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C.C. Zouboulis,[1,2,*,†] J.A.M. van Laar,[1,3,†] M. Schirmer,[1,4,†] G. Emmi,[1,5] F. Fortune,[1,6,7] A. Gül,[1,8] Y. Kirino,[1,9] E.-S. Lee,[1,10] P.P. Sfikakis,[1,11] F. Shahram,[1,12] G.R. Wallace[1,13]

[1]International Society for Behçet's Disease, Dessau, Germany, [2]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Dessau, Germany, [3]Departments of Internal Medicine and Immunology, Division of Allergy and Clinical Immunology, Academic Center for Rare Systemic Immune Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [4]Department of Internal Medicine, Clinic II, Medical University of Innsbruck, Innsbruck, Austria, [5]Department of Experimental and Clinical Medicine, University of Firenze, Firenze, Italy, [6]Centre for Oral Immunobiology and Regenerative Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK, [7]Oral Medicine Unit, Institute of Dentistry, Dental Hospital and Behçet's Centre of Excellence, Royal London Hospital, Barts Health NHS Trust, London, UK, [8]Division of Rheumatology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [9]Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [10]Department of Dermatology, Ajou University School of Medicine, Suwon, Korea, [11]1st Department of Propaedeutic and Internal Medicine and Joint Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [12]Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Teheran, Iran, [13]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, West Midlands, UK

*Correspondence: C.C. Zouboulis. E-mail: christos.zouboulis@mhb-fontane.de

†The authors contributed equally to the manuscript.

References

1 Koutsakos M, Rowntree LC, Hensen L *et al*. Integrated immune dynamics define correlates of COVID-19 severity and antibody responses. *Cell Rep Med* 2021; **2**: 100208.
2 Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev* 2021; **20**: 102792.
3 Welzel T, Samba SD, Klein R, van den Anker JN, Kuemmerle-Deschner JB. COVID-19 in autoinflammatory diseases with immunosuppressive treatment. *J Clin Med* 2021; **10**: 605.
4 Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021; **80**: 384–391.
5 Moosmann T, Veraar C, Brunner J *et al*. Differential clinical presentation of Adamantiades-Behcet's disease in non-endemic and endemic areas: retrospective data from a Middle-European cohort study. *Int J Rheum Dis* 2018; **21**: 2151–2157.
6 Fanlo P, Espinosa G, Adán A *et al*. Impact of novel coronavirus infection in patients with uveitis associated with an autoimmune disease: result of the COVID-19-GEAS patient survey. *Arch Soc Esp Oftalmol* 2021; **96**: 347–352.
7 Espinosa G, Araujo O, Amaro S, *et al*. COVID-19 and Behcet's disease: clinical case series. *Ann Rheum Dis* 2021; **80**: e41.
8 Dursun R, Temiz SA, Özer İ, Daye M, Ataseven A. Management of patients with Behcet's disease during the COVID-19 pandemic. *Dermatol Ther* 2020; **33**: e14063.
9 Yurttaş B, Oztas M, Tunc A *et al*. Characteristics and outcomes of Behcet's syndrome patients with Coronavirus Disease 2019: a case series of 10 patients. *Intern Emerg Med* 2020; **15**: 1567–1571.
10 https://www.eular.org/rheumatism_and_covid_19.cfm; https://www.rheumatology.org/Practice-Quality/Clinical-Support/COVID-19-Guidance

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Purpuric lesions on the eyelids developed after BNT162b2 mRNA COVID-19 vaccine: another piece of SARS-CoV-2 skin puzzle?

Dear Editor,

Vaccination against SARS-CoV-2 has spread around the world since December 2020. Herein, we describe three patients, with no history of SARS-CoV-2 infection, who developed skin reactions after receiving Pfizer-BioNTech (New York, NY, USA) COVID-19 vaccine. The first patient was a 44-year-old woman who presented with purpuric lesions on the right and left eyelid, respectively, 21 and 25 days after the second dose of the BNT162b2 mRNA vaccine (Fig. 1c,d). The lesions were circumscribed on the upper eyelid, totally asymptomatic and resolved spontaneously after ten days. The second patient was a 63-year-old man who presented similar lesions on the upper eyelid three weeks after the second dose of the vaccine (Fig. 1a,b). The lesions were asymptomatic as well and resolved spontaneously after 15 days. Both patients had complete laboratory evaluation for coagulation disorders that resulted unremarkable.

The third was a 67-year-old woman who also developed ecchymotic lesions on upper eyelids 10 days after the first dose of the vaccine. The lesions were moderately itchy and resolved spontaneously after 12 days.

