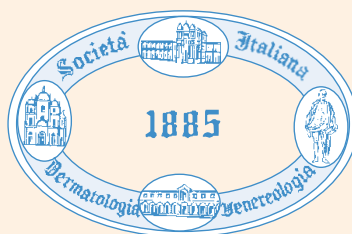


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E D I Z I O N I M I N E R V A M E D I C A

REVIEW

Exploring mechanisms of IgE-mediated autoimmunity through the lens of bullous pemphigoid

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ABSTRACT

Bullous pemphigoid (BP) is the most common autoimmune blistering disease characterized by pathogenic autoantibodies targeting collagen XVII (col XVII), a hemidesmosomal adhesion molecule. Early studies utilizing IgG were critical for establishing col XVII-specific antibodies as primary mediators of blister formation; however, these studies lacked key features of the disease, including urticarial erythema and eosinophilic infiltration, which are often associated with IgE. Although it was recognized that BP patients often had elevated circulating IgE, investigations into the pathogenicity of these antibodies was delayed until discovery of col XVII-specific IgE in BP sera. Since then, a variety of *in-vivo* and *in-vitro* studies have provided clear evidence that IgE autoantibodies are a key component of BP. Furthermore, studies utilizing IgE receptor blockade in BP patients were the first to confirm a pathogenic role of IgE autoantibodies in human autoimmunity. In this review we will utilize BP as a prototypical autoimmune disease to better understand how IgE autoantibodies participate in human autoimmunity.

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There is increasing evidence in support of a role for IgE in immune regulation and the development of autoimmunity. IgE autoantibodies have been reported in a variety of diseases including lupus,¹⁻⁴ Graves' disease,⁵ rheumatoid arthritis,⁶ Hashimoto's thyroiditis,⁷ Crohn's disease,⁸ and multiple sclerosis.⁹ In some cases, IgE autoantibodies correlate with disease activity or the onset of specific complications,^{1, 2, 4} but for the most part, their role in disease pathogenesis is not understood. This knowledge gap has likely persisted due to the difficulty in purification of IgE antibodies for characterization and because the recognized connection between IgE and activation of basophils and mast cells has eclipsed its effects on other immune cells. For example, it was recently shown that interaction of IgE specific for dsDNA with

plasmacytoid dendritic cells modulates disease activity in lupus, although these antibodies were discovered several decades ago.² Furthermore, IgE receptor expression by non-immune cells suggests that all of the downstream effects of IgE are not mediated by immune cells.¹⁰⁻¹²

Bullous pemphigoid (BP) is an autoimmune blistering disease mediated by IgG- and IgE-class autoantibodies specific for collagen XVII (col XVII), also known as BP180. Early studies investigating the pathomechanisms of BP focused on the IgG response; however, there is now overwhelming evidence that IgE-class autoantibodies play an important role in the disease. Over the past several decades, studies utilizing patient samples and murine models of BP¹³⁻¹⁶ have identified key components of disease linked to IgE,

