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RESEARCH ARTICLE

ADVERSE SKIN MANIFESTATIONS FOLLOWING THE ADMINISTRATION OF COVID-19 VACCINATION:REPORT OF 48 CASES

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Abstract

Introduction: Since the first reported case of Coronavirus 19 (COVID 19) outbreak, several vaccines have been developed in a record time and approved for distribution around the globe. The different COVID 19 vaccines showed a good safety and immunogenicity profiles in randomized controlled trial. However since the beginning of mass vaccination, dermatologists have reported various skin reactions following the administration of Covid-19 vaccines. **Material and method** We conducted a prospective study among patients referred to the Dermatology Department at University Hospital of Marrakech, from March 2021 to February 2022 who presented with skin manifestations induced by COVID-19 vaccines. We excluded patients with immediate and/or delayed local site injection reactions as well as the patients whom the reactions couldn't be linked to the COVID 19 vaccine. Data were collected and managed using a questionnaire. The data entry was done using Microsoft Excel. **Results** We collected 48 patients who presented cutaneous reactions after the administration of Covid 19 vaccine. We noted that 24 (50%) of the patients presented cutaneous reactions after the ChAdOx1 nCoV-19, 23 after the BBIBP-CorV (48 %) vaccination and only one patient (2%) presented cutaneous reaction after BNT162b2 vaccine. Twenty-six of our patients were female (54.1%) and 22 were male (45.9%). The patients' mean age was 49.04 years (range 12-80). Of 48 patients, 18 had chronic conditions (37.5%). The majority of the reactions occurred after the first dose of the vaccine with thirty seven patients (77%) and 11 patients (23%) after the second dose. The mean onset time was 7.7 days. Of the ChAdOx1 nCoV-19 vaccine (N=24), 18 reactions (75 %) appeared after the first dose and 6 (25%) after the second. Of the BBIBP-CorV (N=23) 18 reactions (78.3%) appeared after the first dose and 5 (21.7%) after the second. The only reaction noted with the BNT162b2 vaccine occurred after the first dose. The most prevalent cutaneous reaction was herpes zoster in 27% of the patients, followed by lichen planus in 16.6% and urticaria in 14.6% of the cases. Hospitalization was required in 8 cases (16.7%). Of the thirty-seven patients that presented a cutaneous reaction after the first dose: twelve did not develop any cutaneous reaction after the second dose of the vaccine (32.4%), twelve refused to have the second dose (32.4%), seven

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patients had an exacerbation of their reaction(18.9%), three did not show up for the follow up(8.2%) , 2 patients had the exact same reaction following the second dose of the vaccine(5.4%). We noted one death in our series: it was a severe case of pemphigus vulgaris who died from a sepsis complication.

Conclusion: The urge to find a new vaccines has been crucial to stop the spread of the COVID 19 infection. Dermatologist have the obligation to report on the cutaneous adverse reaction, as well as managing all the cutaneous complications of the covid 19 vaccine. Despite of all the cutaneous reactions reported in our study and in the literature, the adverse effects are rarely life threatening, and thus shouldn't discourage the patient to get vaccinated.

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Introduction:-

Since the first reported case of Coronavirus 19 (COVID 19) outbreak, several vaccines have been developed in a record time and approved for distribution around the globe. The different COVID 19 vaccines showed a good safety and immunogenicity profiles in randomized controlled trial [1]. However since the beginning of mass vaccination , dermatologists have reported various skin reactions following the administration of Covid-19 vaccines.

Objective:-

The objective of our study was to evaluate the clinical features and timing of cutaneous reactions following SARS-CoV-2 vaccination.

Materiel and Method:-

We conducted a prospective study among patients referred to the Dermatology Department at University Hospital of Marrakech, from March 2021 to february 2022 who presented with skin manifestations induced by COVID-19 vaccines. We excluded patients with immediate and/or delayed local site injection reactions as well as the patients whom the reactions couldn't be linked to the COVID 19 vaccine. Data were collected and managed using a questionnaire. Variable included patient characteristics: age, sex, medical history , history of allergy, urticaria and/or cutaneous reactions to other vaccines. We collected dates for both vaccine doses, type of the cutaneous reaction, timing and duration of reaction, and treatments. Clinical aspects of the skin manifestations were evaluated by dermatologist. The data entry was done using Microsoft Excel.

