New-onset pemphigus vegetans and pemphigus foliaceus after SARS-CoV-2 vaccination: A report of 2 cases

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INTRODUCTION

New-onset and relapsed pemphigus vulgaris (PV), the most common variants of pemphigus, have been reported in association with vaccination against several infectious agents, including SARS-CoV-2.[1] However, given the rarity of these events, much remains unknown about the clinical course of pemphigus after vaccination with the Pfizer mRNA BNT162b2 and Moderna mRNA-1273 vaccines, particularly among patients with diagnoses of less common subtypes. Here, we report 2 cases of new-onset pemphigus vegetans (PVeg) and pemphigus foliaceus (PF) after administration of the SARS-CoV-2 vaccine.

METHODS

A retrospective study was performed to investigate the clinical course of patients evaluated by the Department of Dermatology at Stanford Medical Center in Stanford, California, between August 2021 and January 2022 for new-onset blistering consistent with pemphigus after SARS-CoV-2 vaccination.

Two patients were identified, and relevant information was reviewed, including patient demographics, SARS-CoV-2 vaccination history, and medical history, including prior dermatologic conditions, clinical course, histopathologic results from skin biopsies, direct immunofluorescence and indirect immunofluorescence results, and treatment course.

Abbreviations used:

PF: pemphigus foliaceus
PVeg: pemphigus vegetans
PV: pemphigus vulgaris

CASE SERIES

Case 1

A 25-year-old otherwise healthy man presented to the dermatology clinic with a 2-month history of an expanding, painful erythematous papule in his right axilla, which began 1 month after his second Pfizer mRNA BNT162b2 vaccination. Physical examination revealed a solitary macerated, erythematous to violaceous plaque with hyperkeratotic crust on the right axilla (Fig 1); no other mucocutaneous lesions were observed. Initial punch biopsy revealed dyskeratosis with a suprabasal epidermal split, brightly eosinophilic cytoplasm in keratinocytes, acantholysis, and prominent acanthosis. Given the isolated plaque on the axilla, the patient was initially given a diagnosis of benign familial pemphigus and was treated with clobetasol 0.05% ointment and intralesional injections of onabotulinum toxin, resulting in mild improvement. Six weeks after the initial evaluation, he developed flaccid blisters with

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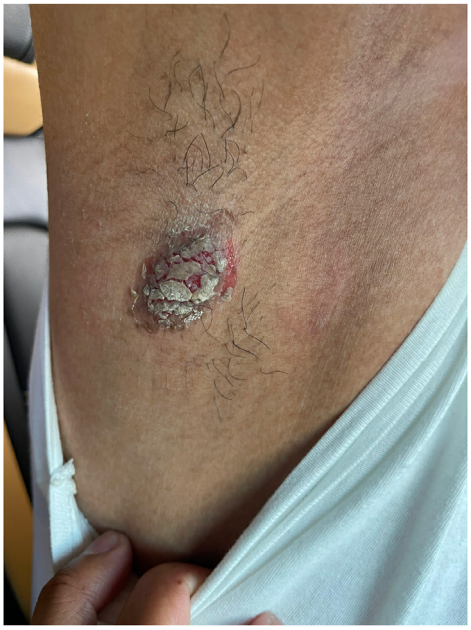

Fig 1. Image of case 1: pemphigus vegetans. The initial presentation of this pemphigus vegetans case revealed a solitary macerated, erythematous to violaceous plaque with hyperkeratotic crust on the right axilla that was initially diagnosed as benign familial pemphigus.

