Delayed Skin Reaction After mRNA-1273 Vaccine Against SARS-CoV-2

Norman-Philipp Hoff1
University Hospital Düsseldorf
Noemi Freise
University Hospital Düsseldorf
Albrecht G. Schmidt
University Hospital, Medical Faculty, Heinrich Heine University
Parnian Firouzi-Memarpuri
University Hospital Düsseldorf
Julia Reifenberger
University Hospital Düsseldorf
Tom Lüdde
University Hospital Düsseldorf
Edwin Boelke (boelke@med.uni-duesseldorf.de)
University Hospital, Medical Faculty, Heinrich Heine University https://orcid.org/0000-0001-9112-1024
Stephan Meller
University Hospital Düsseldorf
Bernhard Homey
University Hospital Düsseldorf
Torsten Feldt
University Hospital Düsseldorf
Björn Erik Ole Jensen
University Hospital Düsseldorf
Verena Keitel
University Hospital Düsseldorf
Livia Schmidt
University Hospital, Medical Faculty, Heinrich Heine University
Kitti Maas
University Hospital, Medical Faculty, Heinrich Heine University
Jan Haussmann
University Hospital, Medical Faculty, Heinrich Heine University
Balint Tamaskovics
Heinrich Heine University Düsseldorf: Heinrich-Heine-Universitat Dusseldorf
Wilfried Budach

University Hospital, Medical Faculty, Heinrich Heine University
Johannes C. Fischer
Institute for Transplant Diagnostics and Cell Therapeutics, Heinrich Heine University
Bettina Alexandra Buhren
Heinrich-Heine-University
Wolfram Trudo Knoefel
Heinrich Heine University
Marion Schneider
University Hospital Ulm
Peter Arne Gerber
Heinrich-Heine-University
Alessia Pedotoa
Memorial Sloan Kettering Cancer Center
Dieter Häussinger
University Hospital Düsseldorf
Olaf Grebe
Petrus Hospital
Martijn van Griensven
Maastricht University, MERLN Institute for Technology-Inspired Regenerative Medicine
Stephan A. Braun
University Hospital Münster
Stefan Salzmann
University Hospital Münster
Amir Rezazadeh
University Hospital, Medical Faculty, Heinrich Heine University
Christiane Matuschek
University Hospital, Medical Faculty, Heinrich Heine University

Research

Keywords: inflammation, Covid-19, dermatitis, injection, hypersensitivity, mRNA-1273 (Moderna) vaccine, erythema, edema

Posted Date: May 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-507024/v1

Abstract

The coronavirus disease 2019 (COVID-19) is associated with a wide clinical spectrum of skin manifestations, including chilblain-like, urticarial, vesicular and vasculitic lesions. Recently, delayed skin reactions following mRNA vaccination against SARS-CoV-2 have been reported. The exact pathomechanisms underlying these skin lesions remain unknown. Here, we describe eleven cases of delayed skin reactions after SARS-CoV-2 vaccination with the mRNA-1273 vaccine, discuss their transient and benign clinical courses and consider their potential pathomechanisms based on histopathological analyses. We conclude that further investigations to characterize the precise molecular and cellular mechanisms underlying this rare phenomenon are warranted.

Introduction

SARS-CoV-2 continues to pose a major threat to health care systems worldwide. Ongoing vaccination programs are anticipated to control the COVID-19 pandemic, eventually. Novel mRNA-based vaccines assessed and made available at unprecedented pace constitute a most critical, enabling advance. At the same time, the novelty of mRNA-based vaccines calls for special attention to potential unexpected or extended spectra of side effects of this novel vaccination technology.[1] Baden et al. reported that immediate injection-site reactions were detected in 84.2% of the participants in the phase III trial after the first dose of the mRNA-1273 vaccine.[2] The authors further reported the rare occurrence of late injection-site reactions with an onset on or after day eight in 244 of the 30,420 participants of their trial after the first dose (0.8%) and in 68 participants after the second injection (0.2%).[2] These reactions involved erythema, induration and soreness, which typically resolved within the next four to five days. Based on histological findings, the research group interpreted the side effect as a type IV hypersensitivity reaction.[3–5] Seemingly similar skin reactions have recently been reported with BNT162b2, the second currently approved mRNA-based vaccine.[6,7] The US Centers for Disease Control and Prevention (CDC) refers to these rare skin reactions associated with mRNA-based vaccines as "COVID arm".[8] “COVID arm” usually neither requires treatment nor should it discourage a 2nd dose vaccination if scheduled.

Here, we report on a series of eleven patients with these responses, all of which appeared near the injection site after complete resolution of the initial local and systemic symptoms associated with vaccination. In addition, we present possible therapeutic approaches and discuss potential pathomechanisms based on histological examinations.

Patients And Methods

We analyzed the reports on acute side effects in the Dermatology Departments at the University of Düsseldorf, Dermatology Department of Münster and in one private practice in Düsseldorf.

Results

Case 1

56-year-old Caucasian male with no history of past medical problems. He developed three days after the injection of the mRNA-1273 vaccine a large local erythema with edema at the injection site. He also complained about local cutaneous hypersensitivity. Use of oral antihistamines gave a quick relief of the symptoms.

Case 2

60 year old Caucasian female with no history of past medical problems. She developed four days after the first injection of the mRNA-1273 vaccine a large local erythema with edema at the injection site. She also developed a cervical lymphnode swelling starting 2 days after the first injection. With use of oral antihistamines no skin symptoms occurred after the 2nd injection

Case 3

41-year-old Caucasian female with erythema, swelling of the arm and soreness exactly 7 days after injection of mRNA-1273-vaccine. No therapy was administered. Symptoms resolved spontaneously.

Case 4

Mild erythema in a 41-year-old Caucasian female exactly 7 days after first vaccination with mRNA-1273. No therapy was required. After 2–3 days the symptoms resolved completely.

Case 5

50-year-old female with local erythema and soreness of the injected arm after vaccination with mRNA-1273. The symptoms appeared 9 days after injection and disappeared after 2–3 days. No therapy was administered.

Case 6

A healthy 30-year-old female developed an indurated plaque (approximately 8 x 5 cm in diameter) on her right upper arm 7 days after her first vaccination with the mRNA-1273 vaccine. She noticed a painful burning sensation at the injection site. Other systemic side effects or further skin changes were denied. Because of the severe discomfort at the injection site, topical methylprednisolone aceponate for a few days as well as a systemic therapy with loratadine was initiated. After a few days, there was complete resolution of the skin lesion. The second vaccination was performed according to standard schedule. No further systemic or cutaneous reactions were observed.

Case 7

A healthy 44-year-old female developed local swelling, redness, and induration at the injection site and the surrounding area 3 days after the second vaccination with the mRNA-1273 vaccine. No other abnormalities were described except for cutaneous tenderness and mild itching. She complained of mild

chills 24 hours after each vaccination. Otherwise, the vaccination was well-tolerated. No topical or systemic therapies were initiated. The skin lesions disappeared completely after a few days.

Case 8

A 63-year-old female noticed redness and swelling at the injection site on her left arm 2 days after her second mRNA-1273 vaccination. Apart from mild itching, no other symptoms were described. Concomitant diseases were denied. Allergies were denied. After the first vaccination, the patient remained at home with a pronounced feeling of illness. Due to the mild symptoms, no therapeutic measures were taken in this case either. There was a significant improvement of the skin findings already after two days and no further symptoms.

Case 9

A 50-year-old healthy female showed redness, swelling, and induration at the injection site 4 days after the second vaccination with mRNA-1273 vaccine, comparable to our other cases. Because of the extensive size of the lesion as well as the pronounced local burning and itching, a skin biopsy was taken. (Figs. 9 and 10).

The histopathologic examination supports the diagnosis of a lymphocyte-triggered inflammatory reaction in response to the vaccination with mRNA-1273. Histologic investigation revealed a dermal perivascular infiltrate of lymphocytes, and a few eosinophils. There was no evidence of granulomatous infiltration as an indication of potential adjuvant response. The patient received topical methylprednisolone aceponate until skin lesions resolved and systemic loratadine for the pruritic symptoms.

Case 10

A 37-year old female patient reported painful swelling on her left upper arm starting 8 days after a first injection with mRNA-1273 vaccine. The left upper arm showed a 10 cm diameter uritcarial plaque with central fading. A painful lymph node could be palpated in the left axilla. The patient was feeling a little listless but had no fever.

