

BRIEF ARTICLE

Development of De Novo Pemphigus Vulgaris Following COVID-19 Vaccination

Faraz Yousefian, DO^{1,2}, Farah Tiab², Sujitha Yadlapati, MD³, Rodolfo E Chirinos, MD, FAAD⁴, Daniel Rivlin, MD, FAAD⁵

¹ Goodman Dermatology, Roswell, Georgia

² University of the Incarnate Word School of Osteopathic Medicine (UIWSOM), San Antonio, Texas

³ HCA Corpus Christi Medical Center- Bay Area Dermatology Residency Program, McAllen, Texas

⁴ Skin and Cancer Associates, Hallandale, Florida

⁵ Larkin Community Hospital, Department of Mohs Micrographic Surgery and Dermatology Oncology, Miami, Florida

ABSTRACT

The vaccines manufactured by Pfizer, Moderna, and AstraZeneca to prevent the spread of SARS-CoV-2 have been reported to cause a wide range of adverse cutaneous reactions. The most common of these include delayed large local reactions, injection site reactions, urticaria, and morbilliform eruptions. The rarest and severe cutaneous reactions include the development of autoimmune blistering diseases such as pemphigus vulgaris and bullous pemphigoid. In this case report, we present a 73-year-old female patient who developed de novo pemphigus vulgaris two weeks after receiving the Pfizer-BioNTech COVID-19 vaccine. To the best of our knowledge, ours is the first case of new-onset pemphigus vulgaris following the Pfizer COVID-19 vaccine in the United States and only the third worldwide. This report confirms a suspected association between COVID-19 vaccination and the onset of pemphigus vulgaris, although it is exceedingly rare. It also highlights the importance of considering the COVID-19 mRNA vaccines as etiologies for new-onset pemphigus vulgaris and potentially other autoimmune blistering disorders. This knowledge may be important for medical providers when considering a differential diagnosis of new-onset blistering disease to expedite accurate diagnosis and initiation of treatment.

INTRODUCTION

A wide variety of adverse cutaneous reactions were reported with the administration of vaccines against the SARS-CoV-2 virus, manufactured by Pfizer, Moderna, and AstraZeneca.^{1,2} The delayed large local reactions, injection site reactions, urticaria, and morbilliform eruptions are the most commonly reported dermatological findings.¹ In addition to these more common

reactions, there have been several case reports in the United States and internationally describing new onset or flaring of existing blistering and autoimmune skin eruptions such as bullous pemphigoid and pemphigus vulgaris.³ These bullous disorders primarily occur in patients over 70 years of age but have also occurred in younger adult patients.³ In this report, we present a case of new-onset pemphigus vulgaris in a 73-year-old female patient following the administration of her second

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dose of the BNT162b2 (Comirnaty®, Biontech/Pfizer) mRNA vaccine. The patient was not taking any prescribed medications and had no history of autoimmune disease.

CASE REPORT

A 73-year-old female presented to our outpatient dermatology clinic with the chief concern of a painful and pruritic rash located on her mouth, abdomen, right flank, and lower back. The patient stated these symptoms started two weeks after receiving her second dose of the Pfizer-BioNTech COVID-19 vaccine six months earlier. On initial examination, there were erythematous vesicles, bullae, and erosions located on her buccal mucosa, anterior abdomen, right flank, and lower back along the T9 and T10 dermatomes (**Figure 1**). She was treated with oral valacyclovir and topical mupirocin ointment for presumed herpes zoster and oral herpes gingivostomatitis. She returned for a follow-up two week later and reported worsening of the painful lesions now consisting of tense, serosanguinous, dome-shaped vesicles, and bullae on an erythematous base with a positive Asboe Hansen sign and negative Nikolsky sign including erosions and ulcers on her tongue and mucosal lower lip (**Figure 2**).

