

Persistent SARS-CoV-2 Spike Protein in Vasculitic Skin Lesions after Infection or mRNA Vaccination: A Retrospective Case-control Immunofluorescence Study

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Vasculitic skin lesions have been reported in association with both SARS-CoV-2 infection and vaccination. Whether viral proteins persist in lesional vessels beyond the acute phase remains unclear. The aim of this study was to investigate the presence of SARS-CoV-2 spike protein in persistent or delayed-onset cutaneous vasculitis temporally associated with COVID-19 infection or vaccination. This retrospective case-control study includes 9 patients with persistent or delayed-onset vasculitic skin lesions following COVID-19 infection ($n=4$) or mRNA vaccination ($n=5$). Skin biopsies were analysed using immunofluorescence for SARS-CoV-2 spike protein. Prepandemic leukocytoclastic vasculitis ($n=3$) and healthy postinfection/postvaccination skin ($n=3$) served as controls. Spike protein was detected in vascular endothelial cells of all 9 patients with COVID-19- or vaccine-associated vasculitis. Staining was absent in all prepandemic vasculitis and healthy control samples. Histopathology showed typical features of leukocytoclastic vasculitis without evidence of viral cytopathic changes. We found that SARS-CoV-2 spike protein can persist in endothelial cells of vasculitic skin lesions weeks to months after COVID-19 infection or mRNA vaccination. These findings suggest that retained viral proteins may contribute to prolonged or delayed-onset vasculitic skin manifestations. Further studies are needed to clarify the mechanisms underlying spike persistence and its clinical significance.

Key words: vasculitis; long COVID; SARS-CoV-2; spike.

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A broad spectrum of cutaneous manifestations has been reported throughout the COVID-19 pandemic. These include maculopapular, urticarial, vesicular and pustular eruptions, chilblain-like lesions, livedoid changes and vasculitic patterns, as described in early

SIGNIFICANCE

Vasculitic skin lesions with SARS-CoV-2 spike protein deposition have been described during acute COVID-19.

We show that similar vasculitic changes with endothelial spike protein deposits can be detected weeks to months after COVID-19 infection or mRNA vaccination.

These findings suggest a potential role of persistent viral proteins in prolonged or delayed-onset inflammatory skin reactions.

cohort studies of infected patients (1). Similar local and systemic dermatologic reactions have also been documented following COVID-19 vaccination (2, 3).

Clinically distinct COVID-related skin reactions show characteristic histopathological patterns, including lymphocytic and neutrophilic infiltrates, urticaria-like changes and small-vessel vasculitis (1). Previous studies have demonstrated that vasculitic changes during acute SARS-CoV-2 infection are associated with deposition of spike protein in endothelial and perivascular cells of dermal microvessels (4, 5). It has been proposed that spike protein may become separated from viral particles during infection or produced transiently following mRNA-based vaccination (6–10).

We previously showed that vasculitic skin changes in acute COVID-19 infection were not associated with direct infection of endothelial cells but rather with accumulation of spike protein (5). In a larger cohort of COVID-related dermatoses, spike protein was detected in some samples despite negative PCR for viral RNA, suggesting the presence of viral proteins independent of active viral replication (4). A spike-associated mechanism has also been hypothesized in vaccine-related skin eruptions (11, 12).

While most COVID-19- or vaccine-associated skin reactions resolve spontaneously, a subset of patients experience persistent or delayed-onset symptoms, falling within the clinical description of post-COVID-19 condition (13). Registry-based analyses have described prolonged cutaneous symptoms after infection (14), but the underlying mechanisms remain unclear. In particular, it is unknown whether spike protein can persist in cutaneous vessels beyond the acute phase of infection or following vaccination.

The aim of this retrospective case–control study was therefore to characterize persistent or delayed-onset vasculitic skin lesions temporally associated with COVID-19 infection or vaccination and to investigate whether SARS-CoV-2 spike protein can be detected in lesional vascular endothelial cells. Pre-pandemic leukocytoclastic vasculitis and healthy skin samples served as negative controls.

