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Case Report
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Successful Treatment of Refractory Childhood Pemphigus with Rituximab

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Abstract

Observation: Rituximab is an anti-CD 20 monoclonal antibody used to treat Chronic Lymphocytic Leukemia and Rheumatoid Arthritis. In dermatology, rituximab has gained popularity for the treatment of refractory pemphigus vulgaris. However, there are only a few case reports regarding the treatment of refractory childhood pemphigus with rituximab. We are reporting this case as childhood pemphigus is rare, and the safety of rituximab in children is unknown due to the paucity of studies.

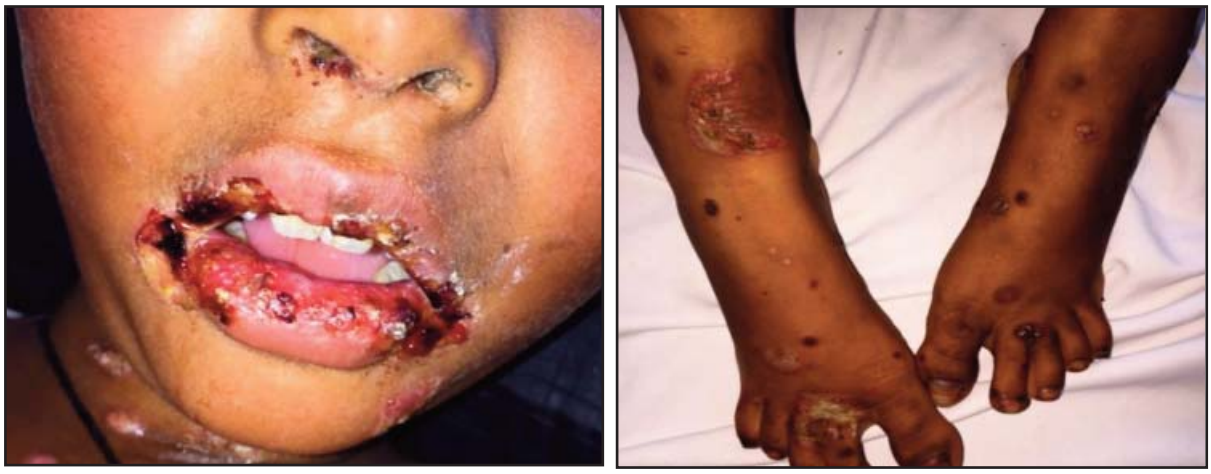
Introduction

Rituximab is an anti-CD 20 monoclonal antibody used to treat Chronic Lymphocytic Leukemia and Rheumatoid Arthritis. Recently, rituximab has been used to treat various other autoimmune diseases like refractory myasthenia gravis, juvenile dermatomyositis, and thrombotic thrombocytopenic purpura. In dermatology, rituximab has gained popularity for the treatment of refractory pemphigus vulgaris. However, there are only a few case reports regarding the treatment of refractory childhood pemphigus with rituximab. We are reporting this case as childhood pemphigus is rare, and the safety of rituximab in children is unknown due to the paucity of studies [**1,2**].

Case Report

A 7-year-old female child presented with oral ulcers, denuded lips, and multiple fluid-filled lesions on the skin involving 20% of the total body surface area. Nikolsky sign was positive. Histopathology showed acantholysis and suprabasal split and direct immunofluoroscence of skin showed intercellular staining of lower epidermis with IgG and C3 diagnostic of pemphigus. She experienced remission with oral prednisolone 1mg/kg and oral azathioprine 2mg/kg. She was then tapered off these medications.

In the second year of her disease, she experienced multiple flares. A prolonged course of oral prednisolone could only temporarily control her symptoms during this time. Therefore, she was hospitalized and the treatment was changed to intravenous methylprednisolone with oral mycophenolate mofetil(MMF) 1g/day. She was discharged from the hospital on MMF 1g/day. However, she developed new fluid filled lesions within 3 months. The patient was then started on high dose oral prednisolone 2mg/kg with MMF. After initial improvement, the patient had flare up of the disease (**Figures 1a and b**) once oral prednisolone was tapered. Her hemoglobin had fallen to 8g/dl and



Figures 1a and b. a) Eroded lips with hemorrhagic crusting in the patient. b) Multiple flaccid bullae and erosions on the lower limb of the patient

WBC count was 3800/mm.[3] Thus, mycophenolate mofetil was stopped.

The patient was planned for intravenous rituximab injection due to poor clinical response and adverse effects of the current therapy. Desmoglein 1 and 3 antibodies (Serum ELISA) before rituximab measured were 274RU/ml and 348RU/ml respectively. (Negative :< 20)

The patient was given one infusion of rituximab 500 mg after premedication with intravenous acetaminophen and promethazine. The infusion was completed in 5 hours. During the infusion blood pressure and blood-oxygen-saturation was monitored half hourly. After fifteen days of the first dose, the second cycle of 500 mg rituximab was given. Following the second dose of rituximab, oral prednisolone was tapered. The patient was off systemic steroids in 2 months.