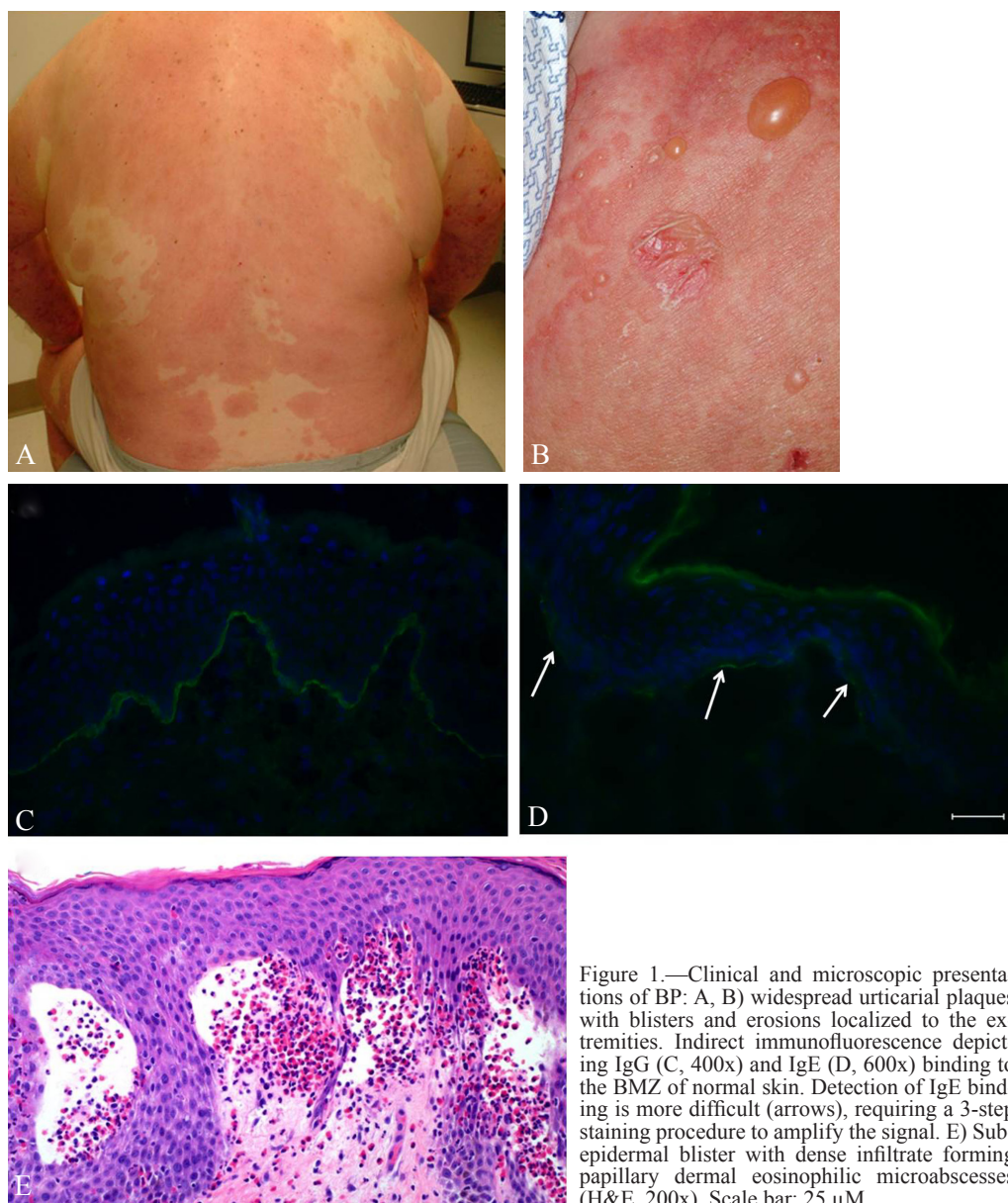


Figure 1.—Clinical and microscopic presentations of BP: A, B) widespread urticarial plaques with blisters and erosions localized to the extremities. Indirect immunofluorescence depicting IgG (C, 400x) and IgE (D, 600x) binding to the BMZ of normal skin. Detection of IgE binding is more difficult (arrows), requiring a 3-step staining procedure to amplify the signal. E) Sub-epidermal blister with dense infiltrate forming papillary dermal eosinophilic microabscesses (H&E, 200x). Scale bar: 25 μ m.

and have laid the groundwork for clinical studies utilizing therapeutic IgE receptor blockade.^{15, 17-20} In this review, we will discuss factors contributing to IgE autoantibody production in BP, experiments identifying disease components attributed to IgE and therapeutic use of IgE receptor blockade. Finally, we will consider how these findings have shaped our concept of BP pathogenesis.

