

Clinicopathological features of cutaneous reactions after mRNA-based COVID-19 vaccines

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Conflicts of interest

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Abstract

Background

Cutaneous reactions, mostly on injection site after mRNA-based COVID-19 vaccines, have been reported but not with detailed histopathological characterization.

Objectives

Characterization and classification of these reactions in a clinical and pathological point of view.

Methods

Monocentric case series of 11 patients with cutaneous manifestations, clinically and histologically characterized after COVID-19 vaccination.

Results

From January to June 2021, we recorded 11 cutaneous reactions to mRNA COVID-19 vaccines from BNT162b2 ($n = 8$) and mRNA-1273 ($n = 3$). Generalized reactions showing erythematous rash or purpura were the most common clinical presentation, and drug-reaction-like pattern was the most common histological finding.

Conclusions

A proper clinicopathological classification will be helpful in the early diagnosis and management of the cutaneous reactions to mRNA COVID-19 vaccines.

Introduction

As in many countries, two mRNA COVID-19 vaccines have been authorized in Switzerland by the Swiss Agency for therapeutic products and are currently administered to the general population: Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273). Cutaneous adverse reactions have been reported for both vaccines. Local injection site reactions (redness and swelling) were few reported, in 5%–7% of the patients after BNT162b2 vaccination.¹ Moderna's trial reported also delayed large local reaction, characterized by erythema, induration and tenderness, called 'COVID-arm' after the first (0.8%) or the second dose (0.2%). Other authors report reactions including « rash » (0.3%), or urticaria (0.2%).² Allergic reactions such as generalized urticaria, diffuse erythematous and pruritic rash with a very short delay were also described in patients with or without allergic history.^{3, 4}

Recently, McMahon *et al.* reported 414 patients with one or more acute or delayed cutaneous reactions to both vaccines.⁵ In this study, the most common cutaneous reactions were delayed large local reaction, followed by local injection site reactions, urticaria, morbilliform rash and erythromelalgia. The median time from first vaccination to onset of cutaneous symptoms was 7 days. They also reported fewer reactions such as swelling at the site of cosmetic fillers, pernio/chilblains, varicella-zoster, herpes simplex flares, pityriasis rosea-like eruption and vasculitis. They also indicated that 90% of the reactions were reported in female patients.⁵

Smaller cohorts or cases described Varicella-zoster virus reactivation, erythematous reaction at the injection site, diffuse morbilliform rash, mild erythema and positive dermographism.^{6, 7} Some rare studies described clinicopathological correlation for delayed large local reactions.^{8, 9}

However, none of these studies focussed on the histological aspect of cutaneous reactions, especially on the lesions located at a distance from the vaccine injection site, which can be of great help for the clinical differential diagnosis.

Our work attempts to improve the clinicopathological description and comprehension of cutaneous reactions to the Pfizer–BioNTech and Moderna vaccines.

Materials and methods

We performed a monocentric retrospective data analysis to characterize clinical and histopathological aspects of skin reactions to BNT162b2 and mRNA-1273 COVID-19 vaccines at University Hospital of Geneva. This vaccination campaign began on January 27. Both vaccines require two doses 3–4 weeks apart. As inclusion criteria, a skin biopsy was needed. Clinical aspects of the skin manifestations were either directly evaluated in the presence of the patients or indirectly assessed through clinical pictures. Allergic reactions, skin or systemic disease history, were recorded, and all patients were re-examined few days later.

A skin biopsy was performed for each patient at admission, was placed into formalin 10%, fixed, embedded in a paraffin block and processed for light microscopy using standard procedures. Serial sections were stained with haematoxylin–eosin. The entire skin biopsy specimen was examined by 3 dermatopathologists.

Results

Cohort

Among 11 subjects, 72.7% received BNT162b2. The mean age was 70 years (range 36–89 years), and 7 (63.6%) patients were female. 81% of the skin reaction appeared after the second dose of the vaccine. A mean delay between injection and symptom was near to 4.5 days (range 1–8) after the first and 11.5 days (range 2–21) after the second injection (Table 1). None were known for allergic history.

