

Generalized morphea induced by the COVID-19 vaccine in a patient with chronic urticaria

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Abstract

Adverse events following vaccinations have been noted for centuries, but as of recently, discussions concerning these adverse effects have increased due to the COVID-19 pandemic and the consequent delivery of vaccinations. Through presenting new cases of such adverse events and reviewing the literature, we aim to facilitate the recognition of COVID-19 vaccine-induced autoimmune diseases that may occur in the years after the pandemic has been contained. We report on a case of biopsy-proven morphea after the COVID-19 vaccine, in which case the patient developed diffuse skin lesions all over her body. The patient was known to have chronic urticaria and received two doses of the Pfizer-BioNTech COVID-19 vaccines (BioNTech, Fosun Pharma,

Pfizer, New York City, USA). The patient started to notice itchy lesions on her arms two months after taking her second dose of the vaccine. This is the first case reported of generalized morphea following COVID-19 vaccination with another autoimmune disease and represents the first case of generalized morphea reported in the Middle East.

Introduction

Morphea, also known as localized scleroderma, is an autoimmune skin disorder characterized by inflammation and sclerosis of the skin and soft tissues.¹ While the pathogenesis of this condition is unknown, several factors are assumed to be involved in the development of the disease, including a genetic predisposition, immune dysregulation, and environmental factors.¹ The COVID-19 vaccination has been linked to immune system dysregulation, which plays a role in the development of morphea.² According to Laxer and Zulian, morphea can be classified into the following variants: circumscribed morphea, linear morphea, generalized morphea, and pan-sclerotic and mixed subtypes. Specifically, circumscribed morphea is the most common variant.³ There are numerous clinical manifestations of morphea. Morphea lesions frequently start as inflamed patches or plaques and progress to firm, sclerotic plaques. The epidermis, dermis, and subcutaneous tissue can be affected, and morphea can also cause functional impairment, including joint contracture.¹ A diagnosis of morphea is made based on the clinical results, but histopathological investigations can also be helpful to exclude other diagnoses.¹

Case Report

The present case focuses on a 56-year-old female with known diabetes, hypertension, and bronchial asthma. She has also had a diagnosis of chronic idiopathic urticaria with angioedema since 2013. The current medications the patient takes for urticaria are as follows: i) omalizumab 300 mg per month; ii) chlorpheniramine 4 mg; iii) montelukast 10 mg orally once daily.

On the 20th of February 2022 at a follow-up clinic, the patient complained of new itchy lesions that started on her arms and then spread to other areas of her body. The lesions started 2 months after the patient received her second dose of the Pfizer-BioNTech COVID-19 vaccine.

On the 27th of February 2021, the patient received her first dose of the Pfizer-BioNTech COVID-19 vaccine, and on the 18th of March 2021, she received her second Pfizer-BioNTech COVID-19 dose. The patient had no history of COVID-19 infection. She denied experiencing any of the following symptoms before the onset of her cutaneous symptoms: fever, chills, night sweats, rhinorrhea, odynophagia, cough, nausea, emesis, arthritis, oral ulcers, other rashes, Raynaud's phenomenon, or weight

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changes. A skin examination revealed multiple linear, atrophic, hypopigmented, brown macules and patches over the bilateral upper arms as well as the axillae, with a few sclerotic depigmented patches and plaques and multiple well-defined irregular erythematous sclerotic plaques over the bilateral thighs. There were lesions on around 45% of the total body surface area, but there was no scalp or face involvement. The mucous membranes and nails were normal. There was no sclerodactyly, lymphadenopathy, or hepatosplenomegaly (Figure 1a-e). The complete blood count, chemistry panel, coagulation parameters, and function tests for the liver, thyroid, and kidneys showed values within the normal ranges. Values within the normal limits were confirmed for the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and complement component C3 and C4 levels. Serologic tests were positive at low titers for antinuclear antibodies (ANA) with a 1:80 NUMA-2 pattern, and rheumatoid factor, hepatitis B, and hepatitis C were negative.

We took two skin punch biopsies. The first one was taken from the left inner thigh and demonstrated a basket-weave keratin layer; additionally, the underlying epidermis showed mild exocytosis (few intraepidermal lymphocytes). In the dermis, there was mild perivascular lymphocytic infiltration, and no neutrophils or eosinophils were seen. There was no evidence of necrotic keratinocytes or increased dermal mucin, no evidence of fungal infection (PAS and GMS stains), and no evidence of atypical lymphocytes. The second biopsy was taken from the right arm; the sections showed a basket-weave keratin layer, epidermal atrophy with underlying thickening of the collagen bundles, and no atypical lymphocytes (Figure 2a-c).

We started the patient on phototherapy, but she experienced photosensitivity from narrowband ultraviolet B exposure. Subsequently, she was started on topical steroids with methotrexate 15 mg and folic acid 5 mg weekly. The patient is still under follow-up and undergoing response evaluation.

