SKIN

BRIEF ARTICLE

# Treatment-Resistant Pemphigoid Following SARS-Cov-2 Vaccination

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## ABSTRACT

As the SARS-CoV-2 vaccinated population increases, there have been many reports of vaccine-induced cutaneous reactions but scarce information on vaccine-induced autoimmune bullous disease. Vaccinations have been associated with the unmasking or development of autoimmune bullous disease; however, there is little data on SARS-CoV-2, specifically. We report a rare case of new-onset pemphigoid in a 70-year-old male following the second dose of the mRNA-1273 vaccine. The patient's disease has been refractory to treatment, thus the underlying pathophysiology in vaccine-induced pemphigoid is likely unique, and further investigation into this pathophysiology is warranted.

## INTRODUCTION

On December 18, 2020, ModernaTX received emergency use authorization from the Food and Drug Administration to release the mRNA-1273 vaccine in order to reduce the severity of SARS-CoV-2 infection.[1] As the SARS-CoV-2 vaccinated population increases, there have been increased reports of cutaneous reactions, the most common being a delayed large local reaction.[1] Additionally, there have been fewer reports of systemic cutaneous reactions, including but not limited to urticaria and morbilliform exanthems.[1] A systematic review published in April 2021 reported no association between COVID-19 vaccination and autoimmune bullous disease (AIBD).[2] However, there have been recent reports of new-onset subepidermal blistering disease following SARS-CoV-2 mRNA vaccination.[3] We report a case of treatment-resistant bullous pemphigoid in a 70-year-old male following the second dose of the mRNA-1273 vaccine.

## CASE REPORT

A 70-year-old male with a past medical history of hypertension, hyperlipidemia, and gastroesophageal reflux disease presented to the clinic with a 2-month history of new lesions on his extremities and trunk. The patient noted the eruption began one week after he had received his second dose of the mRNA-1273 vaccine. He denied oral lesions or systemic symptoms, and he described the lesions as burning and progressively spreading. On exam, several large, geometric, eroded plaques and bullae with surrounding erythema were noted on his right distal leg (Figure 1, A). Smaller, similar lesions were also noted on the abdomen and bilateral arms (Figure 1, B). 4-mm

punch biopsies were performed for further evaluation, and the patient was started on low-dose prednisone.

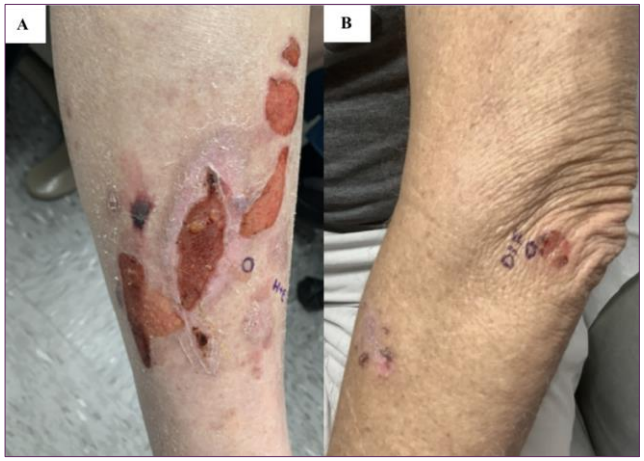


**Figure 1.** Pemphigoid- Clinical images on the day of initial presentation **A)** Several large, geometric, eroded plaques and bullae with surrounding erythema were noted on his right distal leg **B)** Eroded inflammatory plaques on the left arm.

Histopathology revealed a subepidermal blister with eosinophils (Figure 2, A and B). Direct immunofluorescence showed linear deposition of IgG and C3 along the basement membrane zone. These findings supported a diagnosis of bullous pemphigoid (BP). Two weeks later the patient developed new oral lesions. Salt-split skin (SSS) was performed on the initial specimen, which demonstrated linear IgG localizing predominantly to the epidermal side of the blister, labeling the dermal side of the blister to a lesser extent (Figure 3, A and B), favoring BP. Serum basement membrane zone and intercellular skin autoantibodies were negative at this time. The patient's medication list was reviewed and was unremarkable. Treatment was initiated with a combination of high-dose oral prednisone (1 mg/kg/day), doxycycline 100mg twice daily, nicotinamide 500mg three times daily, and triamcinolone 0.1% cream, combined with gentamicin ointment under occlusion. The patient had persistent oral and cutaneous lesions at 2-week follow-up. Therefore, dapsone 12.5mg daily was added to his regimen, which was titrated up to 50mg daily over 2 months. During this time, prednisone was tapered off. The patient had minimal improvement with this regimen and continued to develop breakthrough lesions. Due to the inadequate response to treatment, biopsy was repeated. DIF was positive for thin wavy deposition of IgG and slightly weaker C3 along both the dermal ("N" serrated pattern) as well as the epidermal side of the salt-split (NaCl 1 M x 24 hs) basement membrane zone. These findings confirmed an IgG subepithelial blistering disease. Based on clinical-pathological correlation, BP, or anti-laminin gamma-1 (p200) pemphigoid were considered. Serum enzyme-linked immunosorbent assay (ELISA) for anti-BP180 and anti-BP230 was then performed. Anti-BP180 antibody levels were elevated (22 U/mL; reference value, < 14), thus a diagnosis of BP was favored. Dapsone was discontinued and mycophenolate mofetil was initiated, titrating up to 1g twice daily.

