Introduction

Bullous pemphigoid (BP) is an autoimmune disorder known to be mediated by immunoglobulin G (IgG) autoantibodies. The role of immunoglobulin E (IgE) antibodies is being investigated as their presence has been described in severe cases. Herein, we report a patient of BP who was refractory to most conventional agents and developed hypotension after rituximab but achieved lasting remission after a single dose of the anti-IgE monoclonal antibody omalizumab.

Case Report

A 44-year-old obese lady presented to the Dermatology outpatient department with a 3-month history of tense fluid-filled blisters all over the body. The blisters were preceded by extremely itchy raised weals. Prior to presentation, she had been treated with high-dose oral steroids and dapsone which had led to partial resolution but discontinuation was followed by rapid reappearance of lesions. She had also received one dose of rituximab (500 mg i.v.) but had developed severe hypotension during the infusion consequent to which rituximab had been discontinued.

She was grossly overweight (BMI 40.6) but had no other comorbidities. On muco-cutaneous examination, she had tense bullae some of which were hemorrhagic, mostly overlying urticarial plaques along with extensive erosions and excoriations, involving almost the entire body, especially trunk and thighs [Figure 1a-c]. There was an ulcer on the right buccal mucosa, while the other mucosae appeared normal.

The diagnosis of BP was confirmed on histopathology which showed subepidermal blister with dermal infiltrate of eosinophils [Figure 2a]. Direct immunofluorescence revealed linear staining with IgG (2+) along basement membrane at dermoepidermal junction [Figure 2b]. Both absolute eosinophil count (5500 cells/mm³, normal <350) and serum IgE level (11,579 IU/ml, normal <64) were considerably high. Hypereosinophilic syndrome and hyper-IgE syndromes were ruled out on the basis of absence of any systemic (respiratory/gastrointestinal/ neurologic or rheumatologic) symptoms. There was no history of recurrent upper or lower respiratory tract or skin infections or eczema prior to the onset of presenting lesions. Peripheral smear did not show blast cells, thus ruling out eosinophilic leukemia too. Stool examination for ova/cyst/occult blood, Pap smear, and mammography was all within normal limits. There was no evidence of hepatitis B, hepatitis C, or HIV infection. Cardiomegaly was seen on a chest radiograph and a 2-D echocardiograph showed mild concentric left ventricular hypertension.
hypertrophy with grade 2 diastolic dysfunction. Ultrasound abdomen revealed hepatomegaly with grade 2 fatty liver but no splenomegaly. Immunoglobulin M (IgM) and immunoglobulin A (IgA) levels were within normal limits. Serum vitamin B12 and vitamin D3 levels were both low. She was started on 80 mg prednisolone and potent topical steroids but she continued to develop approximately 50 new lesions daily. She was switched to i.v. dexamethasone 8 mg twice daily (=106 mg prednisolone) and azathioprine 150 mg was added. In spite of this she continued to develop 30 to 50 new lesions daily over the next 2 weeks and, in light of the poor disease control and extremely high serum IgE levels, we administered Omalizumab 450 mg subcutaneously, while dexamethasone 16 mg i.v. was continued. The patient had a dramatic response subsequent to which she developed only ten lesions the day after omalizumab and no new lesion thereafter [Figure 3a-c].

Dexamethasone was replaced by oral prednisolone 60 mg and azathioprine 150 mg was continued. The oral steroids were tapered off over the next 4 months. The serum IgE levels corroborated well with the clinical response – from 11579 IU/mL at baseline they decreased to 8500 IU/mL after 2 months, 5368 IU/mL after 6 months and 2344 after 8 months. The AEC fell dramatically from 5500 cells/cumm at baseline to 220 after 8 months.

The patient is under regular follow up on azathioprine 100 mg and shows no evidence of relapse after 10 months. Notably, she developed extensive milia, especially on her face and dorsa of hands, which decreased on topical tazarotene [Figure 4a and b].

