LETTER TO THE EDITOR

Reply to 'development of severe pemphigus vulgaris following SARS-CoV-2 vaccination with BNT162b2' by Solimani F *et al*

Dear Editor,

We read with interest the article by Solimani *et al*,[1] who reported a case of pemphigus vulgaris developed 5 days after the first administration of SARS-CoV-2 vaccination with the mRNA vaccine BNT162b2 (Comirnaty", Biontech/Pfizer).

We report the case of a superficial pemphigus developed 2 days after the second dose of the same vaccination in an otherwise healthy woman, except for a history of Hashimoto's thyroiditis.

This 63-year-old woman came to our clinic with pruritic erythematous scaly patches, superficial blisters, and erosions on the upper trunk, scalp and face evolving from 1 month (Fig. 1). On her face, she presented crusty patches and plaques mainly over the nose, cheeks and eyelids suggestive of lupus erythematosus or pemphigus erythematosus (PE). (Fig. 1a,c) Mucosal surfaces were not involved. Nikolsky's sign was positive. Line-field confocal optical coherence tomography (LC-OCT) showed a superficial intraepidermal clefting suggestive of PE (Fig. 2c–e).

Given the suspicion of an autoimmune bullous disease, a lesional and perilesional skin biopsy was performed on the back for histopathological examination and direct immunofluorescence (DIF), respectively. Oral methylprednisolone 0.5 mg/kg/day was prescribed based on the clinical and LC-OCT diagnosis with clinical response.

In the following days, DIF showed intercellular epidermal IgG deposition and histology confirmed the clinical and LC-OCT diagnosis of PE. (Fig. 2a,b).

Pemphigus diseases are a group of severe, chronic, autoimmune disorders characterized by the formation of intraepidermal blisters mediated by pathogenic autoantibodies directed mainly against desmoglein 1 and 3. PE is a clinical subtype of pemphigus foliaceus with overlap features with lupus erythematosus.[2]

Following the recent introduction of vaccination campaigns against SARS-CoV-2 virus with mRNA vaccines, there is increasing evidence on associated cutaneous adverse events such as local injection-site reactions, exanthemas, vascular lesions, urticaria, herpes zoster, eosinophilic dermatosis, erythromelalgia and pityriasis rosea-like rash.[3,4] Regarding autoimmune bullous disorders, rare cases of flares or new onset of bullous pemphigoid and pemphigus vulgaris (PV),[1,5–8] and one pemphigus foliaceous have been reported following SARS-CoV-2 vaccination with mRNA vaccine BNT162b2.[8]

COVID-19 mRNA-based vaccines can elicit strong T- and B-cell responses against SARS-CoV-2 and induce type I interferon