Bullous pemphigoid

BP predominantly affects older individuals with a mean age of onset of 75 years old and has no bias in relation to gender, ethnicity or race.^{21, 22} Incidence increases from 13.4-66 new cases per million per year in the general population to 150-330 new cases per million per year in a population aged over 80 years.²¹⁻²³

Clinically (Figure 1), BP is often preceded by pruritic eczematous lesions followed by formation of tense fluid-filled blisters occurring on areas of erythema and normal skin, frequently associated with urticarial plaques.²³⁻²⁵ Blisters correspond histologically to a separation of the skin through the basement membrane zone (BMZ) at the lamina lucida. In addition, there is a superficial and deep perivascular infiltrate of eosinophils, lymphocytes, mast cells and neutrophils.²³⁻²⁵

An immunologic origin of BP was first indicated by the demonstration of IgG and complement (C3) bound to the BMZ of biopsied skin and anti-BMZ autoantibodies in the serum of patients with active disease.²⁶ The cellular targets of BP autoantibodies are two hemidesmosomal proteins, col XVII (BP180), a transmembrane protein known to interact with the dermal extracellular matrix, and BP230, an intracellular component of the hemidesmosomal plaque.^{27, 28} Autoantibody binding to target antigen leads to the activation of complement, recruitment of inflammatory cells and release of proteases. Mast cell degranulation is the earliest identifiable event in lesion formation, followed by infiltration of lymphocytes, eosinophils and neutrophils.^{29, 30}

Immunologic criteria for BP consist of linear deposition of IgG and/or complement (C3) at the BMZ of biopsied skin and confirmation of circulating autoantibodies via indirect IF and/or by ELISA.^{23, 25, 31} If left untreated, the clinical signs and symptoms of BP can last for months or years and lead to significant morbidity or death. In the absence of more targeted therapies, systemic immune suppression remains the treatment of choice; anti-inflammatory agents (oral and/or topical corticosteroids, tetracyclines, dapsone) and immune suppressants (azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide).^{22, 32} The therapeutic regimen is dependent on disease severity and is tailored to individual tolerance to medications or other contraindications. In some cases, strong topical corticosteroid treatment may effectively control disease and avoid adverse effects of systemic steroids.³²⁻³⁴ If the disease is difficult to control, antibody producing B-cells are targeted with anti-CD20 antibody (rituximab) treatment;³⁵⁻³⁸ however, pan B-cell depletion is risky in elderly individuals and does not appear to be as effective as it is in pemphigus.³⁷

IgE autoantibody production and IgE receptor expression

Typically, IgE autoantibodies are associated with protection against parasitic worms or as a mediator of type I hypersensitivity reactions including severe allergy, asthma, chronic urticaria and atopic dermatitis.^{39, 40} In these instances, antibody class-switching to, and plasma cell production of IgE is driven by Th2 cytokines.⁴⁰ It is not known why BP patients develop IgE autoantibodies. In studies of asthma and rhinitis, repeated antigen exposure in lung or nasal epithelium drives class switch combination to IgE.⁴⁰ It is possible that an initial subclinical IgG response to col XVII triggers tissue destruction and inflammation, which would result in increased availability of antigen and Th2 cytokine production — favorable conditions for class-switching to IgE. Indeed, examination of cytokine profiles in the skin and blister fluid from BP patients reveals a prevalence of Th2-type cytokines and chemokines, including IL-4, IL-5, IL-6, IL-8, eotaxin and MCP-4.⁴¹⁻⁴⁵ Because the concentrations of these factors are highest in the blister fluid, it stands to reason that they are produced in the skin.^{41, 44, 45} On the other hand, not every BP patient is characterized by a Th2 cytokine profile,^{41, 43-45} nor is col XVII-specific IgE detected in all sera.⁴⁶⁻⁴⁹ This observation could result from evaluation of patients at different stages of disease or inherent differences in immune profiles of individual patients. To address this, an extensive characterization of autoantibody responses in relation to disease activity and cytokine profiles is needed.

