# Rituximab for linear immunoglobulin A bullous dermatosis

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## Abstract

Linear immunoglobulin A bullous dermatosis (LABD) is an idiopathic or drug-induced vesiculobullous disease typically managed with dapsone or colchicine. We report a case of LABD successfully treated with rituximab in a patient who was intolerant to first-line therapies and recalcitrant to typical immunosuppressants. The patient was initially started on prednisone and mycophenolate mofetil which resulted in minimal response and disease progression. Improvement was seen after two infusions of rituximab 1000 mg at 2 weeks apart with planned maintenance therapy.

## Introduction

Linear immunoglobulin A (IgA) bullous dermatosis (LABD), also known as linear IgA dermatosis, is an idiopathic or drug-induced subepidermal vesiculobullous eruption that occurs in both adults and children. It is characterized by linear deposits of IgA along the basement membrane zone, with the target antigens being the 97-kDa or 120-kDa portions of the BPAG2 carboxy terminus.[1] The most common culprit in drug-induced LABD is vancomycin, less frequently other antibiotics, captopril, and non-steroidal anti-inflammatory drugs (NSAIDs).[2] Its incidence ranges from less than 0.5 to 2.3 cases per million people per year.[3]

The age of onset is usually over 60 for adults and presentation can mimic bullous pemphigoid or dermatitis herpetiformis. Classic lesions are widespread, and annular arrangements of tense blisters are often described as a crown of jewels; however, the presentation can also include urticarial plaques, papules, and vesicles. The trunk, extensor surfaces, buttocks, and face are usually affected.[4] Mucosal involvement can also occur with ocular sequelae, esophageal strictures, or airway obstruction in severe cases.[5,6] Standard therapy begins with topical corticosteroids and dapsone, sulfapyridine, or colchicine, followed by prednisone 0.5 to 1mg/kg/day and steroid-sparing agents if needed. Some reports describe the efficacy of antibiotics.[4] Many cases resolve quickly with dapsone or discontinuing the offending drug.[7] However, in recalcitrant LABD and for patients who cannot tolerate first-line treatments, other immunosuppressants must be used. We present a patient with LABD who could not take dapsone or colchicine but was successfully treated after the addition of rituximab to prednisone and mycophenolate mofetil.

## Case Report

A 71-year-old woman presented with a pruritic eruption consisting of erythematous papules and bullae with excoriations and post-inflammatory hyperpigmentation of the upper extremity extensors, scalp, abdomen, and genitalia. The lesions were present for several months and seemed to come and go. Mucous membranes were uninvolved at the initial exam. The patient denied history of celiac disease or new medications including NSAIDs. She was up to date on age-appropriate cancer screenings and the review of systems was negative. Past medical history was significant for hypertension, chronic obstructive pulmonary disease, asthma, obesity, deep vein thrombosis, arthritis, a benign thyroid nodule, fibroids, esophageal reflux, prediabetes, carpal tunnel syndrome, an accessory kidney, and several orthopedic surgeries. Current medications included metoprolol succinate, telmisartan, hydrochlorothiazide, hydralazine, omeprazole, ezetimibe, advair, spiriva, and montelukast. Importantly, she endorsed an allergy to trimethoprim-sulfamethoxazole causing anaphylaxis in her twenties. Two punch biopsies were taken from the genitalia for hemotoxylin and eosin (H&E) and direct immunofluorescence (DIF) (Figure 1A), with the primary differential diagnoses being bullous pemphigoid and dermatitis herpetiformis. Further workup was negative for tissue transglutaminase IgA and BP180/BP230 serum antibodies. Biopsy results showed a subepidermal bullous der-

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matosis with polymorphonuclear infiltrate in H&E and DIF revealing a linear band of IgA at the dermal-epidermal junction (Figure 1B). The findings were consistent with a diagnosis of LABD.

The initial treatment regimen was challenging due to the patient's medication reaction history. Dapsone was deferred out of concern for sulfa cross-reactivity and anaphylaxis. The patient also declined colchicine because of prior gastrointestinal-related side effects. She was started on mycophenolate mofetil (MMF) 1 g bid and continued with topical clobetasol 0.05% cream and antihistamines. At the two-month follow-up, the patient's presentation worsened (Figure 2 A-C). MMF dosage was then gradually increased to 2 g bid over the next few months, and she was started on prednisone, alendronate, vitamin D, and calcium supplements with some stabilization of the disease. Long-term steroid therapy was undesirable due to the patient's multiple comorbidities, but she was unable to taper prednisone below 30 mg daily without causing flares. Additionally, she developed dysphagia secondary to new erosions in the oropharynx confirmed by an esophagogastroduodenoscopy. Rituximab was considered an adjuvant therapy.

The patient was given two infusions of rituximab 1000 mg two weeks apart on 01/18/22 and 02/04/22. At the one-month follow-up, she reported fewer blisters and improvement in pruritus (Figure 3). By 4 months, there was a resolution of her symptoms with no new blisters. She will continue with MMF 2 g bid and a gradual taper of prednisone. The patient will be evaluated for a reduction in MMF dose if remission is achieved. A second course of rituximab 500 mg is planned for August 2022 as maintenance.

