CASE STUDY

Eosinophil-rich linear IgA bullous dermatosis induced by mRNA COVID-19 booster vaccine

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Abstract

We present a case of eosinophil-rich linear IgA bullous disease (LABD) following the administration of a messenger RNA COVID-19 booster vaccine. A 66-year-old man presented to the emergency department with a 3-week history of a pruritic blistering rash characterized by fluid-filled bullae and multiple annular and polycyclic plaques. He was initially diagnosed with bullous pemphigoid based on a biopsy showing a subepidermal blister with numerous eosinophils. However, direct immunofluorescence studies showed linear IgA and IgM deposition along the basement membrane zone with no immunoreactivity for C3 or IgG. Additionally, indirect immunofluorescence was positive for IgA basement membrane zone antibody. The patient was subsequently diagnosed with LABD and initiated on dapsone therapy with resolution of his lesions at 3-month follow-up. This case illustrates the growing number of autoimmune blistering adverse cutaneous reactions from vaccination. Dermatopathologists should be aware that features of autoimmune blistering diseases can overlap and may not be distinguishable based on these histopathological findings alone. Confirmation with direct immunofluorescence and/or serological studies may be necessary for accurate diagnosis.

KEYWORDS
COVID-19, direct immunofluorescence, linear IgA bullous dermatosis, Moderna booster, vaccine

INTRODUCTION

Cutaneous adverse reactions in the setting of COVID-19 vaccination have recently been the subject of great interest, with several studies and registries reporting various clinical presentations and histopathological findings. Among these, reports of autoimmune bullous dermatoses (AIBD) following COVID-19 infections, as well as vaccinations, are some of the most serious reactions. While bullous pemphigoid (BP) has been the most commonly reported vaccine-related AIBD, linear IgA bullous dermatosis (LABD) has also been reported in the setting of both the recombinant Oxford-AstraZeneca and messenger RNA (mRNA) Pfizer-BioNTech COVID-19 vaccines. Here, we present a case of LABD triggered by the mRNA Moderna COVID-19 vaccine booster with histopathological features resembling BP that required confirmation with direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) studies for accurate diagnosis.

CASE REPORT

A 66-year-old male with a past medical history of hyperlipidemia and nasal congestion presented to the emergency department with a 3-week history of a pruritic blistering rash on both his lower extremities. The eruption began on the bilateral upper thighs 5 days after receiving the Moderna booster vaccine and progressed to involve his trunk and extremities. He reported no other systemic symptoms or other new exposures. His medications...
included rosuvastatin, mometasone furoate nasal spray, and oral montelukast sodium, which had been unchanged.

Physical examination revealed multiple annular and polycyclic blanchable plaques with central areas of clearing spread over his lower extremities, upper extremities, and trunk. There were grouped tense fluid-filled bullae on his upper thighs on an erythematous base (Figure 1). Mucosal membranes were uninvolved.

A shave biopsy of the lateral edge of a bulla was performed, and the resulting specimen with an H&E stain showed a subepidermal bulla with numerous eosinophils within the cavity in addition to a perivascular predominantly eosinophilic infiltrate. At the periphery of the blister, both neutrophils and eosinophils were seen within dermal papillae and lining the dermal-epidermal junction (Figure 2). Based on these histopathological findings, an initial diagnosis of BP was made.

A punch biopsy specimen from perilesional skin was also submitted for DIF and showed linear deposition of IgA and IgM along the basement membrane zone (Figure 3) with no immunoreactivity for C3 or IgG. IIF was positive for IgA basement membrane zone antibody. Antibodies for BPAg1 and BPAg2 were not detected.

A final diagnosis of drug-induced LABD was made. He was initially treated with oral prednisone and a high potency topical steroid for rapid disease control. He then transitioned to dapsone, with resolution of his bullous eruption at approximately 3-month follow-up.

**FIGURE 1** (A) Polycyclic erythematous plaques with central clearing were noticed on the left arm. (B) Yellow tense fluid-filled bullae were present on a background of annular and polycyclic erythematous plaques on the left thigh.

**FIGURE 2** (A) Lesional skin specimen with H&E stain revealed broad subepidermal blister with a superficial perivascular infiltrate (×4). (B) Numerous eosinophils are seen within the blister cavity (×20). (C) Both eosinophils and neutrophils are seen lining the dermal-epidermal junction and within dermal papillae (×40).

**FIGURE 3** (A) Direct Immunofluorescence of clinically perilesional skin revealed a strong linear deposition of IgA (×40) and (B) weaker IgM co-reactivity along the dermal-epidermal junction (×40).
3 | DISCUSSION

We present a challenging case of LABD induced by COVID-19 vaccination. Although the patient presented with polycyclic and annular vesiculobullae that were characteristic of LABD, histopathological examination from a biopsy specimen showed features that more closely resembled BP. Accurate diagnosis and treatment required the detection of IgA deposition along the basement membrane zone on DIF and circulating IgA anti-basement membrane zone antibodies in the patient’s sera.

LABD is a relatively uncommon autoimmune disorder in which IgA autoantibodies develop against heterogeneous antigens of the basement membrane zone. LABD can present in a pediatric form (also known as chronic bullous disease of childhood), an idiopathic adult form, and a drug-induced form. Clinical presentation is polymorphic and variable and can range from polycyclic or annular urticarial papules, to plaques, erosions, or papulovesicles that can be focal or generalized. A characteristic physical exam finding is grouped blisters in an annular configuration around the edges of the plaques (“string of pearls” sign).18–20

In drug-induced LABD, lesions typically present 2–21 days after administration of the offending medication, with vancomycin as the most commonly associated exposure.21,22 Skin involvement tends to be more severe and extensive with large erosions compared to the idiopathic form.23,24 The most common sites involved in drug-induced LABD involve the upper and lower limbs.19,25 Interestingly, mucosal and conjunctival lesions are less likely in drug-induced LABD.26,27 Drug-induced LABD more commonly occurs in men and older patients with a mean age of 66.5 years.22,26 These features are consistent with those of our patient, a 65-year-old male who developed polymorphic papulovesicles in an annular arrangement on the upper and lower extremities that started 5 days after his COVID-19 mRNA booster vaccine.