IgE functions via interaction with cell surface receptors, FcεRI and FcεRII/CD23, expression of which is regulated by cellular activation status.⁵⁰⁻⁵² Expression of FcεRI is highest on mast cells and basophils; however, it is additionally expressed by neutrophils, eosinophils, monocytes, macrophages, dendritic cells, Langerhans cells and platelets.⁵¹ Activation of the tetrameric FcεRI (αβγ₂) isoform triggers activation of effector cells and degranulation, while the trimeric (αγ₂) isoform is thought to be involved in antigen presentation.⁵² *In vivo*, the majority of IgE is not freely circulating, but is bound to the high affinity (10¹⁰ M⁻¹) receptor FcεRI.⁵³ Thus, circulating levels are generally not reflective of IgE production or activity.⁵⁴ Antigen binding to IgE on the surface of effector cells triggers specific release of proteases, toxic proteins, lipid mediators and Th2 cytokines including IL-4, IL-5, IL-13, and eotaxin.^{52, 55} These me-

diators are destructive to surrounding tissue and elicit influx and activation of immune cells.^{39, 55} In particular, eotaxin, IL-4 and IL-5 are responsible for eosinophil recruitment and activation.⁵⁶

The low affinity (10^7 M⁻¹) IgE receptor, FcεRII/CD23, is a single chain glycoprotein expressed by a variety of immune cells including B-cells, monocytes, macrophages, Langerhans cells and mast cells, basophils and eosinophils.^{52, 57, 58} On B-cells, CD23 is a potent regulator of IgE production, capable of stimulating or suppressing IgE production.⁵⁹ In BP patients, expression of CD23 on circulating B-cells is significantly increased, compared to controls or patients with other bullous diseases, and correlated with circulating IgE levels and disease severity.⁶⁰ Thus, elevated CD23 is a potential mechanism of IgE autoantibody production in BP.

CD23 can also be cleaved from the cell surface resulting in several functionally active soluble (sCD23) isoforms which have cytokine-like actions that support growth and differentiation of B-cells and other bone marrow cells and stimulate monocyte cytokine release.^{59, 61} In BP, both cell-bound and soluble CD23 were detected in lesional skin and blister fluid, respectively,⁶² and were correlated with total IgE levels in these patients.^{60, 62, 63} In this context, sCD23 might contribute to the inflammatory response in BP lesions by stimulating cytokine secretion by infiltrating immune cells.

In addition to FcεRI and FcεRII, IgE also specifically interacts with Galectin-3, which is expressed by a variety of cells and tissues, is thought to play a multifunctional role in cellular homeostasis, and has been associated with disease activity in Behçet's disease, another autoinflammatory condition.⁶⁴

Autoantibody specificity in BP

IgG autoantibodies

The immunodominant IgG epitopes recognized by ~90% of BP patients map to the non-collagenous 16A (NC16A) domain of col XVII, whereas 10-15% of the sera recognize epitopes exclusively outside this domain.^{27, 65-68} Disease activity is correlated with the concentration of circulating col XVII-specific IgG.^{49, 69-71} and pathogenicity of these IgG autoantibodies, primarily IgG1 and IgG4,⁷²⁻⁷⁴ has been explored using both in vivo and in vitro models. These studies show that IgG

binding to col XVII at the BMZ results in activation of the complement cascade and Fc-receptor mediated recruitment of granulocytes.⁷⁵⁻⁸⁰ However, strict application of these findings to human disease is difficult since Fc receptor utilization differs in mouse and man.^{52, 81} Autoantibody binding also directly influences keratinocyte adhesion due to hemidesmosomal internalization and depletion of col XVII protein.⁸²⁻⁸⁵ Additionally, autoantibody treatment of primary keratinocytes or human skin stimulates production of proinflammatory cytokines, IL-6 and IL-8, known to be critical for BP lesion development.^{82, 86-88} Although ~50% of BP patients harbor BP230-specific IgG,⁸⁹⁻⁹¹ the pathologic relevance of these antibodies remains controversial.⁹¹⁻⁹⁴