MATERIALS AND METHODS

Study cohort

The retrospective study was conducted on formalin-fixed and paraffin-embedded (FFPE) tissue from patients with vasculitic skin diseases after COVID-19 infection or COVID-19 vaccination.

The study cohort includes patients from the Department of Dermatology at the University Hospital of Tübingen who have been diagnosed with histologically proven vasculitic changes between March 1, 2020 and March 1, 2024 and who have reported a temporal association with COVID-19 vaccination or infection and the beginning of skin symptoms in their medical history. Of 175 patients with histologically confirmed vasculitis, only 9 patients explicitly stated a temporal connection, also providing time points, between COVID-19 infection or vaccination and appearance of skin lesions.

For normal skin as a negative control, patient samples were used in which the time of COVID-19 vaccination or COVID-19 infection was known. For non-COVID-19-related leukocytoclastic vasculitis as a negative control, only patient samples acquired before the start of the COVID-19 pandemic in 2020 were used. Moreover, one patient with COVID arm was added as a nonvasculitis control, who had lesions associated with COVID-19 vaccination, but showed no vasculitis histologically (3).

Histology

FFPE tissue was sectioned at 3 µm, deparaffinized and stained with hematoxylin-eosin (H&E) according to standard procedures. The histological sections of the patients were examined by certified dermatopathologists for vasculitic changes. The presence of vasculitis was defined by the presence of angio-centric or angio-invasive inflammatory infiltrates, destruction of the vessel wall and intramural or intraluminal fibrin deposits (15). The sections were additionally examined for the presence of an epidermal necrosis zone, vasocentric infiltrates, neutrophil nuclear dust, erythrocyte extravasates, fibrin deposits in the vessel walls and vascular occlusions. A classification into 4 levels was carried out (none, mild, moderate and

marked). Semiquantitative classification was performed independently by 2 dermatopathologists.

Direct immunofluorescence (DIF) for immunoglobulin and complement deposition was not systematically performed as part of the study protocol. In a subset of patients, DIF results from routine diagnostics were available but showed heterogeneous findings and were therefore not used for subclassification of vasculitis.

Immunofluorescence staining and confocal microscopy

FFPE skin biopsies were cut into 3 µm thick sections, deparaffinized and blocked with donkey serum. The following primary antibodies were used: mouse anti-SARS-CoV-2 spike (GeneTex), rabbit anti-ERG (Cell Marque), goat anti-CD14 (Abcam). Bound mAb was visualized with Cy3-donkey anti-mouse AB, Alexa 647-donkey anti-rabbit AB, Alexa 488-donkey anti-goat AB. DAPI (Sigma-Aldrich) was used for nuclear staining. The immunofluorescence images were acquired using a LSM 800 confocal laser scanning microscope (Carl Zeiss) and the images were processed and analysed using ZEN Blue software, version 2.6.

Statistics

Statistical analyses were performed using Microsoft Excel (version 16.0). Descriptive statistics were calculated as appropriate.

Ethics statement

The study was approved by the Ethics Committee of the University of Tübingen (Project ID 089/2023BO2) and conducted in accordance with the Declaration of Helsinki.

RESULTS

Clinical characteristics

Of the 175 patients in whom vasculitis has been histologically confirmed at the Tübingen University Department of Dermatology since the beginning of the COVID-19 pandemic, only 9 patients indicated a temporal connection with a COVID-19 infection or COVID-19 vaccination in their medical history documentation. The cohort included 5 women and 4 men, aged 19–85 years. Four patients showed vasculitic changes after a COVID-19 infection. The skin changes first appeared 8–77 days after infection. Five patients had vasculitic changes after a COVID-19 vaccination. Here, the skin changes appeared between 2 and 90 days after vaccination. Although histological confirmation revealed vasculitis in all patients, the clinical picture was very diverse. In addition to the classic skin findings of cutaneous

small vessel vasculitis with palpable purpura on the lower extremities, we observed prurigoform changes, vesicular lesions, urticarial-succulent plaques, livedo racemosa and extensive purpura (see **Fig. 1**). The general epidemiological and clinical findings of the patients are listed in **Table I**.

