated with immediate hypersensitivity to vaccine components and/or a hidden history of allergies to polyethylene glycol and polysorbates with subsequent immunoglobulin E production and degranulation of mast cells.[2] These reactions could arise with any vaccine; therefore, their occurrence is often found in daily clinical practice. These reactions usually resolve with steroid and/or antihistamine therapy.

We also observed type IV reactions (such as COVID-19 arm, erythema multiforme, and eczematous spongiotic reactions). These reactions are induced by recognizing allergen spike peptides by antigen-presenting cells, activating CD4+ lymphocytes. This induces tissue damage and inflammation through the secretion of interferon gamma and tumor necrosis factor alpha.[2] These cutaneous reactions have also been reported after dermal fillers (eg, hyaluronic acid) and other vaccines,[2] but the close association with COVID-19 vaccines, together with the negative history for fillers and/or recent administration of other vaccine types, made it possible to link our type IV reactions cases only to COVID-19 vaccines.

Finally, although erythema multiforme has been described after SARS-CoV-2 infection (with about 23 published reports to date), vaccine-induced erythema multiforme is rarer, with about 10 cases reported in the current literature[14] with a preference for Pfizer and Moderna COVID-19 vaccines. In this setting, the development of type I and type IV reactions and the temporal relationship seem to be indicative of a direct pathogenic role of the COVID-19 vaccines in triggering these skin reactions. Skin tests were not performed in our cohort, because the validity of epicutaneous and intradermal testing to the anti–COVID-19 vaccines has not yet been established.[15,16]

Interestingly, in our cohort, we found different cases of autoimmune diseases, such as bullous pemphigoid (BP), pemphigus vulgaris (PV), pemphigus foliaceus, urticarial vasculitis, and morphea accounting for 27 cases out of 112 (24% of the whole cohort) confirmed by immunopathological studies. As mentioned previously, the high presence of autoimmune conditions in our case series is not surprising, because it has been reported how vaccines could induce autoimmune diseases through molecular mimicry mechanisms.[3] Specifically, as for bullous pemphigoid, there is a series of 21 cases of Pfizer-BioNTech SARS-CoV-2 vaccine–associated bullous pemphigoid (partly included also in the current case series), suggesting that vaccine-induced BP could stem from vaccine-mediated stimulation of pre-existent, subclinical autoreactivity against hemidesmosomal components, as seen in a percentage of pruritic dermatoses of the elderly characterized by immunoglobulin G–mediated autoimmunity against

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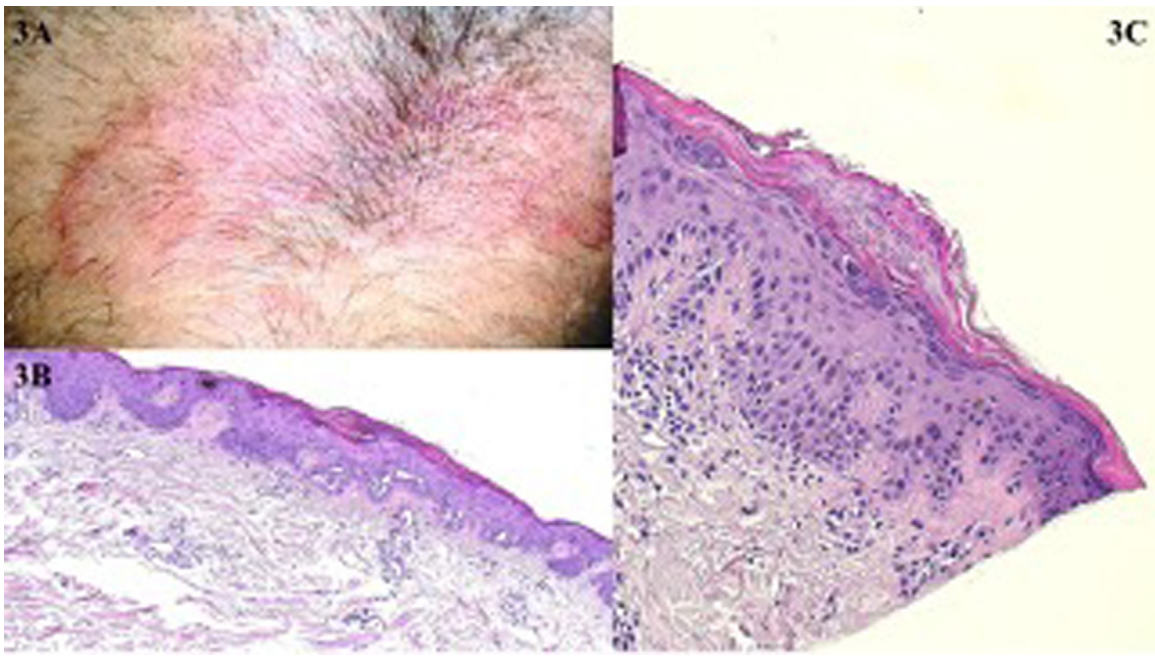