Results:-

We collected 48 patients who presented cutaneous reactions after the administration of Covid 19 vaccine. We noted that 24 (50%) of the patients presented cutaneous reactions after the ChAdOx1 nCoV-19 , 23 after the BBIBP-CorV (48 %) vaccination and only one patient (2%) presented cutaneous reaction after BNT162b2 vaccine. Twenty-six of our patients were female (54.1%) and 22 were male (45.9%). The patients' mean age was 49.04 years (range 12-80). Of 48 patients, 18 had chronic conditions (37.5%) . The most prevalent ones were diabetes and blood hypertension . Five patients had a history of psoriasis , one patient had chronic urticaria , one patient had a history of multiple myeloma in remission and one patient had an allergy to AINS and aspirine. The characteristics of patients are shown in Table 1. The majority of the reactions occurred after the first dose of the vaccine with thirty seven patients (77%) and 11 patients (23%) after the second dose. The mean onset time was 7.7 days. Of the ChAdOx1 nCoV-19 vaccine (N=24), 18 reactions (75 %) appeared after the first dose and 6 (25%) after the second. Of the BBIBP-CorV (N=23) 18 reactions (78.3%) appeared after the first dose and 5 (21.7%) after the second. The only reaction noted with the BNT162b2 vaccine occurred after the first dose. Dermatologic findings and systemic symptoms according to type of vaccine are shown in Table 2. The most prevalent cutaneous reaction was herpes zoster in 27% of the patients, followed by lichen planus in 16.6% and urticaria in 14.6% of the cases. All the different cutaneous reactions are shown in figure 1. Hospitalization was required in 8 cases (16.7%). It was for the patients who presented Dress syndrome (n=2), pemphigus vulgaris (n=2), livedo racemosa (n=1) , flare up of psoriasis (n=1) , sweet syndrome (n=1) and a patient who presented cellulitis complicating herpes zoster (n=1). Skin biopsies were performed in 8 cases (16.7%). Of the thirty-seven patients that presented a cutaneous reaction

after the first dose : twelve did not develop any cutaneous reaction after the second dose of the vaccine (32.4%), twelve refused to have the second dose(32.4%), seven patients had an exacerbation of their reaction(18.9%), three did not show up for the follow up(8.2%) , 2 patients had the exact same reaction following the second dose of the vaccine(5.4%) . Vaccination was withheld in one patient : it was a patient who presented a DRESS syndrome with pancreatitis. We noted one death in our series: it was a severe case of pemphigus vulgaris who died from a sepsis complication.

Table 1:- Characteristics of the patients.

Cutaneous reaction	ChAdOx1 nCoV-19 N=24 (%)	BBIBP-CorV N=23 (%)	BNT162b2 N=1 (%)
Herpes zoster	11 (45.7%)	2 (8.8%)	0
Lichen	1(4.2)	6(26.1%)	1
Urticaria	2 (8.3%)	5(21.8%)	0
Exacerbation of Psoriasis	0	5(21.8%)	0
Rash	2 (8.3%)	1 (4.3%)	0
DRESS syndrome	2 (8.3%)	-0	0
Erythema multiforma	1(4.2%)	1(4.3%)	0
Pemphigus	1(4.2%)	1(4.3%)	0
Erythema nodosum	0	1(4.3%)	0
Exanthem unilateral flexural	1(4.2%)	0	0
Granuloma annular	1(4.2%)	0	0
Livedo	1 (4.2%)	0	0
Sweet syndrome	1(4.2)	0	0
Vitiligo	0	1(4.3%)	0

Table 2:- cutaneous reactions according to the vaccine.

Number of patients		48
Age		49.04 years (12-80)
Sexe,number(%)	Female	26 (54.1%)
	Male	22 (45.9%)
Medical history	diabetes	5
	Psoriasis	5
	hypertension	5
	Rheumatoid arthritis	1
	multiple myeloma in remission	1
	Allergy to AINS-Aspirine	1
	Urticaria chronic	1

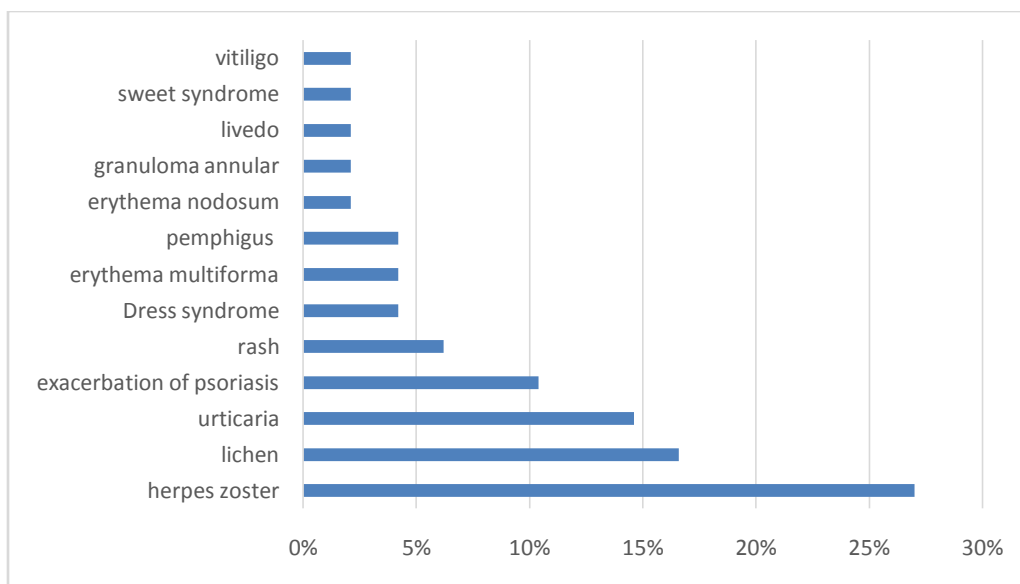


Figure 1:-Cutaneous reaction observed in the patients.



Figure 2:- Herpes zoster following the vaccine in a 12 year-old-boy patient



Figure 3:- Lichen planus lesions in the wrists and forearms occurring after the vaccine.



Figure 4:- Lichen planus lesions affecting both legs and thighs



Figure 5:- A case of severe pemphigus vulgaris following the Covid-19 vaccine.



Figure 6:- Multiple lesions of granular annular in one of our patients.



Figure 7:- Lesions of urticaria after the administration of the Covid-19 vaccine.

Discussion:-

To stop the spread of the Covid-19 infection, different vaccines have been approved. Among those vaccines, BNT162b2 is an mRNA vaccine targeting the Spike protein of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The ChAdOx1 nCoV-19 is based on adenovirus expressing the full-length Spike protein [2]. The BBIBP-CorV is an inactivated vaccine that introduces a dead copy of SARS-CoV-2 into the body [3]. For all those vaccines, the most common adverse cutaneous reactions noted on the clinical trial were local injection site reactions such as erythema, swelling, tenderness, pain, induration and pruritus within 7 days after injection. Mild to moderate injection site pain was the most prevalent event among all COVID-19 vaccine trials [4].

Since the start of the vaccination, several cutaneous side effects following the administration of the Covid-19 vaccine have been reported.

In the literature, the cutaneous reactions were more frequent in women, which is similar to what we found in our study. Women's immune systems might be more responsive to SARS-CoV-2 proteins, resulting in greater vaccine reactogenicity [1].

In a recent study, reactions were more observed in the younger age group. This might be explained by their immunity which boosts a faster and stronger immune response to vaccines compared to older individuals [5]. Same as the literature, the mean age of the patients in our study was 49.04 years. We observed various cutaneous reactions in our study. While some were frequently observed in the literature, other cutaneous reactions were rarely reported.

Herpes zoster reactivation:

Herpes zoster reactivation after administration of the covid 19 vaccine has been reported in the literature. In the cases reported by Santos, 29.2% of the patients that presented the eruption were healthy people aged <50 years old [1]. In our study, none of our patients that presented the reactivation of the herpes zoster had an immunodepression and our youngest patient was 12 years old. It is possible that the vaccine causes certain immunomodulation that allows Varicella-Zona-virus (VZV) to awaken from latency. Activation of VZV in COVID-19 vaccine patients may be also related to physical or emotional stress.

Lichen planus

Both SARS-CoV-2 infection and its vaccines can serve as triggering factors of lichen planus (LP) [6].

The exact pathogenesis is not identified yet. The vaccination probably induces a type 1 T helper (TH1) cell response leading to various cytokine secretion. This may play a key role in the development of this condition [7].

In our study, 7 of our patients presented new onset of Lichen planus, 6 of them occurred after the BBIBP-CorV vaccine, and one presented the affection after the ChAdOx1 nCoV-19 vaccine.

Urticaria

The occurrence of urticaria after the injection of a vaccine is a frequent event. It may be either an immediate hypersensitivity mechanism directed against the vaccine components or a non-immunological inflammatory reaction [8]. Several cases of urticaria have been reported for different Covid19 vaccines [1]. In our series 14.6% of patients presented with urticaria.

Drug reaction with eosinophilia and systemic symptom (DRESS)

Drug reaction with eosinophilia and systemic symptom (DRESS) syndrome is a drug-induced hypersensitivity reaction that usually occurs 2 to 8 weeks after exposure to drug such as anticonvulsants, antibiotics, and allopurinol [9]. While going through the literature, there has been only one case that reported a DRESS syndrome following administration of the COVID-19 vaccine. It was after the administration of the first dose of ChAdOx1 nCoV-19 vaccine [10]. In our study, both our patient developed the dress syndrome following the administration of the first dose of ChAdOx1 nCoV-19 vaccine. Dress syndrome was complicated by an acute pancreatitis in one of our patient.

We believe that the viral antigens in the vaccine might have contributed to trigger the disease.

Maculopapular Rash:

Cases of maculopapular rash after vaccination have been reported for various COVID-19 vaccines. Maculopapular rashes have also been reported in several cases of COVID-19 [1]. The histology performed in those cases revealed spongiosis and mild dermal perivascular lymphocytic infiltrates, suggesting an immune-mediated etiology rather than a direct viral effect. Therefore according to some authors it is plausible that these cutaneous manifestations are also the result of an immune activation [4]. In our study three of our patient presented a maculopapular rash that resolved without sequelae in all the cases.

Psoriasis flare

Psoriasis is a chronic affection that can be provoked by a variety of different environmental factors, particularly infections and drugs. Various COVID-19 vaccine have been associated with exacerbation of psoriasis [11]. In our study, all the patients that presented a worsening of their psoriasis had received the BBIBP-CorV vaccine.

Erythema multiform:

Erythema multiform (EM) following vaccination is rare, it is mostly described with vaccines administered in infancy and childhood [12]. Cases of EM was observed after mRNA-based COVID-19 vaccines, and after CoronaVac vaccination which is an inactivated SARS-CoV-2 virus [13, 14]. In our study we observed 2 cases of EM after covid19 vaccine, one occurred after the BBIBP-CorV vaccine while the other was observed after ChAdOx1 nCoV-19 vaccine. We are not aware of any other cases of EM occurring after the ChAdOx1 nCoV-19 vaccine. It is unclear how vaccines may trigger EM. Vaccine antigens appears to induce cell-mediated inflammation and stimulate immune reactions via the activation of T helper type 1 cells [15].

Pemphigus vulgaris

Pemphigus vulgaris (PV) is a rare and severe autoimmune disorder of skin and mucosa. Single cases of PV after COVID-19 vaccination have been reported [16]. Molecular mimicry is a proposed pathogenesis for autoimmune disorders induced by COVID-19 vaccines. In our study, we observed two new onset cases of PV: one occurred after BBIBP-CorV vaccine and the other was following the chadox ncov vaccine. PV is a potentially life-threatening disease. Indeed in our study the patient who presented PV after ChAdOx1 nCoV-19 vaccine died due to sepsis complication. It was the only death noted in our study.

