Successful Treatment of Refractory Chronic Bullous Disease of Childhood with Rituximab

Abstract
Chronic bullous disease of childhood is a rare subepidermal bullous disease with a hallmark of linear IgA deposition along basement membrane zone seen on direct immunofluorescence. We report a case of a 2-year-old male child, who had recurrent and multiple bullous eruptions over body and he was not responding to conventional therapy. He had earlier developed a drug reaction to dapsone which is considered the drug of choice for this condition. We report successful management of this case with injection rituximab which is a chimeric monoclonal antibody against CD20, which is primarily found on the surface of B cells.

Keywords: Chronic bullous disease of childhood (CBDC), dapsone hypersensitivity, rituximab

Introduction
Linear IgA disease (LAD) is the most frequent autoimmune blistering disease in infants and children characterized by subepidermal blistering and exclusive or predominant binding of IgA along the dermato-epidermal junction (DEJ).

In children, it is commonly known as chronic bullous disease of childhood (CBDC).[1,2] Hallmark of the clinical lesions are tense blisters, vesicles and annular erythema, frequently arranged in annular fashion, which is known as ‘string-of-pearls’ or ‘crown of jewels’ appearance.[3]

The target antigen in its pathomechanism is 97-kDa or 120-kDa proteolytic fragment of BP-180 extracellular domain which gets bound by IgA antibodies.[4,5]

Usually, children of CBDC respond very well to oral dapsone along with topical steroids. In refractory cases, reports of flucloxacinill, erythromycin, tetracycline, nicotinamide, colchicines, methotrexate, ciclosporin, IVIG, azathioprine, mycophenolate, and immunoabsorption have been employed successfully.

There is only one case report of rituximab use in LAD of an adult with good result. We report a case in a 2-year-old child with recurrent blistering who could not respond or tolerate conventional systemic drugs later successfully treated by rituximab.

Case Report
A 2-year-old male child, presented with history of recurrent blisters from the last 18 months. It was insidious in onset, gradually progressive to involve face, trunk, and extremities with a predilection for the lower trunk, genital area and medial thighs. Most of the blisters used to rupture spontaneously with oozing of clear fluid and leaving behind raw areas. New crops of lesions used to appear along the periphery of healed or crusted lesions. There was associated history of recurrent oral ulcers and redness of eyes of same duration. Initially, blisters used to heal over 2 to 3 weeks spontaneously but from the last 9 months he was not disease free even after multiple consultations. There was no history of photosensitivity, prior drug intake, trauma, consanguinity or similar lesions in the family. The child had a past history of developing drug hypersensitivity to dapsone about 5 months back when he had developed fever, transaminitis, hypereosinophilia, and hepatosplenomegaly. He was managed with oral corticosteroids and dapsone was discontinued. He was administered systemic corticosteroid, erythromycin,
cyclosporine, methotrexate, and IVIG over the last 6 months without much benefit.

A general physical and systemic examination was normal. Dermatological examination revealed multiple, tense, discrete as well confluent vesicles, bullae and few erosions all over the body, particularly more intensively distributed over the buttocks, perineal region and lower limbs [Figure 1a]. Few erosions were present inside oral mucosa. The palms, soles and genital mucosae were spared. The characteristic annular arrangement of the vesicles/ bullae around a crusted, erythematous plaque, described as ‘string of pearls sign’ or ‘cluster of jewels’, was seen in many sites [Figure 1b].

Routine hematological and biochemical parameters, Gram stain, and Tzanck smear were essentially normal. Histopathology revealed subepidermal bulla with predominantly neutrophilic infiltration within the bulla and underlying upper dermis composed of neutrophils, eosinophils, and some lymphocytes [Figure 2a: 40× and b: 100 ×]. Direct immunofluorescence of the perilesional skin revealed linear deposition of IgA (++) along the basement membrane zone [Figure 3]. Based on the clinical, histopathological, and immunopathological features, a diagnosis of chronic bullous disease of childhood was made. Considering the past history of dapsone hypersensitivity along with no response to other second-line drugs he was planned for rituximab. He was further evaluated for any focus of infection by viral markers including HAV, HBV, HCV (Hepatitis A, B and C virus) and HIV, chest X-ray PA view, USG abdomen. All tests were essentially normal. The child was premedicated with injection hydrocortisone 100 mg, pheniramine maleate 22.75 mg, and oral paracetamol 200 mg thirty minutes prior to rituximab infusion. Injection rituximab infusion 200 mg was administered over 5–6 hour duration. Two doses of rituximab were given at 15 days intervals. The dose was calculated based on rituximab protocol for Paediatric Rheumatology issued by Oxford Pediatric and adolescent Rheumatology Centre at 375mg/m² and estimated body surface area of 0.53 m² for 11 kg weight. The child was monitored for infusion reactions and acute allergic events and later on monitored for reactivation of opportunistic infections. The skin lesions dried up without any scarring or residual deformity in the next 15 days [Figure 4]. The patient was followed up every month for the next 12 months. He is disease free till date when child is of three and half year of age.

Discussion

CBDC was initially considered to be variant of dermatitis herpetiformis but now it is well-recognized distinct clinical entity with unique clinical features.° It is considered to be the childhood variant of adult-onset disease Linear IgA disease because of overlapping immunogenetics and immunopathology.°

The pathomechanism of blister formation in CBDC is not fully understood, but it is likely that IgA-and complement-mediated neutrophil chemotaxis can create split at DEJ. The drugs like vancomycin and cephalosporine have been implicated in few case reports.°

Histopathology and direct immunofluorescence are diagnostic which will differentiate similar-looking conditions like bullous pemphigoid, dermatitis herpetiformis and mucous membrane pemphigoid.° Usually, this disease responds very well to first-line treatment like oral dapsone and topical steroid. Most children go into complete remission within 2 years of disease onset and only very rarely the disease persists after puberty even after multiple modalities of therapies.
Dapsone rarely can cause serious drug reaction leading to drug rash, eosinophilia, systemic symptoms (DRESS) also known as dapsone hypersensitivity syndrome or drug hypersensitivity syndrome. Our patients had also history of DRESS when he was first prescribed for his disease.

Rituximab, a chimeric monoclonal anti-CD20 antibody, acts by cell-mediated and complement-dependent cytotoxicity. Rituximab infusion not only helped in a quick clinical response in our patient but also led to a long-term remission.

The exact mechanism of action of Rituximab is not clear in CBDC; however, there are reports of disappearance of IgG deposits along dermo-epidermal junction after rituximab treatment, in a patient with IgG- and IgA-mediated mucous membrane pemphigoid.[12-14]

Recent studies also report successful management of recalcitrant adult-onset linear IgA disease with rituximab.[14,15] Rituximab is safe and well tolerated in most pediatric patients.[16] It has been used extensively in pediatric nephrotic syndrome, B-cell non-Hodgkin’s lymphoma, and several pediatric rheumatology patients with autoimmune diseases. However, rituximab has been associated with several serious adverse events, including fatal hepatitis induced by rituximab reactivation of hepatitis B virus[17] and progressive multifocal leukoencephalopathy.[18] The patient was screened for Hepatitis B and long-term follow-up for other complications is being done. Infusion reactions and allergic reactions are common and were avoided by pre-medication and controlling a slow drip rate of infusion.

**Conclusion**

Our case was challenging due to the extent of the lesions, past history of DRESS and no clinical response to short course of oral steroids and multiple other second-line systemic drugs. Our case had excellent outcome and good remission till date following two dosage of rituximab but larger study is required to recommend as an option for refractory CBDC.

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**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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