Several skin manifestations have been reported in association with coronavirus infection while cutaneous reactions to SARS-CoV-2 vaccines have not yet been well documented in

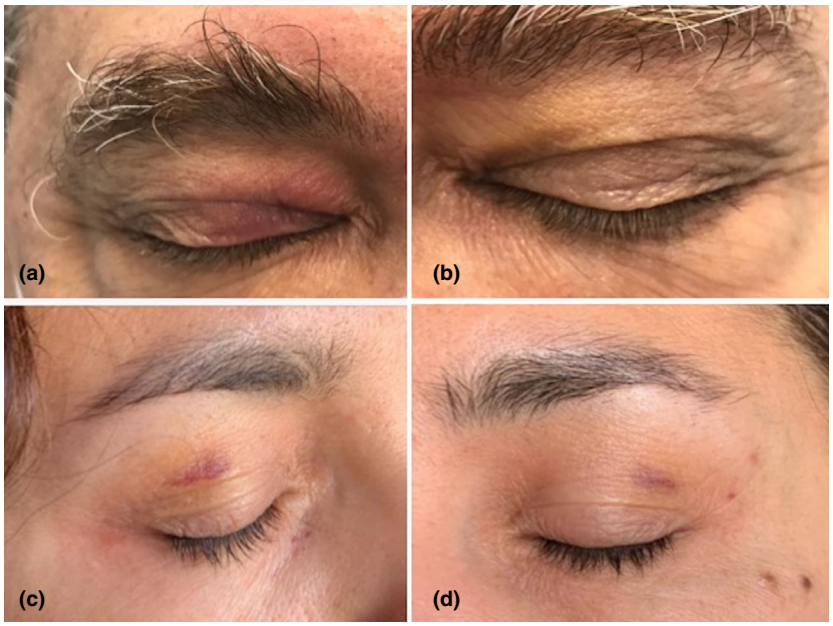

Figure 1 Purpuric lesions on the upper eyelids in patient 2 (a, b) and patient 1 (c, d).

literature.[1] Reported reactions included pain and swelling at injection site and erythematous or urticarial rash, usually associated with itch. The lesions were mostly transient with or without systemic symptoms, except for few cases of angioedema and laryngospasm (usually in patients with a well-known allergic background).[2] However, these adverse events are unspecific and similar to those reported for other vaccines probably related to immune reaction at injection site or allergic reaction to vaccine components.

Herein, we report three cases of eyelid localized purpuric and ecchymotic reaction after BNT162b2 mRNA COVID-19 vaccine, characterized by appearance after a median of 14 days after injection, absence of symptoms and spontaneous clearing after 10–15 days.

After the launch of vaccination campaign, several new potential adverse events have been reported both with BNT162b2 mRNA and ChAdOx1 adenovirus vaccine. In particular, BNT162b2 mRNA vaccine has been associated both with symptomatic and asymptomatic thrombocytopenia,[3] while ChAdOx1 with several cases of a new, life-threatening, thrombotic thrombocytopenic disease resembling the heparin-induced thrombocytopenia, for which the new term vaccine-induced thrombocytopenic thrombosis (VITT) has been proposed.[4] Besides, in severe cases of COVID-19 microthrombotic phenomenon is considered at the basis of the multiorgan microangiopathy associated with the SARS-CoV-2 infection, so that heparin is now one of the cornerstones of severe COVID-19 treatment.

Finally, during the first and second wave of SARS-CoV-2 pandemic several papers reported purpuric and ecchymotic skin eruption on feet and hands, mostly in otherwise healthy adolescents, currently referred as 'chilblain-like lesions'.[5–8]

Hence, in general SARS-CoV-2 infection and immune response to the virus may cause, with different pathogenetic mechanisms, endothelial damage and/or uncontrolled activation of coagulation system.

In this context, the observation of purpuric and ecchymotic lesions on eyelids shortly after receiving BNT162b2 mRNA vaccine could represent a form of very mild and localized form of vaccine-induced microangiopathy. Less likely, these lesions may share similar pathogenetic mechanisms with CLL, which are now considered as a virus-induced interferonopathy associated with a strong activation of innate immune system and fast clearance of antibodies.[9,10]

We are aware that our three cases are not enough to establish a cause–effect relationship between these lesions and the BNT162b2 mRNA vaccine; however, we have described this condition firstly because it is important to report any new postmarketing reaction to vaccine and then to reassure patients of the transience of this clinical manifestation after the first or second dose of BNT162b2 mRNA vaccine. Further larger studies are

desirable to confirm our data and possibly to enlighten the pathogenesis of this phenomenon.

