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Cutaneous Adverse Reactions Associated with COVID-19 Vaccines

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1. Abstract

1.1. Background: SARS-CoV-2 vaccination is crucial to reduce the risk of hospitalization, injury and mortality. However, several adverse cutaneous reactions can occur.

1.2. Objectives: Objective was to collect and classify cutaneous side effects after SARS-CoV-2 vaccination in a Moroccan case series.

1.3. Methods: A cross-sectional observational study among patients referred to the Dermatology Department of Ibn Rochd Hospital from February 2021 to November 2021. Patients of all ages vaccinated against COVID-19 who developed a skin manifestation within 1 month of administration of vaccine that had been approved by the national technical and scientific committee in Morocco (Sinopharm and Astrazeneca then Pfizer-BioNTech). Patients with explainable causes other than SARS-CoV-2 vaccination were excluded.

1.4. Results: A total of 47 patients were identified with cutaneous reactions after COVID-19 vaccination: AstraZeneca (53,19 %), Sinopharm (38,29 %), and mRNAPfizer-BioNTech vaccine (8,51 %). Allergic-type reactions (46.80%): urticaria (10.63%), urticaria with angioedema (10.63%), pruritus (10.63%), morbilliform eruption (4.25%), Quincke's edema (2.12%), DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome (2.12%), Stevens-Johnson syndrome (2.12%), lichenoid drug eruption (2.12%), anaphylactic reaction (2.12%). Inflammatory skin reactions (17.02%): Erythema nodosum (8.51%), psoriasis (4.25%), lupus (2.12%), Shulman fasciitis (2.12%). Autoimmune reactions (14.89%): bullous pemphigoid (6.38%), pemphigus vulgaris (2,12%), urticarial vasculitis (4.25%) and vitiligo (2.12%). Viral reactivation: zoster reactivations (8.51%), herpetic reactivations (4.25%). Reactions described after infection with COVID-19: erythema multiforme (4.25%), Varicella-like rash (2.12%). In addition, a generalized annular rash was noted in a single patient (2.12%).

1.5. Conclusions: Cutaneous reactions to vaccination were mild, self-limiting, and simulate common cutaneous drug eruptions and COVID-19 skin manifestations.

2. Introduction

Since it first described, the coronavirus disease 2019 (COVID-19) pandemic, due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global health crisis [1]. Since then, hundreds of millions of people have been affected, making the imperativeness for developing a safe and effective vaccine, vital to controlling the pandemic.

From December 2020, multitude of SARS-CoV-2 vaccines have been urgently authorized and agreed, including mRNA–vaccines, such as BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna); chimpanzee adenovirus vector vaccine (ChAdOx1- AstraZeneca), human adenovirus 26 (Ad26.COV2. S-Johnson & Johnson/ Janssen), and inactivated SARS-CoV-2 vaccines (Sinopharm and Sinovac) [2]. Morocco approved Sinopharm and Astrazeneca then Pfizer-BioNTech for use in the vaccination protocol on January 2021, and August 2021, respectively.

SARS-CoV-2 vaccines are associated with a vast spectrum of cutaneous reactions. Clinical trials reported different cutaneous adverse events, mainly local injection site reactions, either immediate or delayed. But after global mass vaccination, new cutaneous reactions emerged. In fact, several case series of COVID- 19 vaccine related dermatoses have been published latterly [3].

This case series documents the real experience of the vaccination campaign in a sample of the Moroccan population.

The objective of our study was to collect cases of cutaneous side effects after SARS-CoV-2 vaccination and classify this reaction into different categories. Our second objective was to describe the timing of cutaneous reactions and to clarify the potential associations with other dermatologic or allergic conditions.

3. Materials and Methods

We conducted a cross-sectional observational study among patients referred to the Dermatology Department of Ibn Rochd University Hospital, from February 2021 to November 2021, who presented with skin manifestations induced by COVID-19 vaccines.

Inclusion criteria were patients of any ages vaccinated against COVID-19 who developed a skin manifestation within 1 month of administration of any dose of a vaccine that had been approved by the national technical and scientific committee in Morocco. Patients with explainable causes other than SARS-CoV-2 vaccination were excluded.

Examination was realized by dermatologists to look for skin lesions that could be related to COVID-19 vaccination. Histopathological examination and biological tests were performed when It's required.

