LETTER TO THE EDITOR

Generalized morphea after COVID-19 vaccines: a case series

Editor

In the last months, the detection of adverse muco-cutaneous reactions following COVID-19 vaccines has increased, highlighting not only how SARS-CoV-2 infection but also COVID-19 vaccines may induce adverse cutaneous manifestations.[1,2] In particular, urticaria, angio-oedema and anaphylaxis (as type I hypersensitivity reactions), and inflammatory reactions at the site of injection, morbilliform and erythema multiforme-like rashes (as type IV hypersensitivity reactions) have been the most commonly observed.[1,2] Other manifestations reported in literature include pityriasis rosea-like reactions, herpes zoster reactivations, functional angiopathies, cutaneous vasculitis and lichenoid drug-eruptions.[2–5] To date, only a few cases of COVID-19-induced morphea[1,3] and only one case of morphea induced by COVID-19 vaccine[6] have been reported in the literature. Herein, we described our single centre experience of four cases of generalized morphea following COVID-19 vaccination seen in the last 8 months (Fig. 1a–d).

The mean age of our four patients was 62.5 years (ranging between 52 and 73); three patients were female. All patients developed multiple whitish and sclerotic plaques, with a number of lesions ranging between 5 and 10 and a diameter between 5 and 12 cm. In three patients, the cutaneous lesions appeared after the first and/or second dose of Comirnaty-Pfizer® SARS-CoV-2 vaccine and in one patient 20 days after the second dose of Vaxzevria-Astrazeneca® COVID-19 vaccine. No patient showed an involvement of the area of vaccination (the arm). Of four patients, three patients showed a positivity to anti-nuclear antibodies (ANA) with homogeneous pattern at a low titre, and no patient developed Raynaud's phenomenon, sclerodactyly, facial involvement, nail fold videocapillaroscopy abnormalities or anti-ENA positivity. None of the patients had anti-Borrelia burgdorferi antibodies. The patients have been treated with systemic and/or topical treatments, showing an improvement. All the clinical data are summarized in Table 1.

In our case series, all patients showed a generalized morphea (GM), characterized by ≥4 plaques and ≥3 cm in diameter involving two or more anatomical regions, without cutaneous and systemic symptoms of scleroderma. Besides, in three patients we detected a positivity for ANA, which can be a common finding in more widespread forms of morphea, such as in GM.[7] It is remarkable that one patient presented with a history of eosinophilic fasciitis as this condition is regarded as belonging to the morphea spectrum. As for pathogenesis, since spike protein of SARS-CoV-2 vaccine shares genetic similarities with human proteins, the molecular mimicry and the generation of autoreactive lymphocytes may have contributed to induce this autoimmune disease in a more widespread clinical phenotype.[2] In addition, both mRNA and recombinant adenoviral vector vaccines may induce the activation of chemokines, cytokines

