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COVID-19: Important Updates and Developments

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The clinical and pathologic spectrum of mucocutaneous reactions following COVID-19 vaccines in three tertiary referral centers of Northern Italy.

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Running head: mucocutaneous reactions COVID-19 vaccines.

Conflict of interests: none

Abstract

Adverse cutaneous reactions following COVID-19 vaccines 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 following COVID-19 vaccines, 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 following COVID-19 vaccines and followed at 3 Italian tertiary referral centers in the Metropolitan City of Milan. One hundred twelve patients (35M:75 F; median age 60 years) have been included in the current study; a cutaneous biopsy was performed in 41 cases (36%). The trunk and arms were the most involved anatomic areas. Autoimmune reactions following COVID-19 vaccines, 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 vaccines, which currently have a good safety profile.

Introduction

During the last several months, adverse cutaneous reactions following COVID-19 vaccines 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 sub-classes: i) mRNA vaccines, including Pfizer-BioNTech® BNT162b2, USA and Moderna® mRNA1273; ii) viral vector DNA vaccines, such as Oxford-AstraZeneca®, Sputnik V® and Johnson & Johnson®; iii) recombinant protein subunit vaccines and iv) 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 the daily clinical practice in Europe and USA.

COVID-19 vaccines 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 following COVID-19 vaccines.[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 following COVID-19 vaccines usually consist mainly of non-specific fleeting erythematous reactions, which are mainly evaluated 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 following COVID-19 vaccines, 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 pathological

features for a correct diagnosis and a classification of mucocutaneous reactions related to COVID-19 vaccines.

Materials and Methods

We retrospectively reviewed medical records and skin biopsies of patients diagnosed with mucocutaneous adverse events following COVID-19 vaccines 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 non-regressive 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, gender, personal medical history, comorbidities, type of COVID-19 vaccine performed, the total number of vaccine doses received, type of cutaneous manifestations, the anatomic area involved (e.g., 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 (VC, EB, FR) 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 three days after the first-dose vaccination, while delayed significant local reactions as occurring four 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), while 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 other mucocutaneous manifestations (5.3%). Specifically, after the first dose, autoimmune diseases arose with a mean of 21.5 days from the doses of the anti-COVID19 vaccine (ranging between 10 days and 28 days), inflammatory diseases with a mean of 6 days (ranging between 22 hours and 14 days), 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 vaccines, 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, i.e. 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 only given 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 Caucasian woman with generalized morphea required a different therapeutic regimen. She received methotrexate (MTX) 7.5 mg/week administration, but following 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 follow-up of the patients was six 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), 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-Cov2 virus but also the COVID-19 vaccines could induce mucocutaneous reactions (Figs. 1-3). Molecular mimicry exists between SARS-CoV-2 and human components (e.g., the spike-protein sequences used to design the vaccines), activating autoreactive T or B cells, thus explaining some COVID-19-related diseases as well 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.

Our findings are in accordance with the literature and 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, while the remaining patients had reactions that were *de novo*. As recently reported, most vaccine reactions are "non-allergic" *per se* but due to an autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[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 (PEG) and polysorbates with subsequent IgE 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 arm, erythema multiforme, and eczematous spongiotic reactions). These reactions are induced by recognizing allergen spike peptides by antigen-presenting cells (APC), activating CD4+ lymphocytes. This induces tissue damage and inflammation through the secretion of interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF-α).[2] These cutaneous reactions have also been reported after dermal fillers (e.g., 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 (EM) has been described after SarsCov2 infection (with about 23 published reports to date), vaccine-induced EM 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 (PF), urticarial vasculitis (UV), and morphea accounting for 27 cases out of 112 (24% of the whole cohort) confirmed by immunopathological studies. As mentioned above, 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 twenty-one cases of Pfizer-Biontech® SARS-CoV2 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, sub-clinical autoreactivity against hemidesmosomal components, as seen in a percentage of pruritic dermatoses of the elderly characterized by IgG-mediated autoimmunity against BP230.[4] We also detected two cases of PF 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 4 cases of generalized morphea after COVID-19 vaccines showing a good outcome in all cases.[3] As for the pathogenesis of generalized morphea following COVID-19 vaccines, both mRNA and recombinant adenoviral vector vaccines could activate cytokines, chemokines, and type-I Interferon, that 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 (e.g., 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 paper, 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 histopathological 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. Finally, our report should not be construed to discourage the general population from receiving a vaccination, which currently has a good safety profile.