IgE autoantibodies

Elevated circulating IgE⁹⁵ and deposition of IgE at the BMZ of skin from BP patients⁹⁶ were first reported more than 40 years ago. Despite these early observations, studies aimed at understanding the mechanisms of BP disease focused on the IgG response. This approach was likely due the recognized role of IgG-class autoantibodies in autoimmunity and the overwhelming presence of IgG (mg/mL) compared to IgE (ng/mL) in human serum. Identification of IgE autoantibodies in other autoimmune diseases, and the early urticarial phase of BP, supported a role for IgE in BP. It is now recognized that the majority (≥70%) of untreated BP patients have elevated circulating IgE levels.^{13, 97-101} Similar to the IgG response, the NC16A-domain of col XVII is the primary pathogenic epitope for IgE.⁹⁹ Studies utilizing a variety of methods report that 25-55% of BP sera have IgE antibodies specific for col XVII,^{48, 49, 72, 90, 102} whereas that incidence rises to >70% using an ELISA optimized for the detection of IgE.^{47, 101} Among the patient sera with col XVII-specific IgG, the majority (reports range from ~50-89%) also exhibit specific IgE reactivity.^{13, 47, 72, 99, 101, 103} Similar to col XVII-specific IgG, the IgE autoantibody response can spread to other intracellular regions of the molecule, a phenomenon known as epitope spreading.¹⁰⁴

Within the family of autoimmune blistering diseases, elevated total IgE levels have also been reported in pemphigoid gestationis (PG) and endemic pemphigus foliaceus (PF), and less often in pemphigus vulgaris (PV).^{95, 105-107} In PF and PV, specific IgE reactivity to

desmoglein proteins has been identified, but the pathologic relevance has not been established. In PG, it has been hypothesized that col XVII-specific IgE could play a role in elevated fetal risk since col XVII is also expressed by placental cytotrophoblasts.¹⁰⁶

Similar to the IgG autoantibody response, BP230-specific IgE is also detected in patient sera and, in some cases, these antibodies are more prevalent than those specific for col XVII.^{56, 108, 109} BP230-specific IgE has been associated with local eosinophil accumulation⁹⁰ or disease activity.¹¹⁰ While epitope spreading occurs for BP230-specific IgG,¹¹¹ this same phenomenon has not been described for BP230-specific IgE. Further study is necessary to understand the functional significance of these autoantibodies.

It has been suggested that patients with high levels of col XVII-specific IgE may represent a more severe form of BP because they require longer and more intensive treatment for remission.^{46, 72, 112, 113} Some studies show that the levels of IgE autoantibodies correlate with urticarial erythema, whereas IgG autoantibodies are associated with blister formation.^{48, 114, 115} In others, high circulating concentrations of total IgE are associated with blistering, rather than the presence of urticarial lesions.¹¹⁶ Regardless of these differences, the observation that clinical remission coincided with a disappearance of col XVII specific IgE, but not IgG, confirms that IgE class antibodies feature prominently in the pathogenesis of BP.^{15, 49, 112}

Overall, *in-vivo* deposition of IgE at the BMZ of lesional or perilesional skin is generally reported in a subset (18-65%) of patients who exhibit elevated circulating IgE. Due to the difficulty in detection of ng/mL concentrations, it is not surprising that IgE deposition associates with high circulating concentrations.^{82, 95, 97, 98, 100, 107, 117, 118} It stands to reason that all patients who have col XVII specific IgE in their circulation also have these antibodies in their skin. Nevertheless, attempts have been made to categorize patients based on the detection of *in-vivo* bound IgE. In some cases, IgE deposition was associated with more severe urticarial,¹⁰⁷ while a study of 100 cases did not reveal any clinical phenotype associated with IgE deposition in the skin.¹¹⁵ Interpretation of these studies is further complicated by the very low (18%) incidence of IgE detected at the BMZ, which may reflect sensitivity issues with this assay.¹¹⁵

