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A new eruption of bullous pemphigoid following mRNA COVID-19 vaccination

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Abstract

The rapid development and implementation of COVID-19 vaccines throughout the global population has given rise to unique, rare, adverse skin reactions. This case report describes an elderly man with new-onset bullous pemphigoid following the second dose of the Pfizer-BioNTech (mRNA) COVID-19 vaccine.

Keywords: bullous pemphigoid, COVID-19, vaccine reaction

Introduction

Bullous pemphigoid (BP) is an uncommon autoimmune blistering disease which characteristically affects elderly adults with an incidence of 150–330 cases per million people per year in individuals over 80 years of age. The pathogenesis of BP involves autoantibodies directed against antigens in the hemidesmosome, causing a subepidermal split and subsequent bullae formation [1]. Rare cases of BP have been reported following a variety of vaccinations including those for diphtheria, tetanus, pertussis, polio, influenza, *Haemophilus influenzae* type B, hepatitis B, bacillus Calmette-Guérin, pneumococcus, and herpes zoster, though true association is unclear [2,3]. The following report highlights a case of new-onset bullous pemphigoid occurring the day after an elderly man received his second dose of the Pfizer-BioNTech (mRNA) COVID-19 vaccine.

Case Synopsis

A man in his 70s with a remote history of prostate and renal cancer (in remission) presented with an intensely pruritic eruption of pink plaques that began one day after he received his second dose of the Pfizer-BioNTech (mRNA) COVID-19 vaccine. On examination, brightly erythematous, indurated plaques were present on the trunk, arms, and legs with intact and denuded bullae on the bilateral palms (**Figure 1**). There was no involvement of the soles. Aside from his remote history of malignancy, his past medical history was notable only for hypertension and arthritis, for which he was taking amlodipine and naproxen, respectively. The latter was initiated 6 months prior to the onset of the rash.

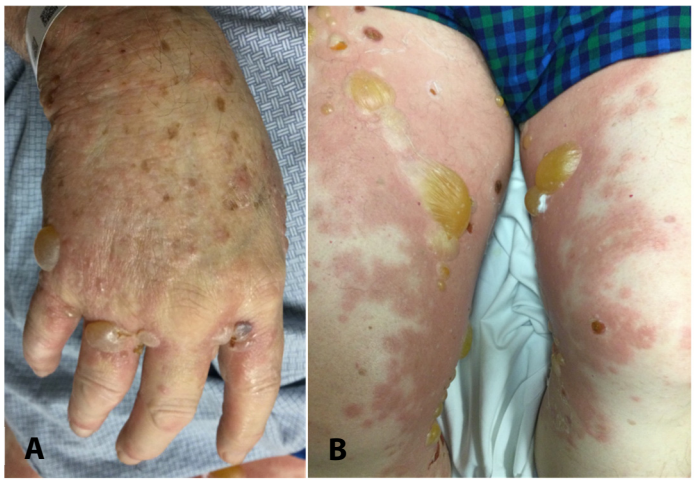

Figure 1. *Bullous pemphigoid eruption with erythematous, indurated plaques with intact and denuded bullae **A)** on the patient's right hand following the second dose of the Pfizer-BioNTech (mRNA) COVID-19 vaccine., and **B)** on the patient's bilateral inner legs following the second dose of the Pfizer-BioNTech (mRNA) COVID-19 vaccine.*

