A Case of Pediatric Pemphigus Treated with Rituximab – Our Experience

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Authors’ contributions

This work was carried out in collaboration between both authors. Author VB wrote the first draft of the manuscript and managed the literature searches. Author SV supervised the clinical and scientific work and contributed valuable remarks. Both authors read and approved the final manuscript.

ABSTRACT

Pemphigus vulgaris is an autoimmune blistering disease with great diagnostic and therapeutic challenge in the pediatric age group. The severe clinical course is often complicated with substantial morbidity and mortality, attributed to treatment side effects. Rituximab proves effective in cases unresponsive to conventional immunosuppressive therapy, corticosteroid-resistant patients and in those who experience unbearable and severe side effects. We present a recalcitrant case of juvenile pemphigus vulgaris treated with rituximab. Additionally, highlights of the currently reported cases of pediatric pemphigus, who received anti-CD20 monoclonal antibody therapy, are provided.

Keywords: Pemphigus; pediatric group; rituximab.

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1. INTRODUCTION

Pemphigus is an uncommon, potentially fatal, auto-immune blistering disease, affecting skin and mucosal membranes [1]. Childhood (0-12y) and adolescent (13-18y) onset is considered very rare [2]. Less than 100 cases have been reported worldwide, as most were misdiagnosed and undertreated [3]. The condition seems to affect both sexes equally, with a medium onset age of 12y [4]. The long-term prognosis and outcome is not known, however, it is largely accepted that morbidity and mortality is highly affiliated to therapeutic side effects, associated with conventional treatment modalities [5]. Safer treatment regimens are a must in the pediatric group, which is extremely vulnerable with lifelong implications.

2. CASE REPORT

A 14-year-old girl of Romani descent presented in our Department with multiple erosions, oval blisters covered with haemorrhagic crusts and flaccid blisters in November 2015 (Fig. 1). The lesions were distributed over the face; trunk and extremities at the total extend of 30% of her body surface area. A few erosions were detected on the hard palate. No past personal medical or family history was revealed. Haematoxylin and eosin staining of a skin biopsy specimen and direct immunofluorescence (IF) examinations were diagnostic for pemphigus vulgaris. Indirect IF on monkey oesophagus was strongly positive. ELISA revealed high values of anti-desmoglein 1 (Dsg1) and 3 (Dsg3) antibodies (Dsg1 = 270 RU/ml Dsg3 = 314 RU/ml, Cut-off < 20 RU/ml). Treatment with methylprednisolone 40 mg/day (body weight 36 kg) was initiated. Despite the quick epithelization achieved in the next 2 months, the reduction of daily dose to 20 mg methylprednisolone, resulted in a new flare. Meanwhile, concomitant side effects from the systemic corticosteroid use, including Cushings features, obesity, skin atrophy, striae, hypertrichosis and secondary skin infections had rapidly evolved (Fig. 2). Dapsone 25 mg/day was tried as a steroid-sparing agent with no improvement. Seven months after the initial manifestation, the patient returned with a relapse, involving mainly the sub mammary folds where extensive painful erosions with maceration and super infection were observed. Severe Cushing syndrome, growth retardation, menstrual irregularity, acne and depression were additional clinical issues. In an effort to achieve long-term control with a minimal steroid need, rituximab was administered. As no formal protocol in the pediatric group exists, we decided to use a body-weight regimen of 375 mg/m² body surface area twice, 30 days apart. Our decision was based exceptionally on financial grounds. The pre-rituximab evaluation included complete haemogram, liver and renal function tests, chest X ray, Mantoux test, viral markers - HBV, HCV, HIV and ECG. Treatment was tolerated well. Partial clinical remission was registered after the first infusion and full clinical response was achieved after the second one. The clinical observations partially correlated with ELISA anti-desmoglein 1 and 3 antibodies results (after the first infusion: Dsg1 = 255 RU/ml Dsg3 = 251 RU/ml; after the second infusion: Dsg1 = 202 RU/ml Dsg3 = 308 RU/ml). Full positive therapeutic response correlation was detected with the flow-cytometric B-cell analysis (before the infusion: B-Ly CD19+ = 14%; after the first infusion: B-Ly CD19+ = 0.4%; after the second infusion: B-Ly CD19+ = 0%). After rituximab treatment the patient continued using low-dose steroid therapy, which was gradually stopped in 6 month-period. No flare has been observed during the next 34 months of follow-up.