Case 11

A 79-year old male patient reported painful swelling on his left upper arm starting 12 days after a first injection with mRNA-1273 vaccine. The patient was feeling a little listless but had no fever

Discussion

The here reported case series of delayed local skin reactions following vaccination with mRNA-1273 mirrors recently published case series of similar findings with both currently approved mRNA-based vaccines mRNA-1273[3,9] and BNT162b2[6;7]. These delayed skin reactions are rare post-vaccination events of both approved mRNA-based vaccines, with incidences reported to be in the order of 0.8-1.0 % following the first and 0.2–1.1% following the second dose[2,6]. Delayed skin reactions are typically observed several days after the vaccination, i.e. following a symptom-free interval and hence distinguishable from acute

allergic and other immediate local reactions attributable to the vaccination intervention itself. The phenomenon is transient and typically resolves within 3–5 days, frequently without any treatment required. In cases in whom pharmacological intervention is needed, the experience of this case series as well as of earlier reports show that the condition may be expected to be well-responsive to topical glucocorticosteroids and oral histamines. In patients in whom a “COVID arm” occurs following the first of two scheduled vaccinations, the recommendation is to seek the second vaccination as scheduled, potentially administered to the opposite arm if needed[8].

An important question unanswered to date relates to the precise molecular and cellular mechanisms underlying the “COVID arm” phenomenon. In response to this question, we noted that the delayed skin reactions observed in our case serious are of two distinct time windows of onset and of two distinct (even though overlapping) clinical phenotypes, indicative of more than a single pathomechanism. Specifically, we observed manifestations of comparatively early onset (days 2–3 post vaccination) characterized by diffuse, poorly demarcated erythema associated with variable degrees of local edema and symptoms of tenderness, local hypersensitivity and itch well-responsive to antihistamines (as exemplified by case 1). These comparatively early skin manifestations appear to be distinct from manifestations of later onset (days 7–10 after the first, days 2–4 after the second vaccination), which are characterized by more sharply demarcated erythema of irregular peri- and intra-lesional morphology. While the former type of skin manifestation clinically reminds of an allergic pathology, we were particularly interested in the pathology and pathomechanisms underlying the latter type of late-onset delayed skin reactions (mirroring events described in earlier reports), with the delayed time window suggesting the involvement of the patient’s adaptive immune response to the vaccination. Even though patient numbers are small, the shorter time to onset following second vaccinations, as observed in our cohort, similarly suggests the involvement of patients’ adaptive immune response, the more so as a similar shortening of time to onset following second vaccination has been observed before[3]. The exact mechanism of these reactions is not known, however a delayed hypersensitivity reaction has been hypothesized.[10]

Focusing on these skin reactions of delayed onset, we considered for reference early skin manifestations associated with COVID-19 infection, *per se*. While COVID-19 associated skin lesions are of a wide clinical spectrum including chilblain-like, urticarial, vesicular and vasculitic lesions, the occurrence of distinct types of skin lesions within distinct windows of onset during the COVID-19 clinical course has been noted[11]. Histopathological skin biopsy analyses of these COVID-19 associated cases show diverse ranges of morphologies. A consistent histological feature, however, appears to be the presence of prominently dilated blood vessels with swollen endothelial layers and vessels engulfed with red blood cells and perivascular infiltrates[12].

The specific mechanisms underlying these endothelial, vascular, and perivascular inflammatory changes associated with COVID-19 infection have not been fully elucidated. A possible lead hypothesis involves direct viral infection of endothelial cells, with preliminary evidence for this derived from existing data of both electron microscopy and polymerase chain reaction (PCR) analyses within skin lesions[13,14 15].

Not dissimilar to the cutaneous histomorphology observed in COVID-19 infection, the histology images of the current mRNA-1273 case series and similarly of a previously reported histology analysis of skin lesions following mRNA-based BNT162b2 vaccination[6] share prominent features of a superficial and deep perivascular dermatitis with scattered eosinophils and intraluminal neutrophil accumulation (Fig. 9, 10). This histology pattern is commonly referred to as dermal hypersensitivity reaction[16]. It is not diagnostic for any specific condition or etiology. Additional analyses will be required, therefore, to further dissect the phenomenon itself as well as its molecular triggers.

At least two categorically different molecular pathomechanisms will need to be considered in these future investigations: Firstly, polyethylene glycol (PEG), an excipient contained in both mRNA-based vaccines yet not in DNA vector vaccines[1] may trigger allergic post-vaccination reactions as a net consequence of prior sensitization to PEG[17] or by direct T cell stimulatory action[18]. With direct proof lacking, the hypothesis of excipient-mediated pathology may appear to be supported indirectly, at least at first glance, by the fact that delayed local skin reactions have not been reported the same with DNA vector vaccines, i.e. with vaccines also encoding the S protein yet neither containing PEG nor other excipients contained in mRNA-based lipid nanoparticle vaccines[1,17,19]. An alternative hypothesis still to be considered, however, is the potential direct transfection of endothelial cells with mRNA locally released from lipid nanoparticles, with aberrantly endothelially expressed S antigen responded to by building adaptive cellular immunity. The seeming absence of similar delayed skin reactions with DNA vector vaccines could find its explanation, if this alternative hypothesis would be proven correct, in the differential distribution, dosage, *in vivo* stability and cargo release characteristics of viral vector DNA vaccines as compared to lipid nanoparticles delivering mRNA.

Therefore, while “COVID arm” is a transient, localized, and clinically benign rare side effect upon vaccination with mRNA-based vaccines encoding the S-protein, the deciphering of the precise molecular and cellular mechanisms underlying this local phenomenon (directly accessible by biopsy) could still become the springboard of a more precise understanding of very rarely occurring endothelitic pathology observed with S-protein encoding vaccines, in general. In-depth analyses of the pathomechanisms underlying delayed skin reactions following mRNA-based vaccinations are called for, in consequence. It could evolve to be of significant clinical relevance to discern whether either (1) excipients exclusive to mRNA-based vaccines (with PEG as the most prominent candidate molecule) or (2) the S-protein encoded by both mRNA-based and DNA vector vaccines and potentially expressed on endothelial cells, or (3) both pathomechanisms in conjunction will constitute the triggering event(s) of very rare and rare adverse events affecting different vascular compartments and endothelial cells, with the spectra of clinical sequelae dependent on the tissue compartments afflicted.

Conclusion

Delayed local skin reactions, also referred to as “COVID arm”, are a rare side effect that can present as a localized, transient erythematous and edematous plaque several days after the first or second dose of the

mRNA-based COVID-19 vaccines. Even though most cases resolve spontaneously, topical glucocorticosteroids and oral anti histamines are effective in resolving the skin lesions and controlling symptoms. Patients should be notified that a “COVID” arm is a non-threatening benign potential side effect that should not discourage from obtaining a second dose of mRNA-based vaccine. Further investigations regarding the precise molecular and cellular mechanisms underlying this cutaneous pathology may inform the understanding of very rare and rare adverse events associated with S protein encoding vaccines, in general, and are called upon, therefore.

Abbreviations

Covid-19: Coronavirus disease 2019

CDC: Centers of disease control

mRNA: messenger ribonucleic acid

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

PEG: polyethylene glycol

Declaration

Authors’ contribution

NH, NF, AGS, EB, SM, BH, TF, BJ, VK, LS, EB, JH, BT, WB, JCF, BAB, TL, CM, OG, MvG, SAB, SS wrote parts of the manuscript. EB and LS did the literature research and prepared the data for analysis. CM, EB and NH contributed significantly to the discussion on the interpretation of the results. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data and materials can be accessed via CM and NH.

Consent for publication

All authors gave consent for the publication

Ethics approval and consent to participate

There was no ethics approval necessary because this is a review of the literature and a case report.

Conflict of Interest: All authors declare that they have no conflict of interest.

Funding

There was no funding for this investigation.

References

1. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract 2020.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403–16.
3. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. N Engl J Med 2021.
4. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5675–84.
5. Greenhawt M, Abrams EM, Oppenheimer J, et al. The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World. J Allergy Clin Immunol Pract 2021.
6. Fernandez-Nieto D, Hammerle J, Fernandez-Escribano M, et al. Skin manifestations of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers. 'COVID-arm': a clinical and histological characterization. J Eur Acad Dermatol Venereol 2021.
7. Ramos CL, Kelso JM. "COVID Arm": Very delayed large injection site reactions to mRNA COVID-19 vaccines. The journal of allergy and clinical immunology In practice 2021.
8. CDC. 2021. April 26, 2021. at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/allergic-reaction.html.).
9. Wei N, Fishman M, Wattenberg D, Gordon M, Lebwohl M. "COVID arm": A reaction to the Moderna vaccine. JAAD Case Rep. 2021;10:92–5.
10. Raap U, Goltz C, Deneka N, et al. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. J Allergy Clin Immunol. 2005;115:1268–75.
11. Gisondi P, Di Leo S, Bellinato F, Cazzaniga S, Piaserico S, Naldi L. Time of Onset of Selected Skin Lesions Associated with COVID-19: A Systematic Review. Dermatol Ther (Heidelb); 2021.
12. Gianotti R, Recalcati S, Fantini F, et al. Histopathological Study of a Broad Spectrum of Skin Dermatoses in Patients Affected or Highly Suspected of Infection by COVID-19 in the Northern Part of Italy: Analysis of the Many Faces of the Viral-Induced Skin Diseases in Previous and New Reported Cases. Am J Dermatopathol. 2020;42:564–70.
13. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417–8.