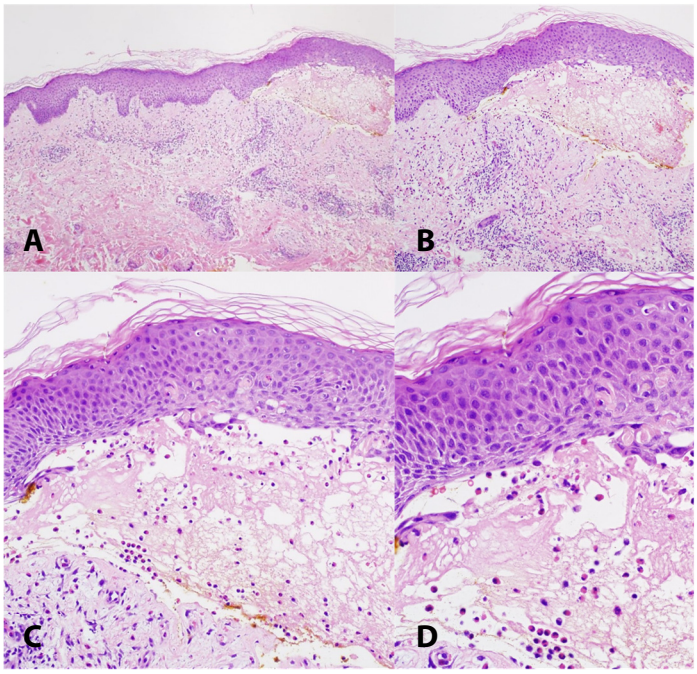

Figure 2. *Biopsy with H&E staining revealed **A)** a subepidermal split with numerous eosinophils along the basement membrane zone, 50×; **B)** a subepidermal split with numerous eosinophils along the basement membrane zone, 100×; **C)** a subepidermal split with numerous eosinophils along the basement membrane zone, 200×; **D)** a subepidermal split with numerous eosinophils along the basement membrane zone, 400×.*

We uncovered no other suspicious medication history. Lesional and perilesional biopsies were obtained for routine histopathology and direct immunofluorescence and revealed a subepidermal split with numerous eosinophils (**Figure 2**), and linear IgG and C3 staining along the basement membrane zone (**Figure 3**). Serum indirect immunofluorescence was notable for a titer of 1:320 on human salt split skin substrate with epidermal localization (1:20 on monkey esophagus substrate) and serum ELISA testing revealed positive IgG BP 180 antibodies (169 units, normal <20). Bullous pemphigoid 230 antibody levels were within normal limits.

Prednisone 40mg and triamcinolone 0.1% cream were initiated with an 80mg dose of intramuscular triamcinolone. After the lesion was confirmed with biopsy, 100mg cyclosporin was initiated twice daily. The eruption subsequently progressed with the development of widespread bullae and rising serum creatinine levels limited further cyclosporin dose escalation. As such, he was admitted to the University of Utah hospital where he received intravenous methylprednisolone (250mg daily × three days) and triamcinolone wet wraps and was discharged on oral methotrexate 15mg weekly, triamcinolone 0.1% ointment, and a prednisone taper starting at 60mg daily at the time of discharge. Halobetasol 0.05% cream and mometasone 0.1% ointment were started on the hands. He experienced a few mild flares of pruritus following discharge but, more than five months later, prednisone has been tapered to 10mg daily with methotrexate 15mg administered weekly and intermittent use of topical triamcinolone 0.1% ointment without recurrence of blistering or rash.

Case Discussion

Bullous pemphigoid is the most common autoimmune subepidermal blistering disease with an estimated incidence between 4.5 and 14 new cases per million each year [4]. It is theorized that cross-reactivity of antibodies produced during the immune response to infectious diseases such as hepatitis B, hepatitis C, *Helicobacter pylori*, *Toxoplasma gondii*, and *Cytomegalovirus* could contribute to the development of disease in