Perilesional biopsies of the periumbilical abdomen were performed and histopathology revealed a suprabasilar blister present with an infiltrate in the dermis comprised mostly of lymphocytes with just a few eosinophils on hematoxylin and eosin (H&E) stains (**Figure 3**) and linear, granular IgG deposits on epithelial cell surfaces on direct immunofluorescent (DIF). Based on the patient's clinical presentation, medical history, review of medications, the onset of symptoms relative to COVID-19 vaccination, and histopathological findings, she was

diagnosed with COVID-19 vaccine-induced pemphigus vulgaris. Initially, the patient was treated with systemic and ultrapotent topical corticosteroids that resulted in the improvement of the mucocutaneous lesions. After four additional weeks of prednisone 60 mg daily, the patient was started on steroid-sparing agents consisting of doxycycline 100 mg BID with Nicotinamide 500 mg. In order to avoid immunosuppression during the COVID-19 pandemic, the trial of dapsone 25 mg twice daily was prescribed after negative glucose-6-phosphate dehydrogenase (G6PD) laboratory testing. Lab work monitoring revealed an elevated desmoglein 3 at 158 units/mL (positive range >20 units/mL). Dapsone resulted in improvement of the mucocutaneous lesions (**Figure 4**), however, it was discontinued due to hemolytic anemia: low RBC (3.24), low hemoglobin (10.7), low hematocrit (33.2), high MCV (103), high LDH (373) and low haptoglobin (<10). The patient was started on mycophenolate mofetil (MMF) 500 mg BID. In her five-week follow-up, the lesions were persistent on her body, but she reported a reduction in pain intensity. Consequently, her MMF dose was increased to 1000 mg twice daily which led to the complete resolution of her symptoms.

DISCUSSION

Pemphigus vulgaris is an autoimmune blistering disease that manifests with painful mucocutaneous serosanguinous vesicles and bullae. The disease process is attributed to the destruction of keratinocyte adhesion initiated by IgG autoantibodies against desmoglein 3,⁴ resulting in acantholysis of the intercellular adhesions between keratinocytes resulting in painful bullae that often rupture.⁴ The etiology of pemphigus vulgaris is poorly understood, but it is thought to be the result of interactions between a



Figure 1. Initial visit. erythematous vesicles, bullae, and erosions located on anterior abdomen (1A) and lower back along the T9 and T10 dermatomes (1B).



Figure 2. Two-week follow-up. Erosions and ulcers on her tongue and mucosal lower lip.

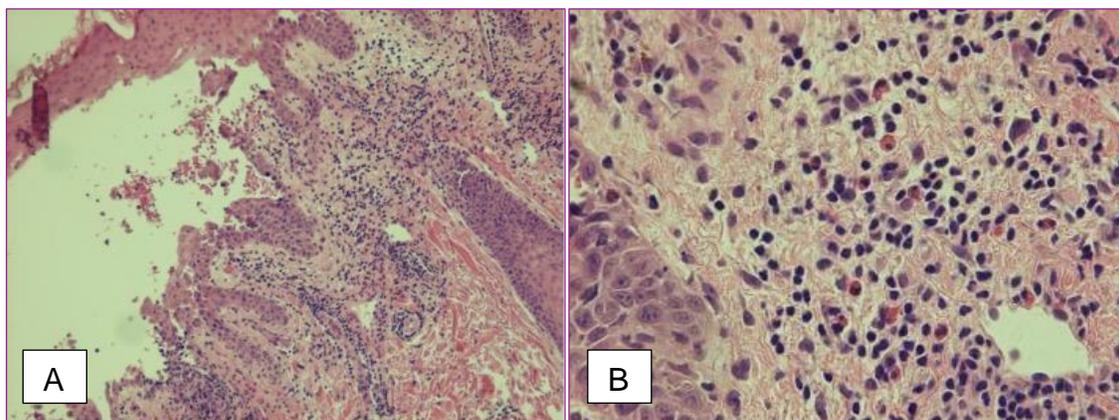


Figure 3. Periumbilical H&E. Suprabasilar blister present with an infiltrate in the dermis comprised mostly of lymphocytes with just a few eosinophils with 10x (3A) and 40x magnification (3B).



Figure 4. Post-treatment with dapson.

genetic predisposition and environmental factors.⁴ Some of these environmental factors include recent infection, immunization, malignancy, and certain medications containing thiol groups such as penicillamine and captopril.^{5,6} An association between certain immunizations and the development of autoimmune bullous diseases like pemphigus vulgaris and bullous pemphigoid has been studied and established over the past 25 years.⁷ A systematic review by Kasperkiewicz et al (2021) explains that the vaccines administered for rabies, influenza, hepatitis B, typhoid, tetanus, and anthrax have all been implicated in the development of pemphigus vulgaris, but at the time of writing it had not yet been seen after COVID-19 vaccines.⁷ Our patient did not have a personal or family history of autoimmune disease, was not recovering from illness or infection and did not take any medications known to precipitate the onset of pemphigus vulgaris, such as penicillamine or captopril.