14. Garrido Ruiz MC, Santos-Briz A, Santos-Briz A, et al. Spectrum of Clinicopathologic Findings in COVID-19-induced Skin Lesions: Demonstration of Direct Viral Infection of the Endothelial Cells. Am J Surg Pathol. 2021;45:293–303.
15. Gambichler T, Reuther J, Stucker M, et al. SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion. J Eur Acad Dermatol Venereol. 2021;35:e187-e9.
16. Fung MA. The clinical and histopathologic spectrum of "dermal hypersensitivity reactions," a nonspecific histologic diagnosis that is not very useful in clinical practice, and the concept of a "dermal hypersensitivity reaction pattern". J Am Acad Dermatol. 2002;47:898–907.
17. Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: possible involvement of polyethylene glycol and IgG-mediated complement activation. Allergy 2021.
18. Ocklind G, Lindahl-Kiessling K. Accessory cell-independent activation of T cells by oxidized red blood cells plus polyethylene glycol. Immunobiology. 1987;176:167–76.
19. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med. 2021;384:643–9.

Figures

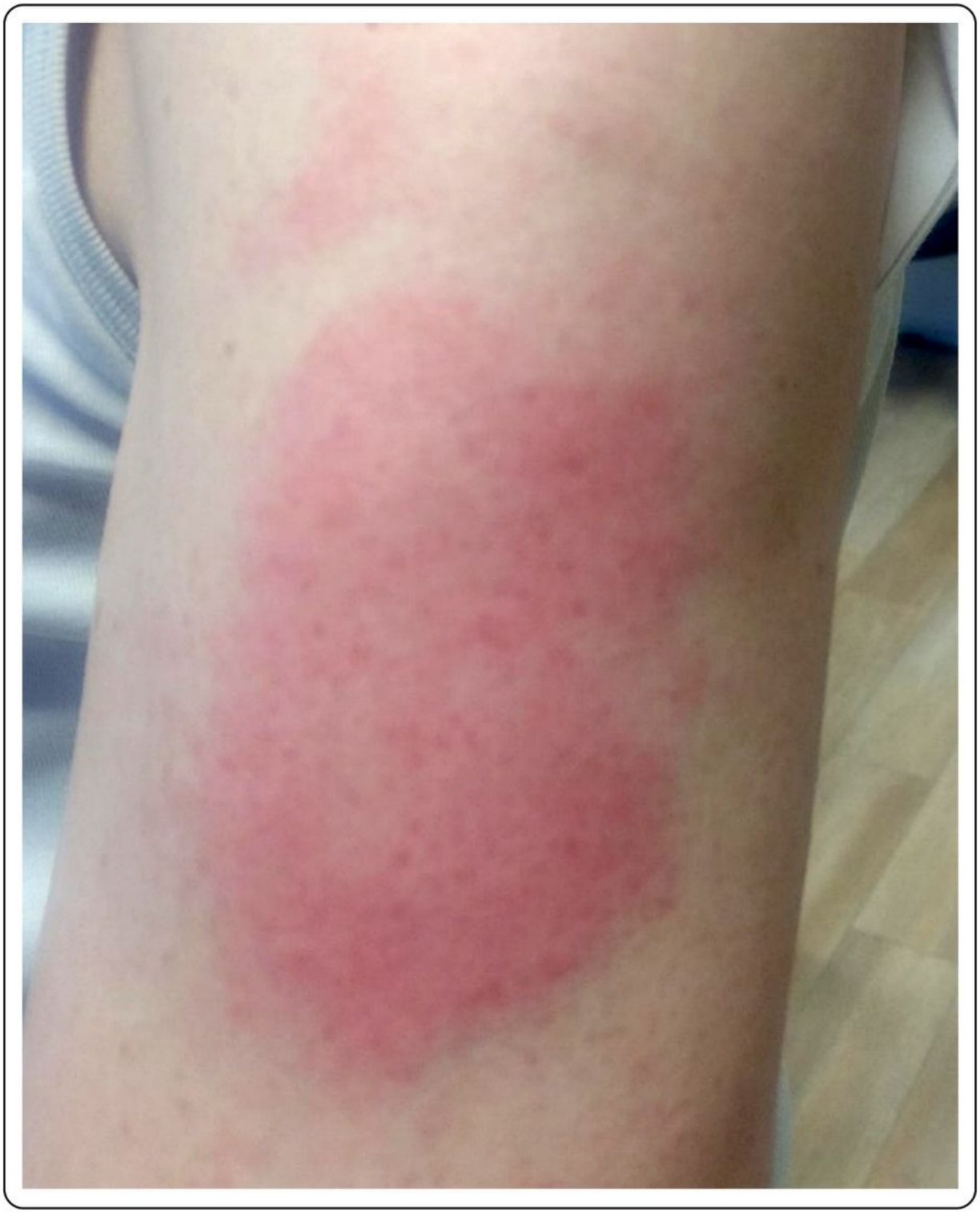


Figure 1

“COVID arm": Delayed cutaneous reaction to the mRNA-1273 vaccine, erythema and induration 72 hours after the injection.

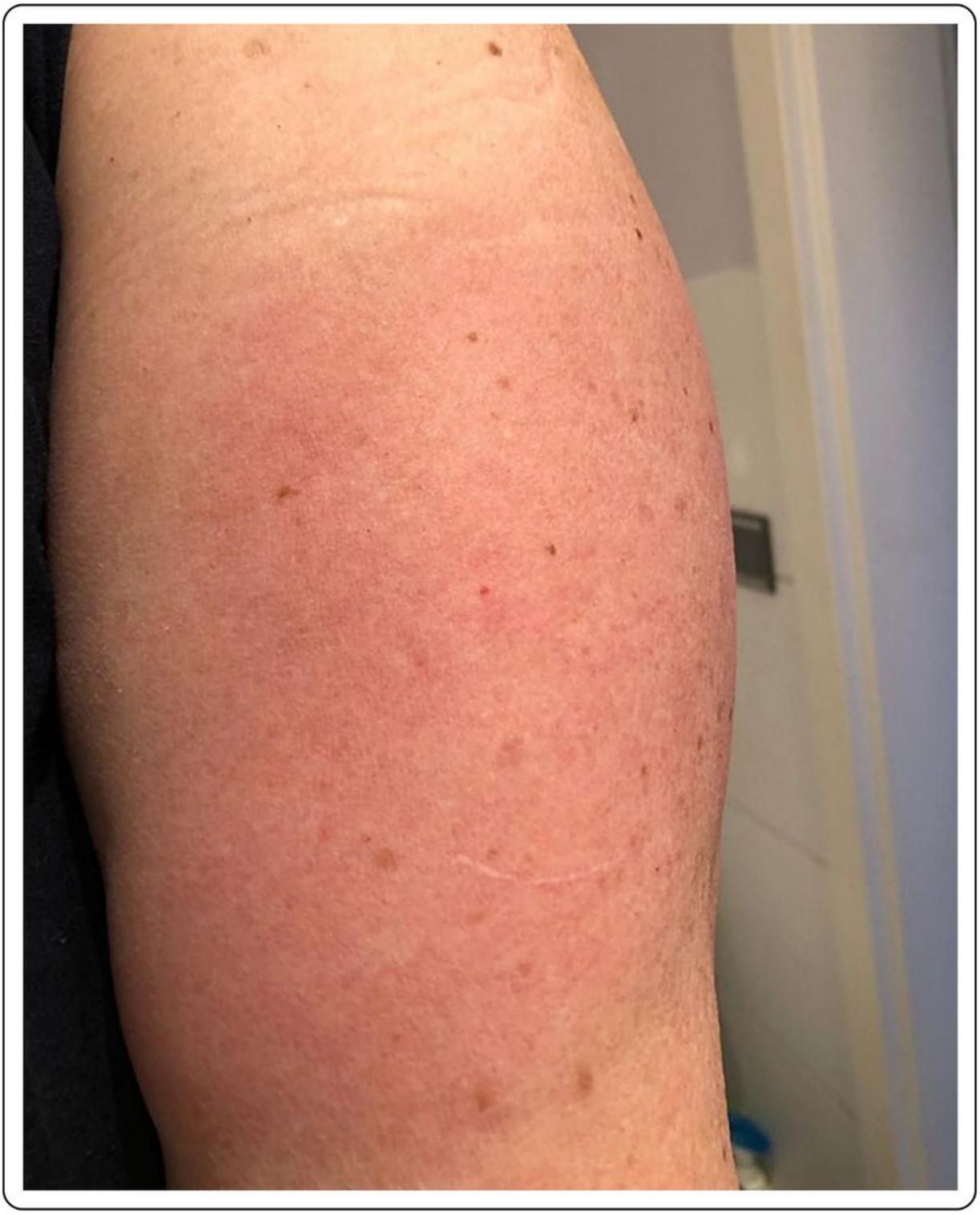


Figure 2

“COVID arm": 48 hours after the injection with the mRNA-1273 vaccine, large local erythema with edema at the injection site. She also developed a cervical lymphnode swelling starting 2 days after the first injection.

