

Figure 2 Photomicrographs showing histopathological changes. (a) (H&E $\times 100$): Microscopy shows compact hyperkeratosis, hypergranulosis, irregular epidermal hyperplasia and a moderately dense lichenoid lymphocytic infiltrate. (b) (H&E $\times 400$): Given the presence of eosinophils (arrow) and parakeratosis a drug-induced lichen planus is favoured.

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‘COVID arm’ – histological features of a delayed-type hypersensitivity reaction to Moderna mRNA-1273 SARS-CoV2 vaccine

Dear Editor,

To prevent SARS-CoV2 infection, mRNA vaccines have been developed including the mRNA-1273 (Moderna, Inc., Cambridge, MA, USA), a lipid nanoparticle-encapsulated mRNA vaccine.¹ In some individuals, a cutaneous localized reaction with erythema and swelling on the upper arm at the injection site occurs which is referred as ‘COVID arm’.^{2,3} It is considered as delayed-type hypersensitivity reaction (DTHR) and occurs mostly in individuals after vaccination with the Moderna vaccine, but rarely with other mRNA vaccines.^{2,3} Whereas the clinical presentation is well characterized, the data on the histological features of this reaction are very sparse.

The clinicopathological features of the patients and biopsies are summarized in Table 1. In all three patients, an erythema

Table 1 Clinicopathological features of localized cutaneous delayed-type hypersensitivity reaction to Moderna mRNA vaccine against SARS-CoV-2

Patient	Age (years)	Gender	Dermatol conditions	Latency	Biopsy time	Biopsy site	CD4	CD8	Treg	CD20	CD56	CD138
1	84	Male	NMSC, CM	7 days	14th day	Periphery	60%	20%	10%	1%	1%	1%
2	86	Female	NMSC	6 days	8th day	Centre	90%	10%	5%	1%	1%	1%
3	81	Female	NMSC, SD	7 days	10th day	Centre	90%	10%	10%	1%	1%	1%

Biopsy time: Time point after injection of the vaccine, on which biopsy was performed.

Dermatol conditions: Other skin diseases, for which patients were under dermatological care during or before administration of the vaccine.

Latency: Period to occurrence of erythema after injection of the vaccine.

CM, cutaneous melanoma; NMSC, non-melanoma skin cancer; SD, spongiotic dermatitis (hand eczema); Treg, regulatory T-helper cells.

occurred on the left upper arm 6–7 days after the first injection of the Moderna (mRNA-1273 SARS-CoV2) vaccine. Skin biopsies were performed from the centre of the erythema in two patients and from the periphery in one patient.

Histology revealed subtle and only very focal epidermal changes with spongiosis and exocytosis of a few lymphocytes in all biopsies. There was a perivascular and occasionally sleeve-like inflammatory infiltrate in the upper and mid dermis which was predominantly composed of small lymphocytes with an admixture of a variable number of eosinophilic granulocytes (Figs 1a and 2a,b).

Immunophenotyping revealed that the lymphocytic component consisted almost exclusively of CD3-positive T cells with an admixture of only very few CD20-positive B cells. CD4-positive T cells accounted for 60–90% of all T cells and CD8-positive T cells for the remaining 10–40% (Fig. 1b,c). FOXP3-positive regulatory T-helper cells (Tregs) accounted for 5–10% of the lymphocytes. In addition, few CD56-positive T/NK cells, scattered CD138-positive plasma cells and CD123-positive plasmacytoid dendritic cells (PDCs) were present.

The histological findings in our series are compatible with erythema annulare centrifugum (EAC) and are similar to the findings of previously reported six skin biopsies.^{2,4,5} Our data expand the immunophenotypic profile as they document the presence of few B cells including plasma cells, PDCs and Tregs. Post-vaccine EAC is an immunological reaction pattern which can be interpreted as a DHRT. It is distinct from the urticarial aspect of an acute-type allergic reaction (urticaria) and from contact allergic spongiotic dermatitis as classic localized DTHR. The predominance of CD4⁺ T cells can be explained by the strong response of CD4-positive type 1 helper T cells elicited by the vaccine.⁶ As in other hypersensitivity reactions, eosinophils are present at variable number. Post-vaccine EAC represents the histomorphological correlate for a localized DTHR known as COVID arm due mRNA vaccines. Remarkably, this immunological reaction pattern was also observed as a complication of COVID-19.⁷ The pathogenesis of EAC has not yet been elucidated in detail. Various triggers have been identified such as food components and drugs including immunotherapy.⁸ Lymphocytes from patients with


EAC showed an increased release of IFN- γ .⁹ The COVID-19 mRNA vaccine BNT162b1 induces T-helper type 1-skewed T-cell immune responses with expansion of CD4⁺ and CD8⁺ T cells which are specific to the receptor-binding domain of the SARS-CoV-2 spike protein and produce interferon- γ .¹⁰ These findings support the concept of EAC as a T-cell-mediated DTHR in which IFN- γ is a crucial pathogenetic factor. It is still unclear which component of the Moderna vaccine is responsible for the induction of post-vaccine EAC. The mRNA encoding the spike protein itself seems not to be the primary culprit as also other mRNA vaccines very rarely induce the same reaction. In conclusion, the histomorphological correlate of the localized cutaneous DTHR to mRNA vaccines against SARS-CoV-2 corresponds to EAC as an immunological reaction pattern.

