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Pathogenicity of IgE in Autoimmunity: Successful Treatment of Bullous Pemphigoid with Omalizumab

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To the Editor

IgE class autoantibodies have been identified in a growing number of autoimmune diseases; however, their pathogenic relevance remains unknown. One such disease, bullous pemphigoid (BP), is characterized by subepidermal blistering caused by autoantibodies against the hemidesmosomal protein BP180. The initial phase of lesion development presents as urticarial plaques consisting of dermal edema and eosinophilic infiltration. As lesions progress, tense, fluid-filled vesicles develop which correspond histologically to skin separation at the basement membrane zone.

Historically, clinical and experimental studies investigating the pathogenesis of BP focused on IgG class autoantibodies; however, IgE class autoantibodies are detectable in 90% of BP patients¹. Additionally, laboratory studies provide strong evidence that IgE class autoantibodies are pathogenic in BP^{1–4}. Based on this evidence and the early urticarial phase of the disease, we initiated treatment of a steroid-unresponsive BP patient with omalizumab, a humanized monoclonal antibody that inhibits IgE binding to its high affinity receptor (FcεR1)⁵. In the case we report, clinical improvement was observed within 16 weeks of treatment. This patient represents the first demonstration of the *in vivo* pathogenicity of IgE class autoantibodies in an autoimmune patient.

When referred to the University of Iowa, this 70-year-old female had a one year history of BP and was under poor control on prednisone 40 mg/day, azathioprine 150 mg/day (initially

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prescribed for myositis several years prior) and minocycline 200 mg/day. The patient had a compression fracture from previous steroid use for myositis and wanted to avoid further steroids. Prednisone was discontinued and she was enrolled in an open-label, randomized trial of omalizumab for bullous pemphigoid (IND 100569). This study was approved by the University of Iowa Institutional Review Board (IRB # 200704726) and was conducted in accordance with the Helsinki principles.

On enrollment the patient's serum level of anti-BP180 IgG was 129 U and anti-BP180 IgE was 44 U. Her total IgE level was 222 IU (normal < 100 IU). The omalizumab dose was calculated according the asthma dosing nomogram and she received 300 mg subcutaneously every two weeks for the 16-week duration of treatment in the study.

One week after her first dose, the patient reported a decrease in itching and the intact blister count was decreased by 44% (89 to 50). By week 16, her body surface involvement with urticarial plaques had declined from 50% to 5%, and the tense blisters characteristic of BP were resolved, although some small 4–6 mm erosions remained (see Figure 1). Eosinophils had dropped from 3427/mm³ to 887/mm³ (normal 0–475/mm³). Measurement of total IgE during treatment is not accurate since the clearance rate of omalizumab:IgE complexes is slower than that of free IgE and these complexes are not biologically active^{6,7}. As expected, no change was seen in IgG antibodies against BP180 (124 U pretreatment, post-treatment 104 U). Four months after discontinuing omalizumab the patient noted a return of pruritus and new blisters on the back and calves. Omalizumab was reinstituted off of the trial and the pruritus subsided and the blisters resolved within two weeks.

The small amount of residual disease present at 16 weeks may be due to several factors. First, the dose and treatment schedule utilized in this study were developed for asthma and may not be optimal for BP. It remains to be determined whether a different treatment regimen would yield a further drop in eosinophils and additional clinical improvement. Second, omalizumab prevents IgE from binding to mast cells and basophils but should not inhibit direct effects of IgE produced by binding to BP180 on the surface of keratinocytes. Finally, if IgG and IgE both play a role in BP lesion development, the remaining IgG may be responsible for the residual disease.

In summary, this case extends the growing evidence indicating IgE class autoantibodies are relevant in autoimmunity. This case is the first to demonstrate the pathogenicity of IgE autoantibodies *in vivo*. The remarkable clinical improvement of this patient despite the relatively high levels of BP180-specific IgG throughout her treatment supports a prominent role for IgE in this autoimmune disease.

We propose that omalizumab may provide a therapeutic option for patients when a broader immunosuppressive therapy is contraindicated. Further studies are needed to determine if omalizumab can be utilized as a monotherapy or as an adjunctive agent to minimize exposure to broad-based immunosuppression in these patients. Based on this study, a larger trial comparing omalizumab to standard prednisone is currently underway.

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Abbreviations

BP bullous pemphigoid

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Figure 1. Bullous pemphigoid patient before and after omalizumab therapy

A, Abdominal involvement of steroid refractory BP patient prior to omalizumab therapy. B, Sixteen weeks after beginning omalizumab treatment the tense blisters and inflammatory plaques had resolved, leaving post-inflammatory hyperpigmentation and a small number of 4–6 mm erosions.