

A Case Report of the Use of Rituximab and the Epidermolysis Bullosa Disease Activity Scoring Index (EBDASI) in a Patient with Epidermolysis Bullosa Acquisita with Extensive Esophageal Involvement

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ABSTRACT A 49-year-old man with recalcitrant mechanobullous epidermolysis bullosa acquisita (EBA) with significant esophageal involvement was treated with rituximab. EBA is a chronic autoimmune subepidermal bullous disease. It is characterized by skin fragility and scarring caused by circulating and tissue bound antibodies to type VII collagen. EBA is often unresponsive or poorly responsive to conventional immunosuppressive therapies such as corticosteroids, methotrexate, and cyclosporine. The burden of long-term use of immunosuppressants also limits their use in the treatment of chronic autoimmune diseases such as EBA. Since a validated and objective way of measuring disease activity in patients with EBA has not been described, we used the Epidermolysis Bullosa Disease Activity Scoring Index (EBDASI), for hereditary EB, as a surrogate to measure disease severity and activity in our patient with EBA. After three courses of rituximab over three years, our patient has achieved near complete clinical remission from disease activity. The patient's response suggests that treatment with rituximab may be a valuable treatment regimen for severe mechanobullous EBA, which is demonstrated by paralleled declines in objective disease activity scores, the EBDASI. This is in line with recently observed beneficial effects of rituximab in the management of EBA.

KEY WORDS: EBDASI, epidermolysis bullosa acquisita, scoring index, rituximab

INTRODUCTION

In 1904, the term epidermolysis bullosa acquisita (EBA) was used for those who had developed features and symptoms similar to hereditary dystrophic EB later in life. This was due to the clinical similarities and overlap of features. EBA is characterized by skin fragility and sub-epidermal bullous formation with light trauma on both mucosal and cutaneous surfaces. Similar to dystrophic EB, the clinical presentation

and severity of disease can vary significantly between patients with EBA. Unlike hereditary EB, EBA is a rare acquired autoimmune bullous disease.

EBA is caused by circulating IgG autoantibodies against the type VII collagen found in anchoring fibrils that are expressed at the basement membrane zone of stratified squamous epithelia. This loss of skin cell adhesion causes severe subepidermal blistering

that presents as a chronic and relapsing disease that can lead to significant comorbidities and impact on patient quality of life. Conventional immunosuppressive therapy is often minimally effective and, due to its rarity, a validated score to measure disease activity does not exist.

The EBDASI was validated to measure the disease activity and damage in patients with genetic epidermolysis bullosa. Due to the clinical overlap between patients with EBA and hereditary dystrophic EB, we have appropriated the use of the EBDASI in our patient with EBA.

We present a case where rituximab was used to treat recalcitrant EBA with significant esophageal involvement. Our patient experienced almost complete clinical remission. The disappearance of mucocutaneous erosions was paralleled by the decline in EBDASI activity scores, the need for esophageal dilatations, and an improvement in quality of life measures and weight.

CASE REPORT

A 49-year-old man was diagnosed with EBA in 1994. His diagnosis was confirmed with a skin biopsy, direct and indirect immunofluorescence, and immunoblotting (1). Previous treatments included prednisone up to 200 mg/day, azathioprine, cyclosporine, dapsone, tetracyclines, photophoresis, and plasmapheresis. He was referred to our dermatology clinic in 2004 with a history of spontaneous blisters and extreme skin fragility especially on trauma-prone sites including the hands, feet, elbows, and knees. He suffered from the effects of extensive cutaneous and

mucosal ulceration with significant involvement of the esophagus and alimentary tract. He experienced pain on a daily basis. He could no longer work, was unable to tolerate solid food, and became socially isolated.

An examination of his skin noted multiple large patches of erosions on his buttocks, legs, shoulders, head and hands, and milia and dystrophy of his nails (Figure 1).

A history of hemoptysis and progressive dysphagia was investigated with a barium swallow. This demonstrated esophageal rings and pharyngeal and cervical webs. He was referred to a gastroenterologist, and severe narrowing of the cricopharyngeus was observed on endoscopic examination (Figure 1).

As his esophageal symptoms progressively worsened over time, he required an increasing number of dilatations. Between November 2006 and November 2012, prior to receiving rituximab therapy, he required ten esophageal dilatations to manage his dysphagia. These were each performed with the prophylactic corticosteroid cover (prednisone 1 mg/kg). Despite the dilatations, his dysphagia symptoms would progressively deteriorate within months of each dilatation. He was no longer able to tolerate solid food and by 2012 he weighed only 55 kg.

He had developed significant treatment-related comorbidities from long term systemic corticosteroid therapy. Skin atrophy, striae, poor wound healing, hypertension, and a bone mineral density scan demonstrated established osteoporosis. Despite aggressive therapy, he was only ever able to achieve poor disease control. After decades of only temporizing treatment, he was reluctant to try any new therapies.



Figure 1. Response of epidermolysis bullosa acquisita (EBA) cutaneous manifestations *before* and *after* rituximab. a) Hands *before*; b) Hands *after*; c) Endoscopic view of arytenoid cartilages *before*; d) Arytenoid cartilages *after*.

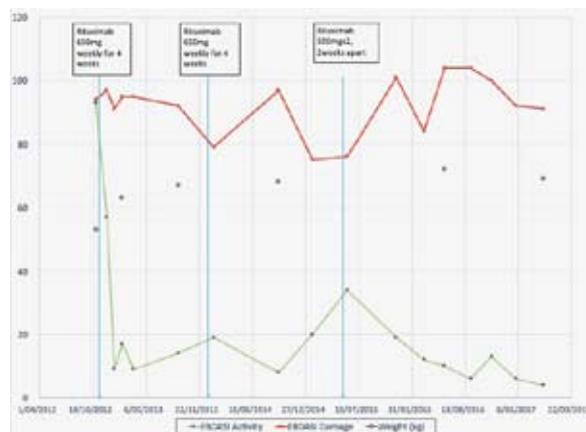


Figure 2. Epidermolysis Bullosa Disease Activity Scoring Index (EBDASI) score over time demonstrating reduction in EBDASI activity with each rituximab treatment (red arrows) and weight (kg).