Table 1. Clinical and demographic characteristics of the subjects with skin reactions after BNT162b2 or mRNA-1273 COVID-19 vaccine

Patient ID	Sex	Age (years)	Vaccine	Number of dose	Onset of reaction after vaccine	Distribution of cutaneous lesions	Clinical features	Histological features
1	M	81	Pfizer	1	8 days after 1st injection	Legs and arms	Erythematous scaly rash	Drug-reaction-like†

Patient ID	Sex	Age (years)	Vaccine	Number of dose	Onset of reaction after vaccine	Distribution of cutaneous lesions	Clinical features	Histological features
2	M	73	Moderna	2	16 days after 2nd injection	Back and arms	Erythematous rash	Drug-reaction-like

AGEP, Acute generalized exanthematic pustulosis.

[†] Drug-reaction-like = variable epidermal keratinocyte necrosis associated with a perivascular lymphocytic infiltrate in the superficial and mid dermis, and a variable number of eosinophils and sometimes neutrophils.

Clinical and histological aspects

Most of the lesions observed were not on the injection site. Skin lesions appeared mostly on the trunk ($n = 8$) followed by the legs ($n = 6$) and the arms ($n = 5$). We did not notice acral or facial lesions.

Clinical patterns were erythematous ($n = 6$), purpuric ($n = 2$), urticarial ($n = 1$), prurigo-like ($n = 1$) and pityriasis rosea-like ($n = 1$; Figs 1,2). Regarding extracutaneous symptoms, 3 patients had systemic symptoms such as fever, fatigue and headache (Patients_2,6,7).

Drug reaction-like rash


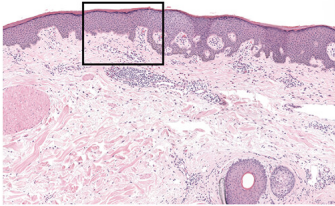
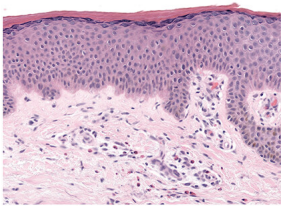
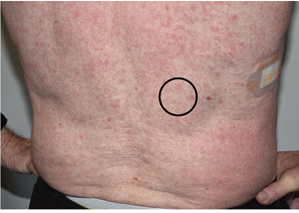
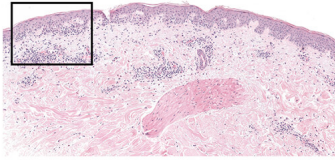
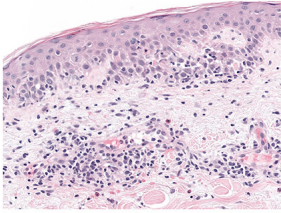

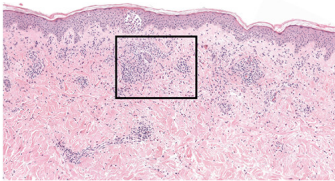
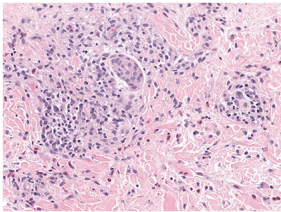

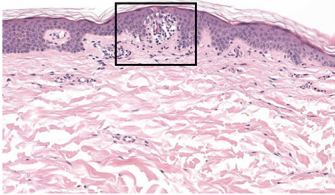
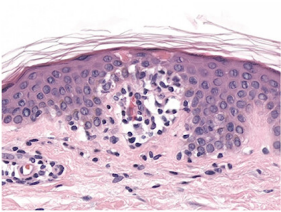

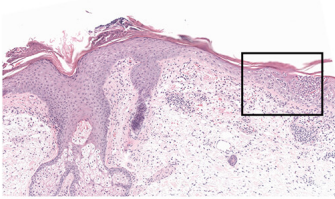
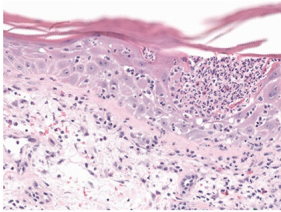