3. DISCUSSION

Pemphigus is extremely rare in pediatric population [6]. Recent study has shown an incidence of less than 5% of all patients with the disease [7]. Most reports are sporadic or with small series that lack data on therapeutic outcomes. Steroids continue to be a mainstream together with azathioprine, dapsone, mycophenolate mofetil, cyclophosphamide and intravenous immunoglobulins [8]. Rituximab, a chimeric anti-CD20 antibody, targets an integral membrane protein involved in B-cell activation and proliferation. It induces apoptosis of matured B cells while sparing progenitor cells and plasma cells, which continue to circulate and additionally produce specific antibodies [9]. This phenomenon may explain the progressive decline in the titers of the target antibodies that probably represent the lifespan of the long-lived plasma cells [10]. Moreover, B lymphocytes function is not strictly limited to clonal proliferation of plasma cell and antibody production. B cells also serve as antigen-presenting cells, produce cytokines and support auto reactive T cells. They may reside in some particular tissues such as joints in rheumatoid arthritis, thus surviving for a long time [10]. This multi-factorial nature of B lymphocytes, give rational of adding adjuvant chemotherapeutic
agents to the single rituximab therapy in autoimmune disease and explains the lack of prophylactic infusions efficacy [11].

Since July 2018 rituximab was labeled for US refractive severe-to-medium pemphigus patients and adapted a year later by the European Committee health authorities. The lymphoma protocol of 375mg/m² of BSA every other week until achieving clinical remission is recognized for adult patients [12,13]. Most of the pediatric cases are treated with a fixed-dose regimen of 500 mg given twice, 15 days apart. Two infusions of 375 mg/ m² of BSA in 15 days have also been used [14]. Clinical outcomes varied from partial clinical improvement with ongoing systemic immuno-suppressive therapy to complete remission off all therapy. The two-dose regimen is considered efficient and safer viable option with minimal risk of subsequent skin and systemic infections [15]. Our patient was treated with a modified two-dose regimen, done 30 days apart, exceptionally due to financial reasons. It proved highly efficient and long-standing, which encourages its further implementation.

![Clinical picture, November, 2015](image1.png)
Rituximab therapy usually ensures prolong remission [16]. The mean period to flare was reported as 13 months (a range of 8-20 months). Most of the relapses in children are mild and easily coped with a short course of steroid and azathioprine [17]. Severe flares, intolerant to conventional therapy, were successfully treated with additional rituximab infusions. Our patient achieved disease control after the first infusion and full clinical remission upon the second dose. The response is still sustained at the 34th month.
Rituximab is very well tolerated [18]. Mild infusion reactions are the most common immediate side effects. Most cases are managed by lowering the infusion rate and administration of antihistamines and systemic corticosteroids. Severe hyperactivity complications such as angiodema are extremely rare [19]. Elevated infection risk is considered higher in children that in adults, probably due to the different state of maturation of B cells in pediatric population. Staphylococcus aureus sepsis and meningitis are exceptional infectious side effects reported in the literature [20]. The suspicious higher infective risk requires a conservative low-dose therapeutic regimen, which therefore, is being recommended in pediatric age group. Our patient did not show any side effects.

4. CONCLUSION

In the era of targeted therapies, pemphigus treatment has also tremendously advanced. Many long-term studies of rituximab patients have left to its official recognition as a first line therapy in adult patients with pemphigus. The vulnerability of pediatric population and the low incidence of pemphigus in this age group do not allow profound clinical trials and exuberant scientific observations. Rituximab proves to be efficient, well-tolerated and safe in a low dose regimen, when used in children and adolescent with pemphigus. Long-term studies with larger numbers of patients to elucidate the perfect dosing recommendations are still required.

CONSENT

As per international standard or university standard, patient’s consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES