Delayed-type hypersensitivity reactions to Pfizer BioNTech SARS-CoV-2 vaccine

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INTRODUCTION

Safe and effective vaccination has become the most important tool to control and prevent the spread of SARS-CoV-2 infection. The Pfizer/BioNTech vaccine was developed using innovative technology and contains messenger RNA (mRNA) encapsulated in lipid-based nanoparticles, stabilised by polyethylene glycol (PEG)-2000 and exhibits high efficiency and safety.[1 2] Like most SARS-CoV-2 virus vaccines produced in 2020, the Pfizer/BioNTech vaccine requires two doses administered 21 days apart.[1] In the phase III study, the Pfizer/BioNTech mRNA vaccine was well tolerated and no cutaneous adverse reactions were reported apart from injection site reactions.[2] Although there is no clear evidence yet on the pathogenesis of immediate and delayed-type hypersensitivity reactions to the SARS-CoV-2 vaccine, vaccine-induced hypersensitivity reactions have been reported.[3] Immediate type hypersensitivity reactions and mild or moderate injection site local reactions were observed more frequently than delayed-type reactions.[3]

Herein, we report two cases of drug-induced eruptions with compatible clinical and histopathological examination findings for delayed-type hypersensitivity reactions following Pfizer/BioNTech vaccine administration.

CASE 1

A 53-year-old female patient, who had no medical history at all, presented with vaccine-induced eruptions in the upper and lower extremities 4 days after the first dose of Pfizer/BioNTech vaccine administration. The day after vaccination, the patient experienced moderate headache, myalgia, and arthralgia without skin lesions. Seventy-two hours after vaccine administration, non-pruritic, erythematous, edematous, slightly warm and tender plaques formed, which started near the injection site and then developed in the periorbital area and various locations of all extremities within 24 hours. The patient was admitted to the emergency department with these complaints and was administered oral antihistamine and 40 mg methylprednisolone. The patient, whose lesions persisted for 24 hours, was evaluated in our outpatient clinic at the 96th hour. In the laboratory findings, no hypocomplementaemia was detected, CRP level increased fivefold, ESR was normal and ANA or other autoantibodies were negative. Skin punch biopsy specimens, which showed superficial, predominantly perivascular lymphocytic infiltrates with some eosinophils and rare polymorphonuclear leukocytes, were consistent with the histopathological findings of urticarial vasculitis (UV). The patient's rash resolved after approximately 3–4 days with topical glucocorticoid treatment and emulsifier. This patient did not receive the second dose of the Pfizer/BioNTech vaccine.

CASE 2

A 49-year-old female patient with no medical history at all was vaccinated with the Pfizer/BioNTech mRNA vaccine. Seven days after vaccination, the patient developed an erythematous macular morbilliform rash that tends to coalesce, most prominent on the lower back and bilateral flanks, and eruptions revealing intervening areas of unaffected skin on the upper back and extremities. Areas such as the face, palms, and feet were spared, and pernio-like lesions were not observed. In the examination, there were no intraoral or mucosal lesions. Medical records confirmed that until this reaction, the patient had not used any medication and had no viral infection. Skin punch biopsy specimens demonstrated perivascular and focal interstitial infiltrate with lymphocytes and eosinophils consistent with a drug hypersensitivity reaction. She had no other systemic symptoms, and all laboratory tests were normal. The patient was prescribed methylprednisolone 60 mg orally (dose reduction was planned 8 mg/every 3 days), hydrocortisone 1% topical, loratadine 40 mg daily and pantoprazole 40 mg daily. Her rash resolved over the following 28 days. This patient did not receive the second dose of the Pfizer/BioNTech vaccine. Demographic and clinical characteristics of patients are presented in table 1 and the morphological findings of patients are presented in figure 1.

DISCUSSION

In this report, we present two cases of delayed-type hypersensitivity reactions to the Pfizer/BioNTech vaccine. These reactions, an UV reaction and a morbilliform rash, differ from the cutaneous reactions observed during vaccine trial studies and from previously reported localised and large-localised delayed-type reactions.

