

# Immunologic overlap in a case of linear IgG/IgA bullous dermatosis responsive to rituximab



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**Key words:** blistering disorder; bullous pemphigoid; dapsone; immunobullous; immunologic overlap; linear IgA; rituximab.

## INTRODUCTION

Autoimmune subepidermal blistering diseases are caused by immunological loss of tolerance to components of hemidesmosomes, triggering humoral and cellular responses.<sup>1</sup> C3 and IgG deposition along the basement membrane zone is characteristic of bullous pemphigoid (BP).<sup>1,2</sup> Alternately, IgA deposition at the basement membrane zone is consistent with linear IgA bullous dermatosis (LABD).<sup>1,3</sup> An immunological overlap spanning the clinical and immunologic spectrum between BP and LABD has been reported and referred to as linear IgA/IgG bullous dermatosis (LAGBD).<sup>3,4</sup> LAGBD has a unique clinical presentation, immunologic properties, and distinct therapeutic options<sup>1,5-7</sup> including rituximab.

## CASE REPORT

A 43-year-old African American man presented with a 7-month history of a worsening erythematous and pruritic rash, which had progressed to blisters and ocular pain 4 weeks prior the presentation. Topical triamcinolone and 2 weeks of 60 mg prednisone had failed to improve the rash. The patient denied any medication changes, history of malignancy, autoimmune disease, or inflammatory bowel disease. Past medical history was significant for end-stage renal disease secondary to hypertension (on hemodialysis) and obstructive sleep apnea. Medications included clonazepam, promethazine, metoprolol, and gabapentin. Physical examination showed numerous erosions with collarettes of scale

### Abbreviations used:

BP: bullous pemphigoid  
 LABD: linear IgA bullous dermatosis  
 LAGBD: linear IgA/IgG bullous dermatosis

and tense bullae in “string of pearls” annular configurations on the bilateral arms, thighs, and trunk (Fig 1, A and B). Mucosal involvement included sloughing of the left eye conjunctiva and tongue.

Histopathology from skin biopsies with hematoxylin-eosin stain and direct immunofluorescence microscopy was consistent with BP, demonstrating a subepidermal split, an eosinophil-rich inflammatory infiltrate (Fig 2), strong linear C3 deposition, equivocal IgG, and absent IgA along the basement membrane zone. However, indirect immunofluorescence with salt split skin revealed both linear IgG and IgA at the roof of the induced blister (epidermal staining pattern). Enzyme-linked immunosorbent assay was positive for circulating anti-BP180 antibodies in the patient’s serum, with IgG and IgA titers of 1:160 and 1:20, respectively. Anti-BP230 antibodies were absent.

After an additional 2 weeks of prednisone without improvement, the patient was started on rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks and mycophenolate mofetil 500 mg twice daily. Prednisone was increased to 80 mg (0.5 mg/kg body weight). Dapsone was avoided due to anemia; methotrexate was avoided due to end-stage renal disease and

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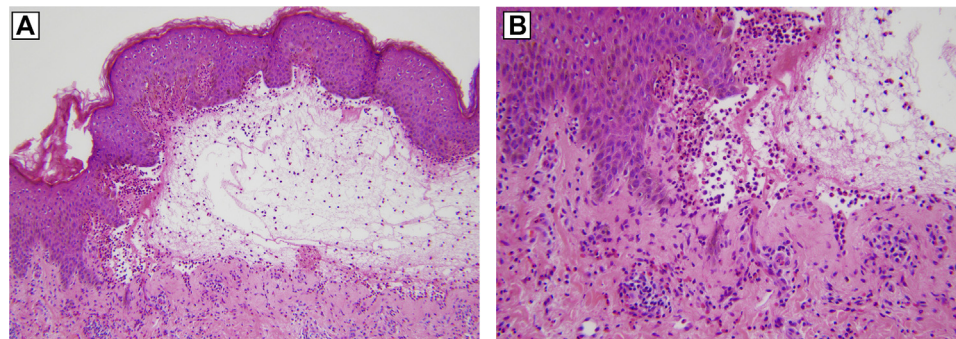
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**Fig 1.** Erosions, collarettes of scale, and tense bullae with examples of annular “string of pearl” configurations. **A**, Left back and arm. **B**, Right thigh. **C**, Resolution of bullae 16 days after initiation of rituximab, mycophenolate mofetil, and prednisone; erosions and collarettes of scale persisted.