erythematous rims scattered on the oral mucosa, face, trunk, genitals, and extremities. Direct immunofluorescence on a perilesional biopsy specimen revealed intercellular deposition of C3 and IgG on keratinocytes at all epidermal levels, with C3 mostly confined to the lower epidermis. Indirect immunofluorescence revealed elevated levels of IgG autoantibodies against desmoglein 1 (81 units/mL) and desmoglein 3 (100 units/mL). Owing to the clinical findings of axillary lesions progressing to involve the trunk and face, in correlation with the initial biopsy revealing prominent acanthosis, the diagnosis was revised from benign familial pemphigus to PVeg, and the patient was started on oral prednisone (1 mg/kg/d). Given a lack of clinical improvement at subsequent follow-up, the patient's prednisone dose was increased to 1.1 mg/kg/d, and adjuvant therapy with oral mycophenolate mofetil (1000 mg/d, up-titrated to 2500 mg/d over 6 weeks) was initiated. At the 6-month follow-up, the patient's blistering had ceased, and he was tolerating an ongoing steroid taper.

Case 2

A 67-year-old woman with a history of osteoporosis presented for evaluation of nonhealing wounds on the chest, shoulders, and back, which appeared approximately 2 weeks after administration of her second Moderna mRNA-1273 SARS-CoV-2 vaccine. Physical examination showed crusted hyperkeratotic plaques on the mid aspect of the back, left aspect of the chest, and left shoulder, but without involvement of the mucosal membranes (Fig 2). Punch biopsy revealed intraepidermal acantholysis, direct immunofluorescence revealed intercellular deposition of IgG and C3, and indirect immunofluorescence revealed elevated serum titer of anti–desmoglein 1 antibodies but absence of elevated serum anti–desmoglein 3 antibodies, consistent with PF. The patient was subsequently treated with oral prednisone (0.36 mg /kg/d) and topical clobetasol and mupirocin. At the 2-month follow-up, the patient had successfully tapered off prednisone. One week later, she noted mild flaring lesions, which healed within days, as well as an isolated, nonhealing wound on her chest.

DISCUSSION

We present 2 cases of new-onset PVeg and PF after SARS-CoV-2 vaccination (Table I). Few cases of PV after SARS-CoV-2 vaccination have been reported.[1] To our knowledge, there have been no reports of other rare pemphigus subtypes, including PVeg and PF, after SARS-CoV-2 vaccination.

Pemphigus is a group of rare, debilitating, and potentially fatal autoimmune bullous dermatoses that includes PV (the most common variant), PF, paraneoplastic pemphigus, and IgA pemphigus.[2] PVeg is considered a subtype of PV and represents 1% to 2% of all pemphigus cases.[3] In all the variants, blistering and erosions occur after autoantibody-mediated damage to desmoglein 1 or desmoglein 3, resulting in the loss of intraepidermal keratinocyte adhesion and acantholysis.[4]

The clinical presentation of different pemphigus variants may vary on the basis of the formation of autoantibodies against additional intraepidermal proteins.[4] PVeg is characterized by erosions appearing predominantly on intertriginous, anogenital, and nasolabial sites that undergo repetitive cycles of incomplete healing to gradually become hypertrophic vegetating plaques; mucous membrane involvement and intense foul odor are common.[5] The characteristic intertriginous distribution of lesions observed in PVeg may be related to semi-occlusion, maceration, and colonization of bacteria or fungi.[5] In contrast, patients with PF often initially develop blisters and erosions in seborrheic areas, such as the face, scalp, and chest, with later development of painful, erythematous erosions and plaques.[2,4] PF may also occur sporadically or endemically among certain Brazilian and North African populations.[2,4]

