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Case Report

Epidermolysis Bullosa Acquisita Responsive to Topical Steroid Therapy - A Report of Two Cases

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Abstract

Epidermolysis Bullosa Acquisita (EBA) is a chronic subepidermal blistering autoimmune disease that is frequently resistant to therapy. Systemic steroids are usually the first choice for treatment of EBA, and other immunosuppressants are sometimes required. Long-term corticosteroid puts patients at risk of serious complications, such as development of hypertension, diabetes mellitus, and osteoporosis. Here we report two patients with generalized EBA, Patient 1 had growth retardation due to the long-time use of systemic steroids and cyclosporin, and patient 2 declined systemic medications due to personal reasons, treated with topical steroids, and achieved complete remission.

Keywords: Epidermolysis bullosa acquisita; Topical steroids; Growth retardation

Abbreviations

EBA: Epidermolysis Bullosa Acquisita; COL7: VII Collagen; BP: Bullous Pemphigoid; DIF: Direct Immunofluorescence; BMZ: Basement Membrane Zone; ROS: Reactive Oxygen Species

Introduction

EBA is an acquired mechanobullous disease, characterized clinically by blisters and erosions of skin and mucous membranes [1]. The circulating immunoglobulin antibodies in EBA react with type VII Collagen (COL7), located at the dermal-epidermal junction. Treatment of EBA can be challenging, primarily consists of systemic steroids, and often with immunosuppressive agents which include azathioprine and cyclophosphamide. In the present report, we describe two patients with generalized EBA, both experienced complete remission with topical steroid therapy.

Case Presentation

Case 1

A 15-year-old girl was referred to our department for treatment of a bullous eruption that began 9 years ago. A diagnosis of Bullous Pemphigoid (BP) was made based on a skin biopsy that demonstrated a sub epidermal blister with few eosinophils. No immunofluorescence examination was performed. She was treated with oral prednisone 35mg per day which soon stopped the blister and erosion formation. Prednisone was gradually decreased to 15mg per day along with cyclosporine A 50mg two times daily. During the past 9 years, she suffered from moon face, hirsutism, and growth retardation, thus she stopped all systemic medications one year ago. Physical examination revealed multiple small tense blisters and erythema on the forearms, hands, legs, and lower back. She had no family history of Epidermolysis Bullosa. Antibodies to BP180, and BP 230 were not detected in the patient's serum by ELISA.

Direct Immunofluorescence (DIF) examination of a biopsy specimen from an erythematous lesion indicated the deposition of Immunoglobulin G (IgG) and C3 at the Basement Membrane Zone (BMZ). Salt-spilt DIF showed linear IgG deposition along the dermal side of BMZ.

Considering the side-effect of long-term steroid and cyclosporin A treatment this patient had experienced, we prescribed topical corticosteroid-0.05% halometasone cream topically (20g/d), lesions mostly healed without developing new blister, reduced to 10g/d for one month, then she stopped the topical medication. During the follow-up for 3 months, no recurrence was observed.

Case 2

A 25-year-old male, presented with a one-year history of many bullae and erythematous lesions on the skin over his entire body. He denied any history of allergic reactions. Physical examination revealed erythematous macules of various sizes, and some tense blisters with clear liquid, involving trunk and limbs. Nikolsky's sign was negative. The oral mucosa and nails were normal. The patient's serum sample was negative for antinuclear antibody, anti-ENA antibody, anti-dsDNA, and antineutrophil cytoplasmic antibody.

Skin biopsies for routine hematoxylin and DIF study were taken from leg lesions. Histological examination showed a subepidermal blister and intense infiltration of lymphocytes and neutrophils in the papillary dermis. Skin DIF revealed linear IgG deposition in the BMZ. Salt-spilt skin DIF revealed linear IgG and C3 fluorescent deposition along the dermal side of the BMZ. IIF showed no fluorescent in the BMZ.

The clinical and immunopathological features were consistent with EBA. The patient rejected the systemic therapy due to his immediate plan to have a child. So he received 0.05% halometasone cream topically (30g/d) for 10 consecutive days, when the lesions resolved partially, halometasone cream was reduced to 20g/d. His skin lesions completely resolved within total 3 weeks, then he stopped the topical medication. During the 6-month follow-up, no new lesion occurred.

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Discussion

EBA has two major clinical subtypes: an inflammatory and a non-inflammatory type. The mechanobullous, non-inflammatory form of EBA, so-called classic EBA, comprises the majority cases, and is characterized by skin fragility, blisters, and erosions at sites of trauma. A less frequent inflammatory type clinically can mimic BP and other blistering diseases [2]. In our report, both cases presented as inflammatory subtype.

COL7 was identified as the autoantigen in EBA approximately 30 years ago [3]. In most EBA patients, the auto antibodies are IgG. DIF demonstrates linear deposits of IgG and/or C3 at the dermal-epidermal junction. Salt-spilt DIF shows linear IgG deposition along the dermal side of BMZ, which differentiates EBA from pemphigoid varians. Based on the clinical presentation, the detection of tissue-bound antibodies by DIF microscopy with salt-spilt skin, we established the diagnosis of EBA for both cases. For EBA, the inflammatory forms are associated with a neutrophils-rich infiltrate with variable numbers of eosinophils and mononuclear cells [4]. An antibody transfer model of EBA has been proposed in which the disease manifestation depends on neutrophils and neutrophils activation [5]. Incubation of neutrophils with fixed immune complex causes the release of Reactive Oxygen Species (ROS) from the neutrophils that ultimately results in a separation of the epidermis from the dermis.

EBA patients are often refractory to high doses of systemic corticosteroids, azathioprine, cyclophosphamide. Long-term systemic corticosteroids have been shown to be associated with systemic infection, gastrointestinal disorders, hypertension, moon face, diabetes mellitus, osteoporosis, hyperlipidemia and obesity. Adverse drug reactions with azathioprine occur in 15% to 30% of patients and include leucopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity. Cyclophosphamide is itself carcinogenic, potentially causing transitional cell carcinoma of the bladder [6]. Other newly reported therapies include IVIG, and rituximab [1]. Although reported effective in some cases and less severe side effects of immunosuppression, it can be costly [7]. Thus, we should take all the risks into consideration to identify a safe and effective therapy of EBA. We used a super potent topical corticosteroid to treat both patients, and obtained satisfactory outcomes. Topical steroid therapy is a known effective treatment for localized forms of EBA [8]. There was only one reported case on successful topical steroid therapy for a generalized EBA, an EBA patient associated with chronic hepatitis C [9]. Topical application of corticosteroids has been documented among the most effective therapeutic options of BP. In 2013, Hellberg et al. investigated the effects of methylprednisolone on human neutrophils as BP can be efficiently treated with either topical or systemic glucocortiocoids [5,10] : 1. methylprednisolone might directly block neutrophils activation. 2. methylprednisolone could block the production of reactive ROSin activated neutrophils. 3. Methylprednisolone dose-dependently inhibits auto antibody-induced dermal-epidermal separation. Besides non-transcriptional mechanisms, steroid use either topically or systemically blocks the expression of pro-inflammatory genes and induces the transcription of anti-inflammatory genes. Hence, topical corticosteroid therapy is effective for BP and due to the absence of systemic adverse effects, it appears to be superior to oral corticosteroid for extensive disease [11].

Our report provides the evidence that topical steroid may be an effective treatment in generalized EBA. We suggest to consider the topical potent steroid as a first-line treatment option for inflammatory generalized EBA, especially for pediatric patients whom the long-term systemic therapy impedes their growth. Whether the topical steroid is effective for non-inflammatory EBA is yet to be investigated.

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