Histopathological findings

Histologically, the 9 patients showed a varied picture. While 8 patients exhibited vasculitis of small capillary vessels with leukocytoclasia, one case (V8) showed vasculitis of a medium-sized subcutaneous arterial vessel structure resulting in a cutaneous panarteriitis nodosa-like disease. Some of the patients showed a histological pattern analogous to classic leukocytoclastic vasculitis (V2, V3, V4), while other patients showed only discrete vasculitic changes, but accompanying epidermal changes in the sense of a prurigo lesion (V1, V5) or with pseudolymphoma-like lymphocytic infiltrates (V6). Three patients had capillary vaso-occlusion with accompanying vasculitic changes (V3, V7, V9). A breakdown of the histological diagnoses

and the characterization of the vasculitic changes and infiltrate can be found in **Table II**.

Spike immunofluorescence in vasculitic lesions

To check for the presence of COVID-19-associated vasculitis, immunofluorescence staining against COVID-19 spike protein was performed on the patients' skin samples. Although the acute COVID-19 infection had been up to 5 months earlier, all of the 4 patients examined (V1, V3, V7, V9) showed a persistent positive reaction to spike protein in the area of the examined vascular endothelia (see **Fig. 2a–b**). Corresponding changes could also be observed after COVID-19 vaccination. Here, all of the 5 patients examined (V2, V4, V5, V6, V8) showed detectable deposits of spike protein up to 18 months after vaccination (see **Fig. 2c–d**). In contrast, no positive reaction to COVID spike protein was found in the vascular endothelia of control samples from leukocytoclastic vasculitis (C14–C16) or healthy skin (C17) before the start of the SARS-CoV-2 pandemic. Likewise, results from samples of healthy skin after a known COVID-19 infection and/or