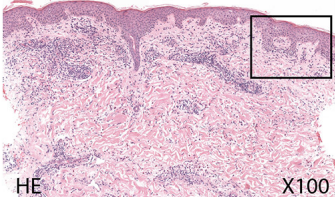
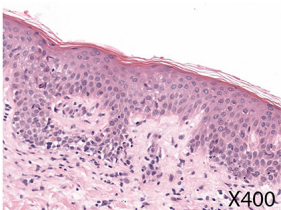
	SeqID	Onset (days)	Clinical features	Histological features	
(a)	1	8			
(b)	2	16			
(c)	3	14			
(d)	4	13			
(e)	5	4			
(f)	6	15			

Figure 1

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Drug-reaction-like rash after BNT162b2 or mRNA-1273 COVID-19 vaccine. Clinical (left) and histological (right) aspects for patients 1 to 6 after mRNA COVID-19 vaccine. Black circle targets the site of biopsies. Black rectangles target where the

zoom is made on the biopsy. (a–f) The 6 patients with clinical features of erythematous rash associated with crusted plaques for patient 5 (e) or with a pityriasis rosea-like features for patient 6 (f). lesions are localized on trunk or back for patient 2 to 6 (b–f), legs for patients 1, 3 and 5 (a,c,e) and arms for patients 1 to 3 (a–c). Histologically, the pattern was a ‘drug-reaction-like’ with epidermal keratinocyte necrosis, perivascular lymphocytic infiltrate in the superficial to mid dermis associated with eosinophils and neutrophils. Patient 5 (e) also showed with subcorneal pustules.