Discussion
BP is an autoimmune blistering disorder characterized by IgG autoantibodies directed against the hemidesmosomal proteins BP180 and BP230. The presence of IgE autoantibodies against the transmembrane protein BP180 has been reported in BP serum samples and is the focus of much research. [1-3] Recent models of the disease have demonstrated that BP IgE can replicate the early
stages of BP lesion formation. Ishiura et al. showed that IgE anti-BP230 levels had a strong association with local eosinophil accumulation and that they may have a role in attracting eosinophils to the skin lesions.[2] High serum IgE levels are associated with more severe BP and thus IgE inhibition could prove to be a valuable therapeutic modality in such patients.[4,5] Our case was a treatment refractory case and this was probably related to the high IgE and AEC levels.

Omalizumab is a humanized monoclonal antibody that inhibits IgE binding to its receptor FcεRI and is FDA approved for severe uncontrolled asthma. The use of this drug in BP is based on certain observations – serum IgE levels are elevated in most BP patients, IgE anti-BP230 antibodies are known to play a role in eosinophil accumulation and IgE levels and eosinophil counts have been known to mirror disease activity in BP.[2‑5] Free IgE levels are seen to decrease within hours of the first dose of omalizumab. There is a remarkable heterogeneity in dosimetry, with the doses varying from 100 mg to 525 mg subcutaneously at 2-8 weekly intervals for durations ranging from 2–20 months [Table 1]. Most authors use the asthma nomogram to decide the dose. This nomogram uses body weight and total IgE levels to determine the dose. Since both these parameters were very high in our patient, we gave a high first dose of 450 mg.

| Authors                  | S. IgE (kU/I)/AEC (cells/mm³) before Omalizumab therapy | Omalizumab dosing regimen                                                                 | Total duration (total number of doses) | Final Outcome                                                                 |
|--------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------|-------------------------------------------------------------------------------|
| Fairley et al.⁶ (2009)   | 222/3427                                               | 300 mg s.c 2 weekly                                                                      | 16 weeks                               | Four months after discontinuing omalizumab, the patient noted a return of pruritus and new blisters On the back and calves. Omalizumab was reinstituted off the trial. The pruritus subsided and the blisters resolved within 2 weeks. Patient was well responsive to monthly Omalizumab without any adverse effects. |
| London VA et al.⁷ (2012) | 881/1640                                               | 300 mg s.c. 6-8 weekly for first 2 months, then every 4 weekly                           | 18 months                               | After a 7-month follow-up period, no clinical relapse had occurred             |
| Dufour C et al.⁸ (2012)  | 636/11,500                                             | 100-mg s.c. Every 2 weeks for 3 months and then monthly for 4 months                     | 7 months                                | Patient remained clear of disease for 5 months and then suffered a relapse. Reinstating Omalizumab was not helpful as she was thus shifted over to prednisolone and azathioprine |
| Yu et al.⁹ (2014)        | 222/3400, 1835/120, 1181/5400, 287/1640, 2135/1810, 5821/17,700 | 300 mg s.c. 2 weekly, 300 mg s.c. 6 weekly, then 8 weekly, then 6 weekly and then 4 weekly, 375 mg s.c. 4 weekly, 300 mg s.c. 4 weekly, then 4-8 weekly, 375 mg s.c. 2 weekly, 375 mg s.c. 2 weekly | 12 weeks, 12 months, 2 years, 12 weeks | Patient remained free of skin lesions for 20 months in follow-up, antihistamines sometimes needed to control mild pruritus. Patient remained disease free 12 months after initiating Omalizumab therapy. After 42 months of initiating Omalizumab therapy, she developed urticarial plaques and one bulla developed; was referred for i.v. rituximab. Patient had concurrent COPD which worsened (unrelated to Omalizumab); hence it was stopped. Patient relapsed 3 months after stopping Omalizumab, and prednisolone, minocycline and azathioprine was started. |
| Yalcin et al.¹⁰ (2014)   | 5000/47%                                               | 300 mg                                                                                   | 13 doses                                | BP lesions exacerbated on stopping Omalizumab therapy for 2 months after 7th dose, but resolved on reinstituting Omalizumab and patient stayed in remission. |
| Gönül M et al.¹¹ (2016)  | 2500/2.9%                                              | 300 mg s.c. 4 weekly                                                                      | 13 months (11 injections; gap of 2 months after 7th dose) |                                                                                     |