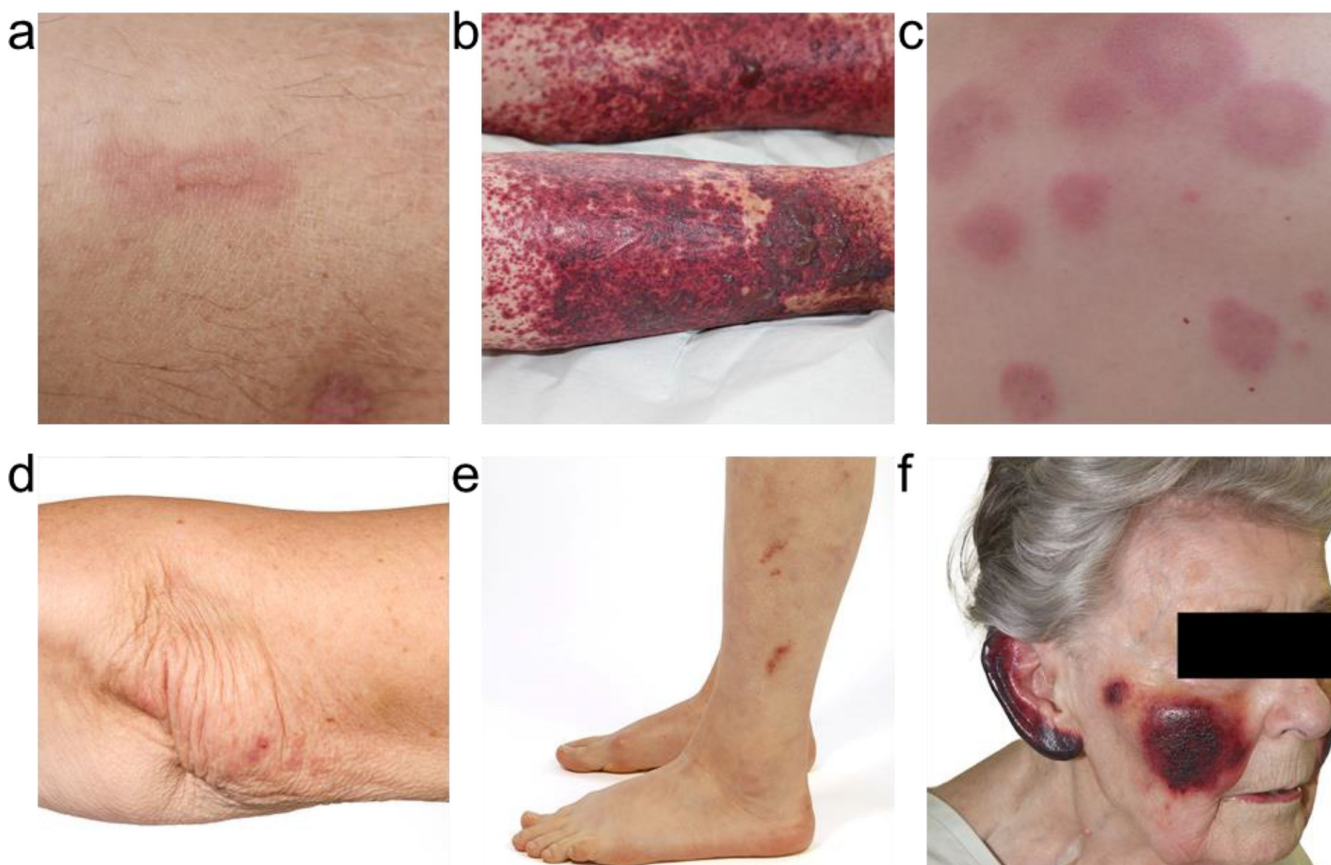


Fig. 1. Clinical findings in 6 patients with post-COVID or post-vac vasculitis. (A) Papules and vesicles (V1), (B) extended palpable purpura (V2), (C) succulent erythematous plaques (V3), (D) papules and small blisters on erythematous skin (V6), (E) livedo racemosa (V8), (F) retiform purpura (V9).

vaccination (C11–C13) show no positive reaction (see Fig. 2e–h).

All patients showed cytoplasmatic spike protein deposits in the endothelial cells (V1–V9). However, in addition to cytoplasmatic deposits, nuclear deposits were also detectable in 2 patients (V8, V9). This was particularly striking in 1 patient (V8) from whom we were able to obtain biopsies from 2 time points 3 years apart. In the first sample, taken in May 2021, spike proteins were found in the cytoplasm, whereas in the biopsy from June 2024, they could be detected in the nucleus (see Fig. 3a and b). Depicted as a line profile graph of an endothelial cell (see Fig. 3c and d).

Spike immunofluorescence in nonvasculitic COVID-associated skin lesions (COVID arm)

In our study, only patients with vasculitic changes were included. However, to test whether corresponding spike deposits can also be detected in other COVID-19 associated skin changes that do not show a vasculitic pattern, a biopsy sample with a confirmed COVID-19 arm was examined (C10). It showed the histological pattern of superficial and deep perivascular dermatitis after vaccination. Despite the absence of vasculitic changes, spike deposits were also found in the vascular endothelium in this sample (see Fig. S1).