Data were collected using a case report form. We recorded several variables including; patient's characteristics: age, sex, history of allergy, atopic dermatitis, urticaria or cutaneous reactions to other vaccines, previous SARS-CoV-2- infections with cutaneous involvement. Vaccine features: type of vaccine, vaccination date, the number of doses, day of onset. Cutaneous and systemic symptoms, location, the clinical nature of the reaction, clinical pictures if possible, treatment and histopathologic findings.

The reactions were classified into five main categories: Allergic-type reactions, inflammatory skin reactions, autoimmune reactions, viral reactivation, reactions described after infection with COVID-19 and then some other reactions.

Statistical Analysis: To ensure accuracy, all obtained data were entered into Microsoft Excel and cross-checked for the presence of any errors. The frequency table, graph, and mean with standard deviation are used to describe the data.

4. Results

A total of 47 patients with cutaneous reaction to the COVID-19 vaccine were identified. The clinical-epidemiological description is shown in (Table 1).

The mean age at diagnosis was 47,40 years, ranging between thirteen and eighty-five years-old. Female predominance was noted with a percentage of 68,08 %, with a female-biased sex ratio of 0,47.

All patients had been given either of the three vaccines. Twenty-five patients had received AstraZeneca vaccine (53,19 %), eighteen had taken Sinopharm vaccine (38,29 %), and four patients had been given Pfizer-BioNTech vaccine (8,51 %).

Skin reactions following the vaccination occurred in twenty-four patients after receiving the first vaccine dose (51,06 %), in twenty patients after the second dose (44,68 %), and in three patients after the third dose (4,25 %)

These reactions appeared within four hours in eight patients (17.02%), between four hours and seventy-two hours in twenty-four patients (51.06%), and later on, after seventy-two hours in fifteen patients. (31.91%).

We have classified into different types shown in (table 2). Allergic-hypersensitivity reactions were seen in twenty-two patients (46.80%): five cases of urticaria, five cases of urticaria with angioedema, five cases of pruritus (10.63%), and two cases of morbilliform eruption (4.25%). Quincke's edema, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens-Johnson syndrome (SJS), lichenoid drug eruption and anaphylactic reaction were also observed, with one case each (2.12%).

Eight patients (17.02%) presented inflammatory skin reactions: four cases of erythema nodosum (8.51%), two cases of psoriasis (4.25%), one case of lupus and one case of Shulman fasciitis (2.12%).

Autoimmune reactions were identified in seven patients (14.89%): three cases of bullous pemphigoid (6.38%), one case of pemphigus vulgaris (2,12%), two cases of urticarial vasculitis (4.25%) and one case of vitiligo (2.12%).

Six patients had a post-vaccination viral reactivation: Four zoster reactivations (8.51%) and two herpetic reactivations (4.25%). Among the reactions described after infection with COVID-19, two cases of erythema multiforme (4.25%) and one case of Varicella-like rash (2.12%) were observed. In addition, a generalized annular rash was noted in a single patient (2.12%).

Table 1: Clinical-epidemiological description of patients with skin manifestations after COVID-19 vaccine

	Total (%)
Gender, n (%)	
Male	15/47 (31.91)
Female	32/47 (68.08)
Age (years)	
MeaN	47.4
Minimum	13
Maximum	85
vaccine type	
ASTRAZENECA	25/47 (51.06)
SINOPHARM	18/47 (38.29)
pfizer	4/47 (8.51)
Onset after dose	
1st dose	24/47 (51.06)
2nd dose	20/47 (44.68)
3rd dose	3/47 (4.25)
ONSET TIME	
0 – 4 hours	8/47 (17.02)
4 – 72 hours	24/47 (51.06)
> 72 hours	15/47 (31.91)
SKIN Reaction type	
Allergic/hyperensitivity	22/47 (46.80)
Inflammatory	8/47 (17.02)
autoimmune	7/47 (14.89)
viral reactivation	6/47 (12.76)
described after covid-19 Infection	3/47 (6.38)
Others	1/47 (2.12)

Table 2: Classifications of adverse skin reactions associated with SARS-CoV-2 vaccinations