## DISCUSSION

Several studies suggest that vaccinations may be associated with unmasking or the development of autoimmune disorders.[4] The pathophysiology remains unclear, however molecular mimicry and bystander activation are reported as possible mechanisms.[4] Kasperkiewicz et. al discusses 28 patients from 1995 to 2021 diagnosed with AIBD occurring 1-day to 3-months status-post vaccination.[2] These vaccinations were most commonly for influenza, tetanus, diphtheria, hepatitis, and varicella-zoster, with no

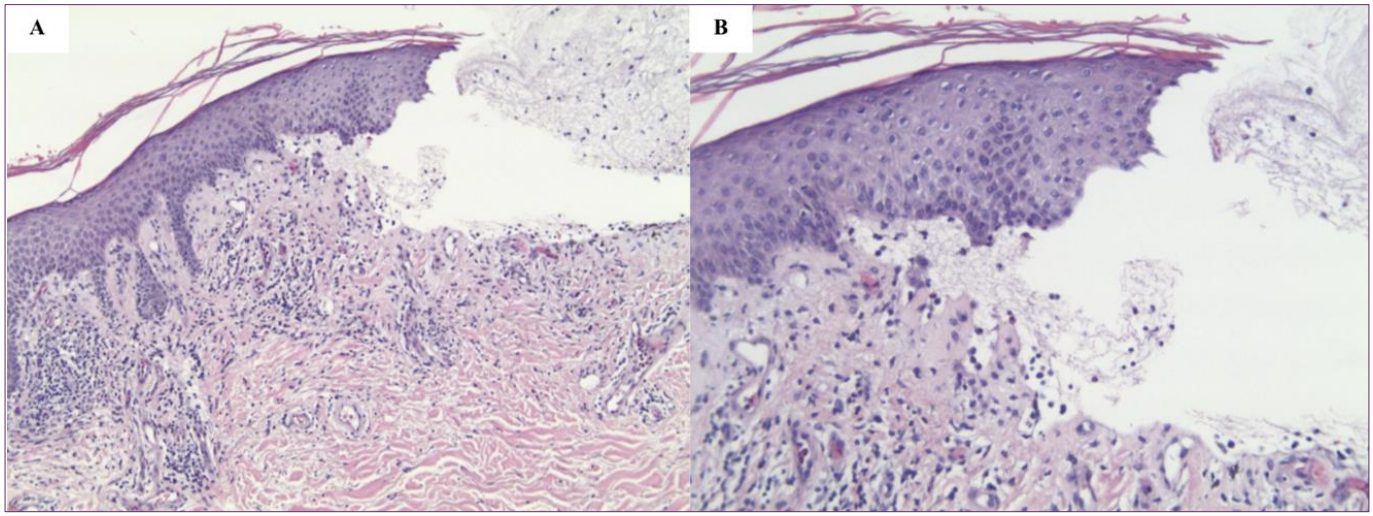


**Figure 2**. Pemphigoid- Histopathology of lesion tissue. A and B, Histopathologic image demonstrating a subepidermal blister with eosinophils. (H&E; original magnification: **A)** ×100; **B)** ×200)