DISCUSSION

In this retrospective study, we identified persistent or delayed-onset vasculitic skin lesions in temporal association with COVID-19 infection or vaccination and detected SARS-CoV-2 spike protein in lesional vascular endothelial cells in all patients. These findings extend previous observations of spike deposition during

Table II. Histological diagnoses and characterization of vasculitic changes and infiltrate

No.	Histologic diagnosis
V1	Prurigo lesion and discrete leukocytoclastic vasculitis
V2	Leukocytoclastic vasculitis
V3	Leukocytoclastic vasculitis
V4	Leukocytoclastic vasculitis with perivascular lymphocytic dermatitis
V5	Prurigo lesion and leukocytoclastic vasculitis
V6	Discrete vasculitis with pseudolymphoma-like lymphocytic infiltrates
V7	Discrete vasculitis with focal vasculopathic changes
V8	Cutaneous polyarteritis nodosa
V9	Extensive vasculopathy with vascular occlusions and leukocytoclastic vasculitis

acute COVID-19-related vasculitic eruptions (5) by demonstrating that spike protein may remain detectable in affected microvessels weeks or months after the triggering event.

Initial reports described spike protein within endothelial cells despite the absence of intact viral particles or detectable viral RNA (4, 5), consistent with ultrastructural studies emphasizing the frequent misinterpretation of virus-like structures in tissue (16). These findings supported the concept that vascular involvement may be mediated by viral proteins rather than direct endothelial infection. In this context, the term leukocytoclastic vasculitis is used strictly as a histopathological descriptor and does not imply a specific etiological classification. Our results align with these observations and further support a protein-associated vascular injury pattern.

Spike protein has also been identified in vaccine-associated skin reactions, including delayed local reactions or persistent dermatoses following mRNA vaccination (3, 11, 12). The detection of spike protein in vasculitic lesions after vaccination in our cohort is therefore compatible with earlier reports of vaccine-related cutaneous inflammation.

Table I. Characteristics of patients' cohort and controls

No.	Sex	Age [years]	Type	Time interval to appearance [days]	Clinical presentation	Time interval infection/ vaccination and skin biopsy [days]	Spike protein in endothelial cells (yes/no)
Vasculitis cohort							
V1	M	55	Post-COVID	35	Ulcerations, prurigo nodules and blisters	150	Yes
V2	M	85	Post-vac	2	Cutaneous small vessel vasculitis	12	Yes
V3	F	64	Post-COVID	77	Sweet syndrome	84	Yes
V4	M	51	Post-vac	Unknown	Exanthema	540	Yes
V5	M	73	Post-vac	Unknown	Prurigo	360	No
V6	F	68	Post-vac	84	Papules	450	Yes
V7	F	56	Post-COVID	8–10	Perniones, COVID finger/toe	42	Yes
V8	F	19	Post-vac	Unknown	Livedo racemosa/panarteriitis nodosa (PAN)	360	Yes
V9	F	83	Post-COVID	60	Retiform purpura	60	Yes
Control cohort							
C10	M	32	Post-vac	10	COVID arm	10	Yes
C11	M	31	Post-COVID, post-vac	n/a	n/a	120	No
C12	F	60	Post-vac	n/a	n/a	120	No
C13	F	48	Post-COVID, post-vac	n/a	n/a	90	No
C14	F	41	n/a	n/a	Cutaneous small vessel vasculitis	n/a	No
C15	F	67	n/a	n/a	Cutaneous small vessel vasculitis	n/a	No
C16	F	68	n/a	n/a	Cutaneous small vessel vasculitis	n/a	No
C17	M	32	n/a	n/a	n/a	n/a	No