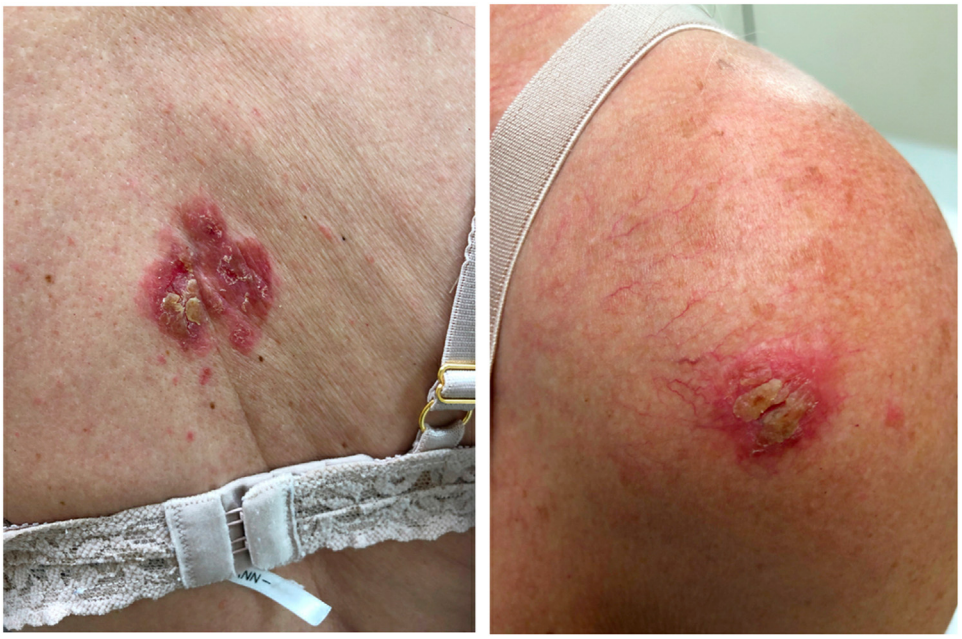

Fig 2. Image of case 2: pemphigus foliaceus. The initial presentation of this pemphigus foliaceus case showed hyperkeratotic plaques on the mid aspect of the back and left shoulder.

In most cases, the underlying inciting event in pemphigus is unknown, although several multifactorial associations have been proposed, including genetic predilection, medications containing thiol or phenol groups, preceding viral infection, ultraviolet radiation, and diet.[6] Pemphigus after vaccination has been reported, including after administration of vaccines against influenza, typhoid, hepatitis B, and anthrax, with symptom onset typically occurring 2 weeks after vaccination.[7] Symptom onset in this report of 2 cases was similar, with new-onset blistering observed 2 to 4 weeks after SARS-CoV-2 vaccination. Prior work has shown that IgG antibodies peak approximately 2 weeks after administration of the second vaccine dose with the Pfizer BNT162b2 vaccine, which may explain the observed timeline of symptom onset in this patient cohort.[8]

Several mechanisms have been proposed for the development of pemphigus after vaccination, including molecular mimicry and epitope spread in genetically predisposed individuals.[9] Molecular mimicry refers to cross-reactivity between a foreign antigen and self-antigens that induces a break of self-tolerance, leading to autoimmunity. Epitope spreading similarly occurs as a result of an immune response against endogenous target antigens secondary to the release of self-antigen during the chronic autoimmune response. In a recent case series of 24 healthy subjects with prior SARS-CoV-2 infections or vaccinations without prior autoimmune bullous dermatoses, no cross-reactivity between anti—SARS-CoV-2 antibodies and pemphigus autoantigens in serum was observed.[10] This work suggests that molecular mimicry may not fully explain the development of pemphigus after SARS-CoV-2 vaccination, although this study was significantly limited by its small sample size and likely absence of patients genetically predisposed to developing autoimmune bullous dermatoses after vaccination.

Alternative pathophysiologic mechanisms have yet to be investigated with experimental approaches, such as nonspecific bystander activation of immune cells or epitope mapping studies. In addition to evidence of associations between vaccinations and pemphigus, there have also been recent case reports discussing similar associations between the BNT162b2 vaccine and other immune-mediated dermatologic conditions. One group noted vitiligo associated with the vaccine, suggesting molecular mimicry or bystander activation as the pathogenic mechanism.[11] Another group noted that toll-like receptor-7 and toll-like receptor-9 stimulation afforded by the new messenger RNA vaccines might upregulate interferon-stimulated genes, contributing to robust early innate immune responses with high type-I interferon, causing erythematous rashes.[12]