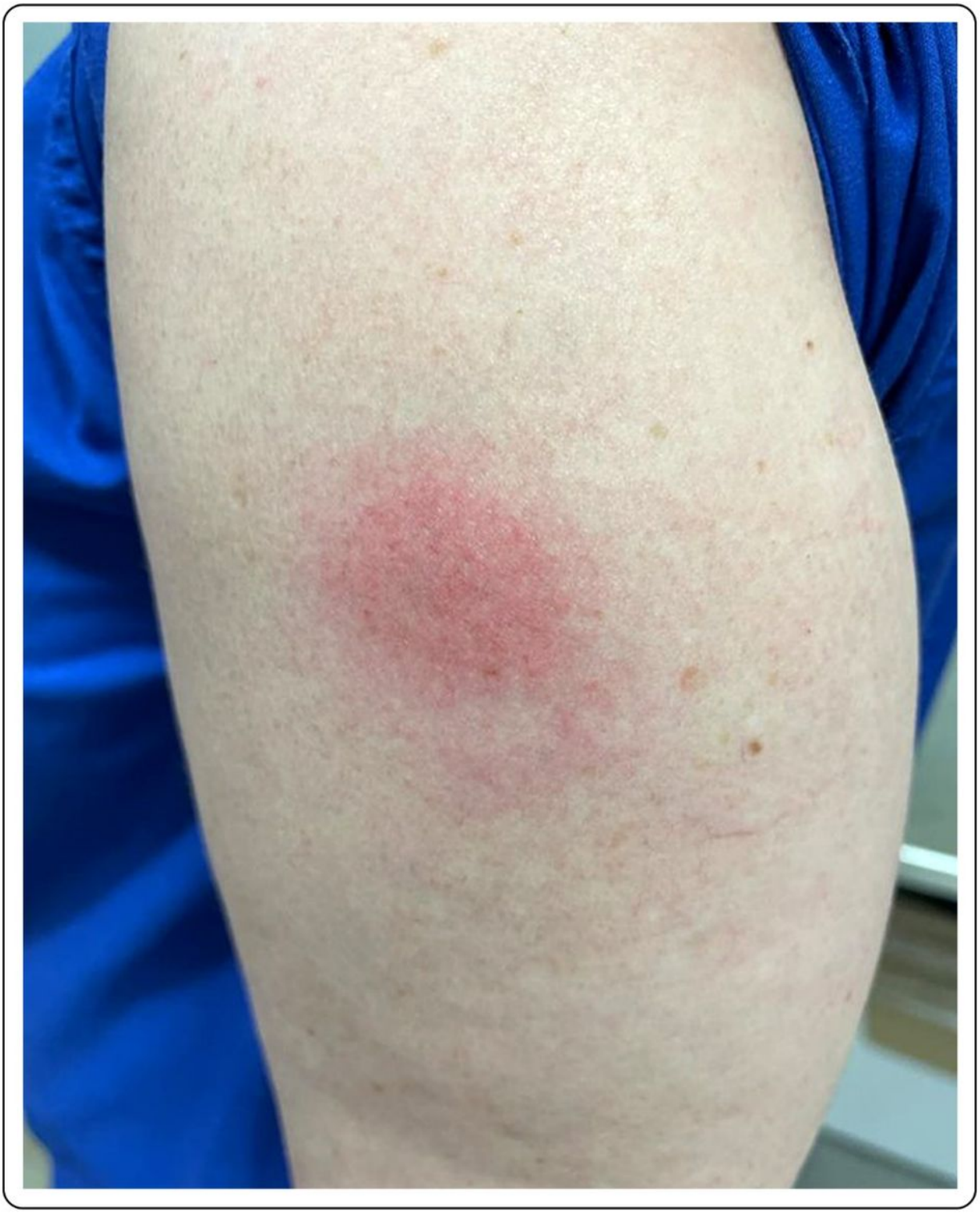


Figure 3

Erythema and edema accompanied by soreness of the upper arm exactly 7 days after injection of mRNA-1273-vaccine.

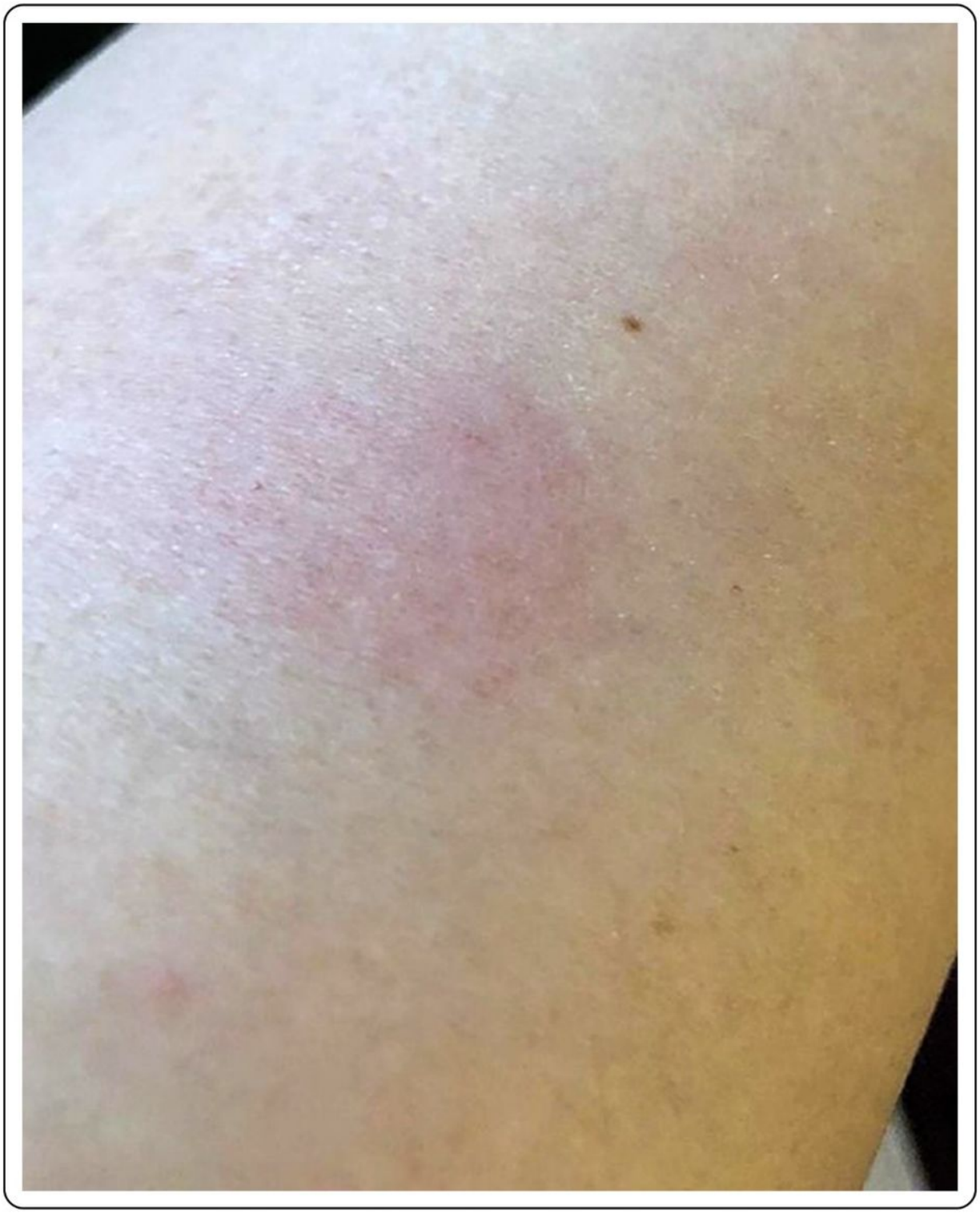


Figure 4

Mild erythema in a 41-year-old Caucasian female 7 days after first vaccination with mRNA-1273.