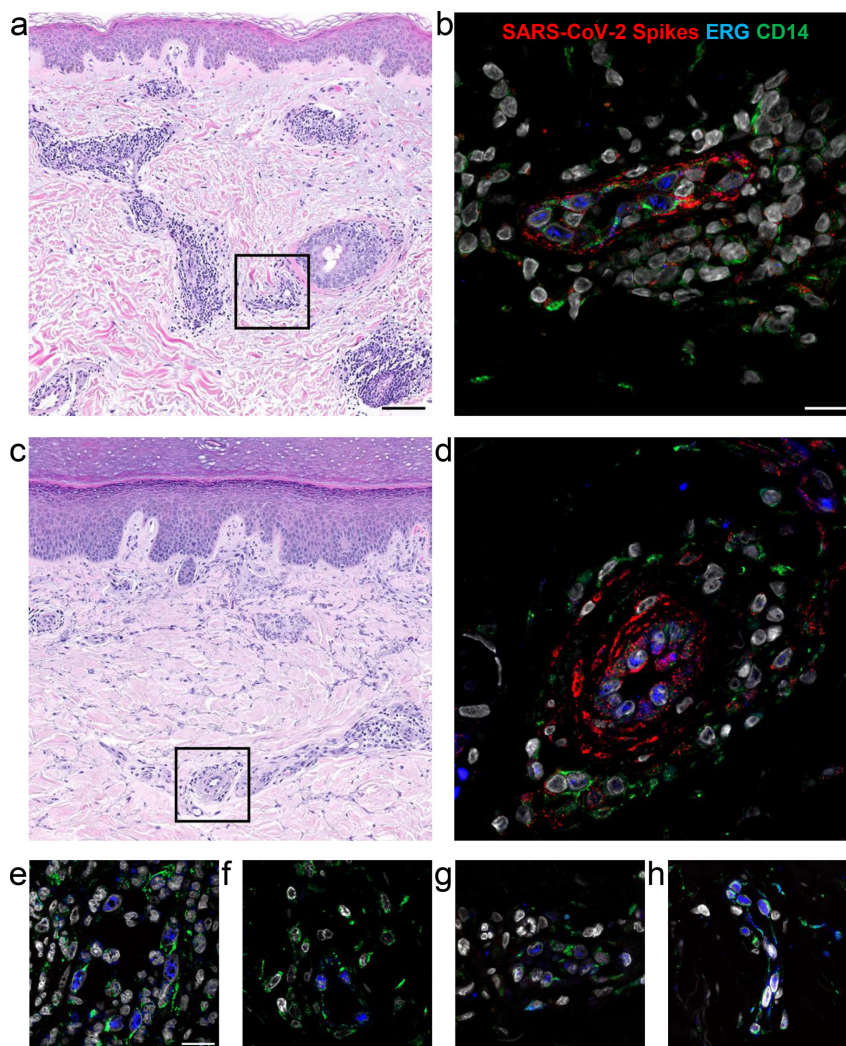


Fig. 2. Dermal microvascular cells. (A) H&E overview of a post COVID skin sample, scale bar 100 µm (V4), square marking the same vessel in a consecutive section seen in (B), stained with immunofluorescence SARS-CoV-2 spikes red, ERG blue, CD14 green, scale bar 20 µm. (C) H&E overview of a post vaccination skin sample (V7) and (D) immunofluorescence, same staining as (B). (E) Vasculitis (C15), scale bar 20 µm and (F) normal skin (C17) before the start of COVID, (G) post-COVID (C11) and (H) post-vaccination of clinically unaltered skin (C13), same staining as (B).

Importantly, spike protein was not detected in pre-pandemic leukocytoclastic vasculitis or in healthy postinfection/postvaccination skin, supporting an association between spike deposition and active vasculitic inflammation. Prolonged dermatologic symptoms after COVID-19 infection have been documented in registry analyses (14), suggesting that delayed inflammatory responses may occur in a subset of patients. Although our data does not establish causality, the presence of spike protein in lesional vessels raises the possibility that retained viral proteins may contribute to persistent vascular inflammation (17, 18).

The mechanism underlying spike persistence in lesional vessels remains unclear. Possible explanations include delayed degradation of viral proteins after infection (6) or transient expression following mRNA vaccination (7–10). Prolonged spike retention in other tissues has also been reported (19), suggesting that

delayed clearance is not unique to the skin. Mechanistic conclusions, however, require prospective studies.