Erythema nodosum

Erythema nodosum (EN) can be associated with infections, drugs and inflammatory diseases. However, approximately 50% of cases are idiopathic. EN associated with vaccines has been rarely reported. Studies suggest that the development of EN was secondary to the antigen of the infectious disease. However the possibility of a hypersensitivity reaction to the adjuvant components of the vaccine was not to be excluded [17]. Previous cases have reported an EN following the administration of Covid 19 vaccine. It was either following mRNA vaccine, or chadox vaccine [18, 19]. In our study EN occurred after the BBIBP-CorV vaccine. To our knowledge, there have been no previously reported cases of EM associated with BBIBP-CorV vaccine. We believe the close association of this vaccination with the acute onset of EM in our patient is more than coincidental.

Unilateral laterothoracic exanthem (UTLE)

Unilateral laterothoracic exanthem (UTLE), also known as asymmetrical periflexural exanthem of childhood, is a relatively rare entity, typically seen in children between 1 and 5 years old[20]. While going through the literature, we only found 3 cases of UTLE linked to Covid-19 vaccine [21, 22, 23]. In our study, we observed one case of UTLE. Our patient was a 40-year-old man with no significant medical history, who presented the rash 14 days after the second dose of ChAdOx1 COV 19 vaccine.

Granuloma annulare

Granuloma annulare (GA) is a benign affection, characterized by annular polycyclic erythematous-vivaceous papules. This affection can be triggered by several causes, such as diabetes mellitus, trauma, medications, vaccinations or viral infections. Very few cases of GA following vaccination have been reported in the literature. The bacillus Calmette-Guérin (BCG) vaccine has been the most reported vaccine[33]. As far as we know, there has been one case report of granuloma annular after Covid 19 vaccination. It was a case of a 58 years old woman, who developed a generalized granuloma annular 2 weeks after the second dose of the RNA-based COVID 19 vaccine[34]. In our study, GA was observed in a patient within 3 days following the first dose of the ChAdOx1 nCoV-19 vaccine. The mechanism inducing GA is unknown. The most probable explanation is a mediated immune response. This immunological activation after vaccination would explain the presence of activated T-cells in the lymphocytic infiltrate of GA[33].

Sweet syndrome

The exact cause of Sweet syndrome (SS) is unknown but sometimes the disease is triggered by infections, malignancies, and by certain drugs. Cases of SS occurring after vaccinations have been reported, including BCG vaccination, influenza vaccine as well as Pneumococcal vaccination[26]. Single cases of SS following Covid 19 vaccination have been reported[27]. In our study, we observed one case of SS that occurred 4 days after the second dose of ChAdOx1 nCoV-19 vaccine.

Vitiligo

Vitiligo has not been frequently reported as a cutaneous reaction after the COVID-19 vaccination[28]. The possible mechanism of its development may be explained by producing type I interferons (IFN-I) after vaccination which play an important role in the initiation of the immune response in vitiligo [29]. In our study, we observed one case of vitiligo in a patient with no personal autoimmune disease history after the injection of the inactivated vaccine (BBIBP-CorV).

Livedo racemosa

More rare vascular reactions such as livedo racemosa have been reported following after the administration of COVID -19 vaccine[30]. The only case of livedo racemosa in our study was a 55 years old female patient that presented the eruption 7 days following the first dose of ChAdOx1 nCoV-19 vaccine.

Conclusion:-

The urge to find a new vaccine has been crucial to stop the spread of the COVID 19 infection. Dermatologists have the obligation to report on the cutaneous adverse reaction, as well as managing all the cutaneous complications of the covid 19 vaccine. Despite of all the cutaneous reactions reported in our study and in the literature, the adverse effects are rarely life threatening, and thus shouldn't discourage the patient to get vaccinated.

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