Complete Remission in a Patient with Treatment Refractory Bullous Pemphigoid after a Single Dose of Omalizumab

Abstract

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.

Keywords: *Bullous pemphigoid, immunoglobulin E, omalizumab, refractory*

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Introduction

Bullous pemphigoid (BP) is an autoimmune disorder with urticarial lesions with/without tense blisters. While immunoglobulin G (IgG) autoantibodies are known to play a pathogenic role; recently, immunoglobulin E (IgE) antibodies have been reported both in serum and lesions, and this is a topic of research that is being translated to its applicability into therapeutic interventions. We report a patient of BP who was refractory to high dose steroids and immunosuppressants and could not tolerate rituximab, but successfully achieved lasting remission after a single dose of 450 mg of 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/mm^3, 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

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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].

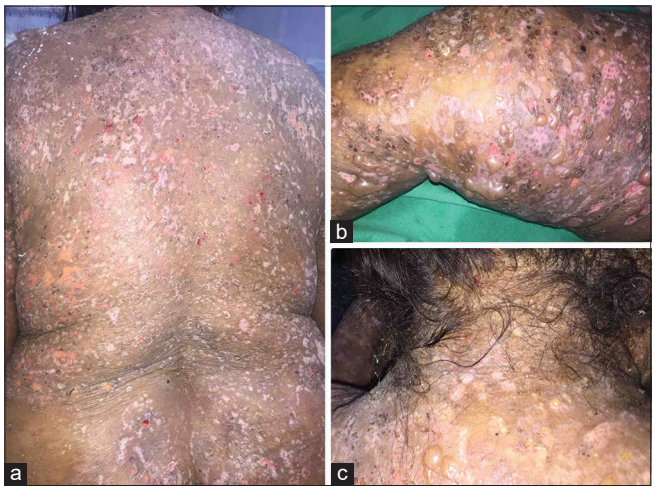

Figure 1: Clinical photograph of patient of bullous pemphigoid after 2 weeks of steroids and azathioprine showing (a) extensive erosions, excoriations and bullae over the whole back, (b) Vesicles and large bullae and erosions on the thigh, and on (c) nape of neck

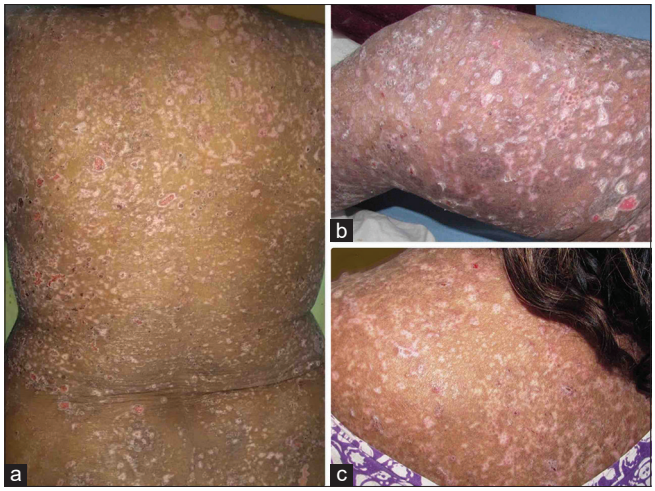

Figure 3: Clinical photographs after administration of single dose of omalizumab showing healing erosions and no vesicles or bullae over (a) back, (b) thigh, and, (c) nape of neck

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 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 BP 180 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

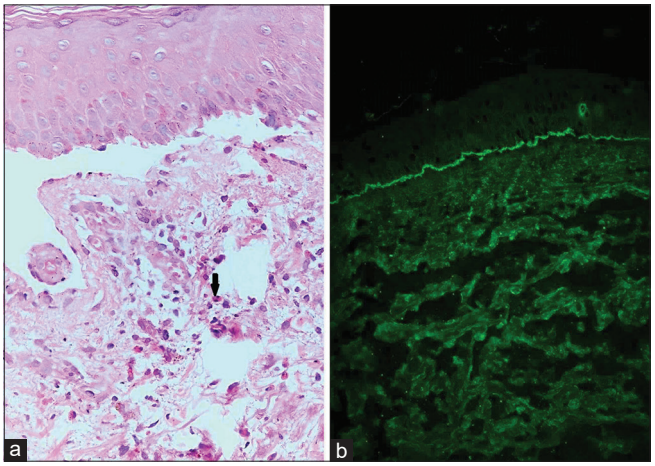

Figure 2: (a) Histopathology showing subepidermal blister with dermal infiltrate of eosinophils (arrow) (H and E × 400), and, (b) direct immunofluorescence showing linear staining with IgG (2+) along basement membrane at dermoepidermal junction (FITC × 200)