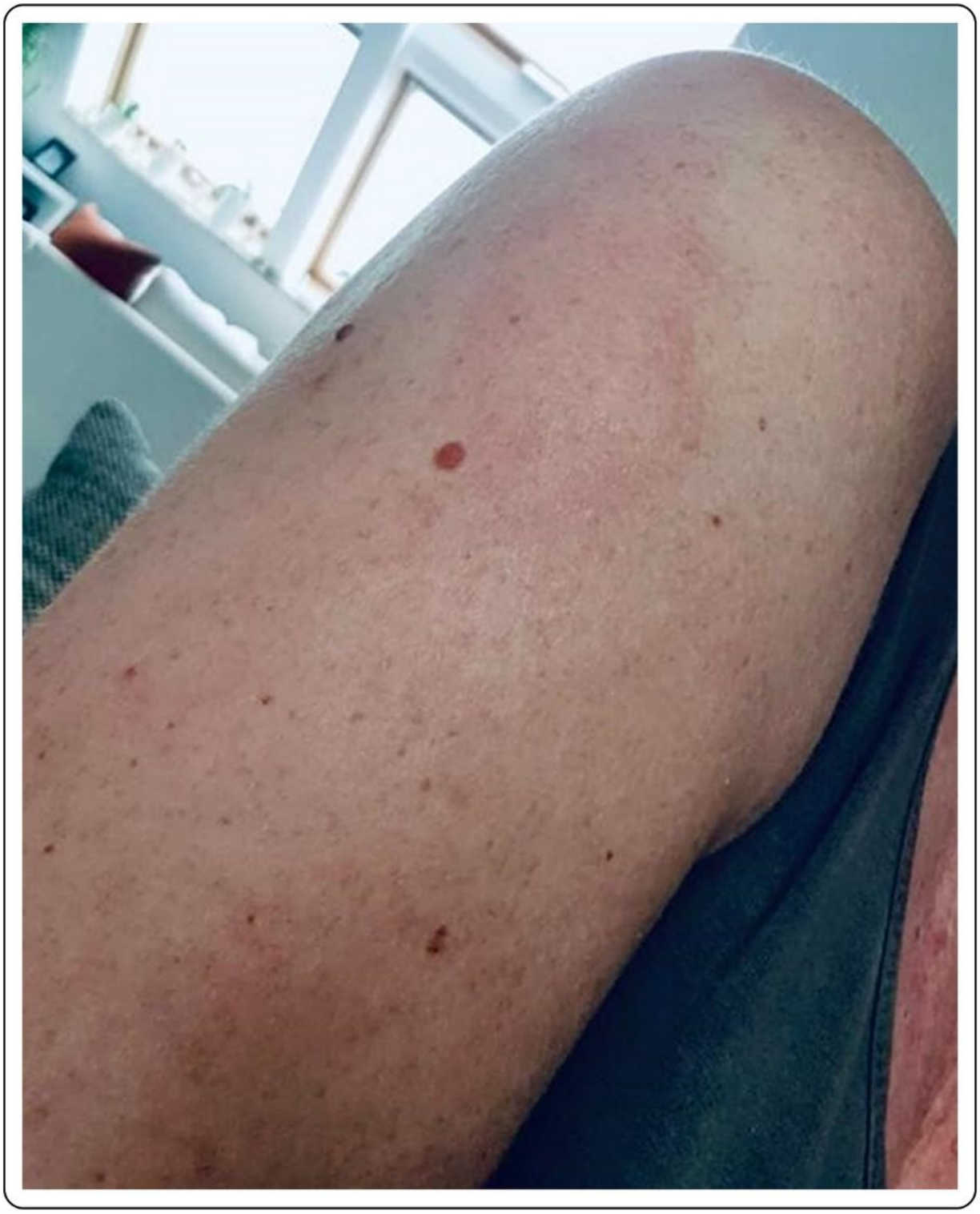


Figure 5

Local erythema after mRNA-1273 vaccination after 9 days.

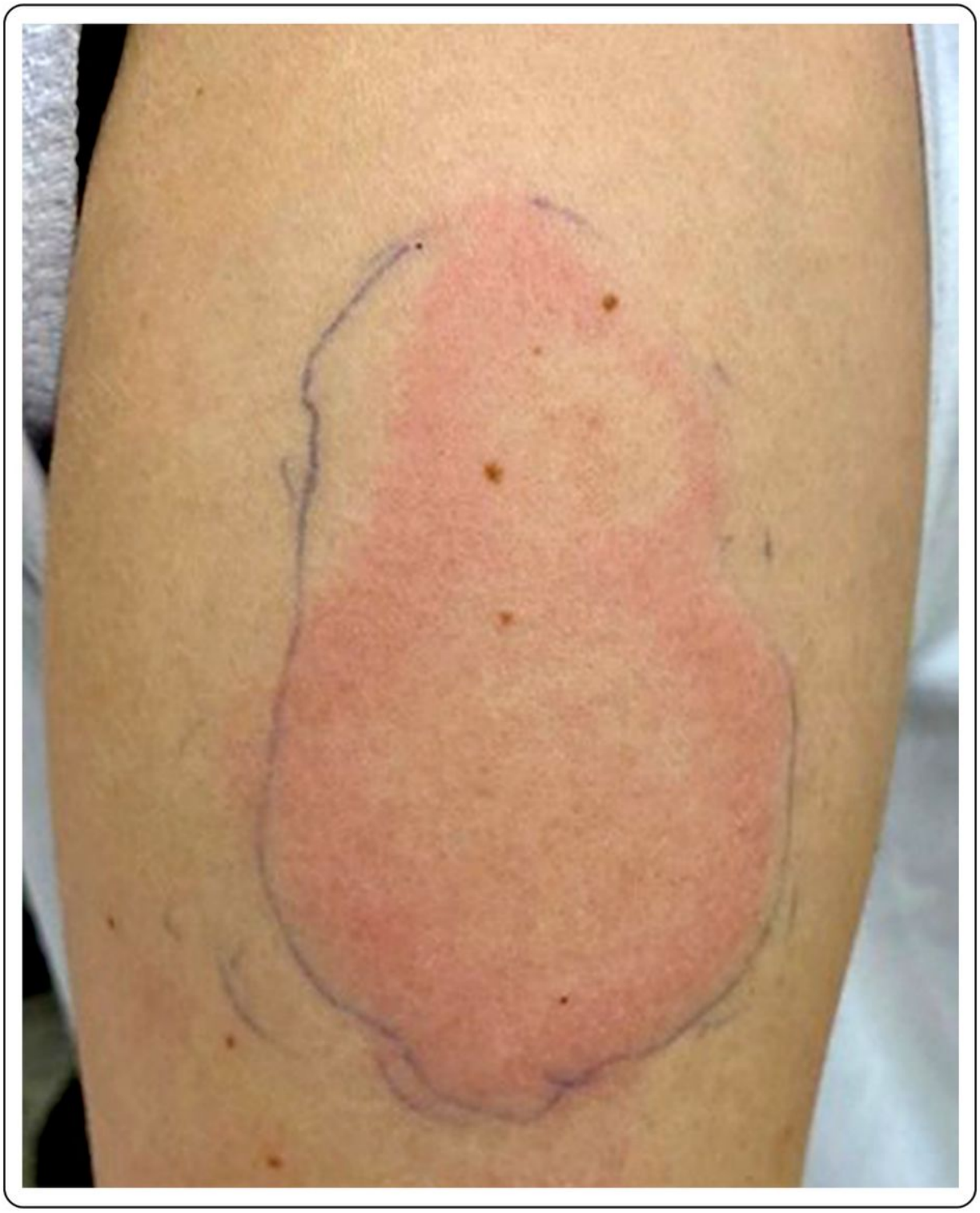


Figure 6

Erythematous and edematous indurated plaque after mRNA-1273 vaccination after 7 days.

