International Journal of Research in Dermatology
Safura BB et al. Int J Res Dermatol. 2024 Jul;10(4):196-200
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20241724

Case Report

Treatment with Rituximab in extensive bullous pemphigoid - recalcitrant to conventional treatment: a report of 2 cases

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Received: 05 April 2024
Revised: 06 May 2024
Accepted: 17 May 2024

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ABSTRACT

Bullous pemphigoid (BP) is the most common autoimmune blistering disease requiring treatment with immunosuppressive medications; however, finding a therapy that has a sustained durable response and an acceptable side effect profile has been challenging. Rituximab (RTX) is a monoclonal antibody targeting CD20, a transmembrane protein expressed on B cells, causing B cell depletion. RTX has shown great efficacy in studies of pemphigus vulgaris, but data of pemphigoid diseases are limited. We report a 60 year old male who presented with widespread fluid filled lesions and raw areas preceded by itching since 3 weeks. Dermatological examination revealed multiple intact bullae, vesicles were seen over urticarial plaques and multiple raw areas, erosions with crust formation over trunk, upper and lower extremities. Histopathological examination (HPE) showed sub epidermal blister. Direct immunofluorescence (DIF) revealed IgG: positive (+3), C3: positive (+2), linear pattern, along the dermoepidermal junction. Based on the clinical features, HPE and DIF findings, diagnosis of BP was made. Patient did not respond to high dose of corticosteroids for 3 weeks. Second case was known case of BP who did not respond to conventional treatment even after 5 years. Both cases were treated with Rheumatoid arthritis protocol of RTX and marked improvement was seen after 8 weeks of treatment with no recurrence of lesions. Our experience shows that in all cases of extensive BP and cases not responding to conventional treatment, injection rituximab should be considered for in view of ease of administration, excellent safety profile and good efficacy.

Keywords: Pemphigoid diseases, Autoimmune blistering disease, Bullous pemphigoid, Rituximab

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering disorder which is usually characterized by urticarial lesions initially and then tense blisters and erosions.[1] It predominantly affects patients over the age of 65 but sometimes can develop in children and young adults. BP is caused by autoantibodies directed against the hemidesmosomal proteins BP180 and BP230.[2] Patients with limited disease involvement may respond to topical therapy. Patients with mild to moderate forms of the disease are often treated with systemic antibiotics with nicotinamide. Alternatively, those with more extensive forms of the disease often require systemic corticosteroids (CS) and immunosuppressive agents (ISA) such as azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF).

The long-term use of such therapy can produce multiple side effects that can potentially reduce the quality of life and result in opportunistic infections, septicemia, and death. Rituximab is a biological agent which is increasingly used in autoimmune blistering diseases especially pemphigus vulgaris. Rituximab selectively destroys CD-20^{+} B-cells that may be producing the pathogenic autoantibodies, which may be the basis for its

use in treating BP. There is a growing tendency to use rituximab in treating other autoantibody mediated diseases.

We have come across one extensive case of BP who did not respond to high dose corticosteroids for 8 weeks and in another case, persistent disease activity with appearance of new bullae with systemic corticosteroids and immunosuppressive agents for more than 5 years. The present case report describes excellent response and prolonged remission achieved in both cases with rituximab.

CASE REPORTS

Case 1

A 60-year old male patient came with chief complaint of widespread fluid filled lesions and raw areas preceded by itching since 3 weeks. Patient was apparently normal 3 weeks ago, then he started developing intensely itchy red raised lesions over extremities and trunk. After 1 week, patient developed blisters initially over arms which then progressed to involve all other limbs, trunk, neck and back. Few blisters spontaneously ruptured to form raw areas. Past history was not significant. Patient is a known diabetic and hypertensive on regular medication.

On dermatological examination, multiple urticarial plaques with well-defined borders were seen diffusely all over the chest, abdomen, back, upper and lower extremities. Multiple intact bullae and vesicles were seen over urticarial plaques with largest bulla of size 4×3 cm and smallest bulla of size 1×0.5 cm (Figure 1). Multiple raw areas, erosions with crust formation were seen over bilateral upper and lower limbs, trunk, neck and back (Figure 2). Nikolsky sign was negative and bulla spread sign revealed round border.

