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SHORT REPORT

Pemphigus vulgaris after SARS-CoV-2 vaccination: A case with new-onset and two cases with severe aggravation

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Abstract

Pemphigus may be induced or aggravated by certain drugs and vaccines. People worldwide are currently vaccinated with several SARS-CoV-2 vaccines which may be associated with increased number of aggravated or triggered autoimmune bullous diseases in subjects with an underlying genetic predisposition. Herein, a case of new-onset pemphigus vulgaris (PV) and two cases with aggravation of PV after vaccinations for SARS-CoV-2 are reported.

KEYWORDS
COVID-19, pemphigus, pemphigus vulgaris, SARS-CoV-2, vaccination

1 | INTRODUCTION

Pemphigus is an autoimmune bullous disease of the skin characterized by flaccid bullae and erosions on mucosal regions and/or skin due to the disruption of intercellular junctions of suprabasal keratinocytes by anti-desmoglein (antidsg) 1 and/or anti-dsg 3 antibodies.[1] Pemphigus may be induced or aggravated by certain drugs and vaccines such as influenza, rabies, hepatitis B, and tetanus vaccination.[2] Herein, the first case of pemphigus vulgaris (PV) developed after inactivated SARS-CoV-2 vaccine (CoronaVac® 3 μg; im) (Sinovac Life Sciences, Beijing, China) is reported. Besides, aggravations of PV in one patient after inactivated SARS-CoV-2 vaccine and in another patient after BNT162b2 vaccine (30 μg, im) (BioNTech/Pfizer®, New York & Mainz, Germany) are presented.

2 | CASES

Patient 1 was a 69-year-old female who presented with a new-onset of mucocutaneous PV 1 week after the second dose of inactivated SARS-CoV-2 vaccine. After obtaining a skin biopsy, she had applied clobetasol ointment on cutaneous lesions for 1 month. On her second visit to the outpatient clinic, cutaneous lesions remarkably regressed, and oral erosions were still moderately severe (Figure 1A–C). Since she had cataracts, steroid therapy was avoided, and methotrexate 10 mg/week was initiated. She is currently on her follow-ups.

Patient 2 was a 58-year-old female who presented with a severe aggravation of PV. She had a history of severe mucocutaneous PV which required multiple immunosuppressive agents. After about 9 months of complete remission off therapy, she had only mild recurrence in her oral mucosa for about 1 month before vaccination. However, after subsequent two doses of inactivated SARS-CoV-2 vaccinations, it gradually became a severe disease, especially for oral mucosa. Due to poor response to systemic corticosteroid therapy, 2 g/kg/d intravenous immunoglobulin (IVIG) treatment was added.

Patient 3 was a 31-year-old female who had moderate–severe aggravation of PV with new multiple erosions on her scalp and genital mucosa and increased oral erosions 1 week after mRNA vaccine, BNT162b2. She had had mild and transient oral erosions and skin blisters for a couple of years without any diagnosis of PV and has managed with topical steroids. About 3 weeks after vaccination, she went on a seaside vacation and had multiple new bullous lesions on her body, sparing the skin under her swimsuit. When examined, additional extensive oral and genital erosions were observed.

Table 1 presents the details of the demographic and clinical features of patients. None of the patients had a history of COVID-19 infection/exposure/related quarantine or medical treatment, which can trigger PV. The presence of high titers of both serum anti-dsg 1 and 3 antibodies, typical suprabasal epidermal acantholysis, blister formation, and intercellular epidermal IgG deposition in the histopathological examinations in all patients confirmed the diagnosis of PV. Informed consent was obtained from patients. All are on their regular follow-ups.

