Treatment of a Refractory Case of Chronic Bullous Disease of Childhood in a Five Year Old Child with Rituximab

Abstract
Patients with chronic bullous disease of childhood (CBDC) generally respond well to treatment with drugs like Dapsone and oral and topical steroids. Refractory cases are additionally treated with immunosuppressants like azathioprine, methotrexate, ciclosporin, colchicine, tetracycline, and IVIG (Intravenous Immunoglobulin). However, there are few patients who fail to respond to these therapies and pose a challenge both to the patient and the treating physician. Rituximab has been widely used to treat pemphigus cases in adults, but its use in children has not been much reported. We hereby report a case of a 5-year-old child with CBDC, refractory to other treatments, who responded favorably to Rituximab.

Keywords: Chronic bullous disease of childhood, pediatric, Rituximab

Introduction
Chronic bullous disease of childhood (CBDC) is a rare, nonhereditary, autoimmune disease occurring most frequently in children with the peak of onset being below the age of 5 years.[1] The disease is characterized by sudden onset of tense vesicles and bullae arranged in a typical pattern termed as “cluster of pearls.” The lesions are predominantly present over the trunk and perineum and on the face mainly in periocular and perioral regions. Mucosal involvement is common (in about 70%), presenting mostly with oral erosions and ulcers.

CBDC is a recurrent disease and the aim of treatment is to achieve long-term remission with minimal side effects. Conventional therapies used include Dapsone, oral and topical corticosteroids, immunosuppressants like azathioprine, sulfapyridine, doxycycline, mycophenolate, and IVIG with variable results.

Rituximab has been widely used in the treatment of pemphigus cases. However, its role in children has not been widely elucidated, with only a few case reports and case series published on its use in the pediatric age group. We hereby report a case of 5-year-old child with CBDC refractory to other treatment options, treated successfully with Rituximab.

Case Report
A 5-year-old female child presented to the skin outpatient department with complaints of recurrent, multiple fluid-filled, itchy blisters all over the body for the last 8 months. The blisters ruptured spontaneously in 2–3 days leaving behind erosions. New blisters continued to appear at the periphery of healing erosions. The lesions healed with postinflammatory hypopigmentation without scarring. There was no history of mucosal involvement, drug intake, or similar lesions in the family. A general physical and systemic examination was normal. On cutaneous examination, multiple tense bullae and vesicles were present all over the body, predominantly on the trunk, arms, and face with the classic “cluster of jewel” appearance present at a few places [Figure 1]. Few areas showed moist erosions with an erythematous base. Palms, soles, mucosae, and nails were spared.

Past treatment history over the past 8 months included the use of oral corticosteroids, Dapsone, and even IVIG based on a diagnosis of CBDC.

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confirmed by histopathology (subepidermal bulla with predominant neutrophilic infiltrate) and direct immunofluorescence (linear deposition of IgA along the basement membrane zone). Despite all these treatments, the patient responded partially and new lesions continued to appear after tapering the dose of corticosteroids.

After admission at our center, all routine investigations were done, i.e. complete blood count, liver function tests, renal function tests, blood glucose levels, chest X-ray, and G6PD levels, which were within normal limits except leucocytosis (20,000 cells per mm\(^3\) with 51% neutrophils and 38% lymphocytes). HIV, Hepatitis B, and C serology were negative. Gram staining and Tzanck staining did not show any significant findings. Histopathological examination revealed the presence of subepidermal bulla. The bulla showed predominantly neutrophilic infiltrate, and overall histomorphology was consistent with CBDC [Figure 2].

Based on clinical and histopathological findings, a diagnosis of CBDC was reconfirmed and the patient was put on Dapsone 25 mg/day (2 mg/kg/day) and Dexamethasone 1 ml/day. The patient did not show any significant improvement after 10 days of therapy, hence Azathioprine 25 mg/day (2 mg/kg/day) was added. The patient still did not show significant improvement, so another cycle of IVIG in the dose of 2 g/kg body weight was given for 3 days.

Despite being treated with all possible conventional therapies, the patient did not show satisfactory response and continued to develop new lesions. At this point, we planned to administer injection Rituximab. The patient was treated with two doses of Rituximab—250 mg (375 mg/m\(^2\)) given 15 days apart while Azathioprine (2 mg/kg/day) and oral Prednisolone (0.5 mg/kg/day) were continued. The patient showed dramatic resolution of lesions after 4 weeks of therapy. Currently, the patient is in complete remission with tablet Azathioprine 25 mg (2 mg/kg/day), since 18 months of Rituximab treatment, while prednisolone has been gradually tapered and stopped [Figures 3 and 4].

**Discussion**

Rituximab is a chimeric anti-CD20 monoclonal antibody whose Fab portion binds specifically to the CD20 antigen located on the surface of pre-B and mature B lymphocytes and depletes the CD20+ B cells from the peripheral blood and lymphoid organs with depletions lasting for around 6 months or more, thus giving a longer remission.\(^{[2,3]}\)

Rituximab has been liberally used in the treatment of adult refractory vesiculobullous disorders, with the recent
upsurge in its use among the pediatric population.\cite{3,5-9} Buch et al.\cite{6} reported five childhood cases of vesiculobullous disorders (3: pemphigus vulgaris, 1: pemphigus foliaceus, and 1: CBDC) who maintained complete remission during the 6 months of follow-up period, along with a decline in the serum anti-DSG titers.

Kanwar and Vinay\cite{7} reviewed ten cases of childhood pemphigus (7: pemphigus vulgaris and 3: pemphigus foliaceus) aged between 9 and 17 years who received Rituximab and were followed up for a median period of 16 months. Overall 35 reported cases of pemphigus vulgaris have been treated with Rituximab, of which 15 of them were below 12 years of age, the youngest being a 2-year-old infant (erythrodermic pemphigus foliaceus).\cite{3,5-9}

A review of these reports shows the significant effectiveness of Rituximab in the treatment of various childhood blistering diseases. Our patient was successfully treated with Rituximab while maintaining long-term remission without any side effects, thus showing that Rituximab can be safely used in the pediatric population with excellent results, especially, if the disease fails to respond to other conventional therapies.

Rituximab is a novel agent for the treatment of refractory vesiculobullous disorders having a good safety profile. However, cost and access to therapy remain its biggest limitation. Use in the pemphigus group of disorders has been widely studied, but the role of Rituximab in pediatric pemphigoid group of disorders still needs to be explored through further studies.

**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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