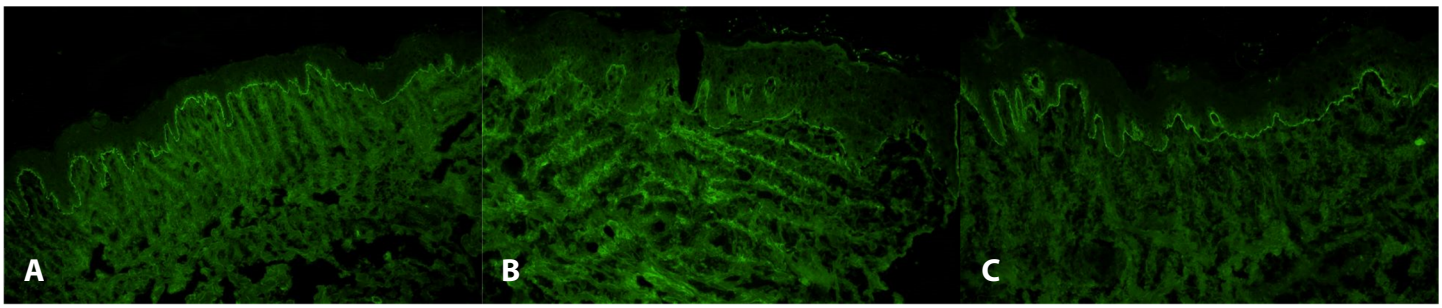

Figure 3. ***A)** Biopsy with direct immunofluorescence showing C3 staining along the basement membrane, 100×. **B)** Biopsy with direct immunofluorescence showing IgG staining, 200×. **C)** Biopsy with direct immunofluorescence showing IgG4 staining along the basement membrane, 200×.*

predisposed individuals [5]. Additionally, there have been anecdotal reports of BP following a variety of vaccinations, as previously mentioned [2]. Dyshidrosiform BP is a unique presentation of this disease with prominent involvement of the palms and soles. This morphologic subtype has been associated with medication exposures. [6,7] The patient described in this report did have involvement of the palms but was without disease on the soles of the feet.

To date, there have been over 1.5 billion doses of COVID-19 vaccines administered throughout the world [8]. As this large-scale campaign utilizing novel vaccines has occurred over a relative short period of time, rare consequences of treatment are still emerging and it is important to recognize uncommon occurrences. The most common cutaneous reactions observed in large-scale studies across mRNA COVID19 vaccines include injection site redness and swelling. However, other cutaneous reactions observed in the phase 3 Moderna mRNA-1273 trial included an exfoliative rash, hand dermatitis, injection site urticaria, generalized urticaria, a maculopapular exanthem, a vesicular rash, and facial swelling [9]. All these reactions were self-limited. Other rare reactions that have been reported outside of clinical trials—in case reports and registries—include flares of chronic, pre-existing dermatologic conditions, perniosis, erythromelalgia, herpes zoster, pityriasis rosea, erythema multiforme, cosmetic filler reactions, vasculitis, and petechia [10]. Among the pre-existing conditions reported, BP and pemphigus flares have been observed in patients with a history of disease following the first dose of mRNA COVID vaccines [11].

A similar case was reported of a patient developing BP after the first dose of the Pfizer-BioNTech COVID vaccine, with more severe features following the second dose [12]. It is worth noting that in both this case and the one presented above that the affected individuals were older than 70 years of age and may have already been predisposed to disease development. In a more recent review of clinical and pathologic correlations between vaccine reaction a total of 12 patients were noted to develop bullous pemphigoid-like reactions (64% following Pfizer vaccination and 36% following Moderna vaccination). These patients ranged in age from 42 to 97 years old [13]. The development of bullous pemphigoid and other new immune-mediated dermatoses is notable as the persistent nature of these reaction are unique among other COVID-19 vaccination reactions which have generally been transient.

In cases, such as the one presented, there has been concern regarding the safety and tolerability of further vaccine doses. Based on data from large registries, it is reassuring to note that most reactions did not lead to subsequent severe adverse events or anaphylaxis with repeat exposure. Most cutaneous reactions can largely be managed—even for patients with "off-target" immune activation—after a second or third dose thus does not automatically preclude further administration [13].

Conclusion

Although it is difficult to establish causality based on anecdotal reports, it is important to recognize that new-onset BP may be a rare consequence of COVID-19 mRNA vaccination, particularly in the elderly. Additional characterization is needed to further explore this association.

Potential conflicts of interest

The authors declare no conflicts of interest.

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