Subepidermal blistering eruptions, including bullous pemphigoid, following COVID-19 vaccination

To the Editor:

The American Academy of Dermatology/International League of Dermatological Societies COVID-19 Dermatology registry has collected 733 cases of skin reactions reported after coronavirus disease 2019 (COVID-19) vaccination between December 24 and April 25, 2021.[1] Here we report the first 12 cases of new-onset subepidermal blistering eruptions (Table I). A total of 7 females and 5 males (median age 82.5-years; range 42-97 years), without a history of bullous pemphigoid (BP) or autoimmunity, developed inflammatory vesicles and bullae a median of 7 days (range 12 hours-21 days) after receiving the first or second dose of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine. All were evaluated by dermatologists, who recorded cutaneous bullae distant from the injection site and skin biopsies demonstrating subepidermal separation and dermal infiltrates with eosinophils. An additional 13th patient with a history of BP had worsened disease but did not undergo further testing.

The diagnosis of BP was confirmed in 8 patients with direct immunofluorescence with or without salt split skin analysis and/or serum BP180-IgG ELISA. Four patients did not meet the full criteria for diagnosis because immunologic testing was either not performed (n = 1) or yielded a negative result (n = 3).

Of the 5 patients who developed blisters after the first vaccine, 3 tolerated the second dose (1 with mild flaring), and 2 of the 5 had a second dose withheld. Three patients diagnosed with dermatitis before vaccination reported worsening dermatitis after the first vaccination and bullae after the second. Blistering resolved or

TABLE I. Diagnosis, treatment, and disease outcomes of patients with BP arising after COVID-19 vaccination

Age (y)/ Sex/Vaccine	History*	Latency to blisters†	H&E staining‡	DIF at DEJ	BP180/230§	Treatment	Outcome
97/F/Pfizer	Psoriasis	(Dose 2) on d 2	+	IgG/C3/IgA SSS, roof	130/81	TCS, DCN, NAM	Improving at wk 2
75/M/Pfizer	Eczematous dermatitis	(Dose 2) on d 10; (dose 1 worsened dermatitis)	+	C3	169/nd	OCS, TCS, DCN, NAM	Improving at wk 3, no longer taking an OCS
64/M/Pfizer	None	(Dose 2) on d 14	+	C3; SSS, floor	26/82	TCS	Improving at wk 4
82/M/Pfizer	Dermatitis	(Dose 2) on d 1; (dose 1 worsened dermatitis)	+	IgG/C3/weak IgA SSS, roof	Neg/Neg	TCS	Resolved at wk 2
95/F/Pfizer	Nonmelanoma skin cancer	(Dose 1) on d 5; (dose 2 no flare)	+	IgG/C3/weak IgA SSS, roof	Neg/Neg	TCS, DCN, NAM	Resolved at wk 8, no longer taking DCN, NAM
87/M/Moderna	Stasis dermatitis, Alzheimer disease	(Dose 2) on d 21; (dose 1 worsened dermatitis)	+	C3	+/+	OCS, DCN, NAM	Ongoing at d 105
42/F/Moderna	Hand eczema	(Dose 2) on d 3	+	IgG/C3/weak granular IgM	>200/59	IMCS, TCS, IVCS	Ongoing at d 23, improving with CS
85/M/Pfizer	Dementia	(Dose 1) on d 5; (dose 2 withheld)	+	IgG/C3	nd	OCS	Ongoing at d 59¶
83/F/Moderna	Raynaud syndrome, major depression	(Dose 1) on d 8; (dose 2 withheld)	+	Neg; IIF result Neg	Neg/Neg	OCS, TCS	Ongoing at mo 2
66/F/Pfizer	Atopic dermatitis	(Dose 1) on d 7; (dose 2) mild flare‖	+	Neg; IIF result Neg	Neg/Neg	OCS, TCS	Resolved at wk 3
70/F/Moderna	Herpes simplex	(Dose 1) on d 9; (dose 2) no reported flare	+	Neg	nd	OCS	Resolved at 1d 5 d
83/F/Pfizer	Dementia	(Dose 2) on d 7	+	nd	nd	OCS, TCS, DCN, NAM	Ongoing at wk 6
83/M/Pfizer	BP¶	(Dose 1) on d 7; (dose 2 withheld)	nd	nd	nd	OCS, TCS	Ongoing at d 45

DCN, Doxycycline; *DEJ*, dermal epidermal junction; *DIF*, direct immunofluorescence histology; *H&E*, hematoxylin and eosin; *F*, female; *IIF*, indirect immunofluorescence; *IMCS*, intramuscular corticosteroid; *IVCS*, intravenous corticosteroid; *M*, male; *Moderna*, Moderna COVID-19 mRNA vaccine; *NAM*, nicotinamide; *Neg*, negative; *OCS*, oral corticosteroid; *nd*, no data; *Pfizer*, Pfizer COVID-19 mRNA vaccine; *SSS*, salt split skin immunofluorescence histology; *TCS*, topical corticosteroid; *Vac*, vaccine.

*Dermatology history, medical conditions associated with BP.

†Blisters were distant from the immunization site in all and widespread unless otherwise noted (by the symbol ‖).

‡Consistent with BP (subepidermal split, infiltrate with eosinophils).

§Serum IgG level according to ELISA, U/mL. Test results were considered negative if BP180 was less than 14 U/mL and BP230 was less than 9 U/mL.

‖Blisters on arms, hands, and lips only after dose 1. A few new blisters on the hands after dose 2.

¶BP was diagnosed in October 2020 (before vaccination). The BP was under control without oral medication before vaccination and flared 5 days after vaccination, requiring systemic treatment. A repeat diagnostic biopsy was not performed.

improved in 7 of the 12 patients in a median of 3 weeks (range 2-8 weeks) with combinations of topical corticosteroids, doxycycline, nicotinamide, and systemic corticosteroids. Disease was ongoing in 5 of the 12 patients at the time of writing of this letter. These outcomes may reflect different pathophysiologies: conventional BP coincident to vaccination with ongoing disease requiring stronger treatment in some versus a vaccine-triggered, benign BP-like condition in others.

These observations raise the question of whether SARS-CoV-2 vaccines might play a role in BP initiation. Certainly, the association could be coincident: the annual incidence of BP worldwide is estimated at between 2.4 and 21.7 new cases per million,[2] so as large populations are vaccinated, some individuals will also develop BP. BP-like disease has been observed after immunization with numerous vaccines, including the measles, varicella zoster, influenza, hepatitis B, and human papilloma virus vaccines.[3,4] It is possible that some individuals who developed BP after SARS-CoV-2 immunization harbored subclinical BP or undiagnosed eczematous-variant BP that was unmasked by vaccination. It is conceivable that in those with more rapid development of bullae (eg, after the first dose), transient bystander immune activation invigorated an existing subclinical autoreactivity. In those with more delayed kinetics, a new cutaneous response may have been primed. However, this is the first use of mRNA vaccines in humans,[5] and a more complete understanding of any potential off-target immunostimulatory properties will require additional investigation.

Dermatologists and other clinicians should be aware that BP-like disease may develop after COVID-19 mRNA vaccination, particularly in older patients. Symptoms may improve rapidly with conservative treatment, as observed in 7 of the 12 patients reported here. Given the risks of SARS-CoV-2 infection, the rarity of these events, and the uncertainty of causality, clinicians should encourage full vaccination, including completion in those with blisters after the first dose. Our experience suggests that the natural history of SARS-CoV-2 mRNA vaccine–associated BP-like disease may differ from that of conventional BP in some individuals, but further studies are required to confirm this hypothesis.

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