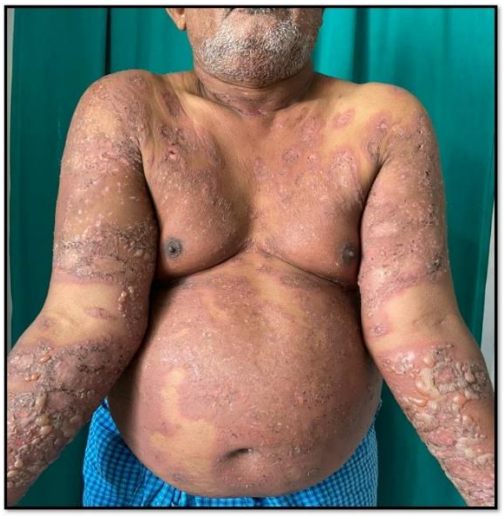

Figure 1: Multiple bullae and vesicles were seen over urticarial plaques with raw areas, erosions with crust formation over bilateral upper limbs, trunk and neck.

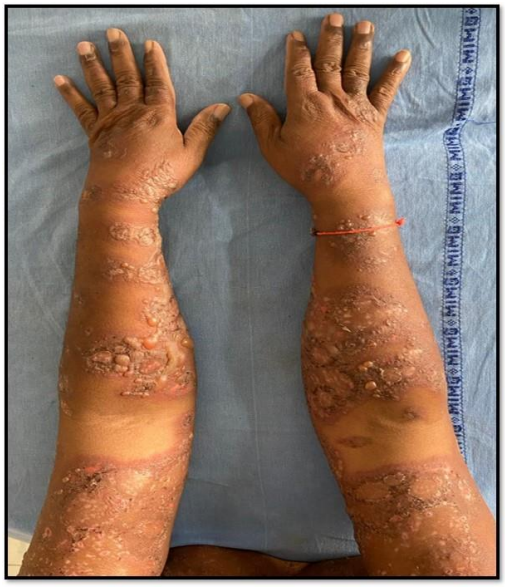

Figure 2: Multiple bullae and vesicles with raw areas on upper limbs.

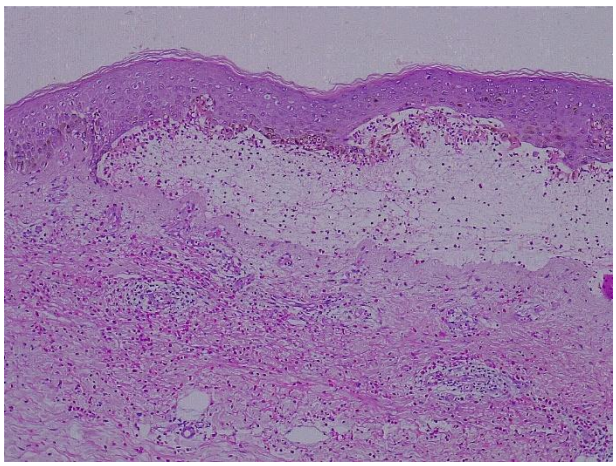

Figure 3: Sub epidermal blister with abundant neutrophils and eosinophils.

Based on history and clinical examination a differential diagnosis of Bullous pemphigoid and Pemphigus vulgaris were considered. Complete blood picture, serum biochemistry were normal except for raised random blood sugar. Tzank smear revealed eosinophils and other inflammatory cells. A 4 mm skin sample sent for histopathological examination showed sub epidermal blister (Figure 3). Blister contained abundant neutrophils and eosinophils. Superficial dermis revealed mild perivascular inflammatory infiltrate, composed of lymphocytes and eosinophils. Deep dermis was unremarkable. A 4mm punch biopsy from perilesional area for direct immunofluorescence revealed Ig G: positive (+3), C3: positive (+2), linear pattern, along the dermo – epidermal junction (Figure 4). Based on the clinical features, direct immunofluorescence and histopathological findings, a diagnosis of bullous pemphigoid was made. Patient was treated with

intravenous (IV) Dexamethasone 16 mg per day in 2 divided doses, antibiotic IV Ceftriaxone 1 gram twice daily for 5 days followed by oral Cefuroxime twice daily for 5 days, tablet dapsone 100 mg once daily, topical Clobetasol Propionate cream 0.05% over affected areas and topical fusidic acid cream application over raw areas. No significant response was seen with above treatment.

