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Brief Communication

IgE blockade in autoimmunity: Omalizumab induced remission of bullous pemphigoid

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ABSTRACT

Bullous pemphigoid (BP) is a blistering dermopathy and a prototypic antibody-mediated autoimmune disease. Detection of IgG autoantibodies against hemidesmosomal proteins BP180 and/or BP230 are diagnostic and levels can correlate with disease activity. Therapies include corticosteroids and oral immunosuppressants, while intravenous immunoglobulin and rituximab are reserved for treatment resistant cases. Here we describe a patient with severe BP which was refractory to standard first line therapy, intravenous immunoglobulin and rituximab induced depletion of peripheral B cells. Use of the monoclonal anti-IgE antibody omalizumab resulted in rapid resolution of blistering despite ongoing high levels of anti-skin IgG antibodies. To our knowledge this is the first case of BP responsive to omalizumab after failure of rituximab to be reported. This case adds to emerging data on omalizumab as a novel BP treatment as well as providing new evidence of an independent role for autoreactive IgE-mediated inflammation in the formation of BP skin lesions.

1. Case report

A 72 year old male presented with a one month history of generalised pruritus and bullae. He had multiple comorbidities including diet-controlled type 2 diabetes mellitus and stage 4 chronic kidney disease. A perilesional skin biopsy demonstrated eosinophilic spongiosis, subepidermal vesiculation and direct immunofluorescence (DIF) revealed linear IgG and C3 at the dermo-epidermal junction. Junctional anti-skin antibodies (3+) were detected by indirect immunofluorescence (IIF) and IgG anti-BP180 antibodies were confirmed positive at a value of 10.68 (reference 0–0.99, Dermatology Profile EIA, Euroimmun). The patient had an eosinophilia of 0.78×10^9/L (reference range $< 0.5 \times 10^9$/L) and a total serum IgE of 6241 kU/L (reference range < 111 kU/L). Prior to admission, the patient was on 10 mg of the antihistamine loratadine daily without any improvement in symptoms. Initial treatment on admission included 50 mg of prednisolone daily, 100 mg of doxycycline twice daily, 500 mg of nicotinamide twice daily and topical corticosteroids which were commenced simultaneously. In addition, the dose of loratadine was increased to 20 mg twice daily. There was a partial response with reduced blisters, however, pruritus persisted and any reduction in prednisolone dose resulted in severe disease flares. The corticosteroids destabilised his diabetic control and a non-healing foot ulcer necessitated forefoot amputation. His poor renal function and disease severity limited use of slow acting oral immunosuppressive agents. The patient was treated with 2 cycles of monthly intravenous immunoglobulin, and as there was no change in disease, rituximab was administered (two 1 g doses at week 0 and 2). Complete B cell depletion was documented within 6 weeks of rituximab, however the patient had progression to extensive tense, haemorrhagic bullae affecting > 80% of his body surface area. At this point the disease had been active for 5 months, the eosinophil count was 2.19×10^9/L and anti-skin antibodies remained high (3+). Omalizumab at a dose of 300 mg subcutaneously was trialled, based on standard fixed dosing in chronic spontaneous urticaria and used in previously described cases of BP [1,2]. Within 4 days of the first dose of omalizumab, the patient had resolution of pruritus and cessation of new bullae formation. By day 8, the erythematous base had resolved and there was wound healing (Fig. 1). Within 2 weeks the eosinophil count normalised and prednisolone was tapered to a low maintenance dose. Three weeks after the first injection, recurrence of mild pruritus and a few isolated blisters coincided with an increase in blood eosinophil count, which subsequently resolved again with a second dose of

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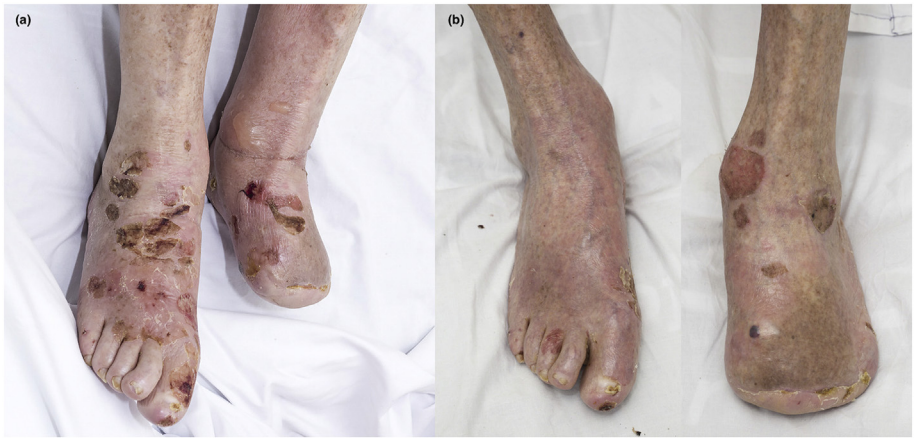

Fig. 1. Clinical appearance of lower limbs (a) before and (b) 8 days after treatment with omalizumab.