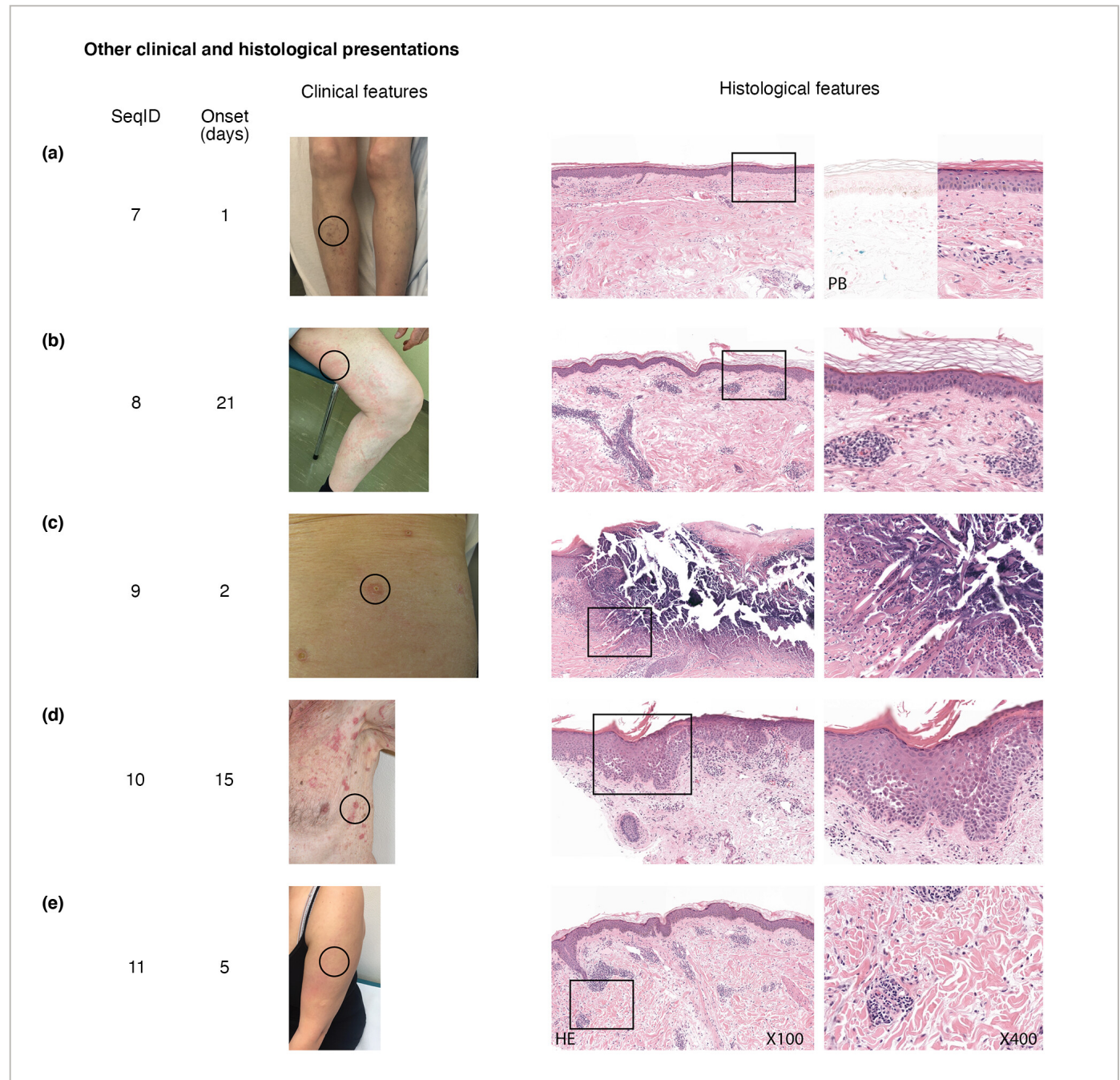


Figure 2

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Other cutaneous manifestations after BNT162b2 or mRNA-1273 COVID-19 vaccine. Clinical (left) and histological (right) aspects for patients 7 to 11 after mRNA COVID-19 vaccine. Black circle targets the site of biopsies. Black rectangles target

where the zoom is made on the biopsy. (a) Patient 7 with a clinical features of purpuric lesions on the right leg. Histologically, this is a perivascular lymphocytic infiltrate associated with red blood cell extravasation and hemosiderin deposits, confirmed by Prussian blue (PB) staining. (b) Patient 8 with a clinical features of Papules and urticarial plaques on the thighs and abdomen. Slice showed a perivascular infiltrate with neutrophils, foci of leucocytoclasia, extravasated red blood cells. (c) Patient 9 with a excoriated prurigo localized on trunk, arms and legs. Histological examination revealed a crust and superficial ulceration filled with thick, eosinophilic and verticalized collagen fibres perforating the crust. (d) Patient 10 with a clinical features of erythematous scaly plaques on the Trunk, thighs and arms. Histological examination was characterized by suprabasal acantholysis, and balloon-like keratinocytes with no dyskeratosis. (e) Patient 11 with a 'COVID-arm' reaction. Histologically, we observed dilated capillaries and venules in the superficial and mid dermis, lymphocytic perivascular infiltrate with rare neutrophils and eosinophils.

Histologically, the most common pattern was a 'drug-reaction-like' pattern and was characterized by variable epidermal keratinocyte necrosis associated with a perivascular lymphocytic infiltrate in the superficial and mid dermis, and a variable number of eosinophils and sometimes neutrophils. This pattern was found in 6 patients (Fig. [1a–f](#)) with an average time of onset of 11.6 days (range 4–16; Patients_1-6).

One of these patients (Patient 5), presented an erythematous rash, associated with crusted plaques. She had many medications without no recent changes. Histological examination showed the abovementioned features and also acute generalized exanthematous pustulosis-like features with subcorneal pustules (Fig. [1e](#)).

Another patient, with no previous medical history or medication, presented with an erythematous scaly annular and oval patches of the trunk, two weeks after the second injection of the vaccine. She had a fever 24 h after the injection and diffuse lymph nodes that had disappeared before rash. Clinical picture was consistent with pityriasis rosea (Patient_6). However, histological examination revealed epidermal spongiosis and keratinocyte necrosis associated with lymphocytic infiltrate in the superficial and deep dermis with few eosinophils and was therefore consistent with a 'drug-reaction-like' pattern (Fig. [1f](#)). Blood PCR test was negative for HHV6 and HHV7.

Besides this pattern, five patients presented other clinical and histological aspects.

One patient presented petechial and purpuric macules on legs, one day after the first injection (Patient_7). Histological examination was consistent with pigmented purpuric dermatosis, with a perivascular lymphocytic infiltrate associated with red blood cell extravasation and hemosiderin deposits, confirmed by Prussian blue staining without vascular fibrinoid necrosis (Fig. [2a](#)).