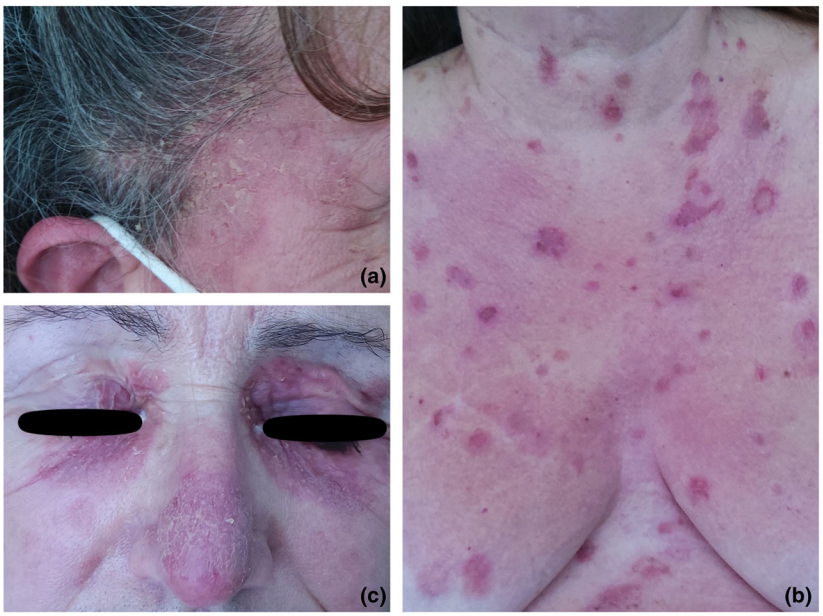

Figure 1 Clinical features of pemphigus erythematosus in a patient vaccinated against SARS-CoV-2. (a) Crusted plaques on the scalp; (b) erythema, erosions, scaly and crusty patches on the upper trunk; (c) scaly patches and plaques on nose, cheeks and periocular.

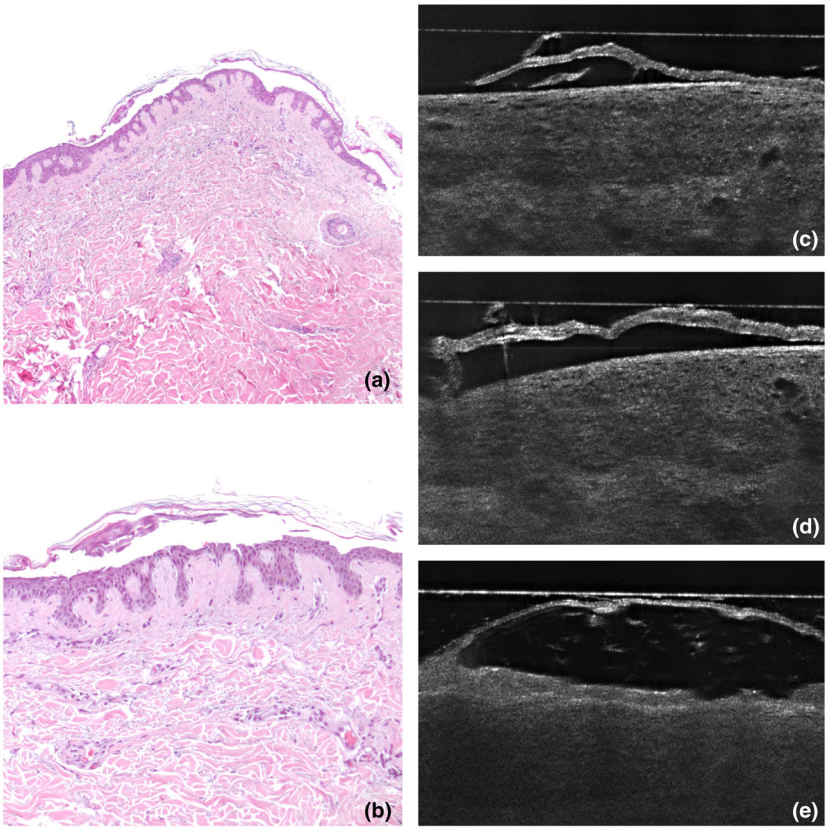

Figure 2 Histopathology and LC-OCT examination of pemphigus erythematosus in a patient following SARS-CoV-2 vaccination. (a) Orthokeratosis overlying a superficial bulla directly benath the stratum corneum; the upper dermis shows a slight oedema with a perivascular and sparse mononuclear inflammatory infiltrate (Haematoxylin and eosin; original magnification ×4); (b) At higher magnification the bulla appears high in the granular layer and contain scattered acantholytic keratinocytes (Haematoxylin and eosin; original magnification ×10). (c–e) *In vivo* 2D LC-OCT examination showing a superficial intraepidermal clefting consistent with the histological features of PE.

responses, which has been associated with inflammation and potentially with autoimmunity, especially in genetically susceptible individuals.[9] Moreover, autoimmune bullous disorders could be secondary to a delayed T-cell-mediated hypersensitivity response to vaccination or molecular mimicry driven by off-target immune activation against pathogenic elements similar to human proteins.[3,8]