***In-vivo* studies demonstrating the pathogenicity of IgE autoantibodies**

Paradoxically, the failure of IgG-based models of disease to reproduce features of human BP launched investigations into the role of IgE autoantibodies in BP.^{75, 119-121} Initially, two passive transfer models were used to examine the pathogenicity of IgE autoantibodies *in vivo*. Since the pathogenic NC16A domain of the col XVII protein is not conserved, Fairley¹⁴ utilized IgE purified from BP patient sera, utilized IgE purified from BP patient sera injected into human skin grafted onto nude mice. Injection of BP IgE (6 ng/graft) resulted in deposition of IgE at the BMZ of grafted skin and development of erythematous plaques, engorgement of blood vessels, degranulation of mast cells and dermal infiltration of neutrophils and eosinophils. When a higher dose of IgE was used (47 ng/graft), separation at the BMZ was confirmed histologically. To overcome the limitation of low circulating concentrations of IgE available for purification, Zone¹⁶ utilized a murine IgE hybridoma directed against the shed ectodomain of col XVII (LABD97). Intradermal injection of the hybridoma in SCID mice with engrafted human skin led to high titers of col XVII-specific IgE, erythema, eosinophilic infiltration, mast cell degranulation and histologic blisters. These studies were the first to demonstrate the pathogenicity of IgE autoantibodies in a human disease model.

More recently, Hirose *et al.*¹²² utilized repetitive immunization of mice with recombinant fragments of murine col XVII to produce an active BP disease model. All of the immunized mice developed col XVII-specific IgG and elevated total IgE, lesions were characterized by erythema and crusts, and histologic examination revealed a subepidermal split accompanied by a dense inflammatory infiltrate consisting of granulocytes, including eosinophils. These studies did not identify col XVII-specific IgE in the sera or IgE deposition at the BMZ, although the authors did not rule out technical issues with detection. When taken together, these *in-vivo* studies indicate that IgE autoantibodies are involved in erythema, urticaria and eosinophilic infiltration, and can produce subepidermal blistering in the absence of IgG autoantibodies.

Mechanisms of IgE pathogenesis

The earliest events in BP lesion formation are the degranulation of dermal mast cells and the infiltration and

degranulation of eosinophils.^{29, 123-127} Degranulation is evidenced by ultrastructural changes within both cell types and the presence of intact granules or granule proteins in the skin, blister fluid and circulation of BP patients.^{29, 101, 123, 125-128} Below, we discuss the modulation of mast cells and eosinophils as the primary pathogenic mechanisms of IgE autoantibodies in BP.

MAST CELLS

Mast cells have been implicated in a number of autoantibody-mediated diseases, including rheumatoid arthritis, lupus, multiple sclerosis and thyroiditis.^{129, 130} Mast cell degranulation, typically via FcεRI, releases a number of mediators that are important chemoattractants for eosinophils and neutrophils.^{51, 52} Several lines of evidence suggest that interaction of IgE autoantibodies and mast cells is critical for lesion formation in BP. First, using immunofluorescent staining, IgE and NC16A, but not IgG, co-localize to the surface of lesional mast cells.^{13, 14, 99} Likewise, freshly isolated basophils from BP patients exhibit surface-bound IgE and release histamine after exposure to recombinant NC16A.^{13, 99} Third, degranulated mast cells are observed in the first 24-hours after autoantibody treatment in an IgE-based mouse model of BP.¹⁴ *In vivo*, free antigen is available for interaction with cell surface bound antibodies *via* constitutive shedding of the col XVII ectodomain.¹³¹ Finally, mast cells are also required for neutrophil recruitment and activation and subepidermal separation in IgG-based mouse models of BP.^{127, 132} The caveat of these studies is that while neutrophils are the predominant cell type IgG-based mouse models of BP, eosinophils are more common in human disease.^{29, 123, 124} It is also unlikely that both IgE and IgG participate equally in mast cell activation in BP lesions, since co-engagement of Fcε and Fcγ receptors results in cellular inhibition.^{130, 133, 134} Rather, IgG: Fcγ might provide an additional mechanism of degranulation in the absence of IgE.