Contd...
Remarkably, our patient achieved complete control with the single dose. This may be related to the extremely high IgE levels (>11000 IU/ml), hitherto unreported in any case of BP on omalizumab. While we did not repeat the dose due to monetary constraints, this was probably serendipitous as there was remarkable and lasting control with a single dose. We believe that possibly, there is a subset of patients, with pruritic urticarial lesions preceding the bullae, and very high IgE and/or AEC levels, which may not require repeated dosing with omalizumab to achieve disease control and may be eventually managed on conventional therapy alone. Further studies would be needed to clearly define this subset of patients but this could significantly decrease the cost of treatment.

To the best of our knowledge, a single dose of omalizumab leading to complete remission has not been reported as yet in BP. While we are unable to offer an explanation for the remarkable response with one dose, possibly omalizumab may be used as a form of “rescue therapy” in cases of treatment refractory BP.

**Conclusion**

Omalizumab could prove to be a valuable reserve option

| Authors          | S. IgE (kU/I)/AEC (cells/mm³) before Omalizumab therapy | Omalizumab dosing regimen | Total duration (total number of doses) | Final Outcome                                                                 |
|------------------|--------------------------------------------------------|---------------------------|----------------------------------------|-------------------------------------------------------------------------------|
| Balakirski et al. (2016) | 1697/5.5%, 1074/11% | 300 mg s.c. 4 weekly, then 3 weekly, 300 mg s.c. 3 weekly | 15 months (20 doses) | 8 weeks after discontinuation of therapy, patient developed exacerbation of the disease, hence oral prednisolone reintroduced. Patient is free of pruritus but kept having few isolated blisters. |
| Menzinger et al. (2017) | 4994/1450 | 300 mg s.c. monthly | 7 months | After 7 months, the follow-up was lost for 2 months and a relapse occurred. Omalizumab monotherapy was resumed with disease control after 8 weeks. Complete clinical response |
| Uysal et al. (2017) | -100/-700/-1000/-400/-1400/-1400/-100/-3800/-100/-900/-200 | 300 mg s.c. 2 weekly, final dose 3 weekly, 300 mg s.c. 4 weekly, final dose 4 weekly, 300 mg s.c. 2 weekly, final dose 4 weekly, 300 mg s.c. 2 weekly, final dose 4 weekly, 300 mg s.c. 2 weekly, final dose 4 weekly, 300 mg s.c. 2 weekly, final dose 4 weekly, 300 mg s.c. 2 weekly, final dose 4 weekly | 21 doses | Complete clinical response |
| Temel et al. (2017) | 1598/- | 525 mg s.c. every 2 weekly for 8-weeks followed by 450 mg s.c. every 2 weeks for 2-months | 4 months | No significant clinical improvement on Omalizumab therapy. Patient responded eventually to rituximab therapy. Complete clinical response |
| James et al. (2018) | 6241/2190 | 300 mg 3 weekly | 10 months | Patient is disease free and off steroids. Patient recovered and other adjuvant treatments were tapered and stopped. |
| Vick-Alonso et al. (2019) | 235/- (No eosinophilia) | 300 mg 4 weekly, final dose every 7 weekly | - | |

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for treatment refractory BP, especially in patients with very high IgE and/or AEC levels. Attempts should also be made to switch the patient to conventional modes of treatment once initial control is achieved to cut down treatment cost.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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