Another one was characterized by urticarial papules and plaques lasted more than 24 h (Patient_8). Histological examination showed a picture of early leucocytoclastic vasculitis with a

perivascular infiltrate with neutrophils, foci of leucocytoclasia, extravasated red blood cells and without vascular fibrinoid necrosis. The clinical and pathological correlation was consistent with urticarial vasculitis (Fig. [2b](#)).

One of these cases was characterized clinically by an intense pruritus, associated with excoriated papules and nodules on trunk, arms and legs 15 days after the second dose (Patient_9). Histological examination revealed a crust and superficial ulceration filled with thick, eosinophilic and verticalized collagen fibres perforating the crust, and was consistent with prurigo nodularis with excoriations (Fig. [2c](#)).

One patient presented with eczematiform erythematous and squamous plaques with a nummular aspect on trunk and legs. He was not known for atopic dermatitis or nummular eczema (Patient_10). Histological examination was characterized by suprabasal acantholysis, and balloon-like keratinocytes with no dyskeratosis. The direct immunofluorescence examination was negative and not suggestive of pemphigus. Furthermore, the clinical aspect and topography of the lesions were not consistent with Grover's disease (Fig. [2d](#)).

We also observed a delayed large local reaction or 'COVID-arm'. (Patient_11). Histological examination showed dilated capillaries and venules in the superficial and mid dermis, lymphocytic perivascular infiltrate with rare neutrophils and eosinophils, without leucocytoclasia or vascular fibrinoid necrosis. These findings were reminiscent of erythema annulare centrifugum, as recently proposed for COVID-arm lesions induced by Moderna vaccines (Fig. [2e](#)).¹⁰

For all the patients, the lesions decreased in size, number or disappeared completely during the 2 weeks after the first consultation.

Discussion

The clinical presentations were erythematous, purpuric, urticarial, prurigo-like and pityriasis rosea-like.

Histologically, the main finding was drug-reaction-like pattern. We also observed pigmented purpuric dermatosis, prurigo nodularis with excoriations, vasculitis and acantholytic dermatosis.

This study included only patients with skin biopsy. Other patients with clinically characteristic post-vaccination skin lesions were not included. Biopsies were performed to help on the differential diagnosis and for the pharmacovigilance reporting.

Clinical differential diagnosis was sometimes challenging. For example, one patient was known to have transplanted chronic myeloid leukaemia, and graft-versus-host disease was a

differential diagnosis (Patient_2).

All reactions were benign and resolved inside 2 weeks.

Although our cohort is predominantly female, it is not possible to draw a trend because we only included patients who had a biopsy and more women were vaccinated at the beginning of the vaccination phase in Switzerland.¹¹

Also note that our cohort is on average older than those already published. Indeed, the previous cohorts were mostly composed of healthcare workers which is mostly not the case in our study.

Even though the skin reactions are quite rare in comparison with the number of vaccinations,¹² it remains important not to misdiagnose a cutaneous reaction related to the vaccine. All of these reactions have been described clinically and histologically with other vaccines.¹³ Moreover, unusual vaccine reaction should be notified as for any adverse drug reaction. A previous drug or vaccine allergy seems to be a risk factor for COVID-19 vaccine adverse reaction.⁷ However, we did not find it in any of our patients.

Our study has several limitations, first of all, few patients were collected; we had a spontaneous, retrospective recruitment, and some patients may have been missed. We did not analyse serological anti-SARS-CoV-2 antibody responses or RT-PCR for SARS-CoV-2 during vaccination to exclude asymptomatic infection. However, little is known about this point; moreover, none of the patients had presented a previous episode consistent with COVID-19 infection. However, the exploration of the presence of viral proteins using anti-SARS-CoV-2 antibodies by immunohistochemistry on the skin samples of patients would give some clues about the immunopathogenesis of these skin reactions.

As mRNA vaccines are based on a totally new mechanism to deliver an immunogenic response, we insist on a meticulous description of cutaneous adverse effects. A proper clinicopathological classification will be helpful in the early diagnosis, management of these cutaneous reactions, and give clues of physiopathological mechanisms.

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