Blistering Papulosquamous Erythema with Arthralgia: A Quiz

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A healthy 54-year-old woman was referred to our dermatology clinic with oedematous pruritic erythema and squamous papules symmetrically distributed on her trunk and extremities (Fig. 1a and b). The patient did not have mucosal lesions, but reported arthralgia and stiffness involving the toes, knees, elbows and wrists. She was referred to our clinic from rheumatology due to the symptoms persisting for 3 weeks. Despite treatment with topical corticosteroids, blisters gradually appeared over a period of several weeks with sign of Köbnerization (Fig. 1c). Laboratory findings were unremarkable, and she was seronegative for antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-BP180 (NC16A)/BP230 antibodies. Hepatitis B/C virus infection was ruled out.

What is your diagnosis? See next page for answer.

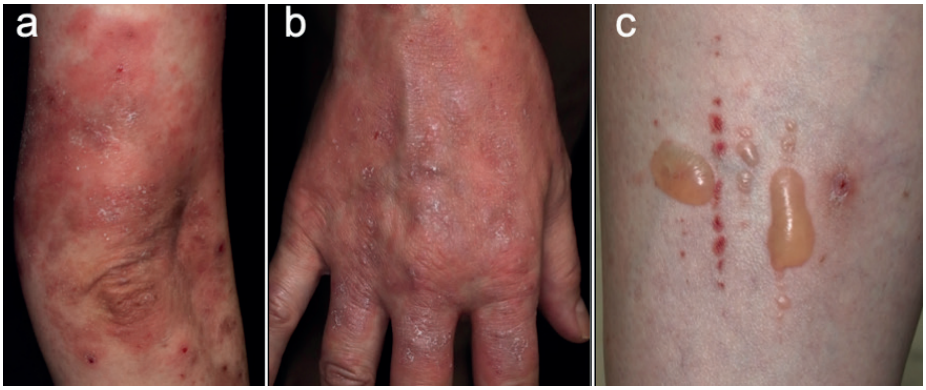

Fig. 1. (a, b) Symmetrically distributed pruritic papulosquamous erythema. Tense bullae appeared on the lower leg after several weeks of follow-up with (c) sign of Köbnerization.

ANSWERS TO QUIZ

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Diagnosis: **Lichen planus pemphigoides associated with mRNA coronavirus disease 2019 (COVID-19) vaccination**

Skin biopsy taken from squamous erythema comprised a typical lichenoid tissue reaction (band-like infiltration of small round cells in the upper dermis, liquefaction degeneration, and foci of wedge-shaped hypergranulosis), albeit occasional eosinophil infiltration was noted (Fig. 2a). The blistering part was composed of the subepidermal bulla, and the blister roof had occasional necrotic figures of keratinocytes (Fig. 2b). Indirect immunofluorescence revealed linear IgG deposition along the blister roof (Fig. 2c). Collectively, the final diagnosis of lichen planus pemphigoides (LPP) was given.

LPP and bullous lichen planus (BLP) are rare subepidermal blistering disorders that share clinicopathological features of lichen planus (LP). Because of the presence of circulating autoantibodies, blisters can appear in normal-looking skin in LPP, whereas BLP primarily affects pre-existing LP lesions (1–3). Therefore, immunofluorescent studies are instrumental in differentiating LPP from BLP, the latter of which shows negativity (1, 3). Both LPP and bullous pemphigoid (BP) autoantibodies recognize the extracellular domain of type-XVII collagen (BP180); however, it has been shown that LPP autoantibodies preferentially react with the carboxy-terminus, whereas BP autoantibodies recognize the amino-terminus of the BP180 non-collagenous 16A (NC16A) domain (2). Thus, we undertook a flow cytometric analysis to determine if the patient's serum reacts with the full-length BP180 expressed in HEK293T cells (Appendix S1). The patient's serum reacted with the BP180 protein comparably to the sera of patients with BP (Fig. 2d and Fig. S1). Titration of antibodies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) proteins revealed positivity and negativity for anti-spike and anti-nucleocapsid IgG, respectively (5), refuting the possibility of community-acquired COVID-19 infection. As previously suggested, the clinical symptoms were manageable with administration of oral corticosteroid (6).