Fig. 3 (A) Grover-like eruption characterized by arciform, papular, and erythematous lesions in a 60-year-old male patient, occurring 7 days after AstraZeneca COVID-19 vaccine. (Reproduced with permission from Erika Schmitt, MD.) (B) Suprabasal Groover-like acantholysis and parakeratotic scale (hematoxylin and eosin, × 20). (C) Higher view of parakeratosis and dyskeratosis (hematoxylin and eosin, × 30).

BP230.[4] We also detected two cases of pemphigus foliaceus and PV, confirming that COVID-19 vaccines could upregulate the production of interleukin (IL)–4, IL-17, and IL-21, already involved in the pathogenesis of PV.[5] Finally, we also detected four cases of generalized morphea after COVID-19 vaccinations, showing a good outcome in all cases.[3] As for the pathogenesis of generalized morphea after COVID-19 vaccinations, both mRNA and recombinant adenoviral vector vaccines could activate cytokines, chemokines, and type-I interferon, which play a pivotal role in the pathogenesis of morphea and systemic sclerosis, thus correlating also with disease activity.[17,18] We did not find purely mucosal manifestations induced by COVID-19 vaccines, but the mucosal involvement (eg, tongue edema, eyelids edema, lips edema, bullous lesions in pemphigus) fell within systemic manifestations (such as bullous diseases and urticarial with angioedema), confirming a lower tropism of COVID-19 vaccines for mucosal manifestations compared to the cutaneous ones, as it has also been reported in a recent review.[19]

A strength of our contribution, when compared with previous reports,[2,6-13,20] is the number of biopsy samples collected out of the total sample. In another report, out of 803 reported vaccine reactions, only 58 (7%) cases had been biopsied.[2] In contrast, out of 112 vaccine reactions in our cohort, a biopsy with histopathologic confirmation was performed in 41 cases (36%). Among the analyzed samples, a diagnosis of lichenoid drug eruption, urticarial vasculitis, erythema multiforme, and Grover-like eruptions could be identified only on histopathologic grounds. Although rare, acantholytic dyskeratosis mimicking Grover disease has already been reported[20-22] in the setting of COVID-19 vaccine reactions,[21] highlighting that a differential diagnosis includes reactivation of Grover disease by the vaccine as a possible trigger factor.[22] We also observed erythroderma consistent with a drug eruption in an 81-year-old man. Some cases of erythroderma induced by COVID-19 vaccines, although rare, have been previously reported in the literature.[23-25] These have been related to an abnormal release of IL-6 with the recruitment of Th17 cells induced by the viral components and vaccine adjuvants.[23-24]

A limitation of our study is that it is a retrospective study carried out in tertiary referral centers, where many more common cutaneous reactions may not have been referred and could not be evaluated.

Conclusions

Our report shows how, in a high percentage of cases, COVID-19 vaccines could mainly induce autoimmune cutaneous diseases due to molecular mimicry rather than pure allergic reactions. Compared to the currently available literature, we were able to perform a high number of histologic examinations that have allowed us to make more precise diagnoses.

Although our case series concerns patients sent to tertiary centers with more difficult-to-manage and potentially more severe skin diseases, most of these COVID-19-associated cutaneous reactions were self-healing and/or responded to topical and systemic steroids and systemic antihistamines. Fi-

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nally, our report should not be construed to discourage the general population from receiving a vaccination, which currently has a good safety profile.

Conflict of interest

The authors declare no conflicts of interest.

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