Correspondence

Can Covid-19 vaccines cause or exacerbate bullous pemphigoid? A report of seven cases from one center

Dear Editor,

A wide range of dermatological manifestations following different types of SARS-CoV-2 vaccines have been reported in the literature since the beginning of implementation of mass immunization programs.[1] Here we report a case series of seven patients with bullous pemphigoid (BP), four of which had a new-onset BP following vaccination and three had a post-vaccine exacerbation of a previous BP.

In Turkey, the vaccination program against COVID-19 was started in January 2021 with inactivated CoronaVac vaccine (Sinovac, Beijing, China), and it was the only vaccine available for the population at that time. Later, in March, BNT162b2 mRNA vaccine (Pfizer-BioNTech, Germany) also became available in the country, and people who had previously been vaccinated with inactivated CoronaVac were given the opportunity to be vaccinated with BNT162b2 mRNA Pfizer-BioNTech if they preferred. To date, in our tertiary referral center, which also includes a specialized Autoimmune Blistering Disease Outpatient Department, we have observed four patients with new-onset BP and three patients with exacerbation of previous BP following COVID-19 vaccination (Table 1). In two of four cases with new-onset disease, BP was observed after the second dose of inactivated CoronaVac and in two of them after the first dose of BNT162b2 mRNA Pfizer-BioNTech which was administered as a third vaccine. On the other hand, all three patients who experienced a flare of previous BP were vaccinated with inactivated CoronaVac. The duration of BP before the flare was 5 months in Case 5, 2 years in Case 6, and 6 months in Case 7. Of note, in Case 5, the disease was in pre-bullous stage, and the first bullous lesions have emerged only after the first dose of inactivated CoronaVac (Fig. 1). The latency period for the new-onset BP varied between 2 weeks to 1 month after vaccination, whereas it was as short as 1 week after the first dose in a patient with post-vaccine exacerbation.

The diagnosis of BP was confirmed with histopathology and direct immunofluorescence in all patients. In terms of treatment, topical and oral corticosteroids, dapsone, doxycycline, methotrexate, and azathioprine were used in different combinations. In a majority of the patients, BP showed improvement with treatment; however, Case 1 was diagnosed with SARS-CoV-2 infection while under immunosuppressive therapy with systemic corticosteroids and methotrexate for BP. After the diagnosis of SARS-CoV-2 infection was confirmed with PCR, her immunosuppressive doses were reduced, and the patient was recovered from COVID-19 within a few weeks.

Recently, Tomayko et al.[2] described a case series of 12 patients with new-onset BP following either Moderna mRNA-

Table 1 Data of patients with new-onset BP and exacerbation of previous BP following SARS-CoV-2 vaccination

Case number	Age / Sex	New-onset BP	Flare of previous BP	1st dose of vaccination	2nd dose of vaccination	3rd dose of vaccination	Time interval between vaccination and blisters	H&E staining	DIF	Treatment	Outcome
1	88/F	+	–	March/CoronaVac	April/CoronaVac	–	1 month after 2nd dose	+	+	TCS, OCS, MTX	COVID-19 infection while under OCS + MTX
2	82/F	+	–	February/CoronaVac	March/CoronaVac	July/Pfizer	2 weeks after 3rd dose	+	+	TCS, OCS, Dapsone	Improvement
3	65/M	+	–	February/CoronaVac	March/CoronaVac	July/Pfizer	2 weeks after 3rd dose	+	+	TCS, DCN	Improvement
4	82/F	+	–	January/CoronaVac	February/ CoronaVac	–	2 weeks after 2nd dose	+	+	TCS, OCS	Improvement
5	74/F	–	+	February/CoronaVac	April/CoronaVac	–	1 week after 1st dose	+	+	TCS, DCN, OCS, MTX	Improvement
6	65/F	–	+	February/CoronaVac	March/CoronaVac	August/Pfizer	1 week after 2nd dose	+	+	TCS, MTX	Improvement
7	71/M	–	+	February/CoronaVac	March/CoronaVac	July/ CoronaVac	1.5 month after 2nd dose	+	+	TCS, OCS, AZA	Improvement

AZA, azathioprine; DCN, doxycycline; DIF, direct immunofluorescence histology; H&E, hematoxylin and eosin; F, female; M, male; OCS, oral corticosteroid; TCS, topical corticosteroid.