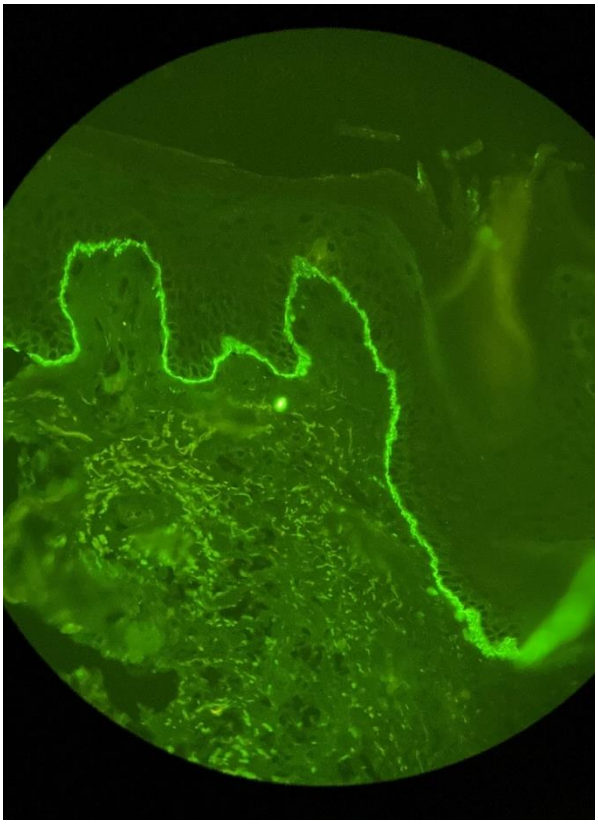

Figure 4: Ig G: positive (+3), C3: positive (+2), linear pattern, along the dermo - epidermal junction.

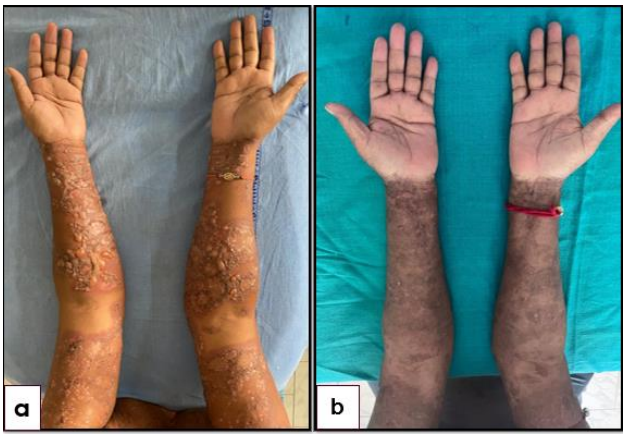

Figure 5: (a) Before treatment and (b) after 1 month of treatment with marked improvement of lesions.

Development of new bullae and large erosions was seen all over body even after 6 weeks of treatment. In view of extensive involvement and recalcitrant nature of the disease, patient was treated with 2 doses of injection rituximab 1 gram IV at an interval of 2 weeks. Marked improvement with resolution of all bullae was noticed after 2nd dose of rituximab (Figure 5). No adverse effects observed.

Case 2

A 50- year old female patient came with chief complaint of widespread fluid filled lesions preceded by itching since 1 month. Patient was apparently normal 1 month back, then she started developing blisters initially over extremities later involved trunk and face. Few blisters spontaneously ruptured to form raw areas. Patient had past history of similar recurrent episodes of bullous lesions since 5 years. She had taken treatment previously which resolved in partial remission and relapse.

On dermatological examination, multiple intact bullae and vesicles were seen diffusely all over the face, chest, abdomen, back, upper and lower extremities with largest bulla of size 3×2 cm and smallest bulla of size 1×1 cm (Figure 6). Multiple raw areas, erosions with crust formation were seen. Few lesions healed with post-inflammatory hyperpigmentation and hypopigmentation. Nikolsky sign was negative and bulla spread sign revealed round border.

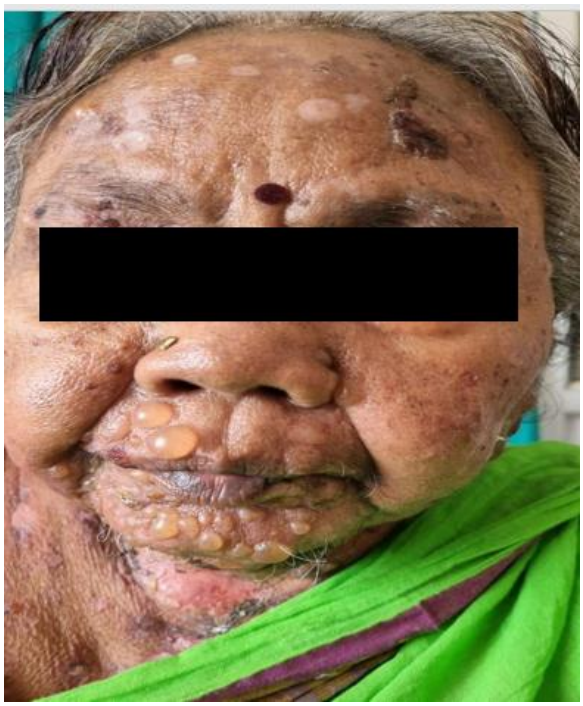

Figure 6: Multiple tense bullae over face.