This study has several limitations. The sample size is small, reflecting the rarity of clearly documented temporal associations between vasculitis and COVID-19 exposure. The retrospective design introduces potential inaccuracies in timing, and asymptomatic infections cannot be excluded. Direct immunofluorescence data were not systematically available and showed heterogeneous findings in individual cases, limiting further subclassification of vasculitis. As most biopsies were obtained at only one time point per patient, we cannot evaluate the time course of spike protein persistence. Nevertheless, the consistency of spike detection in temporally associated vasculitis cases, combined with the absence of staining in pre-pandemic controls, supports the robustness of the main finding.

In conclusion, SARS-CoV-2 spike protein can be detected in the vascular endothelial cells of vasculitic

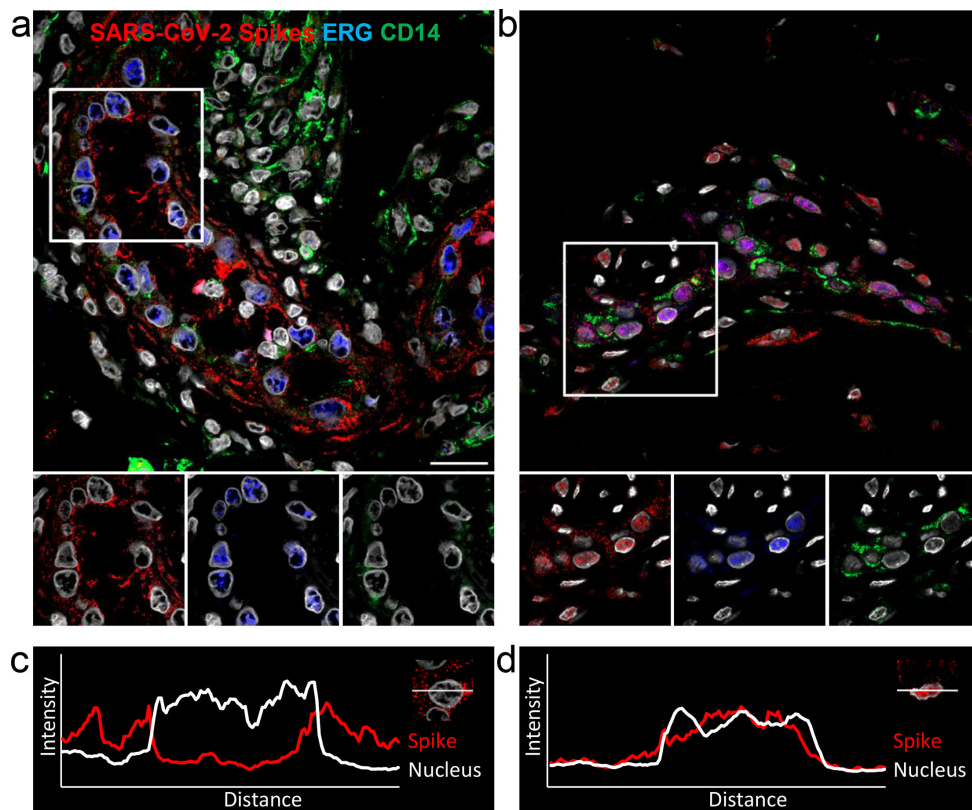


Fig. 3. Post vaccination skin sample of V8. (A) 12 months, scale bar 20 µm and (B) 46 months after vaccination, SARS-CoV-2 spikes red, ERG blue, CD14 green. (c+d) Intensity graphs indicate colocalization of SARS-CoV-2 spikes red and DAPI white, (C) 12 months and (D) 46 months after vaccination.

skin lesions not only during acute COVID-19 infection but also after prolonged latency following infection or vaccination. These findings contribute to the understanding of COVID-19-associated inflammatory skin disease. Larger prospective studies are needed to clarify the mechanisms underlying spike persistence and to determine its clinical significance.

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Data availability statement: All data generated or used during the study appear in the submitted article.

Ethics committee: The study was approved by the Institutional Review Board of the University of Tübingen (project ID: 089/2023BO2) and conducted in accordance with the Declaration of Helsinki.

The authors have no conflicts of interest to declare.

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