The vaccines developed to prevent the spread of COVID-19 have been shown to be extremely safe and effective, with the

majority of adverse effects being extremely mild.⁸ The most common reactions associated with COVID-19 vaccines include local injection site reactions, delayed local reactions, urticaria, angioedema, and morbilliform eruptions, but the development of new-onset autoimmune disorders is rare.^{5,8} The mRNA vaccines developed by Pfizer and Moderna contain no adjuvants that are commonly added to other vaccines to ensure the elicitation of a strong immune response, which may contribute to the mild side effect profile. However, starting in 2021, case reports have emerged describing the association between the administration of the Pfizer, Moderna and AstraZeneca COVID-19 vaccines and cases of new-onset or reactivation of autoimmune bullous diseases. Providers should maintain a high index of suspicion in patients with new-onset pemphigus vulgaris or flaring of previously well-controlled disease.

Solimani et al (2021) published the first case report of a patient in Germany who developed new-onset pemphigus vulgaris following the administration of the BNT162b2 (Comirnaty®, Biontech/Pfizer) mRNA

vaccine.⁹ Since this first report, there have been two additional cases of new-onset pemphigus vulgaris after receiving the Pfizer vaccine specifically, one by Knechtel et al (2022) in Switzerland and one by Calabria et al. (2022) in Italy.^{10, 11} To the best of our knowledge, our report is the third example of this specific case in the world and the first to be reported in the United States.¹¹ Of note, there was a case report of new-onset pemphigus vulgaris in Minnesota, but this occurred after the administration of the Moderna mRNA COVID-19 vaccine.¹² Similar case reports in the same time frame describe new-onset and flaring of preexisting pemphigus vulgaris in response to other COVID-19 vaccines, such as the AstraZeneca and CoronaVac vaccines, but this is more rare when compared to the frequency of occurrence after the mRNA vaccines.^{2,7, 11} This is due in part to the fact that they are the most frequently administered.⁸ This may also be due to the immune response elicited by the mRNA vaccines, as they are thought to upregulate the expression of cytokines that are important mediators of the pathogenesis of pemphigus vulgaris, namely interleukin 4 (IL-4), interleukin 17 (IL-17), and interleukin 21 (IL-21).⁹

In addition to the development of de novo pemphigus vulgaris following COVID-19 vaccination, there have been several reports of severe flares of previously controlled pemphigus vulgaris. Damiani et al (2021) described flares of preexisting pemphigus vulgaris and bullous pemphigoid in patients who had received the Pfizer or Moderna COVID-19 vaccines.¹³ Avallone et al (2022) also reported a case of severe flaring of pemphigus vulgaris following the first dose of the Pfizer COVID-19 vaccine.¹⁴ The patient's lesions got progressively worse after receiving the second dose of the vaccine with a corresponding increase in antibodies

against desmoglein 1 and 3 after each administration.¹⁴ A report by Ong et al (2022) described a similar case in which a patient experienced a flare of previously well-controlled pemphigus vulgaris after the first dose of the Moderna COVID-19 vaccine.¹⁵ The patient opted to receive the Johnson & Johnson COVID-19 vaccine instead of the second dose of the Moderna vaccine to avoid further flaring.¹⁵ Our patient decided to not receive future COVID-19 vaccine boosters to avoid reoccurrences or flares of her resolved condition.

Taking all of these case reports into account can help providers better anticipate the adverse dermatological effects of COVID-19 immunizations, particularly in older patients with a personal or family history of the autoimmune bullous disease. Patients should be instructed to consult a dermatologist for the diagnosis and treatment of adverse cutaneous reactions to the vaccines, especially if they are experiencing severe symptoms such as painful blistering. These reports are also important for the ongoing accumulation of information about the potential effects of COVID-19 vaccination but should not be used as a deterrent to vaccination as they are exceedingly rare. Further studies are warranted to elucidate how mRNA vaccines might interact with the immune system to produce autoantibodies against desmoglein in addition to other adverse autoimmune effects.

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Corresponding Author:

Faraz Yousefian, DO

2500 University Drive Unit 208, Roswell, Georgia

Email: Yousefian.faraz@gmail.com

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