On histopathology, LABD is typically characterized by a subepidermal separation with a neutrophil-rich infiltrate that can line the dermal-epidermal junction or concentrate within dermal papillae. In drug-induced cases, however, eosinophils may predominate and mimic BP.29–33 The histopathological differential diagnosis for classical LABD includes dermatitis herpetiformis (DH), epidermolysis bullosa acquista (EBA), neutrophil-rich BP, mucous membrane pemphigoid (MMP), and bullous systemic lupus erythematosus (SLE). In cases of LABD in which eosinophils predominate, it may be indistinguishable from BP.

DIF studies are, therefore, a critical component of appropriate workup and accurate diagnosis. LABD can be confirmed through DIF studies showing deposits of IgA with or without C3 in a linear fashion along the basement membrane zone. While IgA is often the sole immunoreactant,33 weaker co-reactivity with IgG or IgM have been reported.34–36 DIF findings in DH are characterized by microgranular or fibrillar IgA deposition along the basement membrane zone and in the dermal papillae.37 In BP, there is linear C3 with or without weaker IgG along the basement membrane zone. Linear C3 and IgG along the basement membrane zone can also be seen in EBA, MMP, and bullous SLE. Not uncommonly, IgA deposition can be seen in BP, EBA, MMP, and bullous SLE.38–41 Distinction between pemphigoid and non-pemphigoid group of disorders can be made through serralation patterns, where immunoreactants exhibit an n-serration pattern in pemphigoid and a u-serration pattern in non-pemphigoid groups, and through salt-split studies to determine the localization of immunoreactant deposition to the roof, which favors pemphigoid, or to the floor, which points to EBA or bullous SLE.

Salt-split studies are less useful in LABD as immunoreactants can localize to either the roof or floor depending on the location of the autoantigen in the basement membrane zone.42 This is because of the development of IgA autoantibodies against a heterogenous group of antigenic targets. These include the NC16a domain of BP180, 97- and 120-kDa neoeptopes of BP180,33 laminin-332, laminin-γ1, integrin α6β4,43 and type VII collagen.20,44–46

While histopathological examination with DIF is sufficient to diagnose many autoimmune blistering disorders, IIF or serological studies may be necessary to ultimately confirm the diagnosis, as in our case. As LABD generally responds well to dapsone, accurate diagnosis is of the utmost importance for selecting treatment.

With the recent COVID-19 pandemic, AIBD, such as BP, has been found to be induced not only by COVID-19 infections,29,30 but also by newly developed vaccines to COVID-19.19–21 The exact mechanism of action is unknown for vaccine-induced AIBDs, including LABD. One hypothesis is that vaccinations, in general, can lead to elevations of pre-existing autoimmunity in patients with an immunological predisposition to blistering disorders.47 For instance, there is evidence that some patients have circulating anti-basement membrane antibodies but subclinical disease activity.48,49 Another explanation for the development of AIBD after administration of a vaccine proposes that antigenic components of a vaccine share structural similarity to a host’s antigen at the basement membrane zone.50 In addition to molecular mimicry, it has been proposed that vaccines can activate interleukin and transforming growth factor-beta production, leading to an increase in IgA synthesis.51

While no cases of LABD have been reported with COVID-19 infection, there are two reports of LABD being triggered by the recombinant Oxford-AstraZeneca and mRNA Pfizer-BioNTech COVID-19 vaccines. In both these cases, eosinophils were seen in the infiltrate, although not as dense as seen in our patient.16,17 In these reports, a 61-year-old male developed LABD 3 days after the second dose of the Oxford-AstraZeneca COVID-19 vaccine and was treated with oral prednisolone with improvement.16 While a 71-year-old male developed LABD 3 days after the second dose of the Pfizer-BioNTech COVID-19 vaccine and was treated with topical corticosteroids with improvement.17

The Oxford-AstraZeneca vaccine, available in other parts of the world but not in the United States, is a recombinant vaccine containing an altered adenovirus with the gene of the coronavirus spike protein.52 The Pfizer-BioNTech vaccine and Moderna vaccine utilize mRNA technology to prevent symptomatic COVID-19 disease.53 It has been proposed that cross-reactions between SARS-CoV-2 spike protein antibody and interprotein crosslinks of the epidermis such as transglutaminase (TGase)2, TGase3, S100B, and collagen may play a role in the immune-mediated response with vaccine-induced LABD.17 Additionally, COVID-19 mRNA vaccines can induce spike-antigen-specific IgG and IgA levels in the serum of patients.54 Thus, skin reactions could potentially occur months after vaccine administration.5

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With the recent recommendation of a second booster COVID-19 vaccine, an increased number of immune-mediated cutaneous reactions may potentially be observed.  

Blistering disorders are being increasingly recognized as a cutaneous side effect of COVID-19 vaccination. Dermatopathologists should continue to be aware of the various clinical and histopathological presentations of vaccine-related reactions. In particular, appropriate workup for bullous diseases should be accompanied by DIF studies or other serological studies as histopathological features alone may not be adequately specific.

AUTHOR CONTRIBUTIONS
Williams J. Nahm: writing—original draft. Michelle Juarez: supervision, writing—review and editing. Julie Wu: acquisition of data, writing—review and editing, supervision. Randie H. Kim: conceptualization, data analysis, writing—review and editing, supervision.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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