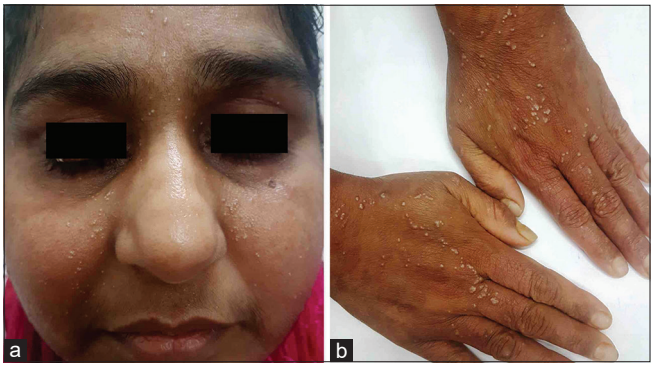

Figure 4: Clinical photograph showing milia over sites of healing of vesicles over (a) face and (b) dorsa of hands

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.

Table 1: Summary of published cases of bullous pemphigoid patients treated with omalizumab till date

Authors	S. IgE (kU/l)/AEC (cells/mm^3) 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.
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	Patient was well responsive to monthly Omalizumab without any adverse effects.
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	After a 7-month follow-up period, no clinical relapse had occurred
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 20 months 12 months 2 years 1 dose 12 weeks	Patient remained clear of disease for 5 months and then suffered a relapse. Reinstituting Omalizumab was not helpful a d she was thus shifted over to prednisolone and azathioprine 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	
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)	BP lesions exacerbated on stopping Omalizumab therapy for 2 months after 7th dose, but resolved on reinstituting Omalizumab and patient stayed in remission.

Contd...

Table 1: Contd...

Authors	S. IgE (kU/I)/AEC (cells/mm^3) before Omalizumab therapy	Omalizumab dosing regimen	Total duration (total number of doses)	Final Outcome
Balakirski G *et al*.[12] (2016)	1697/5.5%	300 mg s.c. 4 weekly, then 3 weekly	15 months (20 doses)	Patient is free of pruritus but kept having few isolated blisters.
	1074/11%	300 mg s.c. 3 weekly	24 weeks (8 doses)	8 weeks after discontinuation of therapy, patient developed exacerbation of the disease, hence oral prednisolone reintroduced
Menzinger *et al*.[13] (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.
Uysal *et al*.[14] (2017)	-/100	300 mg s.c. 4 weekly, , final dose 5 weekly	21 doses	Complete clinical response
	-/700		40 doses	Partial clinical response
	-/1000	300 mg s.c. 2 weekly, , final dose 3 weekly	16 doses	Complete clinical response
	-/400		10 doses	Complete clinical response
	-/1400	300 mg s.c. 2 weekly, , final dose 4 weekly	Single dose	Omalizumab therapy was discontinued in view of elevated liver enzymes (unrelated to omalizumab)
	-/1400		Single dose	
	-/100	300 mg s.c. 2 weekly, final dose 8 weekly	9 doses	Omalizumab therapy was discontinued because patient suffered MI and died (unrelated to omalizumab)
	-/3800	300 mg s.c. 4 weekly	9 doses	
	-/100	300 mg s.c. 4 weekly	11 doses	Omalizumab therapy was discontinued because patient suffered from MI and thrombocytopenia (unrelated to omalizumab)
	-/900	300 mg s.c. 2 weekly	11 doses	
	-/200	300 mg s.c. 2 weekly, final dose 4 weekly	3 doses	Complete clinical response
		300 mg s.c. 2 weekly, final dose 4 weekly		Complete clinical response
		300 mg s.c. 2 weekly, final dose 4 weekly		Complete clinical response
		300 mg s.c. 4 weekly		Patient failed to complete treatment and did not follow up
Temel *et al*.[15] (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.
James *et al*.[16] (2018)	6241/ 2,190	300 mg 3 weekly	10 months	Patient is disease free and off steroids.
Vick-Alonso *et al*.[17] (2019)	235/-(No eosinophilia)	300 mg 4 weekly, final dose every 7 weekly	-	Patient recovered and other adjuvant treatments were tapered and stopped.

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

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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