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Table legend.

Table 1. The results of the clinicopathologic analysis of this case series included 112 patients.

	N	%											
Gender Women Men	77 35	69 31											
Median age	60 (22 - 93)												
Autoimmune history Negative Positive	104 8	92.9 7.1											
Allergy history Negative Positive	89 23	79.5 20.5											
Anatomic area[≠] Trunk Limbs Head/Neck Genitals	102 90 4 1	91 80 3.51											
Symptoms Itching Burning Others*	335 2	83 13 6											
Vaccine Pfizer® Moderna ® Astrazeneca ® Missing	48 225 37	42 205 33											
Biopsy No Yes	71 41	64 36											
Cutaneous reactions ● ***Allergic diseases*** Urticaria Anaphylactic shock	241 17	21.5 0.9	T1 34 hr 72 hr	T2 NA NA	T3 7.5d NA NA	FU 3mont	Trunk 23 0	Limbs 24 0	Head/Neck 0 1	Mucosal*** 17 1	AH 8 1	AIH 2 0	TV 8Pfizer;1 Moderna Pfizer 11 Pfizer;2

●***Autoimmune diseases***	4	15			NA	hs	17	17	0	0	0	2	Astrazeneca;2Moderna
Bullous pemphigoid	2	3.5	25d	13	17d	10	4	4	0	0	0	1	3 Moderna; 1 Astrazeneca
Morphea	2	1.8	15d	d	15.5	month	1	0	0	0	0	0	1 Pfizer
Pemphigus foliaceus	1	1.8	28d	16	d	s	1	1	0	2	0	1	1 Pfizer 1 Moderna
Pemphigus vulgaris	1	0.9	NA	d	NA	6	1	1	0	0	0	0	1 Astrazeneca
Urticaria vasculitis	20	0.9	10d	N	NA	month	1	1	0	0	0	0	
Small vessel vasculitis	15	17.	28d	A	15d	s	20	20	1	0	8	1	
● ***Inflammatory diseases***	9	8	22h	N	NA		15	2	0	0	2	0	
Eczematous dermatitis	5	13.	r	A	NA		7	9	0	0	3	1	10 Pfizer; 10 Moderna
Morbilliform eruption	2	4	20h	N	NA		5	2	0	0	0	0	
Lichenoid drug eruption	1	8	r	A	NA		0	2	0	0	0	0	10 Pfizer; 2 Moderna
Pityriasis rosea-like	1	4.5	NA		NA		1	1	0	0	0	0	
Covid-arm	1	4.5	14d		NA		1	1	0	0	0	0	4Pfizer; 2 Moderna
Erythema multiforme		0.9	9d	N	NA		1	1	0	0	1	0	
Erythroderma		0.9	NA	A		6							3 Pfizer, 2 Moderna
Psoriasis	3	0.9	5d	N		month							
● ***Others***	3		NA	A	NA	s	3	1	0	0	0	0	2 Moderna
Grover-like eruptions				N	NA	2	1	0	2	0	0	0	1 Moderna
Herpes simplex reactivation		2.6		A		month							1 Pfizer
		2.6	7d	N		s							1 Pfizer
			15d	A									
				N									
				A									1 Astrazeneca
				N									3 Pfizer
				A									
				5d									
				N									
				A									
				N									
				A									

* others included diarrhea/ headache/difficulty in breath;
**Type I reactions included urticarial and angioedema + one case of anaphylaxtic shock with angioedema;
≠ including different anatomic areas in the same patients;
*** including more mucosal manifestations in the same patients (1 genital, 9 edema lips, 1eyelids, 2 throat, 7 tung)
∞ morbilliform eruptions include erythema and generalized maculo-papular exanthem.
T1 Mean time from the first dose
T2 Mean time from the second dose
T3 Mean time from the third dose
β including 9 edema lips, 1 eyelids, 2 throat, 7 lung

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 nickel including 1 case of allergy to profillins and 3 cases of chronic urticaria; eczematous dermatitis: 7 allergy to pollens and 1 to nickel; morbilliform eruption: 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

Figure legends.