With counselling and support he was persuaded to undergo his first course of rituximab, 375 mg/m²/week for four weeks in November 2012. Within the first month of the rituximab infusion there was progressive improvement of his clinical symptoms. An objective improvement in his EBDASI score was documented three months after his first treatment.

Over the following year there was a slow return of his symptoms and he received a second course of rituximab in April 2014. In June of 2015 he received his third course of rituximab, given as 1000 mg doses two weeks apart (Figure 2).

There was a discernible reduction in the number of esophageal dilatations our patient had required after commencing rituximab therapy. Within the initial 30 months after his first dose of rituximab from November 2012 to March 2016 he required eleven dilatations. Since April 2016 he has not needed any further esophageal treatments. Furthermore, since receiving rituximab he has been able to tolerate a solid diet with reduced discomfort and has subsequently gained 13 kg in weight, back to his pre-morbid weight of 68 kg.

To date, the disease continues to be manageable. More importantly he has gained a significant improvement in his quality of life demonstrated by a reduction in Autoimmune Bullous Quality of Life (ABQOL) score that has been reduced from 39 to 7 and Treatment Autoimmune Quality of Life (TABQOL) scores, 26 to 14. He no longer requires special diet modifications and he has been able to return back to the workforce.

DISCUSSION

Epidermolysis bullosa acquisita (EBA) is very rare, autoimmune sub-epidermal bullous disease. It is characterized by skin fragility and scarring caused by antibodies to type VII collagen. This is the main collagen found in the anchoring fibrils that bind the epidermis to the dermis at the dermal epidermal junction. Damage to the anchoring fibrils causes potentially severe subepidermal blistering. There are five clinical variants of EBA: the traditional mechanobullous type, inflammatory bullous type, the MMP-like EBA, IgA EBA, and Brunsting Perry like (2). His phenotype was unusual in being classical and extensive in his skin but also severe in the esophagus. The severity of disease can vary across a wide spectrum, from some patients only experiencing skin fragility to those who suffer significant epithelial and mucosal involvement, including esophageal and anorectal disease. Esophageal involvement can lead to stricture formation and significant morbidity.

As the name suggests, EBA is an acquired disease that has characteristics similar to that of the genetic dystrophic epidermolysis bullosa. However, unlike hereditary EB, a validated disease activity scoring system does not exist for EBA. In 2012, the EBDASI was validated to measure the disease activity and damage in patients with the genetic disease epidermolysis bullosa (EB). It scores disease activity and damage separately. It measures skin, mucous membrane, and hair and nail involvement (3). This scoring tool has been valuable in objectively measuring and monitoring disease progression and treatment response in patients with genetic EB. Due to the clinical overlap between dystrophic EB and EBA, we have used it in a patient with EBA. We also used the Autoimmune Bullous Quality of Life (ABQOL) and Treatment Autoimmune Bullous Quality of Life (TABQOL) to measure the effect of disease and treatment on the quality of life (QOL) in our patient (4).

EBA often fails to respond to conventional therapy or only provides short term improvement. Conventional therapy is usually considered to be high-dose systemic corticosteroids in conjunction with adjuvant immunosuppressive therapy. With the management of esophageal involvement several reports suggest a variety of treatments, varying from conservative management, dilation with prophylactic prednisone therapy, and endoscopic treatment with thermoplastic dilators and intra-lesional steroid injections (5-7). Esophageal dilatations with prednisone or dexamethasone cover provided temporary relief for our patient and he continued to require an increasing number of dilatations to maintain their effect.

The burden of adverse effects due to the long-term use of systemic corticosteroids limits their use in a chronic and relapsing disease such as EBA. In recent times, rituximab has been described as presenting an alternative modality for patients with EBA that is unresponsive to conventional treatment or limited by the adverse effect profile (8-13). B-cells in autoimmune diseases such as EBA play a role in antigen presentation, regulation of inflammation, and production of autoantibodies. Rituximab is a humanized monoclonal antibody which causes B-cell depletion by binding to the CD20 molecule expressed on these cells. Our patient initially received the more often used lymphoma dosing regimen (375 mg/m² weekly for four weeks) for the first two doses. He then received the rheumatoid arthritis regimen (1000 mg doses given two weeks apart) for the third dose. This is based on the idea that autoimmune diseases such as EBA have a lower B-cell burden than lymphoma and therefore should not require such high doses. However, the optimal dosing for rituximab in EBA has not been established.



With the introduction of rituximab therapy, the patient has not required any further dilations since April 2016. The reduction in his EBDASI activity scores parallels this clinical improvement. There was a marked reduction in his disease severity scores within three months of his initial dose of rituximab. Over time, there was progressive return of his symptoms and he consequently received a second dose a year later. This was followed with further improvement of his symptoms that was consolidated with his last dose of rituximab in 2016.

CONCLUSION

The EBDASI is a useful surrogate scoring tool to measure the disease severity, damage, and activity in patients with EBA. This tool was used to demonstrate the response to rituximab in our patients with recalcitrant EBA. Rituximab, used as a sole agent, achieved near complete remission in a patient with severe, recalcitrant EBA resulting in considerable improvement in QOL and weight, with the use of the EBDASI to document the reduction in disease activity in a patient with EBA.

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