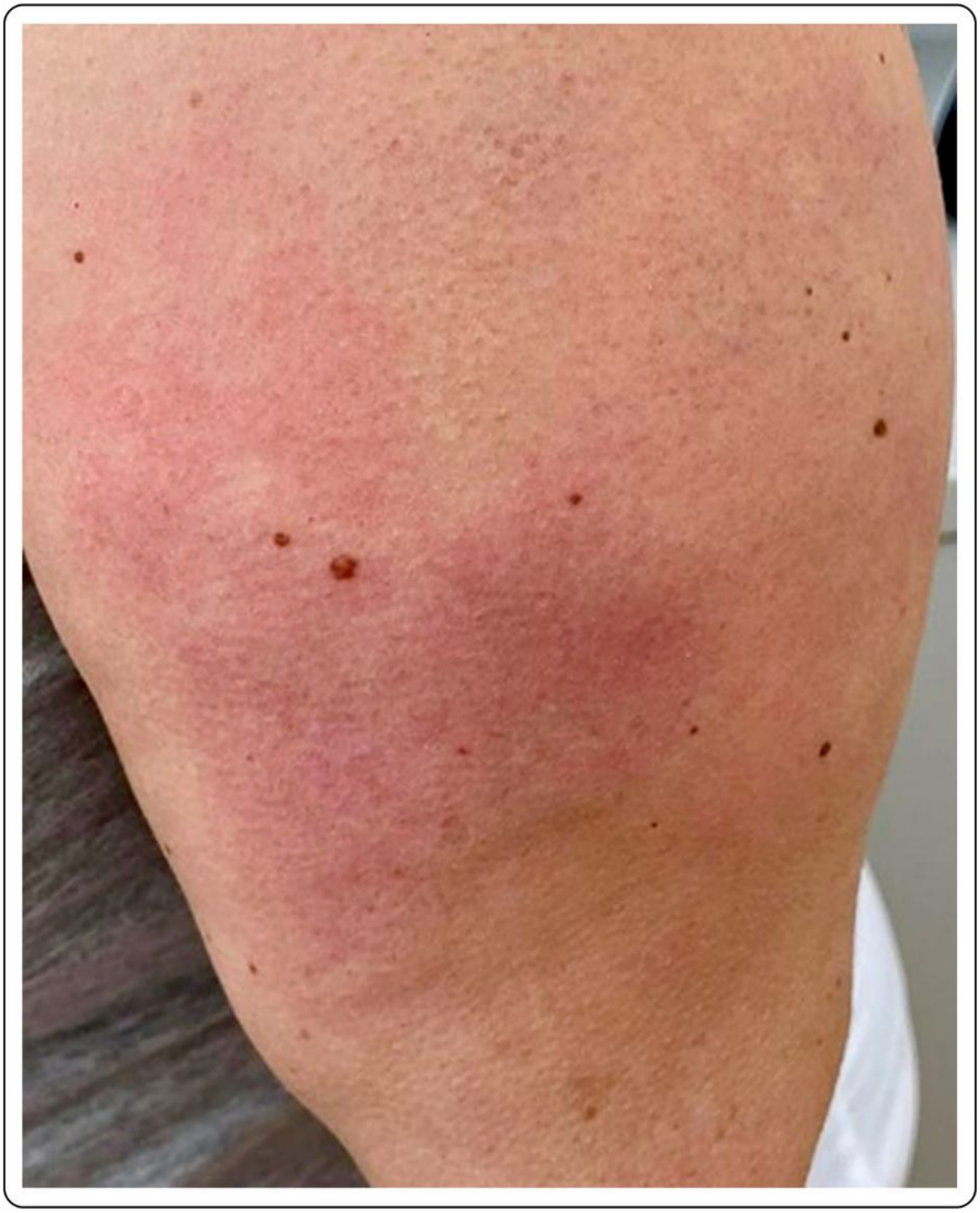


Figure 7

Local erythema and edema after mRNA-1273 vaccination after 3 days.

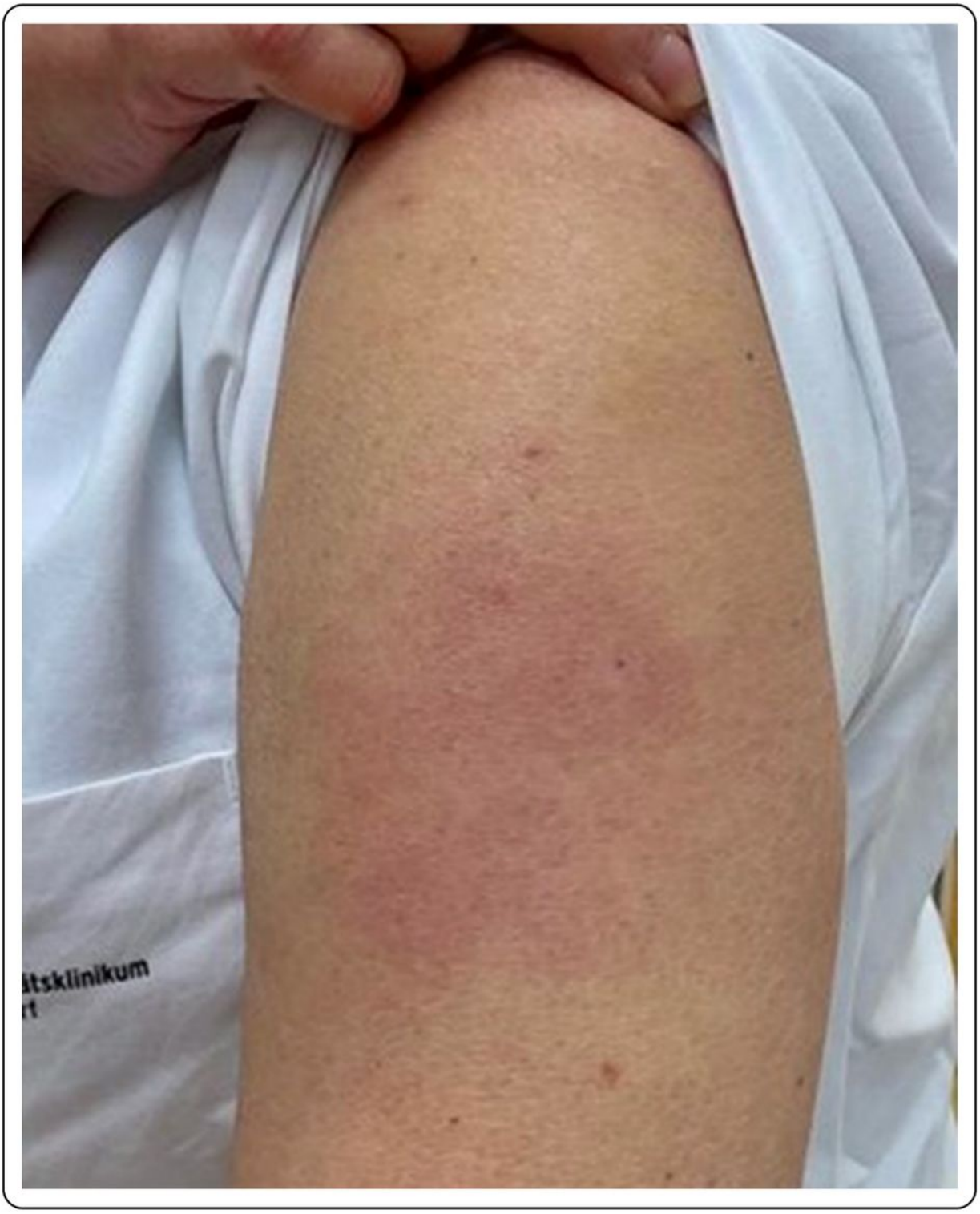
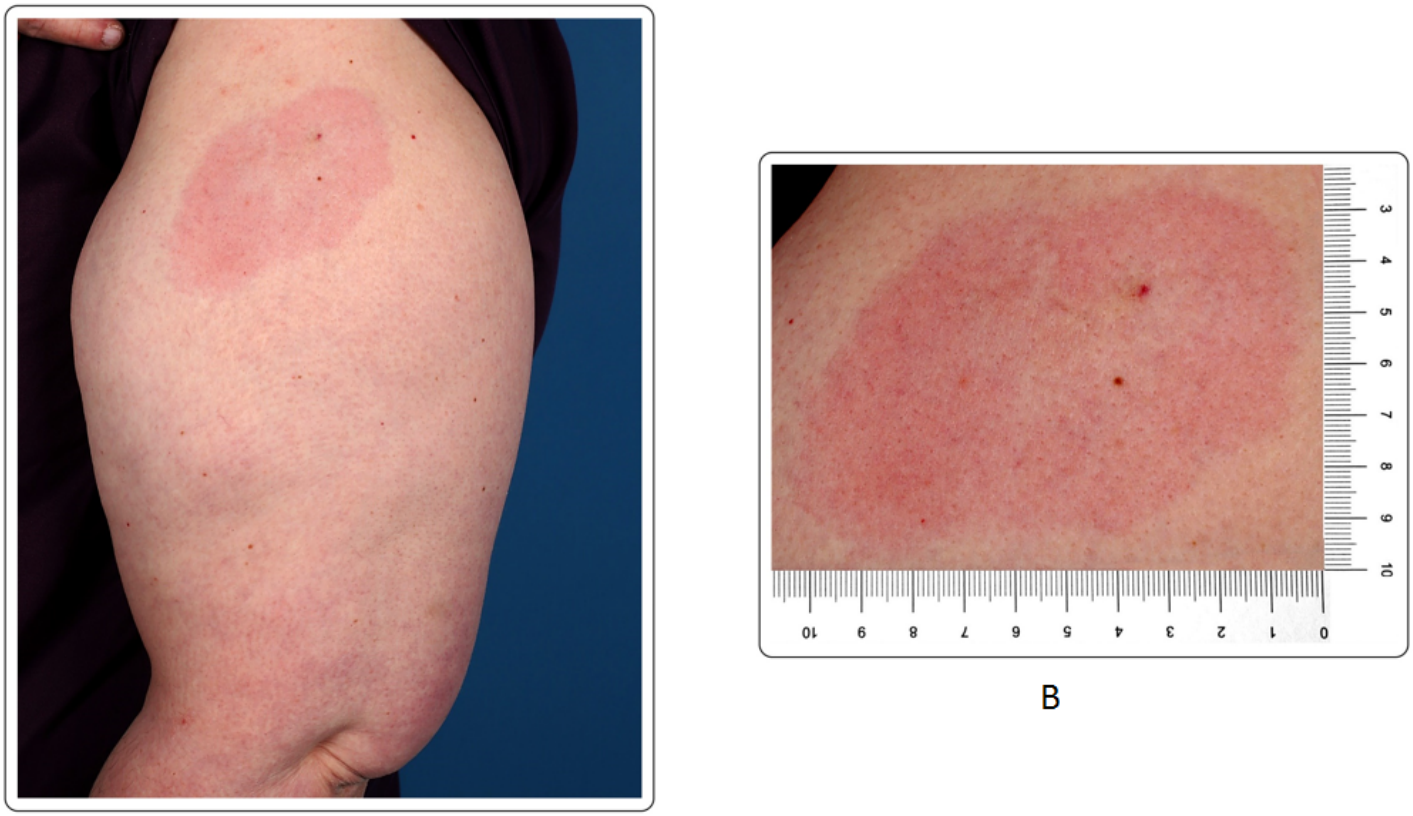


Figure 8

Redness and swelling after second shot with mRNA-1273 vaccination after 2 days.