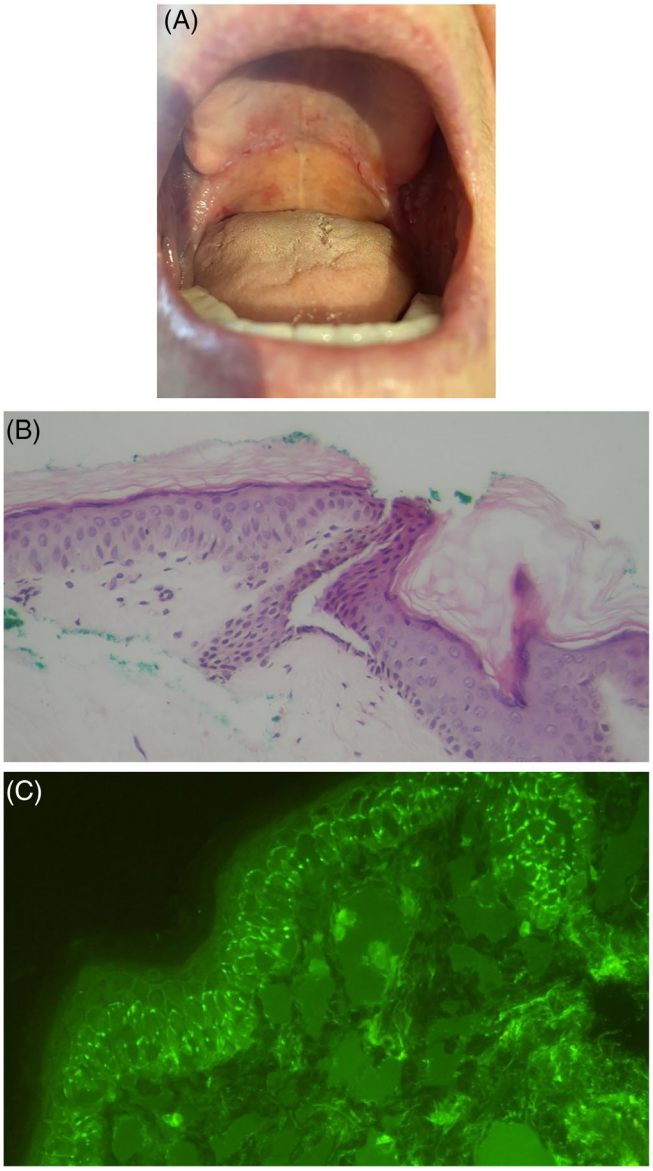

FIGURE 1 Patient 1, new onset of PV lesions on (A) palatal region, (B) histopathological section of skin lesion demonstrating suprabasal acantholysis (H&E, ×40); (C) direct immunofluorescence from perilesional skin showing honeycomb-like pattern intercellular epidermal IgG deposition (×20)

3 | DISCUSSION

In this report, the second case of PV developed after the COVID-19 vaccination is presented. To date, there is only one case reported to have developed new-onset PV after COVID-19 vaccination, mRNA vaccine.[3] The reported case was a 40-year-old female, a younger patient than our case, who had oral lesions occurring 5 days after the first dose of BNT162b2 vaccine. Oral lesions had become worse and cutaneous erosions and blisters had evoked 3 days after the second dose. In contrast, my patient had new-onset PV lesions 1 week after the second dose of inactivated vaccine. The purpose of all COVID-19 vaccines is to create a potent immunological response to COVID-19. After BNT162b2 vaccination, strong adaptive humoral and poly-specific cellular immune responses against SARS-CoV-2 are detected.[4] CoronaVac is an inactivated vaccine which is conjugated with alum for the proper stimulation of immune cells. Both vaccines produce a high level of neutralizing antibodies against SARS-CoV-2.[5] Although the antibody response after both doses of inactivated vaccine could not be measured, production of anti-dsg antibodies may likely have slowly and gradually increased. The clinical manifestations of PV may have shown up after a "silent" period due to the potentially weaker or slower T/B cell responses in older people than younger ones.[6] Although currently there is no report about the T cell responses after CoronaVac vaccine, the possible weak T cell immune response after the first injection may be speculated. The second dose of vaccine may have a booster effect on the intended humoral and adaptive immune response to COVID-19 and unintended T/B cell interaction leading to autoimmunity to desmosomes.

Up to now, there are two cases with PV who experienced a disease flare after the first dose of vaccination during their remission period.[7] In all cases, mRNA vaccines were considered to be causative factors. I observed aggravation of PV after both mRNA vaccine and inactivated vaccine for COVID-19. The remarkable feature of Patient 2 is that she already had a history of severe PV, which needed therapy with potent immunosuppression with rituximab previously. I may speculate that increase in disease severity after two doses of inactivated vaccine may be related to immune activation along with robust activation of B and plasma cells that were currently ready to produce more and more anti-dsg antibodies in this patient. When compared with rituximab, IVIG treatment is a non-immunosuppressive agent and recommended in managing patients with PV during COVID-19 pandemic.[8] Therefore, to avoid potent immunosuppression with high dose systemic steroids and additional rituximab, IVIG was administered as adjuvant therapy for the patient.