EOSINOPHILS

Eosinophils are increasingly recognized as participants in a broad array of human diseases in association with IgE.^{135, 136} In BP, eosinophils are a prominent feature of the lesional inflammatory infiltrate and cir-

culating eosinophilia is often observed.^{101, 117, 123, 137-139} The observation that eosinophil infiltration precedes blister formation indicates that these cells are not just a consequence of inflammation.¹²³ To understand the significance of eosinophilia in BP, several studies have aimed to determine relationships between eosinophil numbers and other measures of disease activity or disease phenotype. Blood eosinophilia has been correlated with disease severity¹⁴⁰ or the number of blisters and erosions,¹¹⁶ whereas others have found an association with the extent of urticaria and erythema.¹⁰⁷ These discrepancies are not wholly unsurprising since tissue eosinophilia is not dependent on circulating eosinophil numbers.¹³⁵ Perhaps a clearer picture would result from comparison to lesional or perilesional eosinophilia?

It is probable that eosinophil accumulation in the skin is dependent on skin-derived chemotactic factors, such as eotaxin, IL-4 and MCP-4.^{44, 137, 141} In support of this, blister fluid eotaxin levels correlated with the number of dermal infiltrating eosinophils.¹³⁷ Although we maintain that IgE mediated degranulation of mast cells is a critical step in BP, many of these same factors are also made by keratinocytes.¹⁴² Furthermore, it is not surprising that circulating levels of these factors does not always reflect the level of eosinophilia, since local production in the skin is necessary for migration.^{128, 143, 144}

In lesional skin, eosinophil degranulation is confirmed in ultrastructural studies and by the presence extracellular granules or proteins in blister fluid and/or circulation.^{29, 101, 124, 128, 145, 146} In BP, eosinophil degranulation is observed at all stages of disease, but is most prominent in early erythematous and urticarial lesions and is not observed in uninvolved skin.¹²³ Understanding the contribution of eosinophil degranulation to blister formation is complicated by the concurrent release of proteases and inflammatory factors from other immune cells. Along this vein, studies using a human cryosection model of BP show that eosinophil localization to the BMZ is dependent on antibody-mediated complement fixation and suggest that unidentified factors derived from infiltrating cells may be required for eosinophil degranulation.¹⁴⁶ On the other hand, peripheral eosinophils from a subset of BP patients do degranulate upon exposure to recombinant NC16A,¹⁰¹ which might be attributed to differences in Fc receptor expression or activation signals that are provided *in vivo*. A number of inflammatory mediators known to be



Figure 2.—Omalizumab monotherapy for BP. IgE receptor blockade for treatment of BP. A steroid-unresponsive patient was treated with omalizumab as a monotherapy using asthma dosing. A) Pre-treatment the upper legs show widespread urticarial plaques, bullae and erosions. B) After 28 days of treatment (two doses of drug) and C) 42 days of treatment (3 doses of drug), there was a significant reduction in erythema and blistering.

elevated in BP skin can provide the stimulus required for eosinophil degranulation, including cytokines, CC chemokines (eotaxin and RANTES) and platelet activating factor.^{147, 148}

The relationship between IgE and eosinophilia in several diseases has prompted evaluation of IgE receptor expression as a mechanism of direct interaction.^{101, 149-152} Indeed, the degree of eosinophilia in BP correlated with circulating total and col XVII-specific IgE.¹⁰¹ Characterization of FcεRI expression by eosinophils from BP patients determined that eosinophils from both the blood and skin express the trimeric αγ² receptor form and lesional eosinophils additionally express the tetrameric αβγ² receptor.¹⁰¹ Furthermore, CD23 was identified on circulating basophils and lesional mast cells and eosinophils.