Discussion

Over the recent months, many studies have reported the mucocutaneous consequences of COVID-19 vaccine injections. Nine cases have been reported of generalized morphea after COVID-19 vaccine injection with different sites, time of onset post vaccination, and types of vaccine used: Pfizer in six cases, AstraZeneca in two cases, and Moderna in one case (Table 1).^{2,4-7} Overall, 25 cases of various cutaneous manifestations following COVID-19

vaccination have been reported, one of which was a case of generalized morphea that was observed in a female patient 10 days after the AstraZeneca vaccine.⁴ Another case series has been presented of four cases of generalized morphea with multiple whitish and sclerotic plaques following COVID-19 vaccination. For one

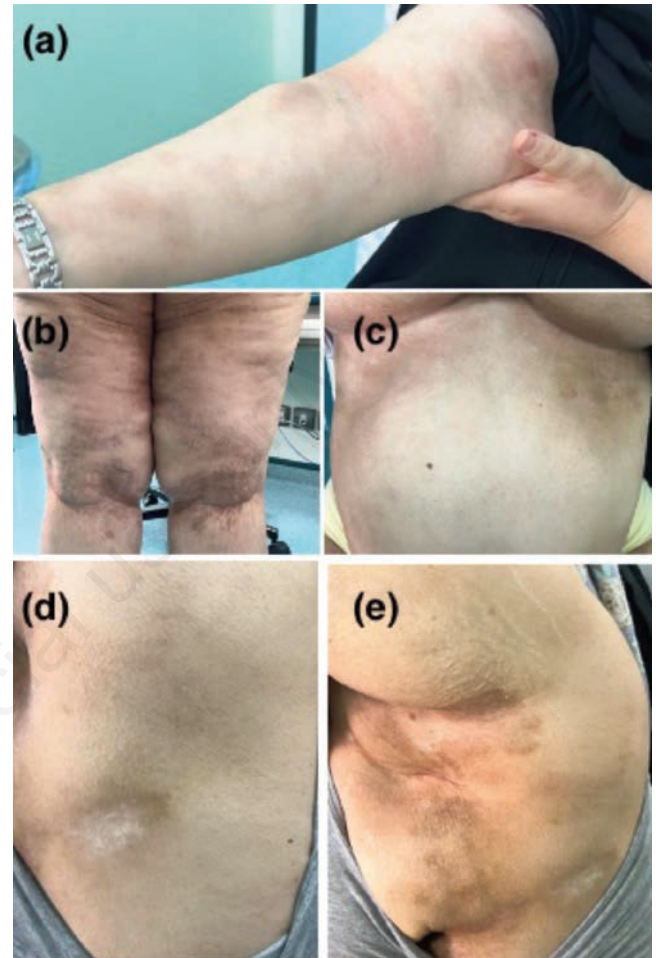


Figure 1. Multiple linear atrophic hypopigmented and brown macules and patches. a) Multiple well defined irregular erythematous sclerotic plaques; b) few sclerotic; c-e) depigmented patches and plaques at axile and inframammary areas.

Table 1. Reported cases of generalized morphea induced by COVID-19 vaccine.

Cases	Cases, n.	Time from COVID-19 vaccine	Vaccine
Metin Z <i>et al.</i> ⁶	1	4 weeks after the second dose	Pfizer-BioNTech (BNT162b2) (Pfizer)
Oh DAQ <i>et al.</i> ⁷	1	3 weeks after receiving the second dose of the vaccine	Pfizer-BioNTech vaccine (tozinameran) (Pfizer)
Paolino G <i>et al.</i> ⁵	4	15 days from 1st dose and 15 days from 2 nd dose 7 days after the 2 nd dose 20 days after the 1 st dose 20 days after the 2 nd dose	Comirnaty-Pfizer® (Pfizer) Comirnaty-Pfizer® (Pfizer) Vaxzevria-Astrazeneca® (AstraZeneca) Comirnaty-Pfizer® (Pfizer)
Antoñanzas J <i>et al.</i> ²	2	2 weeks after receiving the first dose of the vaccine 6 weeks after receiving the second dose of the vaccine	mRNA-1273 COVID-19 vaccine (Moderna) BNT162b2 COVID-19 vaccine (Pfizer)
Shakoei S <i>et al.</i> ⁴	1	10 days	AstraZeneca
Present case	1	2 months after receiving her second dose	Pfizer-BioNTech (BNT162b2) (Pfizer)