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Conflict of interest

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C. Mazzatenta,[1] V. Piccolo,[2,*] G. Pace,[3] I. Romano,[4] G. Argenziano,[2] A. Bassi[1]

[1]UO Dermatologia Lucca- Azienda USL Toscana Nordovest, Lucca, Italy, [2]Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy, [3]Pediatrician Self Employed, Treviso, Italy, [4]Dermatology Unit - Department of Medicine DIMED, University of Padua, Padova, Italy

*Correspondence: V. Piccolo. E-mail: piccolo.vincenzo@gmail.com

References

1 Corbeddu M, Diociaiuti A, Vinci MR *et al*. Transient cutaneous manifestations after administration of Pfizer-BioNTech COVID-19 Vaccine: an Italian single centre case series. *J Eur Acad Dermatol Venereol* 2021; **35**: e483–e485.

2 Ring J, Worm M, Wollenberg A *et al*. Risk of severe allergic reactions to COVID-19 vaccines among patients with allergic skin diseases – practical recommendations. A position statement of ETFAD with external experts. *J Eur Acad Dermatol Venereol* 2021: **35**: e362–e365.

3 Lee EJ, Cines DB, Gernsheimer T *et al*. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol* 2021; **96**: 534–537.

4 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021; **384**: 2092–2101.

5 Piccolo V, Neri I, Manunza F, Mazzatenta C, Bassi A. Chilblain-like lesions during the COVID-19 pandemic: should we really worry? *Int J Dermatol* 2020; **59**: 1026–1027.

6 Piccolo V, Bassi A, Argenziano G *et al*. Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: a multicenter study on 10 patients. *J Am Acad Dermatol* 2020; **83**: 1749–1751.

7 Piccolo V, Bassi A. Acral findings during the COVID-19 outbreak: Chilblain-like lesions should be preferred to acroischemic lesions. *J Am Acad Dermatol* 2020; **83**: e231.

8 Piccolo V, Bassi A, Russo T *et al*. Chilblain-like lesions and COVID-19: second wave, second outbreak. *J Eur Acad Dermatol Venereol* 2021; **35**: e316–e318.

9 Hubiche T, Cardot-Leccia N, Le Duff F *et al*. Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic. *JAMA Dermatol* 2020; **157**: e204324.

10 Sekine T, Perez-Potti A, Rivera-Ballesteros O *et al*. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell* 2020; **183**: 158–168.e14.

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Recurrent injection-site reactions after incorrect subcutaneous administration of a COVID-19 vaccine

To the Editor,

Local reactions to SARS-CoV-2 vaccination are common and mainly occur within the first week, albeit also seen later.[1] Here, we address another aspect of cutaneous side effects to SARS-CoV-2 vaccination and draw attention to implications in clinical practice.

A 33-year-old woman with type-2 diabetes and obesity (BMI 43 kg/m^2) was incorrectly given the first SARS-CoV-2 vaccination dose (BNT162b2, Pfizer-BioNTech) in the middle of her left upper arm. There were no complications to the procedure. One week later, she developed fever, myalgia, arthralgia and malaise and tested PCR-positive for SARS-CoV-2. Five days after symptom onset, she noticed an asymptomatic rash at the injection site (Fig. 1a). A lesional 3 mm skin punch biopsy showed perivascular lymphocyte infiltration in the dermis. Using ELISA,[2] serology testing performed on postvaccination day 13 and 35 initially demonstrated an IgG response towards the receptor-binding domain (RBD) of the spike protein but was negative for response against viral N-protein. At follow-up, antibodies against both RBD and viral N-protein were detected. The rash disappeared without treatment. Following correct re-vaccination in the left deltoid, the patient, within hours, developed skin erythema, intense soreness and warmth at the first injection site (Fig. 1b). The exanthema cleared spontaneously within a few days.

In this case, the first SARS-CoV-2 vaccine dose was accidentally injected subcutaneously due to incorrect anatomical location and high patient BMI. The significant skin reactions at the original injection site following SARS-CoV-2 infection and re-vaccination, respectively, are most likely caused by immunological reactivity towards vaccine antigens trapped in the subcutaneous tissue. As RBD is contained in the vaccine and N-protein is not, the patient's primary immune response was most likely raised against the vaccine, while both vaccine and virus antibodies were identified at follow-up.

Like most vaccines, SARS-CoV-2 vaccination should be administered intramuscularly to optimize immunogenicity and minimize local adverse reactions. Compared with muscle tissue, subcutaneous fat is less vascularized, which may harm the processing and presentation of antigens. In addition, superficial administration of vaccines more likely causes local side effects.[3] Obese individuals are at greater risk for severe SARS-CoV-2 infection and seem to generate poorer humoral vaccination responses compared with normal-weight persons.[4] Therefore, correct administration of SARS-CoV-2 vaccines is essential in the obese population. Deltoid fat pad thickness varies greatly,[5]