## Discussion and Conclusions

To the best of our knowledge, only 4 cases of LABD and one report of an overlap linear IgG/IgA bullous dermatosis case have been successfully treated with rituximab to date.[1,8-10] It is a chimeric, anti-CD20 monoclonal antibody currently approved by the Food and Drug Administration for pemphigus vulgaris among other conditions.[1] Rituximab depletes CD20+ B cells in the periphery without affecting stem cells or existing plasma cells.[11] Data regarding its effectiveness for IgA-mediated disease is mixed. One study showed that four out of five IgA-dominant pem-

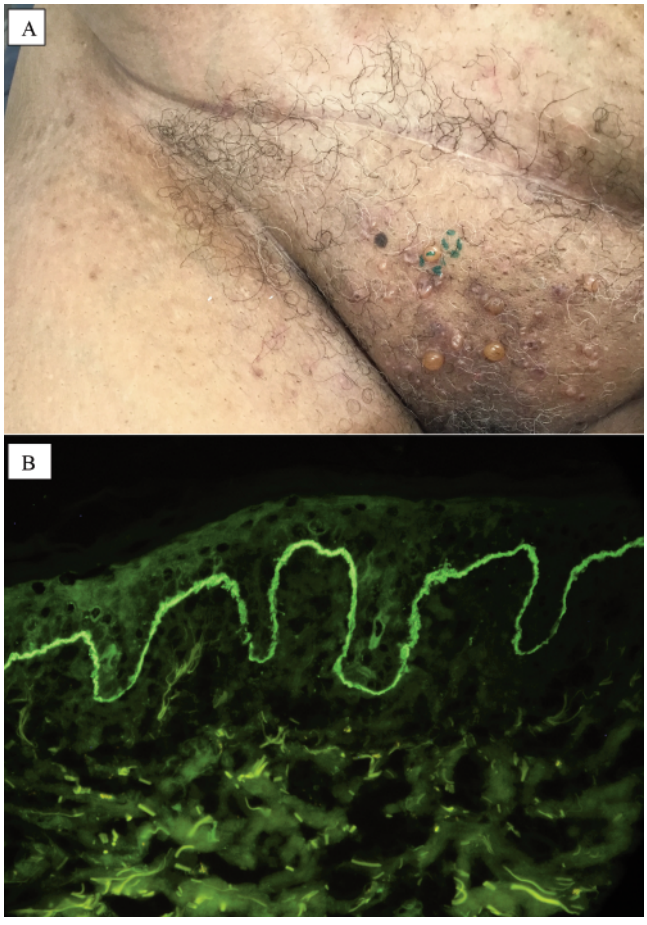


**Figure 1.** A) Punch biopsy sites for hemotoxylin and eosin and direct immunofluorescence; B) Direct immunofluorescence with a linear band of IgA at the dermal-epidermal junction.

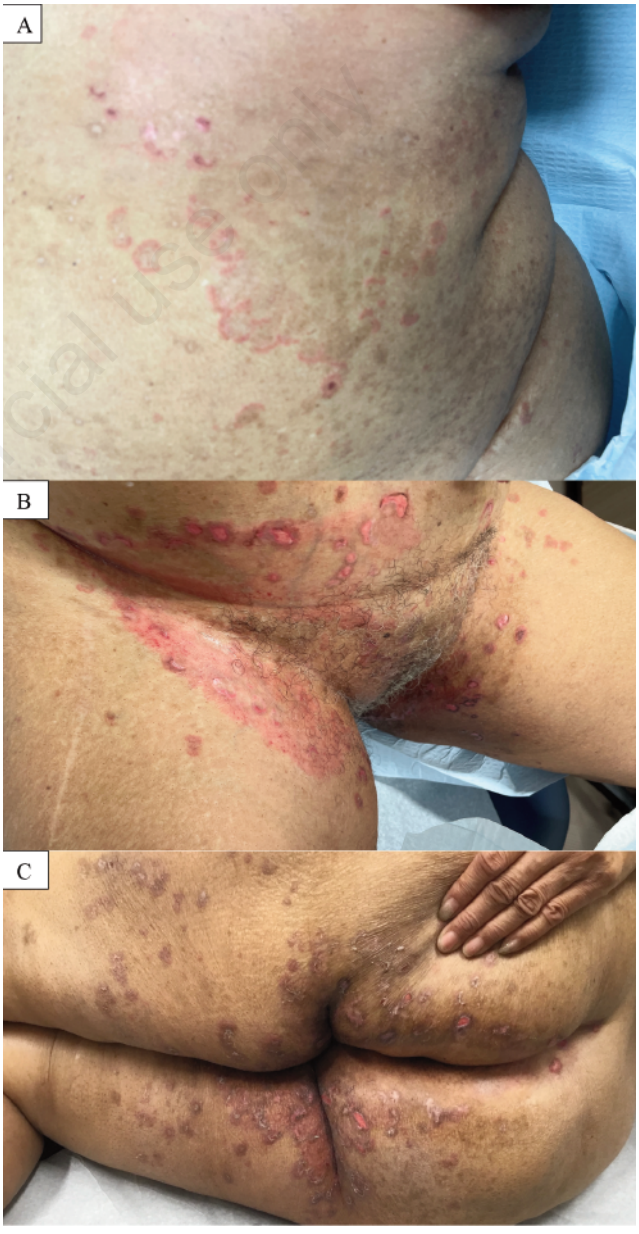


**Figure 2.** A-C) Worsening blisters, erosions, and erythematous plaques on the lower abdomen, genitalia, and thighs while on prednisone and mycophenolate mofetil.