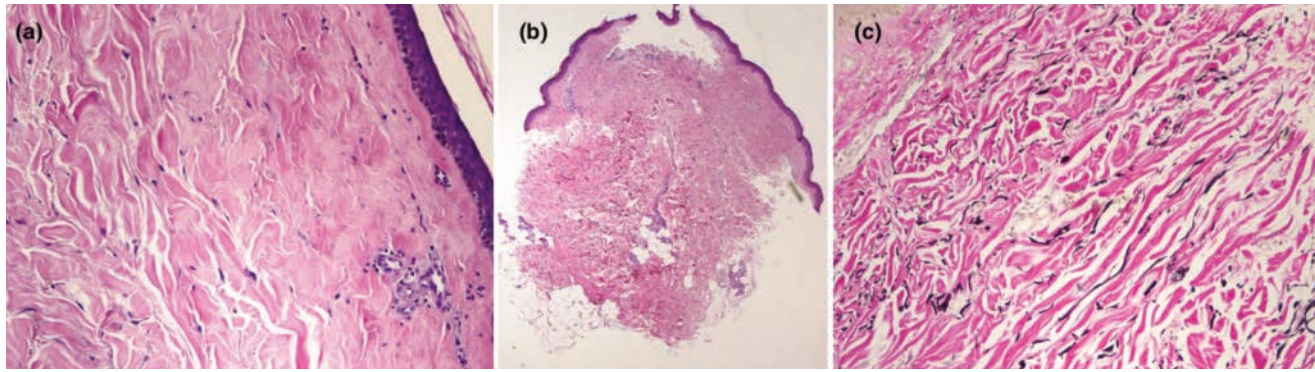


Figure 2. Photomicrograph of skin punch biopsy show basket weave keratin layer, epidermal atrophy with underlying thickening of collagen bundles. No atypical lymphocytes seen (H/E stain, original magnification 200x).

case, the cutaneous lesions developed 20 days following the second dose of Vaxzevria (AstraZeneca). The arm, which is the area of the vaccination injection, was not affected in all the patients. Three of the patients had positive tests for ANA with a homogeneous pattern at a low titer. None of the patients developed the following symptoms: sclerodactyly, Raynaud's phenomenon, facial involvement, nail fold video capillaroscopy abnormalities, or anti-ENA positivity. The conditions of the patients improved with systemic and/or topical treatments.⁵ Furthermore, two cases have been reported involving generalized morphea after receiving COVID-19 vaccination. In the first case, the patient experienced generalized morphea after the first dose of the Moderna vaccine, and this was treated with betamethasone and topical calcipotriol. In the second case, the patient developed generalized morphea after receiving the second dose of the Pfizer vaccine, and this was treated with topical corticosteroids followed by oral methotrexate at a dose of 15 mg/m² per week.²

It is worth noting that the first case of morphea reported following the COVID-19 vaccine was in a 55-year-old female with no medical conditions and no family history of morphea. This patient complained of nonpruritic red rash on the armpit and left breast 4 weeks after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. Histopathologic examination revealed morphea with a positive immunohistochemical analysis using the COVID-19 anti-spike protein antibody, suggesting that the source of the spike proteins was most likely the vaccine. The lesions improved 1 month after the patient started treatment with topical clobetasol propionate pomade and calcipotriol pomade.⁶ This case was followed by another case published in China of a 47-year-old Chinese woman who received her second dose of the Pfizer-BioNTech vaccine (Tozinameran) in May 2021. Three weeks later, she noticed a rash progressively spreading from her thighs to her calves over a period of weeks.⁷

In our case, a 56-year-old female known to have chronic urticaria developed generalized morphea 2 months after taking the second dose of the Pfizer-BioNTech COVID-19 vaccine. There was progressive involvement of the extremities and trunk. In addition, she showed a positive test for ANA at a low titer. The patient did not develop Raynaud's phenomenon, sclerodactyly, facial involvement, or nail fold video capillaroscopy abnormalities. Despite the fact that circumscribed morphea is the most common variant for 60-65% of the patients,³ all cases reported to date of morphea preceded by the COVID-19 vaccine, including ours, involved generalized morphea.

Generalized morphea has been linked to COVID-19 vaccination, and the cause of this association has been hypothesized to be

virus-induced inflammation. Indeed, virus-induced inflammation may activate the immune system or cause a cross-reaction between the virus and the host skin antigens.⁸ Interferons play a key role in the pathogenesis of morphea and systemic sclerosis, and all types of interferons have been identified to correlate with disease activity.⁹ Finally, with respect to morphea, endothelial cell damage causes changes in the soft tissue, and viruses (as well as the associated vaccines) can lead to vascular disorders through the overproduction of profibrotic cytokines (such as TGF- β 1 and β 2, PDGF- α , and PDGF- β).¹⁰ An evaluation was undertaken with the patient to assess for autoimmune rheumatologic diseases, autoimmune thyroiditis, hepatitis C virus and hepatitis B virus, and immunoglobulin E, and all the tests were negative.

This case study was undertaken to address the scarcity of both local and international studies on this topic. It is important to report new cases of skin diseases to acknowledge new or rare cases and evaluate therapeutic effects. It is essential to recognize and understand the possible adverse events following COVID-19 vaccination in patients with chronic urticaria as they have different immune system reactions to different factors.

Conclusions

Recent COVID-19 vaccines have been linked to some types of dermatologic conditions and different types of morphea. Therefore, it is imperative to consider these links if a patient presents with an exacerbated or new-onset cutaneous disease. It is important to report and understand the possible adverse events following COVID-19 vaccination in patients with chronic urticaria.

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