A

B

Figure 9

A Redness, swelling and induration 4 days after second vaccination with mRNA-1273. B Redness, swelling and induration 4 days after second vaccination with mRNA-1273.

Image not available with this version

Figure 10

A 50-year-old healthy female showed redness, swelling, and induration at the injection site 4 days after the second vaccination with mRNA-1273 vaccine, comparable to our other cases. Because of the

extensive size of the lesion as well as the pronounced local burning and itching, a skin biopsy was taken. (Figures 9 and 10).

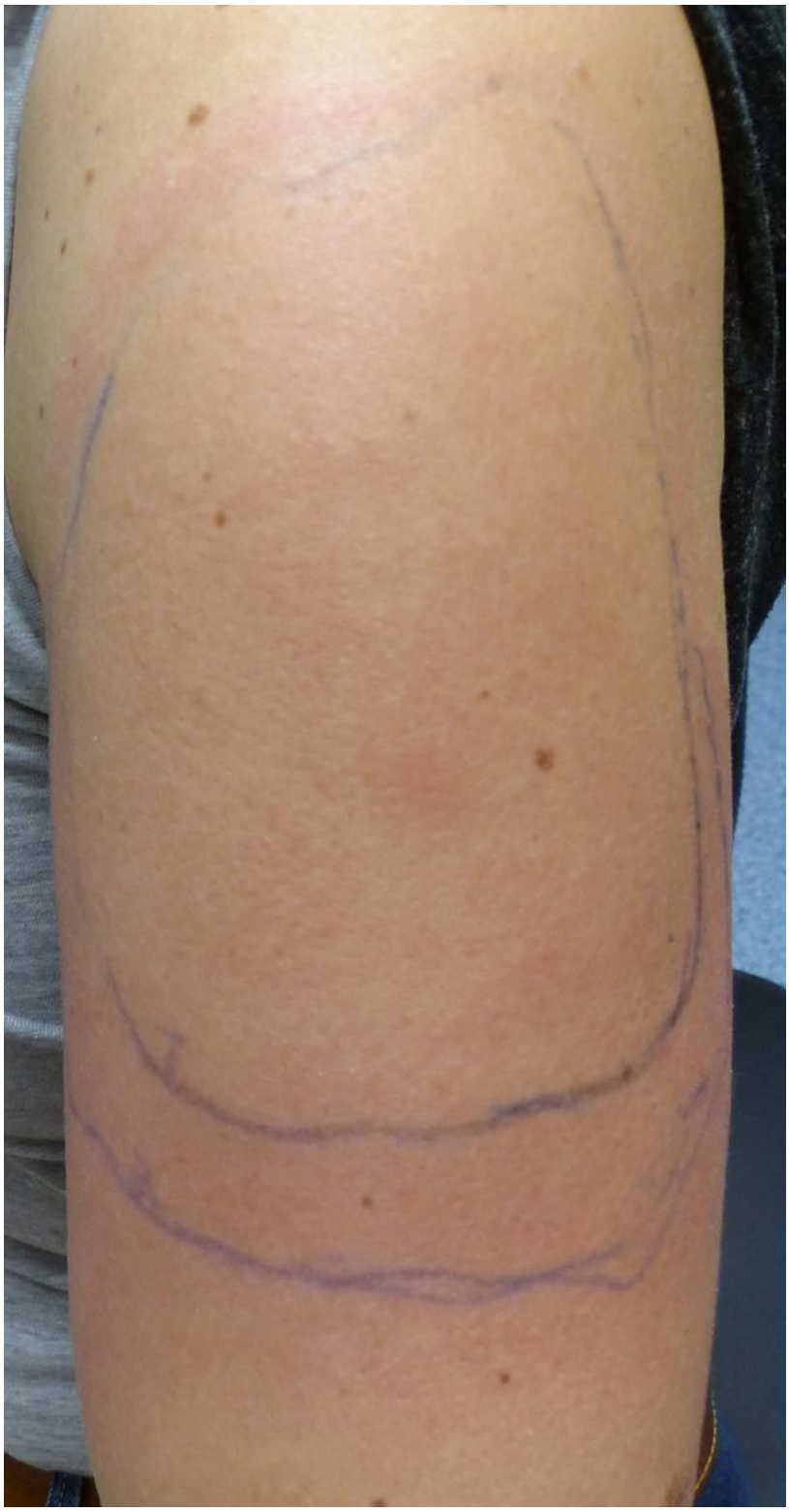


Figure 11

Redness, swelling and induration 8 days after second vaccination with mRNA-1273

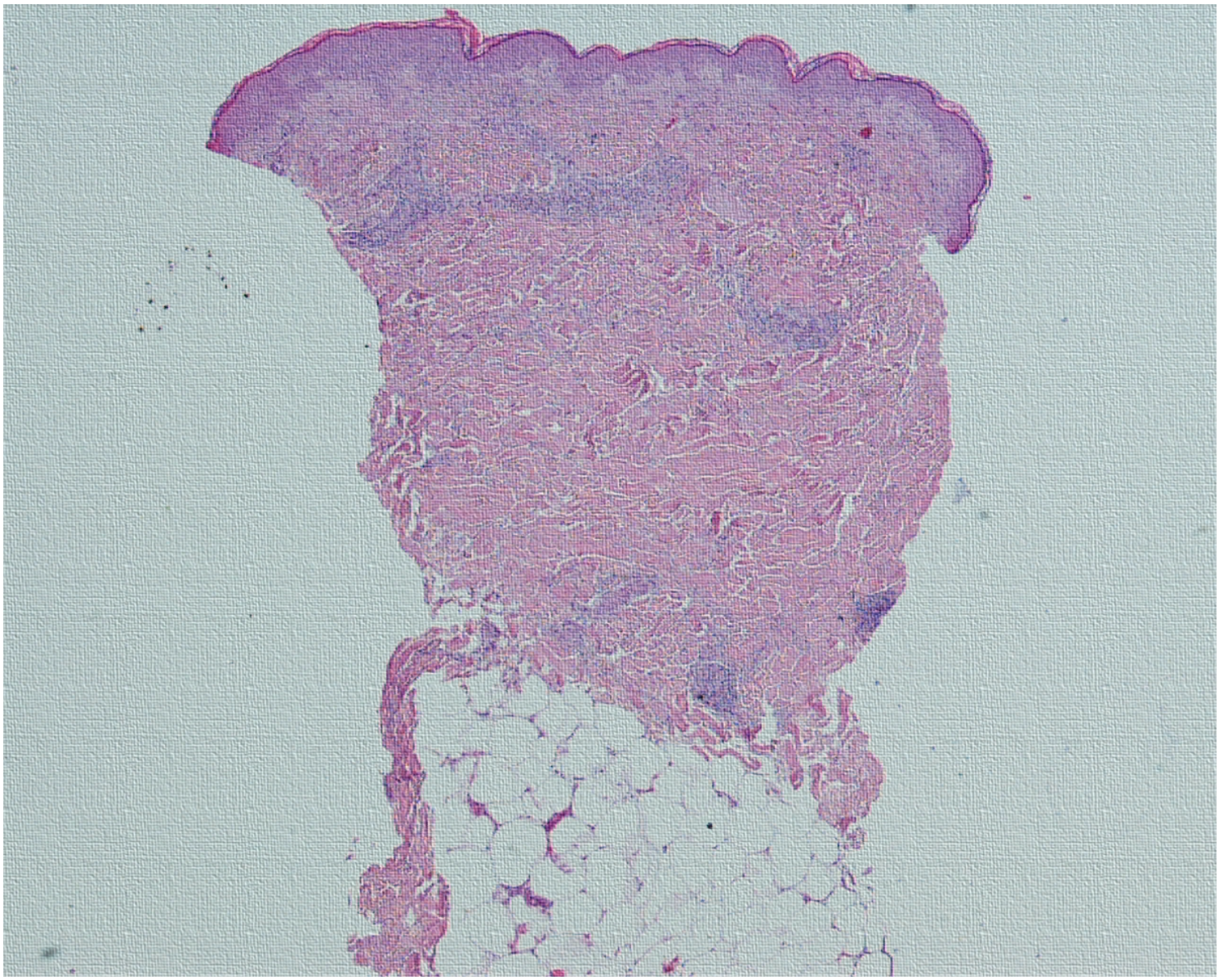


Figure 12

Skin biopsy from left upper arm revealing superficial and deep perivascular inflammatory infiltrate after mRNA-1273 vaccination. (Hematoxylin & Eosin, 40-fold magnification).