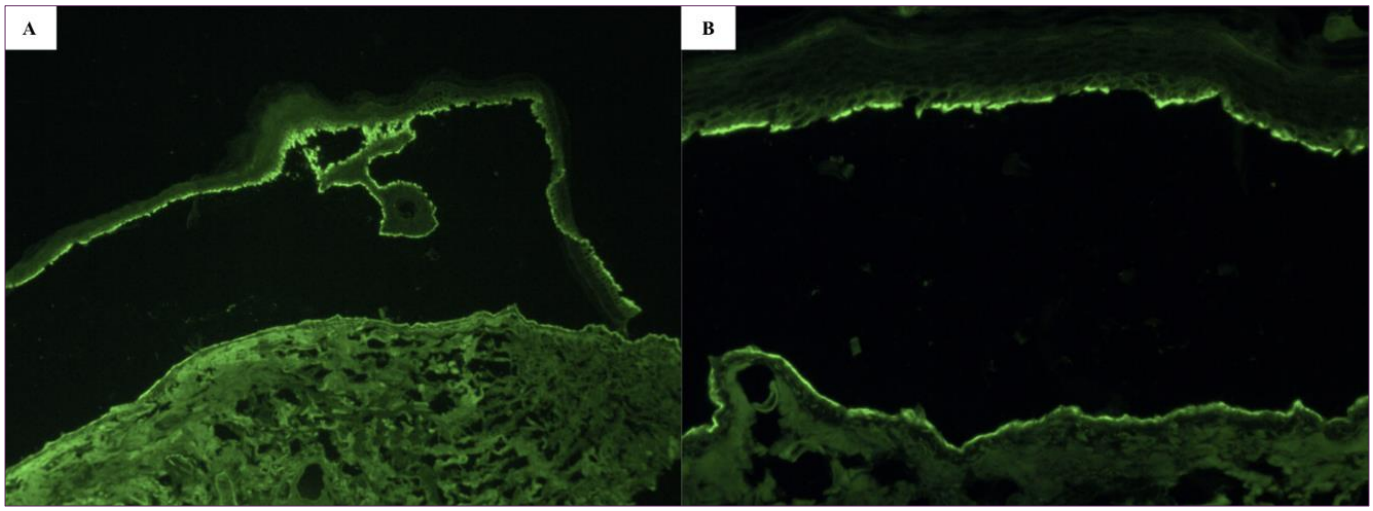


**Figure 3.** Pemphigoid- Salt-split skin (NaCl 1 M x 24 hs) demonstrating linear IgG localizing predominantly to the epidermal side of the blister, labeling the dermal side of the blister to a lesser extent (Original magnification: **A)** x100; **B)** x400)

reports of SARS-CoV-2.[2] Of the biopsy-proven reports of SARS-CoV-2 vaccine-associated BP in a letter to the editor, 75% of these patients exhibited symptoms 1-21 days after the second dose,[3] which is consistent with our patient's timeline. In these cases, 7 out of 12 patients had resolution or improvement of lesions at a median of 3 weeks after treatment with topical and systemic steroids, doxycycline, and nicotinamide.[3] Of the 5 patients with ongoing disease, Tomayko proposed the possibility of a different pathophysiology.[3] Our patient had persistent disease despite treatment, and thus a different pathophysiology should be considered. Interestingly, our patient had oral mucosal lesions in the setting of both dermal and epidermal staining on SSS. This could suggest BP with recognition of more distal epitopes near the non-collagenous domain of BP180. Another possible explanation is that our patient has anti-p200 pemphigoid with epitope spreading and the additional

targeting of BP180. Further testing for anti-p200 pemphigoid was not pursued in our case, however, this could be a future consideration. Thus, the underlying pathophysiology in vaccine-induced pemphigoid is likely unique, and further investigation is warranted.

The authors suspect this to be a true vaccine-triggered case of pemphigoid. BP affects the elderly and is typically seen in patients 70 years of age and older.[5] Considering our patient is a 70-year-old male, his initial presentation following SARS-CoV-2 vaccination could represent coincidental unmasking of subclinical BP, although the authors feel this is less likely given the timeline, refractory course, and similar reports of BP after vaccination.[3]

Additional reports discuss inconclusive or BP-negative, bullous-like eruptions related to SARS-CoV-2 vaccination.[3,6] This is due to either patient loss to follow-up or negative direct immunofluorescence.[3] Additionally, new-onset BP has been reported in patients with acute SARS-CoV-2 infection.[7-8] Our patient was not tested for SARS-CoV-2 at the time of diagnosis, as he was asymptomatic and had just completed the mRNA vaccine series. Therefore, the possibility of SARS-COV-2 infection was not ruled out, but highly unlikely.

## CONCLUSION

The SARS-CoV-2 vaccination is the first approved use of an mRNA vaccine in humans and a more complete understanding of potential off-course immunostimulatory properties will require more investigation.[9] It is important to be aware that pemphigoid and pemphigoid-like diseases may develop after SARS-CoV-2 vaccination. However, given the significant health risks of SARS-CoV-2 infection and the rarity of these events, clinicians should continue to encourage full vaccination.

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