Although it is not certain that the new-onset PVeg and PF reported in these 2 cases were caused by SARS-CoV-2 vaccination, the lack of prior cutaneous disease, onset of symptoms within 1 month of vaccination, known tendency for vaccines to trigger immune-mediated skin conditions, and rarity of

Table I. Characteristics of patients with pemphigus

Case	Age, sex, race	Pertinent history	Vaccine type, dose	Weeks to onset	Abnormal preceding serologies? (CBC)	Prodromal symptoms?	Pemphigus type	Mucosal involvement	BSA%, OSA %	Serum Dsg1 & Dsg3 antibodies upon diagnosis	Treatment	Duration of treatment before remission	Retried vaccine?
1	25 y, M, Asian	None noted	BNT162b2, second	4	No	None	PVeg	Oral and genital	10% BSA 2% OSA	Dsg1: 81 RU/mL (H) Dsg3: 100 RU/mL (H)	Prednisone 1.1 mg/kg/d; MMF up to 2500 mg/d; TAC 0.1%	5 mo	No
2	67 y F, White	COVID-19 (after development of PF)	mRNA-1273, second	2	No	Pain	PF	None	5% TBSA	Dsg1: 47 RU/mL (H) Dsg3: 8 RU/mL	Prednisone 0.36 mg/kg/d (20 mg for 55 kg person)	2 mo	No

BSA, Body surface area; *CBC*, complete blood cell count; *Dsg1*, desmoglein 1; *Dsg3*, desmoglein 3; *F*, female; *M*, male; *MMF*, mycophenolate mofetil; *OSA*, oral surface area; *PF*, pemphigus foliaceus; *PVeg*, pemphigus vegetans; *RU*, relative units; *TAC*, triamcinolone; *TBSA*, total body surface area.

pemphigus all suggest that the observed relationship may not be coincidental, and further studies are needed to elucidate causality.

Dedicated treatment modalities for vaccine-associated pemphigus remain unexplored, and current treatment strategies in cases of pemphigus after SARS-CoV-2 vaccination have relied on existing treatment paradigms used in the broader population. Systemic glucocorticoids, such as prednisone, are considered immediate first-line therapy for moderate to severe pemphigus at a preferred initial dose of 1 mg/kg/d.[2] Rituximab is also first-line maintenance therapy in moderate to severe pemphigus to achieve disease remission and reduce cumulative glucocorticoid exposure for moderate to severe pemphigus.[13] Steroid-sparing treatments, such as mycophenolate mofetil, azathioprine, methotrexate, intravenous immune globulin, and dapsone, among others, may also be added.[5] However, we know that patients who receive rituximab are at higher risk of complications from SARS-CoV-2 infection compared with those not treated with rituximab, although this risk decreases gradually after infusion.[14] Thus, guidelines for management of pemphigus during the ongoing pandemic highlight the need for an individualized approach when selecting therapies.[15] Further work to investigate specific treatment regimens and modalities to manage new-onset pemphigus after SARS-CoV-2 vaccination, including rare variants such as PVeg and PF, are needed.

Limitations

This study has limitations, including its retrospective design, which preclude the ability to infer a causal relationship between SARS-CoV-2 vaccination and the development of new-onset pemphigus. In addition, this study was performed at a single academic center, which limits the diversity of our patient population.

CONCLUSION

New-onset pemphigus, including the less common variants PVeg and PF, may be associated with the administration of the Pfizer BNT162b2 and Moderna mRNA-1273 vaccines. In these 2 cases, patients successfully achieved remission of their pemphigus with treatment; however, the risk of disease relapse and optimal treatment regimen for vaccine-associated pemphigus remain unknown at this time. In addition, further research clarifying the relationship between messenger RNA SARS-CoV-2 vaccines and new-onset autoimmune diseases, including pemphigus, is warranted. Clinicians must weigh the benefits of vaccination given the severity

of the ongoing COVID-19 pandemic against the risk, which may encompass new-onset pemphigus.

Conflicts of interest

None disclosed.

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