UV, a type III hypersensitivity reaction, is a rare inflammation of small blood vessels of the skin characterised by long-lasting (>24 hours) urticarial eruptions and histopathological leukocytoclastic vasculitis.[4 5] UV can be idiopathic or it can develop due to connective tissue diseases, neoplasms, viral infections or drug reactions.[4 6] In the present case, there was no underlying disease or drug use that could cause UV save for vaccine administration. To our knowledge, this is the first reported case of UV following Pfizer/BioNTech COVID-19 vaccination. There are two types of UV: normocomplementaemic

Table 1 Demographic and clinical features of patients with delayed-type reactions to the Pfizer/BioNTech vaccine

Variables	Patient 1	Patient 2
Gender	Female	Female
Age	53	49
Atopy history	None	None
Drug allergy history	None	None
Vaccine allergy history	None	None
Symptoms	Erythematous, edematous and tender plaques	Morbilliform eruptions
Other systemic symptoms	Headache, myalgia, arthralgia	None
Time of onset	72 hours	7 days
Treatment	Topical glucocorticoid and emulsifier	Oral antihistamines and oral and topical glucocorticoids
Residual hyperpigmentation	Yes	Yes
Time of resolution	5 days	28 days

and hypocomplementaemic.[4] Our patient's complement (C) 1q, C3 and C4 levels were normal. Skin lesions (patches) in UV, which cause itching, pain and burning sensations, are red, can last for over 24 hours, and may leave skin discoloration.[4 5] Skin lesions like those described above were seen our patient, lasted longer than 24 hours, and healed with a slight discolouration. Treatment of UV depends on the extent of the affected organs and symptoms. Acute UV was usually associated with drug reactions, and in cases of drug-induced UV, discontinuation of the drug resulted in reduction or healing of the lesions.[5 6] When symptoms affect the skin, the lesions may resolve on their own or with treatments such as antihistamines or corticosteroids.[4] In our patient, the lesions resolved with glucocorticoid therapy and non-repetition of exposure to the vaccine.

Morbilliform eruptions, which are characterised by diffuse and symmetric erythematous macules or papules, often develop due to viral infection or drugs.[7] As demonstrated by our patient, eruptions usually occur within a week after administration of the drug. The clinical features are variable, and the lesions usually begin on the trunk, neck, and upper extremities and then spread symmetrically to the lower extremities.[7] However, palms, feet and mucous membranes are usually spared.[7] Itching and fever may also be observed in patients.[7] In our patient, the lesions developed as described above, and the palms, feet and mucous membranes were not involved. Morbilliform eruptions secondary to SARS-CoV-2 infection have been previously reported.[8 9] In addition, morbilliform eruption due to the Pfizer/BioNTech vaccine was reported previously.[10] In patients with a maculopapular rash due to COVID-19, the underlying cause was thought to be immune activation, not the virus itself.[9] Our case with morbilliform rash secondary to the Pfizer/BioNTech vaccine was like previously reported cases. Although the vaccine-related eruption of our patient suggests an immune-mediated aetiology, it is difficult to explain the underlying mechanism because the patient was not administered the second dose and did not accept in vivo tests.

A key factor to consider is the possibility that our patients' reaction may have been caused by PEG. We could not confirm this hypothesis, as neither of our patients accepted testing with the vaccine itself or PEG.

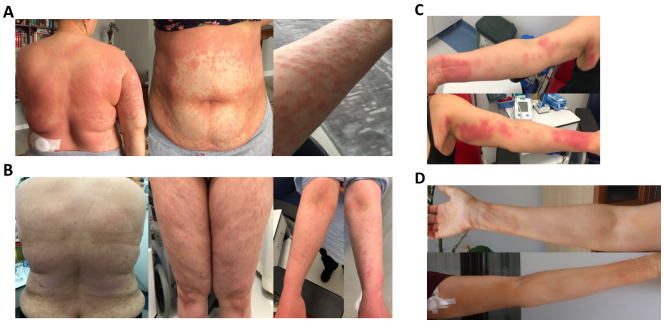

Figure 1 Delayed-type reactions to the Pfizer/BioNTech vaccine. (A) Erythematous maculopapular patches on the back and front of the trunk and forearms of case 2 (onset of reaction). (B) All eruptions started to resolve with residual discolouration on day 21 (case 2). (C) Erythematous mildly edematous plaques on the upper extremities of case 1 (second day). (D) Residual hyperpigmentation on arm and forearm on day 4 (case 1).

CONCLUSIONS

In the current report, the time of onset and histopathological findings of the lesions suggest immunocomplex and cell-mediated immunity. Since it is not clear how the vaccine triggered the delayed-type reaction, these case reports presenting the timing, morphology and histopathology will be key to fully understanding the pathomechanism of delayed-type reactions. With these results, we hope to provide physicians and other healthcare professionals with awareness of potential adverse drug reactions when using these novel vaccines.

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