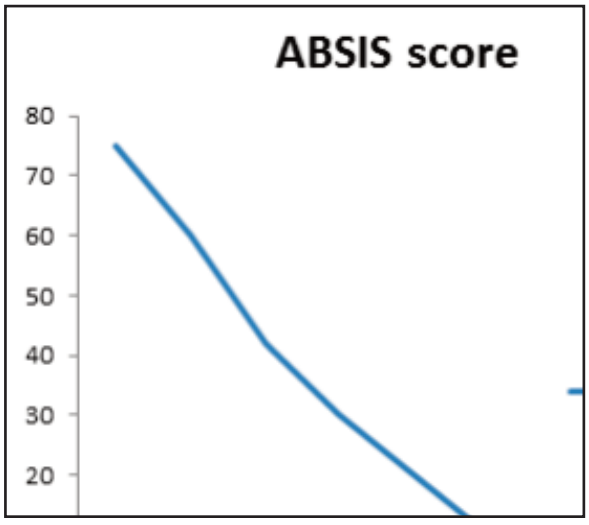


Figure 2. All the lesions healed well leaving behind hyperpigmented patches.

The patient was monitored biweekly till the 12th week and monthly thereafter, for 1 year. The patient did not develop any adverse effects during or post-infusion and is still in complete remission1, at the end of first year of treatment with rituximab.

The outcome was assessed using Autoimmune Bullous Skin disorder Intensity Score.(ABSIS) There was steady decline in ABSIS score (**Figure 2**). All the lesions healed well leaving behind hyperpigmented patches. Desmoglein 1 and 3 levels after 4 months of first rituximab infusion were 28RU/ml and 42RU/ml respectively

Discussion

PV is due to antibodies against desmoglein antigens 1 and 3. It is mainly a B-cell mediated disease. Systemic steroids are currently the mainstay of treatment in patients with PV. Steroid-sparing agents like azathioprine, mycophenolate mofetil, and cyclophosphamide are some of the immunosuppressants that are used in order to decrease the steroid induced toxicity. The efficacy of these steroid sparing agents has been controversial in treatment of PV2. Due to re-occurring nature of PV and side effects of the current therapy, we are compelled to look for other alternatives.

Based upon the rationale that pemphigus is a primarily an autoantibody driven autoimmune disorder, therapies that deplete auto reactive B cell clones have been investigated for the treatment of pemphigus [**3, 4, 5**]. Rituximab infusion decreases the CD 20 B cells levels but has no effect on plasma cells and stem cells. These plasma cells may produce antibodies

Tablo 1. Pemfigus Vulgaris Managements with Rituximab

Reference	Age (years)	Gender	Previous therapy	Rituximab Dosage	Side effects due to Rituximab	Outcome
Kanwer et al.(6)	9	Male	Systemic CS+AZA	375 mg / m2 BSA 2 doses 15 days apart	Angioedema	CR
Fuertes et al.(7)	14	Male	Systemic CS+AZA+DAP+oral gold	375 mg / m2 BSA weekly for 4 weeks	None	CR
Kanwer et al.(8)	11.5	Male	Systemic CS+AZA	375 mg / m2 BSA 2 doses 15 day apart	None	CR
Schmidt et al.(9)	14	Male	Systemic CS+AZA+IVIG+MMF+CYC+DAP	375 mg / m2 BSA weekly for 4 weeks+IVIG 1st and 4th week	None	CR

CS- corticosteroid; AZA-Azathioprine; DAP-Dapsone; IVIG-immunoglobulin; MMF-Mycophenolate Mofetil; PP- Plasmapheresis; CYC-Cyclosprine; CR- Complete remission

even after rituximab infusion, 5 with time as plasma cells die there is a decline in antibody titre as seen in our patient.

On reviewing the literature, we came across only four cases of childhood PV in which rituximab was used below the age of 15 years [**6,7,8,9**]. In all the reported cases, the PV was successfully managed with rituximab with no or minimal adverse effects (**Table 1**).

TOur case is the youngest patient to receive rituximab among them. We decided to use rituximab as the patient did not achieve long lasting remission with steroids, azathioprine or mycophenolate mofetil. The patient tolerated rituximab well and there was a significant decrease in desmoglein levels pre and post rituximab infusion.

Conclusion

To conclude, we suggest that rituximab can be an effective and safe treatment choice for refractory childhood PV not responding to conventional therapies. It's exact dosage and long term safety in the pediatric population is still unknown. Since childhood PV is a rare disease, large multicentric trials are required to explore the full potential of this drug in treating childhood PV.

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