**Fig 2.** Biopsy specimens obtained from the right posterior shoulder. **A**, subepidermal blister. No necrosis of keratinocytes noted. **B**, Mixed inflammatory infiltrate including lymphocytes, histiocytes, and abundant eosinophils extending down to the level of the superficial vascular plexus. (Hematoxylin-eosin stain.)

morbid obesity. Gabapentin was discontinued due to the possibility of drug-induced BP.<sup>1,8</sup> Ophthalmology recommended prednisolone acetate ophthalmic suspension, and tobramycin, and dexamethasone ointments. Age-appropriate cancer and autoimmune disease screenings were recommended. Bullae completely cleared after 4 rituximab infusions (Fig 1, C), and prednisone was tapered over a month. The disease relapsed 9 months after initial treatment, but cleared with 2 additional rituximab infusions.

## DISCUSSION

Autoimmune subepidermal blistering diseases are rare. The BP incidence is 6-13 per million people and typically affects adults over 60 years of age. The

LABD incidence is 0.3-2.3 per million and may present both in children and adults.<sup>1</sup> A review of 45 LAGBD cases in Japan showed that 49% of the patients were younger than 60 years of age.<sup>9</sup>

In BP, the most common antigens are BP230 (a 230-kDa intracellular protein) and BP180 (a 180-kDa transmembrane glycoprotein).<sup>1</sup> Antibodies against BP180 are believed to induce the initial blisters, while anti-BP230 antibodies enhance the inflammatory reaction.<sup>1,2</sup> In LABD, the target antigens are the 97-kDa or 120-kDa fractions of BP180 carboxy-terminus. In LAGBD, IgG and IgA antibodies target BP180 most commonly,<sup>4,10-14</sup> and, less often, laminin-332<sup>11,15,16</sup> and BP230.<sup>11,14,17</sup> Drug-induced BP and LABD have been reported<sup>1</sup>; there is, however, no specific association of LAGBD with drugs.<sup>7,10-18</sup>

**Table I.** Comparison of clinical, histological, and immunological findings in BP, LAGBD, and LABD

	<b>Bullous pemphigoid (BP)</b>	<b>Linear IgA/IgG bullous dermatosis (LAGBD)</b>	<b>Linear IgA bullous dermatosis (LABD)</b>
Epidemiology	<ul style="list-style-type: none"> <li>• 6-13 cases per million</li> <li>• Onset over 60 years of age</li> <li>• Mean presentation age, 80 years</li> </ul>	<ul style="list-style-type: none"> <li>• 6.7% of the patients 0-15 years of age</li> <li>• 42.3% 15-60 years of age</li> <li>• 51% &gt;60 years<sup>9</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 0.3-2.3 cases per million</li> <li>• Childhood disease with mean age of 4.5 years; adult disease onset &gt;60 years</li> </ul>
Associated conditions/triggers	<ul style="list-style-type: none"> <li>• Medications</li> <li>• Autoimmune diseases</li> <li>• Neurological diseases</li> <li>• Trauma, burns, UV radiation</li> </ul>	<ul style="list-style-type: none"> <li>• Gastrointestinal diseases<sup>13</sup></li> <li>• Malignancy<sup>11,17</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Medications</li> <li>• Autoimmune diseases</li> <li>• Gastrointestinal diseases</li> <li>• Malignancy</li> <li>• Infections</li> </ul>
Pathogenesis (autoantibodies)	<ul style="list-style-type: none"> <li>• BP180</li> <li>• BP230</li> </ul>	<ul style="list-style-type: none"> <li>• BP180<sup>4,10-14</sup></li> <li>• BP230<sup>11,14,17</sup></li> <li>• Laminin-332<sup>11,15,16</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 97-kDa and 120-kDa fraction of BP180</li> <li>• BP180</li> <li>• BP230</li> <li>• Anti-Type VII collagen</li> </ul>
Clinical presentation	<ul style="list-style-type: none"> <li>• Pruritus</li> <li>• Tense blisters and vesicles</li> <li>• Erosions and crusting</li> <li>• Urticarial and infiltrated papules and plaques</li> <li>• Oral involvement in 10%-30%</li> <li>• Eye, nose, pharynx, esophagus, and anogenital involvement is rare</li> </ul>	<ul style="list-style-type: none"> <li>• Pruritus</li> <li>• Tense blisters and vesicles</li> <li>• Annular vesicular pattern<sup>10,13,16</sup></li> <li>• Erosions and crusting</li> <li>• Erythema</li> <li>• Ocular and oral mucosa involvement<sup>7,11</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Pruritus</li> <li>• Tense blisters and vesicles</li> <li>• Annular or hepetiform vesicular pattern</li> <li>• Erosions and crusting</li> <li>• Oral, ocular, nasal, pharyngeal, and esophageal involvement in up to 80% of patients</li> </ul>
<b>Subepidermal blisters</b>			
Pathology findings	Eosinophilic and mononuclear cell infiltrate	Mixed eosinophilic and neutrophilic infiltrate <sup>10,11,13,15</sup>	Neutrophilic infiltrate
Direct immunofluorescence	IgG and/or C3	IgG + IgA and/or C3	IgA and/or C3
Indirect immunofluorescence	<ul style="list-style-type: none"> <li>• IgG</li> <li>• Mainly epidermal pattern</li> <li>• Combined epidermal/dermal pattern</li> </ul>	<ul style="list-style-type: none"> <li>• IgG and IgA</li> <li>• Mainly epidermal pattern<sup>10,12-14,17,21</sup></li> <li>• Combined epidermal/dermal pattern<sup>16</sup></li> <li>• Rarely dermal pattern<sup>16</sup></li> </ul>	<ul style="list-style-type: none"> <li>• IgA</li> <li>• Mainly epidermal pattern</li> <li>• Combined epidermal/dermal pattern</li> <li>• Rarely dermal pattern<sup>9</sup></li> </ul>