Skin reactions after covid-19 vaccine		**TOTAL (%)**
Allergic reaction	Urticaria	5/47 (10.63)
	Urticaria with angioedema	5/47 (10.53)
	Pruritus	5/47 (10.63)
	Maculo-papular rash	2/47 (4.25)
	Angioedema	1/47 (2.12)
	DRESS syndrome	1/47 (2.12)
	SJS	1/47 (2.12)
	Lichenoid drug eruption	1/47 (2.12)
	Anaphylactic reaction	1/47 (2.12)
Inflammatory reaction	Erythema nodosum	4/47 (8.51)
	Psoriasis	2/47 (4.25)
	Lupus	1/47 (2.12)
	Shulman fasciitis	1/47 (2.12)
autoimmune reaction	Bullous pemphigoid	3/47 (6.38)
	Urticarial vasculitis	2/47 (4.25)
	Pemphigus vulgaris	1/47 (2.12)
	Vitiligo	1/47 (2.12)
VIRAL REACTIVATION	Zoster	4/47 (8.51)
	Herpes	2/47 (4.25)
REACTION AFTER COVID-19 infection	Erythema multiforme	2/47 (4.25)
	Varicella-like rash	1/47 (2.12)
OTHERS	Generalized annular rash	1/47 (2.12)

DRESS: drug reaction with eosinophilia and systemic symptoms; SJS: Stevens-Johnson syndrome

5. Discussion

In clinical trials, initial reports mostly described were local injection site reactions such as erythema, swelling, pain, induration, and pruritus within 7 days after injection and, subsequently, other miscellaneous skin reactions [3,4,5].

In this series, there was no local reaction at the injection site, either early or delayed. This is due to the type of the study and the fact that the patients are not referred or do not consult for this type of reaction.

A large number of hypersensitivity reactions accounted for approximately 50% of all events was described. They ranged from simple pruritus to anaphylactic reactions. Cases of severe drug eruption have also been described. It is essential to distinguish immediate hypersensitivity reactions, defined by the Centers for Disease Control that occur within the first four hours of the injection, from the same reactions that occur beyond 4 hours after injection [6]. This distinction is important to recognize because the former are potential contraindications to the second dose.

Autoimmune bullous reactions are uncommon, and few cases of autoimmune sub epidermal bullous diseases have been reported [4,7]. Their clinical presentations shows itchy, urticated, erythematous plaques and tense bullae developing 3–21 days after the first or second dose. We report four cases with onset intervals ranging from 3 days to 3 weeks.

In our experience, only one case of lupus has been identified. Both mRNA and adenoviral vaccines trigger immunity to SARS-CoV-2 through the production of high levels of spike proteins [8]. They also trigger innate sensors resulting in the production of type 1 interferons, which play an important role in the pathogenesis of autoimmune rheumatic diseases [8].

Exacerbations of psoriasis have been clearly documented, including cases of new onset psoriatic arthritis have been reported after the mRNA and adenovirus-vectored vaccines [9]. Etiological relationship between psoriasis and vaccination remains uncertain [9]. The immunologic reaction to vaccination might rely on the production of interleukin IL-6 and IL-22, producing Th17 that play a role in the development of the epidermal changes of psoriasis [9].

Cutaneous vasculitis were described following mRNA, adenovirus-vectored vaccinations, and inactivated whole-virus vaccines including vasculitis urticarial [10]. The two cases in our study were described after AstraZeneca vaccine. It is probably secondary to abnormal immunological activation with vaccine-related antigens promoting antibody development and deposition of immune complexes [10].

Here, we report also one case of vitiligo after AstraZenca vaccine. The temporal relationship between the vaccine and development of the disease is interesting. An underlying autoimmune disease is probably the cause of this reaction [11].

We additionally observed a number of viral reactivations. A plausible mechanism is that vaccination induce a strong specific immune response against SARS-CoV-2 or the spike protein from vaccine causing an immunomodulation that allows varicella-zoster virus to emerge from its latency phase [6,9].

Skin manifestations that were previously described after SARS-CoV-2 infection, were also described after vaccination [3]. It is probably triggered by an immunogenic epiphenomenon to viral antigens.

Our study has several limitations which is inherent to the type of the study. Firstly, it does not permit the quantification of incidence of skin reactions after vaccination. Secondly, it cannot determine cause and effect relationship. And finally, we could not evaluate the incidence of reaction's severity by vaccine type, because distribution depended on vaccine availability.

Overall, skin reactions were generally mild, self-limited, and simulate common drug rashes and COVID-19 skin manifestations, although severe reactions have been described. Other studies on vaccine safety are required to strengthen confidence in the vaccine, and for a better understanding of risk factors of vaccine side effects.

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