

Linear IgA bullous dermatosis treated with rituximab



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Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering disease with an incidence of 0.5 cases per million inhabitants per year.¹ Pathogenic IgA autoantibodies mostly bind to a 97-kDa or 120-kDa proteolytic fragment of BP-180 extracellular domain.² Most cases of LABD involve children and usually heal with dapsone within a few months. Drug-induced LABD also have a favorable course in most cases after stopping the culprit drug.

However, some idiopathic LABD occurring in adult patients may be recalcitrant to dapsone and require systemic corticosteroids or immunosuppressive drugs. To the best of our knowledge, only 1 case of severe LABD and 1 case of dermatitis herpetiformis successfully treated with rituximab have been published to date.^{3,4} Despite the fact that dermatitis herpetiformis is a different disease from LABD, both diseases are mediated by IgA deposits. We report 2 patients with severe and recalcitrant LABD successfully treated with rituximab.

CASE REPORT

Case 1

A 35-year-old man with a history of sclerosing cholangitis and Crohn's disease was referred in May 2009 for a urticarial and vesiculobullous eruption of the neck, trunk, and upper limbs (Fig 1). Standard histology showed a subepidermal blister with a dermal infiltration of neutrophils and few eosinophils. Direct immunofluorescence on the patient's salt-split skin showed linear IgA deposits on the dermal side of the detachment. Indirect immunofluorescence examination of the patient's serum on salt-split normal human skin and immunoblotting on

Abbreviations used:

LABD: Linear IgA bullous dermatosis
MMF: mycophenolate mofetil

dermal and epidermal extracts were negative. No anti-BP-230 or anti-BP-180 antibodies were detected by enzyme-linked immunosorbent assays.

The patient was initially treated with dapsone and topical corticosteroids. Because he did not achieve disease control and refused to be treated with oral corticosteroids, cyclosporine (3.75 mg/kg/d) was started in February 2014 but did not allow achievement of disease control. Two infusions of 1 g of rituximab 2 weeks apart were administered in July 2014. Because the LABD was not completely controlled, a second infusion of 1 g was administered 6 months after the initial infusion. Because of renal toxicity, cyclosporine was switched to mycophenolate mofetil (MMF), 3 g/d, in February 2015. The patient achieved complete remission in September 2015, corresponding to 9 months after the second infusion of rituximab. The patient had a relapse in March 2016, and 2 additional infusions of 1 g of rituximab were administered in April 2016 and March 2017. The patient achieved complete remission again (Fig 2) allowing to progressively decrease the dose of MMF from 3 g/d to 500 mg/d, without relapse to date.

Case 2

A 30-year-old man was referred in August 2016 for severe and recalcitrant LABD diagnosed 20 years

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Fig 1. Urticarial eruption of the trunk.

previously. He presented with oral mucosal erosions and cutaneous blisters. Histology showed a subepidermal blister with a dermal infiltration of neutrophils. Direct immunofluorescence on the patient's salt-split skin showed linear IgA deposits on the epidermal side. Indirect immunofluorescence on salt-split skin showed IgA antibodies on the epidermal side. Anti-BP-230, anti-BP-180 and anti-collagen VII antibodies were not detected in the patient's serum. The patient had remained in complete remission after dapsone was stopped from November 2000 to November 2002, then he experienced relapse.

Despite a gradual increase in dapsone, the patient did not improve. Low doses of oral prednisone, 0.1 mg/kg/d, were then given in September 2009. MMF was started in June 2014 at a dose of 1 g/d because of thrombocytopenia. The disease was still active with dapsone, 200 mg/d, oral prednisone, doxycycline, 200 mg/d, and MMF, 1 g/d. Two infusions of 1 g of rituximab were administered 2 weeks apart in December 2016. Because the patient did not achieve complete remission, 2 new infusions of 1 g of rituximab were administered 2 weeks apart in August 2017. Twelve months after the last infusion of rituximab, the patient achieved long-lasting remission. Doxycycline was stopped, and the doses of dapsone and MMF were decreased to 150 mg/d and 750 mg/d, respectively.

DISCUSSION

These case reports suggest the efficacy of rituximab in these 2 severe and recalcitrant cases of LABD. In addition to dapsone, rituximab was associated with MMF in both cases, which might question the efficacy of rituximab. It is likely that rituximab was effective in these patients, as both of them had an LABD that was evolving for many years without disease control despite the prolonged use of corticosteroids, dapsone, and various conventional immunosuppressants. However, their condition greatly



Fig 2. Complete remission after 4 infusions of rituximab.

improved after a first infusion of rituximab and then resolved after repeated infusions of rituximab, which allowed to decrease or stop immunomodulants/immunosuppressants in both cases. Some recalcitrant cases of LABD, in particular sublamina densa-type LABD as in our first observation, have been described and may be difficult to differentiate from IgA epidermolysis bullous acquisita.⁵ Interestingly, in our 2 observations, the delay of efficacy of rituximab was much longer than that in pemphigus, as long-lasting remission of LABD was obtained 14 and 20 months after the initial infusion of rituximab, respectively, and repeated infusions of the drug were needed. Indeed, only an improvement of LABD lesions, but not a complete remission, occurred in the first patient after the initial infusion of rituximab. He achieved complete remission 9 months after a second infusion of rituximab administered at month 6. The second patient also needed 2 additional infusions of 1 g of rituximab and finally achieve remission 12 months after the second cycle of rituximab. Such a long delay of action of rituximab was previously reported in a patient with dermatitis herpetiformis whose disease was not controlled by gluten-free diet, dapsone, and conventional immunosuppressive agents. Indeed, complete resolution of pruritus and skin symptoms occurred 13 months after the initial infusion of rituximab.³ The persistence of IgA deposits along the dermoepidermal junction, although IgG deposits disappeared after

rituximab treatment, was recently reported in a patient with IgG- and IgA-mediated mucous membrane pemphigoid. In this patient, a persistent population of IgA-secreting plasmablasts/plasma cells could still be observed after rituximab despite the depletion of CD20⁺ B cells.⁶

Overall, these observations suggest considering the use of rituximab in patients with severe cases of LABD that are recalcitrant to conventional immunosuppressants.

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