phigoid diseases were unresponsive to rituximab.[12] Another report of mucous membrane pemphigoid treated with rituximab found persistent IgA deposits in the skin and serum IgA-secreting plasmablasts despite the elimination of IgG deposits and CD20+ B cells. However, there are also cases of recalcitrant dermatitis herpetiformis, an IgA-mediated disease, successfully managed with rituximab and a negative serum tissue transglutaminase one year after treatment.[13,14] The reason for this discrepancy between disease processes is unclear and additional studies are warranted.

The case presented provides further evidence that rituximab may be considered an adjuvant therapy for LABD. The patient initially required a high dose of oral prednisone and was started on steroid-sparing MMF. She continued with an increased dosage of 2 g bid for several months providing ample time to evaluate her clinical response to MMF before initiating rituximab. The development of mucosal involvement was worrisome for the disease progression and prompted the need for more aggressive therapy. The patient had resolution of mucosal erosions and no new lesions 4 months following the rituximab course, allowing for a reduction in steroid dose and potential taper of MMF.

The most effective combination of immunosuppressants with rituximab is unclear. Other LABD cases referenced above were on a multidrug regimen with either corticosteroids, dapsone, MMF, cyclosporine, doxycycline, intravenous immunoglobulin, or a combination of them.[1,8-10] Dapsone and MMF were the most frequently used. As monotherapy, rituximab was superior to MMF and resulted in a greater reduction in glucocorticoid use for pemphigus vulgaris in one study.[15] However, more patients in the rituximab group had serious adverse reactions which is important when considering a patient's individual comorbidities. 2 of the LABD cases described had relapses occurring up to a year after rituximab therapy and required a second course of infusions for complete remission.[8] Therefore, management of LABD can require multiple courses of rituximab and concurrent immunosuppressive drugs prior to clearance. Controlled clinical trials are still needed to clarify the role of rituximab in LABD management. There is limited data on monitoring serum levels of IgA autoantibodies against the basement membrane zone as a measure of disease activity and response to therapies.[4] Further studies in this area may help guide treatment plans.

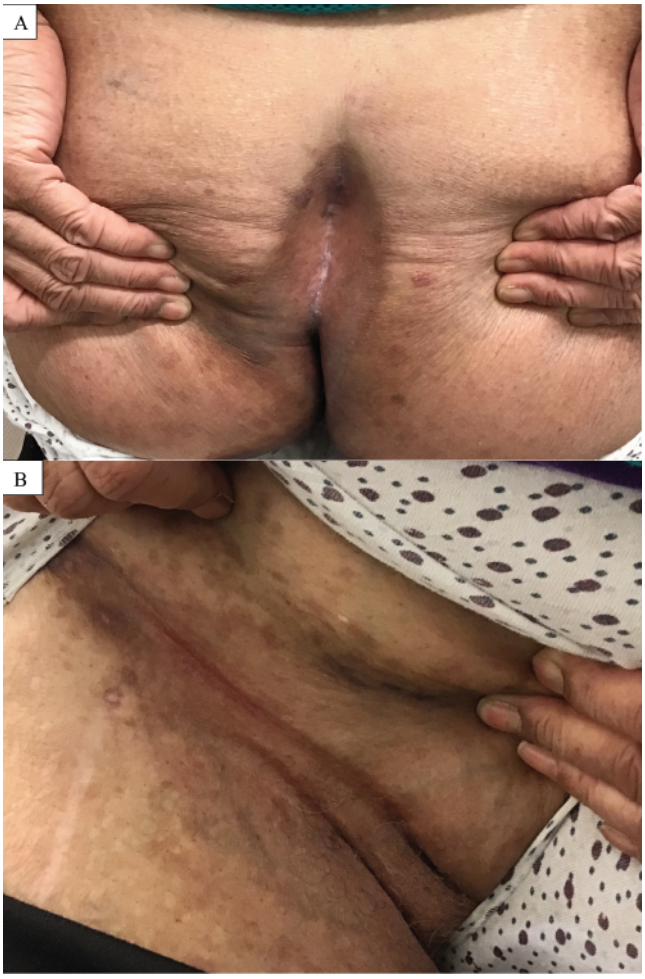


**Figure 3.** A,B) 6 weeks following two infusions of rituximab 1000 mg.

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