To the best of our knowledge, this is the first case reported of PE occurring a few days after the second dose of vaccination with BNT162b2. LC-OCT a new non-invasive imaging technique, developed to perform *in vivo* analysis with quasi histological resolution, was used to early identify the disease and to start treatment .[10] Our patient would have to do the third dose of the vaccine and thus we raise the question whether this dose should be contraindicated. To date, Avallone *et al*[5] reported a case of worsening of PV after the second dose despite maintaining low-dose steroid therapy and there are various cases of flares of pre-existing autoimmune bullous disorders.[6,7]

The risk–benefit ratio is difficult to assess in these patients because this is the first time that any mRNA vaccine has been approved for human use and a complete understanding of any potential off-target immunostimulatory properties will require further investigations.

Aknowledgments
None.

Conflict of Interest
There are no known conflicts of interest to disclose.

Funding sources
None.

Informed consent
The patient in this manuscript has given written informed consent to the publication of her case details.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

F. Falcinelli,[1,*] A. Lamberti,[1] C. Cota,[2] P. Rubegni,[1] E. Cinotti[1]

[1]Dermatology Unit and Skin Bank, Department of Medical, Surgical and Neurosciences, Siena University Hospital, Siena, Italy, [2]Dermatopathology Unit, San Gallicano Dermatological Institute, IRCCS, Rome, Italy

*Correspondence: F. Falcinelli. E-mail: f.falcinelli@student.unisi.it

References

1 Solimani F, Mansour Y, Didona D, Dilling A, Ghoreschi K, Meier K. Development of severe pemphigus vulgaris following SARS-CoV-2 vaccination with BNT162b2. *J Eur Acad Dermatol Venereol* 2021; **35**: e649–e651.

2 Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet* 2019; **394**: 882–894.

3 McMahon DE, Kovarik CL, Damsky W *et al*. Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: a registry-based study. *J Am Acad Dermatol* 2022; **86**: 113–121.

4 Cinotti E, Perrot J-L., Bruzziches F, Tognetti L, Batsikosta A, Sorrentino E, et al. Eosinophilic dermatosis after AstraZeneca COVID-19 vaccination. *J Eur Acad Dermatol Venereol* 2022; **36**, e171-e172.

5 Avallone G, Giordano S, Astrua C *et al*. Reply to 'the first dose of COVID-19 vaccine may trigger pemphigus and bullous pemphigoid flares: is the second dose therefore contraindicated?' by Damiani G *et al*. *J Eur Acad Dermatol Venereol* 2022; **36**: e433–e435.

6 Tomayko MM, Damsky W, Fathy R *et al*. Subepidermal blistering eruptions, including bullous pemphigoid, following COVID-19 vaccination. *J Allergy Clin Immunol* 2021; **148**: 750–751.

7 Damiani G, Pacifico A, Pelloni F, Iorizzo M. The first dose of COVID-19 vaccine may trigger pemphigus and bullous pemphigoid flares: is the second dose therefore contraindicated? *J Eur Acad Dermatol Venereol* 2021; **35**: e645–e647.

8 Lua ACY, Ong FLL, Choo KJL, Yeo YW, Oh CC. An unusual presentation of pemphigus foliaceus following COVID-19 vaccination. *Australas J Dermatol*. 2021; **63**: 128–130.

9 Wack S, Patton T, Ferris LK. COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: review of available evidence. *J Am Acad Dermatol* 2021; **85**: 1274–1284.

10 Tognetti L, Cinotti E, Suppa M, Guazzo R, Habougit C, Santi F, Diet G., Fontaine M., Berot V., Monnier J., Pianigiani E., Marmol V., Malvehy J., Perrot J.L., Rubegni P. Line field confocal optical coherence tomography: an adjunctive tool in the diagnosis of autoimmune bullous diseases. *J Biophotonics* 2021; **14**: e202000449

DOI: 10.1111/jdv.18398