Anti-IgE therapy for bullous pemphigoid

In the past several decades, our understanding of the pathogenesis of blistering disorders has improved greatly; however, progress in disease therapy has been less remarkable. Omalizumab (OMZ) is a humanized monoclonal antibody that binds the Cε3 region of the Fc fragment of IgE, thus preventing interaction with FcεRI,^{153, 154} and is approved for the treatment of severe allergic asthma in the United States (2003) and Europe (2005) as well as chronic urticaria in both the EU and US. (2014). Omalizumab limits allergic inflammation by decreasing IgE available for receptor interaction, which limits activation of effector cells and decreases expression of FcεRI.¹⁵⁴ Simply, OMZ prevents mast cell degranulation and subsequent recruitment and acti-

vation of eosinophils.^{154, 155} Furthermore, OMZ therapy reduces circulating eosinophil numbers.^{153, 154, 156, 157}

The effect of IgE receptor blockade with OMZ has been examined in a handful of BP patients.^{15, 17-20} All patients were selected based on their presentation with severe recalcitrant disease and elevated IgE and/or eosinophilia. All patients were treated using the asthma dosing regimen, which considers total serum IgE levels and patient body weight.¹⁵⁴ None of the patients have experienced any side effects, although one patient ceased treatment due to complications that were deemed unrelated to omalizumab therapy.¹⁹ The earliest report of successful treatment of a recalcitrant BP patient with OMZ as monotherapy was the first demonstration of the pathogenicity of IgE autoantibodies in human autoimmunity.¹⁵ Since then, OMZ has been used as a monotherapy or as a steroid-sparing agent in BP. Therapeutic benefit was evidenced by decreased use of immunosuppressants, a decline in blister formation, less pruritus and dramatic decreases in eosinophil counts. In one particularly severe case,¹⁸ OMZ therapy was given to a patient who continued to develop new blisters, covering 50-60% of her body surface, while receiving high dose intravenous methylprednisolone and cyclophosphamide. One day after her first treatment, her eosinophil count decreased to within normal limits and blister formation ceased by day 2. Similar results have been obtained in a case of infant BP¹⁷ and a 28-year old patient with severe pruritic BP.²⁰

It is difficult to know if OMZ treatment resulted in complete binding of free IgE since routine laboratory serum IgE assays will measure both free and complexed (inactive) IgE. As assays that measure biologically active IgE become available, it can be determined if standard asthma dosing regimens are adequate for BP patients with very high IgE levels. Indeed, a survey of IgE levels indicates that ~15% of BP patients fall outside the recommended maximum dose.¹³⁴ Investigation of new therapies with higher affinity to IgE will also address this issue.

A universal observation with OMZ treatment is the decline in eosinophil numbers.^{153, 154, 156, 157} It was noted that peripheral eosinophils paralleled disease activity even more closely than col XVII-specific IgG. Although the mechanism of this is not established, studies in allergic inflammation and asthma note that IgE blockade reduced eosinophil migration and Th2 cytokine produc-

tion and increased eosinophil apoptosis.¹⁵⁷ Our demonstration of eosinophil FcεRI expression provides a direct route for IgE antibodies to modulate cell function through positive feedback. Careful in vitro analysis will be necessary to test this hypothesis.

It is not known if BP patients with milder disease or normal serum IgE level would also have a good response to OMZ therapy. Furthermore, the optimal utilization of OMZ as a continuous versus intermittent therapy for BP has yet to be determined. Recently, OMZ therapy has been explored in other conditions related to IgE, such as chronic urticaria, atopic dermatitis.^{155, 158} and an ongoing trial (NIH, NCT01716312) will determine its effectiveness in lupus.

Conclusions

There is a rising incidence of autoimmune diseases worldwide. In many cases, the fundamental cause of the disease is not understood so therapies rely on global immunosuppression, which is associated with significant morbidity. In the past two decades, IgE autoantibodies have been identified in an increasing number of autoimmune diseases. BP is an ideal model to study the role of IgE in human autoimmunity due to the accessibility of the target organ. Studies designed to understand the significance of IgE in BP have confirmed the pathogenicity of IgE in mouse models and in patients treated with OMZ. Going forward, understanding the events leading to IgE autoantibody production in BP and the precise role of these antibodies in disease pathogenesis will provide novel therapeutic targets for a variety of IgE-mediated diseases.

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