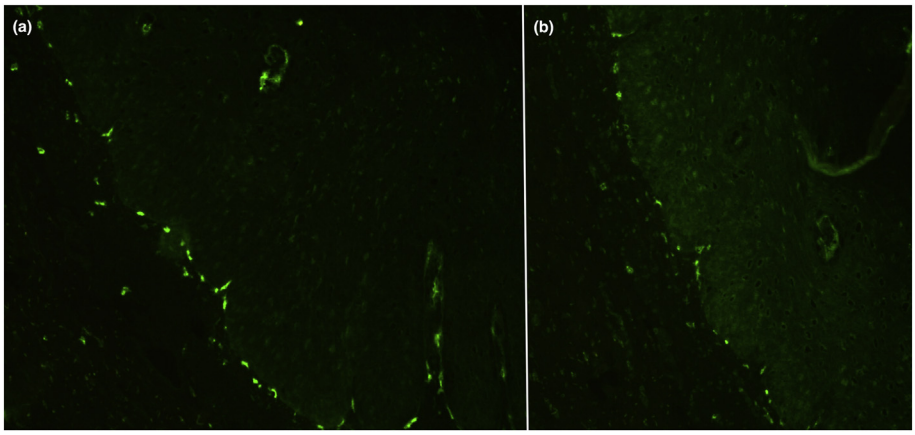

Fig. 2. Indirect immunofluorescence with monkey oesophagus substrate and FITC-conjugated IgE antibody using patient sera before (a) and after (b) omalizumab treatment.

omalizumab. Given these observations, IIF was retrospectively performed using the patient's stored serum on monkey oesophagus substrate, with FITC-conjugated anti-human IgE detection antibody. This revealed discontinuous junctional fluorescence with pre-omalizumab serum, and lesser binding in a similar distribution with post-omalizumab serum (Fig. 2). This pattern was not seen with healthy control serum. DIF using a stored skin sample was uninterpretable due to poor tissue preservation. At the time of reporting, after 10 months of omalizumab therapy (300 mg, 3 weekly) the patient remains disease-free off prednisolone, with good diabetic control, normal eosinophil count and undetectable B cells, but with persisting IgG anti-skin antibodies (3+).

2. Discussion

Recent case reports have suggested omalizumab may be an effective treatment for refractory BP, including as monotherapy [1,2]. As previously reported, we observed a strikingly dramatic response in very severe disease which had not responded to standard therapies. However, this case uniquely demonstrates that new blisters can form in the absence of peripheral blood B cells, which is a standard serological marker of rituximab effect in a range of autoimmune diseases. Persisting IgG and IgE autoantibodies implies ongoing production by autoreactive plasma cell clones. However, in this case, a near resolution of blisters occurred despite no demonstrable change in the circulating anti-skin IgG antibody level. This challenges the idea that autoreactive B cells and IgG autoantibodies alone mediate blister formation in all phenotypes of BP.

There has been increasing evidence to suggest that IgE has a role in BP pathogenesis [3–10]. Up to 70% of patients with untreated BP have elevated serum IgE [4,5]. Messingham et al detected circulating IgE against NC16A, a domain of BP180, in up to 77% of BP sera and demonstrated BP180-specific degranulation of IgE coated basophils in untreated BP patients compared to health controls [5]. Similarly, Dimson et al detected BP180-specific IgE in 86% of patients and in all but one, the IgE reacted with the NC16A domain [4]. Linear IgE deposits along the dermoepidermal junction have also been demonstrated in up to 41% of patients with BP [6]. Kalowska et al reported that patients with anti-NC16A IgE have twice the body surface involvement than those without [7]. Additionally, anti-NC16A IgE correlated better with disease course compared to anti-NC16A IgG and total IgE. In mouse models of BP with engrafted human skin, IgE alone mediated blister formation [8,9]. Recently, the integral role of eosinophils in this process has been demonstrated [10]. In a humanised IgE receptor mouse model Lin et al demonstrated that disease severity was anti-NC16A IgE dose dependent and was associated with eosinophil infiltration, with a lack of effect in eosinophil deficient mice. These findings suggest that IgE specific for self-antigens have a direct role in blister formation. One hypothesis is that IgE autoantibodies bind to mast cells and basophils *via* the high affinity IgE receptor FcεRI [6]. These then bind to the antigenic NC16A domain of BP180 causing receptor cross-linking, release of histamine, cytokines and proteases and triggering of a destructive immune cascade at the basement membrane. Another proposed mechanism is that IgE antibodies bind to the BP180 NC16A domain resulting in internalisation by basal keratinocytes and release of pro-inflammatory cytokines. Omalizumab targets the Fc region of free, circulating IgE, and forms IgE–anti-IgE complexes,

inhibiting IgE crosslinking and downregulating FcεRI expression on mast cells and basophils and has also been shown to reduce peripheral eosinophil numbers. Given that omalizumab cannot bind cross-linked or cell bound IgE *in-vivo*, the rapid clinical effect in BP may favour the latter hypothesis. Our findings of junctional IgE deposition by IIF may also be supportive, though more studies are needed to confirm this.

3. Conclusion

The ideal patient selection and regimen of anti-IgE therapy *versus* other second line agents for BP is yet to be established. At a broader level, the nexus between IgE-mediated inflammation and autoimmunity may be relevant to other conditions such as chronic spontaneous urticaria and potentially other autoimmune diseases. Cases such as these may help to elucidate these understudied pathogenetic links and inform future therapeutics in autoimmunity

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Declaration

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