In the other patient (Patient 3), disease manifestations demonstrated consecutive evolution from a mild PV to progression into severe mucosal erosions and milder scalp lesions after the BNT162b2 vaccine. Then extensive cutaneous lesions evolved due to ultraviolet radiation. Since the disease severity of cutaneous lesions has possibly changed due to intervening another trigger, ultraviolet radiation, the sole effect of vaccination on cutaneous lesions could not be evaluated.

Although I observed only two cases with aggravation of PV after COVID-19 vaccination, it is clear that the common feature of these two patients was the high titers of anti-dsg antibodies. Damiani et al. reported the time from vaccination to first aggravation to be 3 days for their patients with PV during their remission.[7] When compared, patients in the current report were not in remission, and mild lesions aggravated after about 1 week after vaccination, which is also a short period.

Today, people are massively vaccinated with several SARS-CoV-2 vaccines to prevent deaths due to COVID-19 infection and to end the pandemic. Although vaccination-induced PV is rarely reported, this kind of intense vaccination is likely to bring along with an increased number of aggravated or triggered autoimmune bullous diseases in subjects with an underlying genetic predisposition. These

TABLE 1 Demographic and clinical features of patients who experienced new-onset of PV and aggravation of PV after SARS-COV-2 vaccines

Patient no	Age (years), gender	Comorbidities; related medications	Previous PV diagnosis	PV duration at admission	Previous PV treatments	PV lesions before vaccination	Vaccine; injection time	Time to onset/ aggravation[a]	Vaccine related PV manifestation	Anti-dsg 1 antibody	Anti-dsg 3 antibody	Intervention	Outcome
1	69, female	Thyroidectomy Cataracts	No	5 months	None	None	Inactivated vaccine (First dose: February 13, 2021	-	New onset of oral, scalp, trunk, and limb lesions (moderate PV)	83.8 RU/ML	>200 RU/ML	MTX 10 mg/week has been initiated	Rapid control within 2 weeks, almost complete remission after 12 weeks, no adverse reaction
							Inactivated vaccine (Second dose: March, 13, 2021)	1 week					
2	58, female	HT Right thyroid lobectomy; amlodipine	Yes	8 years	RTX, AZA, systemic steroids	Mild oral erosions since March 2021	Inactivated vaccine (First dose: April 4, 2021)	Within a few days	Increase in oropharyngeal erosions	>200 RU/ML	100 RU/ML	0.8 mg/kg/day prednisolone; then additional 2 g/kg/day IVIG within 5 days (3 cycles)	Complete regression of cutaneous lesions; rapid response for oral mucosal lesions after IVIG treatment, almost complete remission with therapy
							Inactivated vaccine (Second dose: May 7, 2021)	Within 1 week	Extension to severe oral lesions, new genital, nasal mucosal and umbilical lesions (severe PV)				
3	31, female	No	No	History of transient skin bullae and mild oral erosions	Topical potent corticosteroid ointments	Mild oral and cutaneous lesions	BNT162b2 (June 19, 2021)	1 week	New cutaneous lesions on scalp and genital mucosa; increase in oral erosions (severe PV)	>200 RU/ML	>200 RU/ML	0.8 mg/kg/day prednisolone has been initiated	All lesions regressed after 8 weeks, currently on complete remission on minimal therapy

Abbreviations: AZA, azathioprine; HT, hypertension; MTX, methotrexate; PV, pemphigus vulgaris; RTX, rituximab.

observations are shared to pay attention to vaccine-related new manifestations, not to diminish the importance of vaccination against the COVID-19 pandemic, which affects the whole world. Future studies are needed to enlighten the exact cause-and-effect relationship.

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

ENDNOTE

[a]time period for first symptom or manifestation of onset or of significant aggravation of PV lesions after vaccination.

DATA AVAILABILITY STATEMENT

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

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