Figure 1. A. Bullous pemphigoid after Moderna® anti-COVID-19 vaccine. **B.** Subepidermal blister, with underlying inflammation and infiltrates with eosinophils. (Hematoxylin and Eosin, 4X)

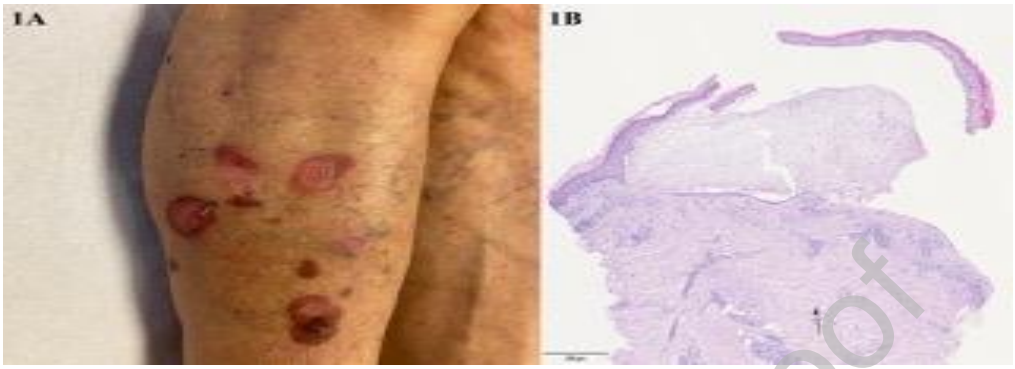

Figure 2. A Erythroderma in an 81-year-old man occurring five days after the Pfizer-Biontech® COVID-19 vaccine. **B.** Hyperkeratosis, acanthosis, focal spongiosis with exocytosis, slight perivascular lymphocytic infiltrate with some eosinophils and occasional apoptotic keratinocytes. (Hematoxylin and Eosin, 20X) **C.** Scattered eosinophils are present in the inflammatory infiltrate (Hematoxylin and Eosin 30X)

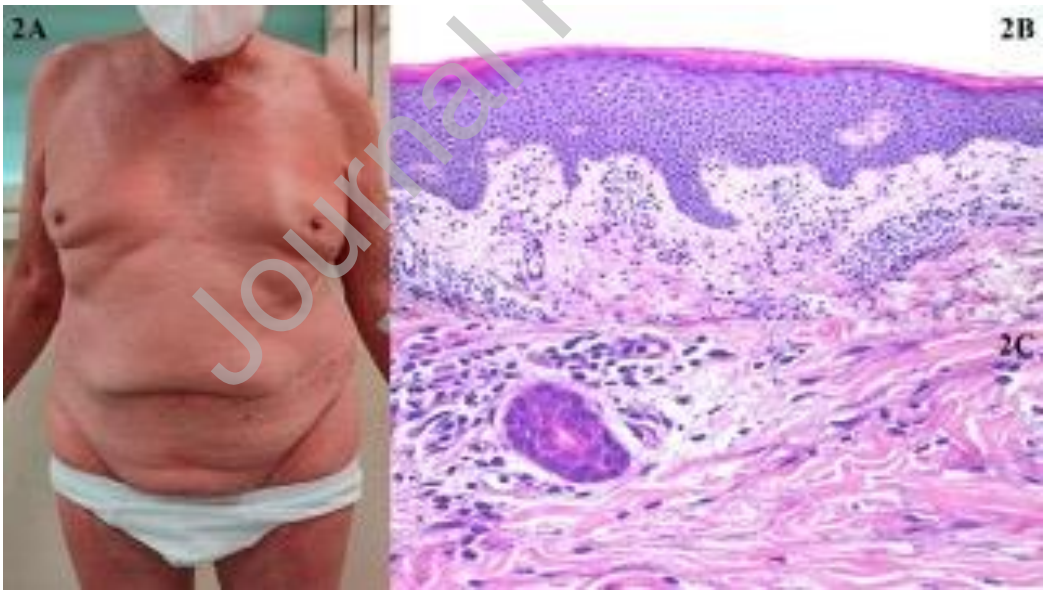

Figure 3. A. Grover-like eruption characterized by arciform, papular, and erythematous lesions in a 60-year-old male patient, occurring seven days after Astrazeneca® COVID-19 vaccine. (Courtesy of Erika Schmitt, MD) **B.** Suprabasal Groover-like acantholysis and parakeratotic scale. (Hematoxylin and Eosin, 20X) **C.** Higher view of parakeratosis and dyskeratosis. (Hematoxylin and Eosin, 30X)