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Conflict of interest

None to declare.

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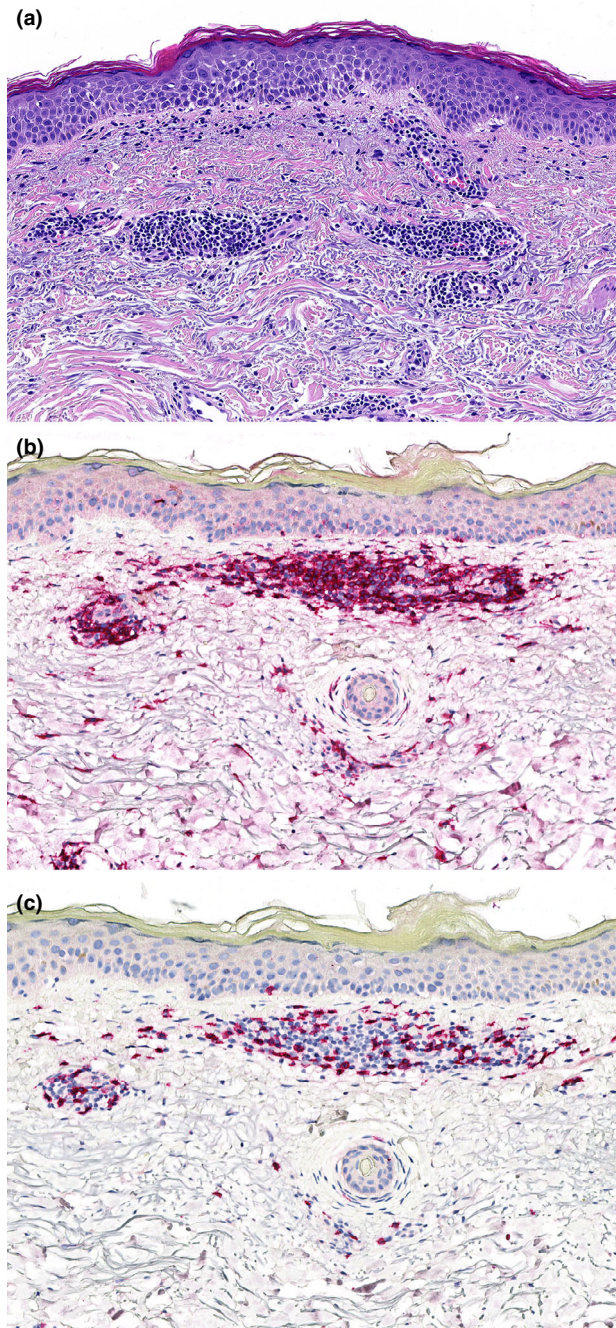


Figure 1 Histology and immunophenotyping of post-vaccine erythema annulare centrifugum. Sleeve-like infiltrate in the upper and mid dermis predominantly composed of small lymphocytes with admixture of a few eosinophilic granulocytes (H&E, original magnification $\times 100$) (a). The lymphocytic component of the infiltrate is predominantly composed of CD4⁺ T cells (b) and to a lesser extent of CD8⁺ T cells (c) (immunohistochemistry, original magnification $\times 100$).

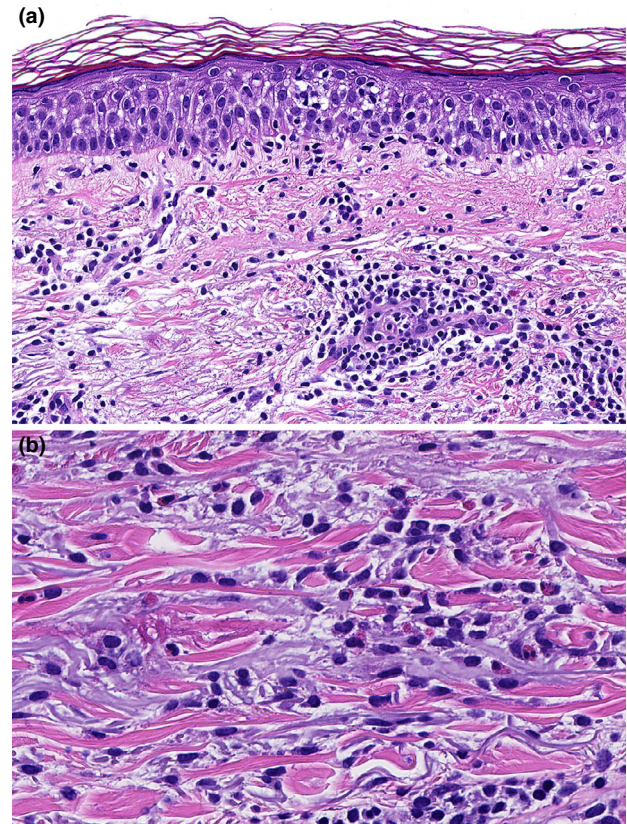


Figure 2 Epidermis with focal spongiosis and exocytosis of lymphocytes (H&E, original magnification $\times 200$) (a). Admixture of numerous eosinophilic granulocytes (indicated by blue arrow) (H&E, original magnification $\times 400$) (b).

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