BP, Bullous pemphigoid; LAGBD, linear IgA/IgG bullous dermatosis; LABD, linear IgA bullous dermatosis.

LAGBD has been reported in patients with ulcerative colitis,<sup>13</sup> B-cell lymphoma,<sup>17</sup> and colorectal carcinoma.<sup>11</sup>

Clinical manifestations of BP and LABD are variable and can overlap. LAGBD presentations include erythema,<sup>10,14</sup> pustules,<sup>14</sup> tense bullous lesions<sup>7,10-12,16,17</sup> and small vesicles in annular patterns.<sup>10,13,16</sup> Ocular and oral mucosa<sup>7,11</sup> involvement, as well as a case of LAGBD-related interstitial pneumonia,<sup>19</sup> have been reported. The relationship between LAGBD clinical manifestations and the type of predominant antibody highlights that BP, LAGBD, and LABD are on a spectrum.<sup>20</sup>

Histopathologic evaluation shows subepidermal bullae.<sup>1</sup> Eosinophilic spongiosis and/or dermal infiltrate of eosinophils are seen in BP. LABD shows

predominantly neutrophilic infiltrates.<sup>1</sup> LAGBD has mixed eosinophilic and neutrophilic infiltrates.<sup>10,11,13,15</sup> Direct immunofluorescence typically reveals the presence of linear deposits of IgG, IgA, and C3. LAGBD has been reported to have IgA and IgG binding mostly to the epidermal surface (as seen in this case),<sup>10,12-14,17,21</sup> and rarely combined epidermal-dermal<sup>11,15</sup> or dermal<sup>16</sup> sides.

Treatment starts with a review of medications to identify and discontinue drugs potentially inducing the disease.<sup>1,8</sup> Age-appropriate screening for malignancy may be appropriate.<sup>11</sup> Systemic and topical corticosteroids are first-line treatment<sup>1,2</sup>; however, significant side effects are common. Dapsone treatment is an effective option in LAGBD, limiting systemic immunosuppression.<sup>2,7,13,16,17</sup> Dapsone



inhibits neutrophil adhesion and release of tissue-damaging oxidants and proteases.<sup>6</sup> Side effects include hemolytic anemia, methemoglobinemia, neutropenia, neuropathy, and hepatitis. It is contraindicated for patients with anemia (as in our case), liver disease, or low glucose-6-phosphate dehydrogenase enzyme levels.<sup>6</sup>

Steroid-sparing adjunctive therapies include azathioprine, mycophenolate mofetil, intravenous immunoglobulin,<sup>1</sup> and targeted therapies such as rituximab, an anti-CD20 monoclonal antibody. Rituximab is Food and Drug Administration-approved for the treatment of pemphigus vulgaris. Case reports describe rituximab use for both BP and LABD with higher efficacy observed in IgG-dominant disease.<sup>19</sup> In BP, rituximab has a reported complete response rate of 85%, a recurrence rate of 29%, and an adverse effects rate of 24%.<sup>22</sup> Side effects include infections, anemia, syndrome of inappropriate antidiuretic hormone secretion, drug fever, acute pruritus, peripheral arterial occlusive disease, and tachycardia.<sup>22</sup> Rituximab is an important treatment option for patients with multiple medical comorbidities and severe disease as presented in this case report.

The case presented here highlights the importance of distinguishing between BP, LABD, and LAGBD (Table I). The young age of the patient, mucosal involvement, and bullae in an annular configuration were not typical for classic BP. Only by further evaluation with indirect immunofluorescence and enzyme-linked immunosorbent assay were IgA antibodies identified. The LAGBD diagnosis allows treatment with dapsone (not readily used for BP) or rituximab in severe cases. Due to distinct clinical features, immunologic findings, and treatment modalities, it is important for LAGBD to be recognized as a subtype of subepidermal blistering disease.

#### Conflicts of interest

Henry K. Wong discloses contracted research for Solegenix, Abbot Laboratories, and Galderma. Dmitry Nedosekin, Kelsey Derrick Wilson, Katelynn Campbell, and Sara Shalin have no conflicts of interest to disclose.

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