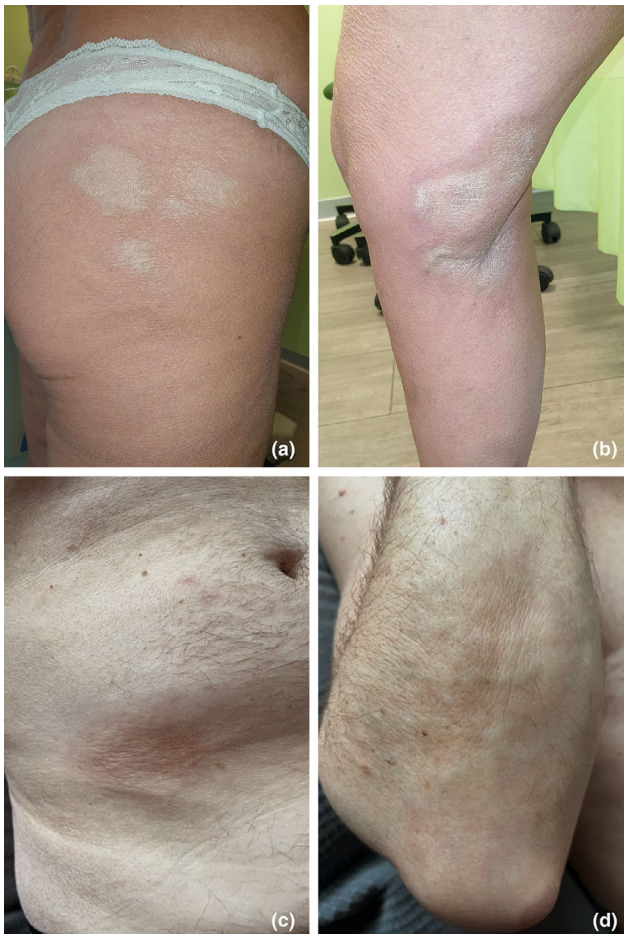

Figure 1 (a–b) Figures show the presence of multiple cutaneous lesions involving more anatomic areas in the same patient (Case patient 1). (c–d) Figures show the presence of multiple cutaneous lesions involving more anatomic areas in the same patient, with an improvement after local treatment with tacrolimus 0.1% cream, which makes the lesion in the forearm slightly perceptible (Case patient 3).

Table 1 Clinical features of patients that developed generalized morphea after COVID-19 vaccines

n	Gender	Age	Past medical history	Ongoing therapies	COVID-19 vaccine	Time from COVID-19 vaccine	Number and diameter of the lesions	Body area	Antibodies	Histology	Direct immunofluorescence	Treatment	Outcome
1	F	61	Negative	None	Corminaty®	15 days from 1st dose and 15 days from 2nd dose	*n* = ≥ 10 ø = 5–12 cm	Abdomen Back, lower limbs	ANA 1:160 Homogeneous	Dermal sclerosis consistent with morphea	Not performed	Clobetasol 0.05% cream and MTX 7.5 mg/week. Because hepatotoxicity MTX has been replaced with Mycophenolate.	Good improvement
2	F	52	Eosinophilic fasciitis	Abatacept and Methotrexate from 2018	Corminaty®	7 days after the 2nd dose	*n* = 5 ø = 5–6 cm	Abdomen, chest, upper limbs	None	Dermal sclerosis consistent with morphea	Not performed	Methotrexate 7.5 mg/week	Good improvement
3	M	64	Negative	None	Vaxzevria®	20 days after the 1st dose	*n* = ≥ 7 ø = 7 cm	Upper limbs, abdomen	ANA 1:160 Homogeneous	Dermal sclerosis consistent with morphea	Not performed	Tacrolimus 0.1% cream	Improvement
4	F	73	Atrio-ventricular block	Pacemaker	Corminaty®	20 days after the 2nd dose	*n* = > 5 ø = 5–6 cm	Lower limbs, abdomen	ANA 1:320 Homogeneous	Dermal sclerosis consistent with morphea	IgG -, IgA-, IgM-, C3-, C1q -, Fibrinogen -	Tacrolimus 0.1% cream	Good improvement

N means patient number; ANA means antinuclear antibodies; n means number; ø means diameter of the lesions; MTX means methotrexate.

and above all of type-I Interferon, which plays a pivotal role in the pathogenesis of morphea and systemic sclerosis, correlating also with disease activity.[8] Finally, endothelial cell damage represents the initial and pivotal step in the development of soft tissue changes in morphea, and viruses (as well as related vaccines) may trigger vascular damage *via* neo-intimal proliferation through overproduction of profibrotic cytokines (such as TGF-beta, PDGF-alpha and PDGF-beta).[9,10]

In conclusion, dysregulation of immune system, as well as genetic and environmental factors have an important role in the pathogenesis of morphea.[6] In this setting, although a coincidence cannot be excluded (given the large number of people who have received COVID-19 vaccines in last months and who may have developed the disease independently), the time elapsed between vaccination and the onset of skin lesions suggests a close correlation between COVID-19 vaccination and GM, especially considering that morphea remains a rare disease.

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Conflicts of interest

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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