Including LPP, skin rashes are a well-recognized side-effect of vaccination against infectious diseases, such as influenza (7), hepatitis B (8), or human papillomavirus diseases (9). According to reports from Europe, eruptions associated with the the mRNA SARS-CoV-2 vaccine vaccine are phenotypically diverse, mimicking urticaria, pityriasis rosea, or chilblains (10). Pruritic blisters accompanied by eosinophil infiltration observed in the current case resemble BP-like eruptions associated with the the mRNA SARS-CoV-2 vaccine (11). Subepidermal blistering eruptions can occur after the first or second doses (6). The patient developed LPP the day after the second dose of mRNA COVID-19 vaccine (Comirnaty®, BioNTech/Pfizer (Mainz, Rhineland-Palatinate, Germany/New York, NY, USA)). This rapid onset implies transient bystander immune activation (6), presumably related to pattern recognition receptor activation in antigen-presenting cells that took up nucleic acids (12). It may also be possible that the vaccination activated pre-existing subclinical autoimmunity (6), given that the patient allegedly had itchy non-blistering erythema on her upper arm several decades before vaccination. The inherent adjuvant effect that augments recall responses (12), in addition to deduced cross-reactivity of the SARS-CoV-2 spike protein with endogenous tissue proteins (13), may underlie the cutaneous adverse reactions.

It should be noted that mRNA vaccination can incrementally evoke inflammatory responses, including fever, fatigue,

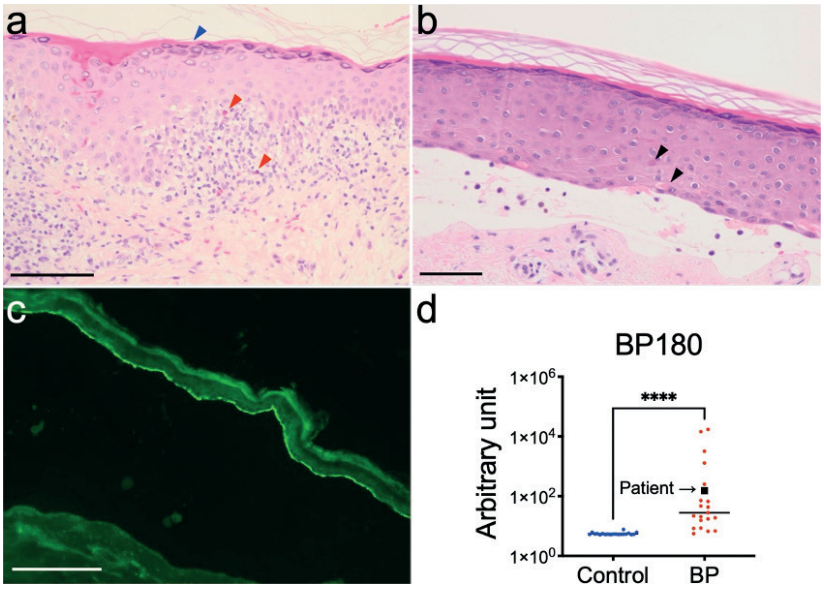

Fig. 2. Skin biopsy results. (a) Lichenoid tissue reaction, with hypergranulosis (*blue arrowheads*), and eosinophils (*red arrowheads*), and (b) subepidermal blistering, with necrotic figures of keratinocytes (*black arrowheads*). (c) Linear immunoglobulin G (IgG) deposits along the blister roof shown by indirect immunofluorescence on salt-split normal human skin. *Bars:* 100 μm. (d) Detection of antibodies against the full-length type-XVII collagen (BP180) extracellular domain using flow cytometry. BP180 was exogenously expressed using a plasmid vector and incubated with serum from the patient (*black square*) together with sera of patients with bullous pemphigoid (BP; $n = 20$, *red dots*) and healthy controls (Control; $n = 20$, *blue dots*). Immunoreactivity was determined by mean fluorescence intensity. Statistical significance was determined with the Mann–Whitney *U* test (****$p < 0.001$).

headache, arthralgia (12), or myocarditis (14). Therefore, in the current case, the second dose of mRNA vaccination appears to be primarily responsible for the strong adverse reactions, i.e. widespread blistering papulosquamous erythema with arthralgia, as indicated previously (12).

More than 50% of people are fully vaccinated against COVID-19 worldwide and awaiting the third booster shot (15). Dermatologists need to be aware of vaccination-related complications in the skin during the ongoing COVID-19 pandemic.

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