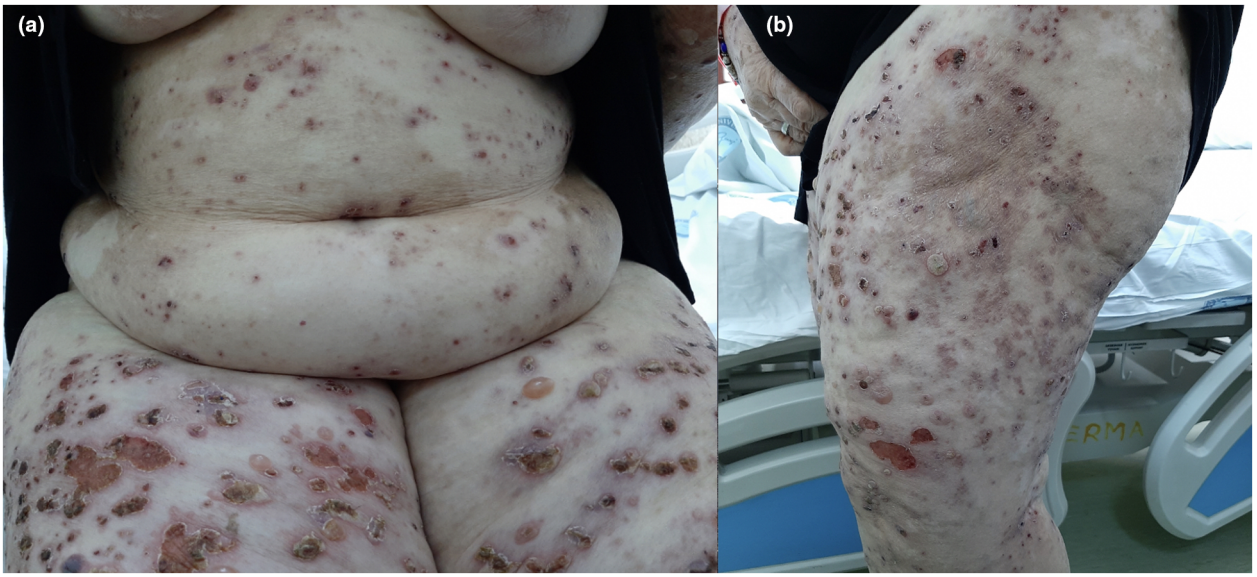

Figure 1 Case number 5 demonstrating first bullous lesions following the first dose of inactivated CoronaVac vaccine, (a) abdomen and upper thighs, (b) lateral thigh

1273 or Pfizer mRNA BNT162b2 vaccine and an additional 13th patient with exacerbation of known BP after Pfizer mRNA BNT162b2. Additionally, Damiani et al.[3] reported two cases of pemphigus and three cases of BP flares triggered by Moderna mRNA-1273 or Pfizer mRNA BNT162b2 vaccine in patients with previous history of autoimmune bullous disease. Anectodal evidence also suggests that BP and other autoimmune bullous diseases can be observed after immunization with several vaccines, including influenza, hepatitis B, tetanus, and herpes zoster vaccines.[4] To the best of our knowledge, our case series includes the first patients in the literature that developed new-onset BP and flare of previous BP after inactivated SARS-CoV-2 vaccine (CoronaVac, China). As far as we can observe in our seven cases, there was no notable clinical difference between the vaccine related new-onset BP/BP flare and idiopathic BP, however the number of patients was too small to comment on the subject. Moreover, there is not enough data in the literature yet regarding the possible cutaneous side effects of the 'heterologous vaccination regimens' or 'mix and match' approach of priming one vaccine and boosting with another in COVID-19 vaccine administration.[5] Although large-scale future studies are needed to elucidate the relationship between the BP and heterologous SARS-CoV-2 vaccine regimens, we believe that our data will contribute to the existing literature.

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The patients in this manuscript have given written informed consent to publication of their case details.

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