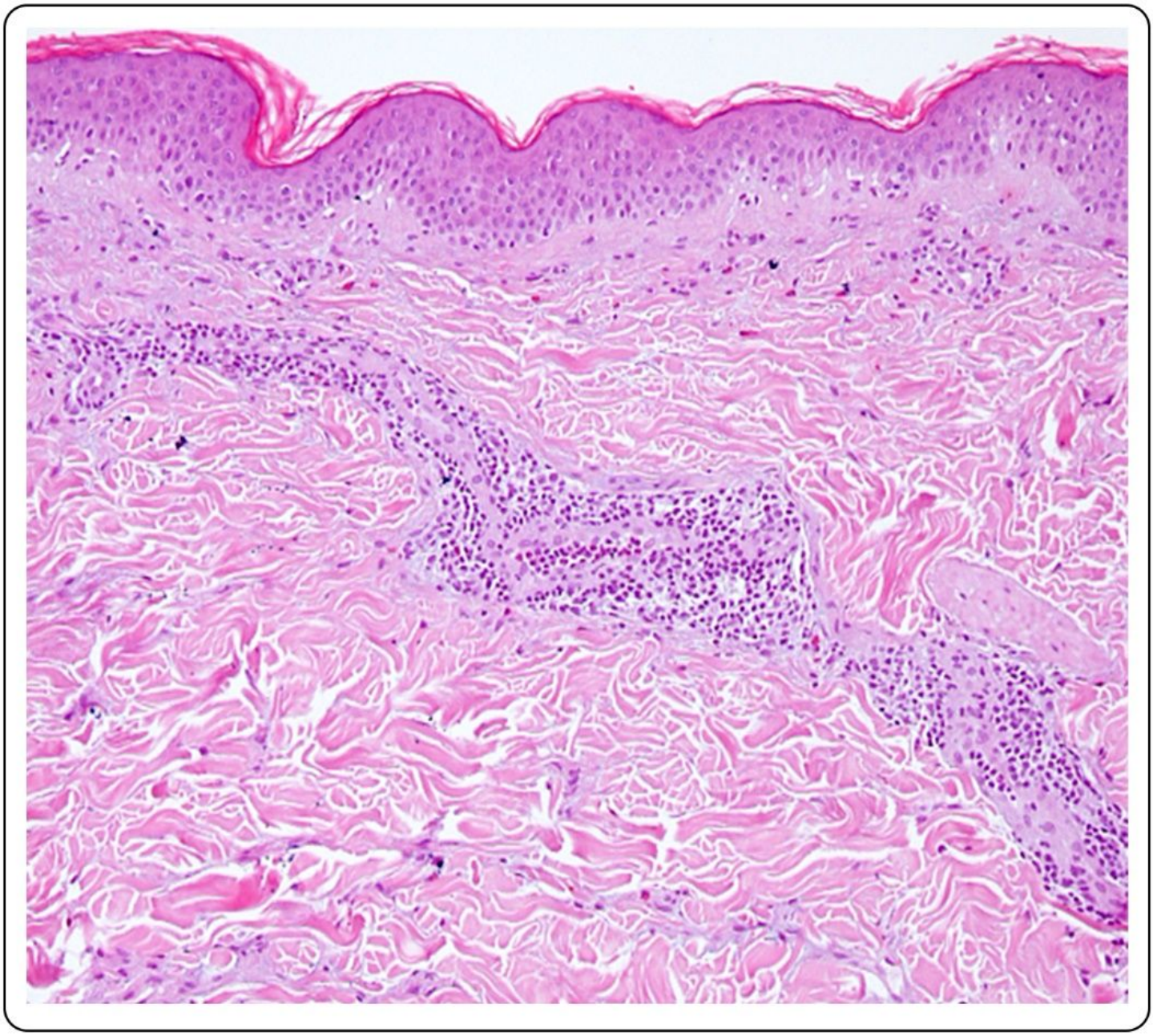


Figure 13

Skin sample from the area of induration on the left upper arm. Note the perivascular infiltrate composed of mainly of lymphocytes and a few eosinophils. Accumulation of neutrophils within the vessel's lumen. (Hematoxylin & Eosin, 100-fold magnification)

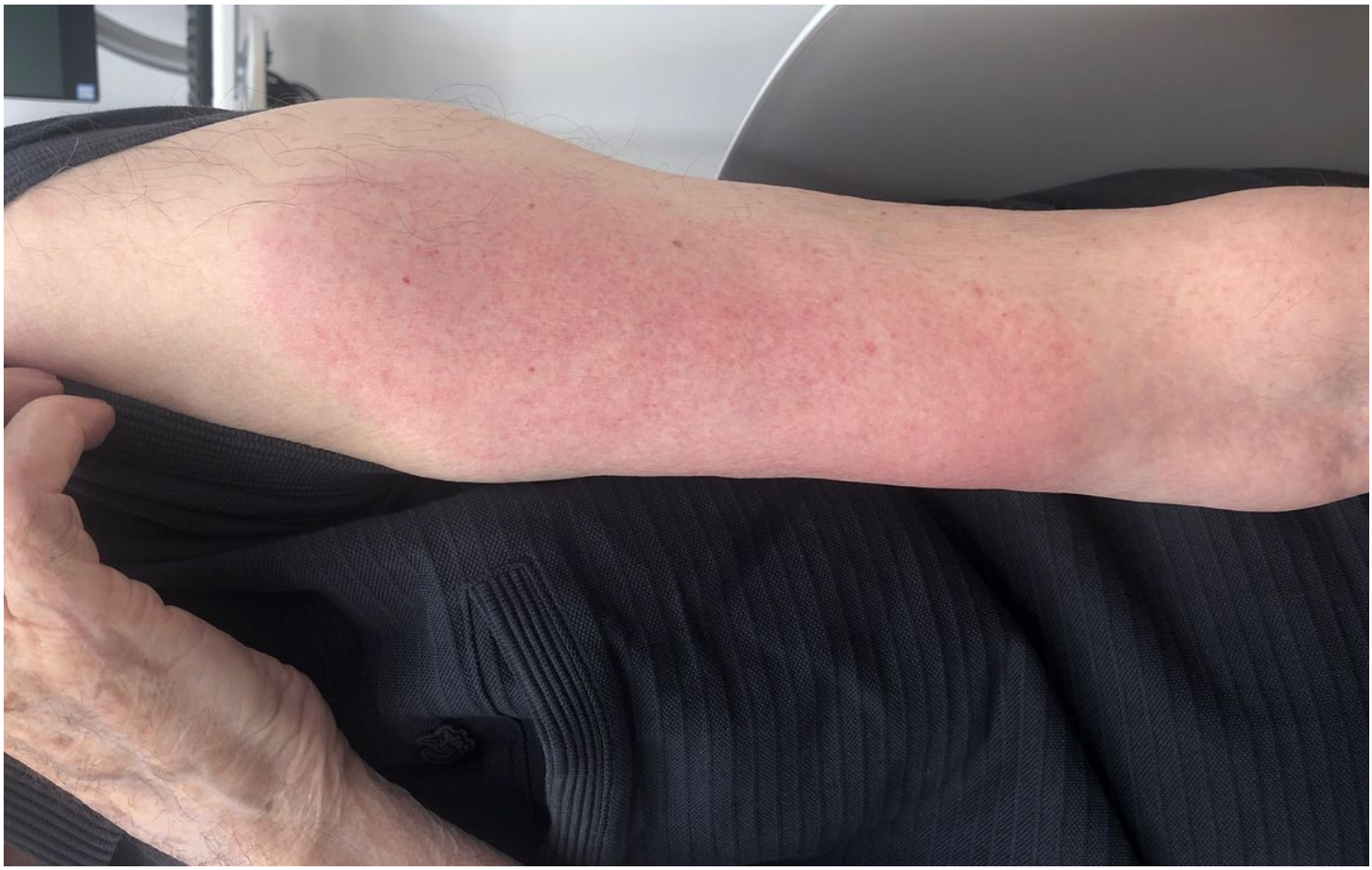


Figure 14

Redness, swelling and induration 12 days after second vaccination with mRNA-1273