Based on history and clinical examination, differential diagnosis of Bullous pemphigoid and Pemphigus vulgaris were considered. Complete blood picture, serum biochemistry were normal. Tzank smear revealed eosinophils and other inflammatory cells. A 4 mm skin sample sent for histopathological examination showed

sub epidermal blister. A 4mm punch biopsy from perilesional area for direct immunofluorescence revealed Ig G, C3: positive (+2), linear pattern, along the dermo–epidermal junction. Based on the clinical features, direct immunofluorescence and histopathological findings, a diagnosis of bullous pemphigoid was made.

Patient was treated with oral glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil on multiple occasions previously with partial response and relapse within one month of stoppage of treatment. In view of recalcitrant disease, she was treated with 2 doses of 1 gram rituximab two weeks apart resulting in satisfactory improvement with resolution of active skin lesions and absence of new skin lesions after 4 weeks of 2nd dose of rituximab.

DISCUSSION

BP is not only the most common disorder within the group of sub-epidermal immunobullous disorders but also represents the most frequent autoimmune blistering disease in general.[3] It mainly affects elderly people although younger patients may also be affected and often starts with pruritus and urticated and erythematous lesions. Later, tense blisters are characteristic both on erythematous and on normal skin. Histopathology of a lesional biopsy reveals subepidermal splitting. Autoantibodies, chiefly IgG, recognize two proteins of the dermoepidermaljunction, BP180 (type XVII collagen) in almost all patients and, in about half of them, BP230.[4]

Bullous pemphigoid is nowadays a therapeutic challenge, as the only validated therapies consist of steroids and steroid-sparing immunosuppressants like dapsone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF).[5] The rate of efficacy is counterbalanced by their low safety profile over long-term use. The latest discoveries on the pathogenesis of BP, however, have given an insight for further research aiming to identify new target treatments for refractory cases, with the hope of guaranteeing long-term-effective and safe treatments for patients.[6] The choice of possible targets ranges from $CD20^+$ lymphocytes with rituximab, Th2 axis using dupilumab and omalizumab and IL-17/IL-23 axis to the inhibition of certain molecules of the complement system or the inflammasome.[7]

Rituximab has already entered into the therapeutic armory of dermatologists, but only for treatment of PV.[8] Preliminary evidence has demonstrated high rates of remission, steroid-sparing activity, and an acceptable safety profile in patients with severe BP or disease refractory to conventional therapies.[9] A reason for long lasting therapeutic results with this drug as compared to conventional oral immunosuppresive agents is it's ability to increase regulatory B cells that helps in prolonged remission.[10]

The patient is premedicated with injection hydrocortisone 100 mg IV stat, injection pheniramine maleate 22.75 mg IV stat, Tablet paracetamol 500 mg; 30 minutes prior to RTX infusion. It would be easier to administer as follows with an infusion pump: 30 ml/hour for half an hour (15 ml), 60 ml/hour for half an hour (30 ml), 90 ml/hour till infusion is over (455 ml) (5 hours), total infusion period – 6 hours.

Various protocols include lymphoma protocol- most commonly followed protocol. Rituximab is administered at a dose of $375mg/m^2$ body surface area weekly for four weeks. Rheumatoid arthritis protocol -two doses of rituximab 1gm is administered at an interval of 15 days. Advantage over the lymphoma protocol include less cost and fewer infusions. Adverse effects include cutaneous: early –infusion reaction, cytokine release syndrome, night sweats, skin rash, urticaria, and pruritus. Late - SJS, TEN, serum sickness and vasculitis. Noncutaneous - fatal infusion reactions usually in the first infusion, tumor lysis syndrome, Hepatitis B reactivation with related fulminant hepatitis and severe life-threatening cardiac arrhythmias. In the above 2 cases, no adverse effects were noted during follow up period of 12 months and patients were under remission with marked improvement.

CONCLUSION

Our experience shows that in all cases of extensive BP and cases not responding to conventional treatment, injection rituximab should be considered for in view of low cost, ease of administration, excellent safety profile and good efficacy.

ACKNOWLEDGEMENTS

We would like to thank Dr. Sudhir MD, Pathologist.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Safura BB, Gopal KVT, Raju PVK, Rani BR. Treatment with Rituximab in extensive Bullous Pemphigoid - Recalcitrant to conventional treatment: a report of 2 cases. Int J Res Dermatol 2024;10:196-200.