Childhood-Onset Epidermolysis Bullosa Acquisita Successfully Treated with Colchicine and a Super-potent Topical Corticosteroid: A Case Report

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ABSTRACT:
Epidermolysis bullosa acquisita (EBA) is an uncommon autoimmune disorder that results in subepidermal blister formation. The clinical manifestations vary depending on subtype. In the classical form, tense bullae or erosions present on non-inflamed skin, accompanied by scars and milia in trauma-prone areas. In the non-classical form, blisters can appear on both non-inflamed and inflamed skin, resembling other autoimmune blistering diseases. The diagnosis relies on histology, immunofluorescence, and serological testing demonstrating autoantibody targeting type-VII collagen which is an element of anchoring fibrils located at sublamina densa of the basement membrane in skin and mucosal tissues. The treatment is challenging since the data on the efficacy of therapeutic options is still scarce. Herein, we reported a rare childhood-onset EBA case successfully treated with colchicine and a super-potent topical corticosteroid.
Key words: Epidermolysis Bullosa Acquisita, Subepidermal Autoimmune Bullous Disease

Case report

A 23-year-old female had generalized bullous lesions without history of mucosal involvement for 15 years, which have appeared both spontaneously and following trauma. Initially appearing in childhood, she was evaluated at a pediatric hospital, where a skin biopsy demonstrated subepidermal blisters containing eosinophils admixed with neutrophilic infiltration. Direct immunofluorescence (DIF) exhibited linear deposits of immunoglobulin (Ig) G (IgG), n M IgM, IgA, and complement 3 (C3) at the dermo-epidermal junction (DEJ). Furthermore, anti-basement membrane zone antibodies titer of 1:640 was detected by indirect immunofluorescence (IIF). Treatment with systemic prednisolone partially improved symptoms; however, she stopped follow-up and used over-the-counter topical corticosteroids. Persistent lesions prompted her visit to our institution. She had no family history of bullous diseases.

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Physical examination revealed generalized erythematous plaques with superficial erosion, crust, and a few tense bullae on urticarial plaques on face, trunk and extremities without mucosal or nail involvement. Scarring and milia were also evident (Figure 1). Multiple dental caries were noted.

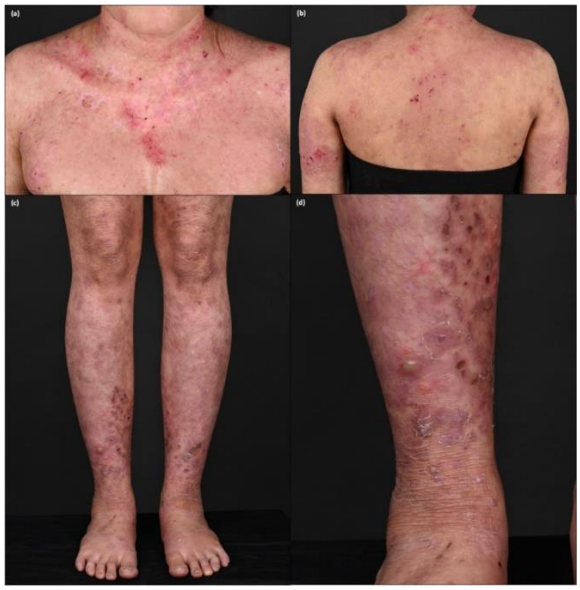

Figure 1 The patient presented with generalized erythematous erosive plaques (a-d) and a tense bulla on the lower leg (c-d). Scar and milia formation is noted (a-b)

Histopathology revealed the predominant eosinophilic infiltration with some neutrophils within a subepidermal blister (Figure 2). DIF showed linear deposits of C3 and IgG at the DEJ, and IgM exhibited a granular pattern at the DEJ and colloid bodies. Direct salt-split skin testing revealed IgG and C3 staining at the blister floor (Figure 2). Based on the clinical presentation, histopathology, and linear floor staining on DIF, the differential diagnoses encompass epidermolysis bullosa acquisita (EBA), anti-p200/laminin gamma-1 pemphigoid, anti-laminin 332 pemphigoid, and bullous systemic lupus erythematosus (SLE).

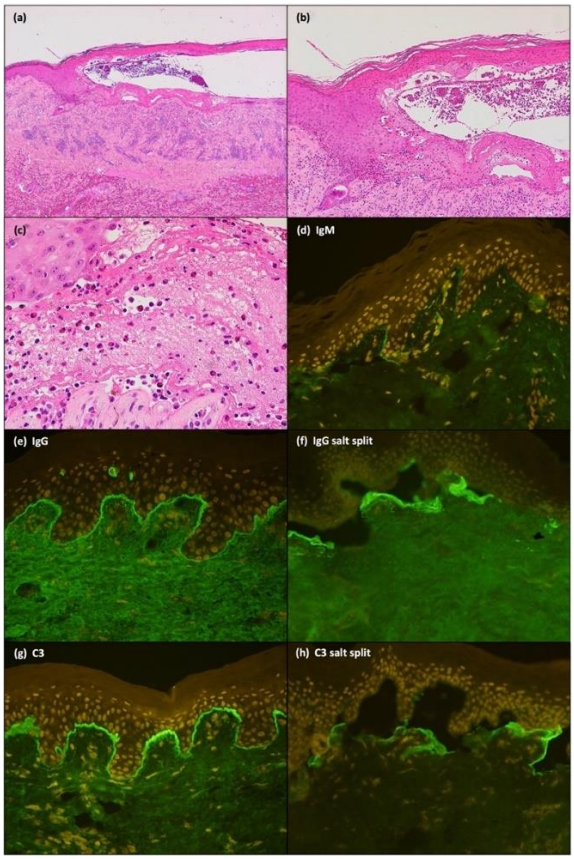

Figure 2 Histopathology revealed subepidermal separation with predominant eosinophilic infiltration, along with some neutrophils (a-c; X40, X100, and X400 magnifications, respectively). A DIF study showed granular deposition of IgM at the DEJ (X400 magnification) (d), and linear deposits of IgG and C3 with staining of the blister floor upon direct salt-split skin testing (X400 magnification) (e-h)

IIF testing was negative, while the anti-type VII collagen enzyme-linked immunosorbent assay (ELISA) detecting non-collagenous domain 1 (Euroimmun, Lübeck, Germany) reported a positive result of 34.37 RU/mL (positive > 20 RU/mL). The differential diagnosis was narrowed down to bullous SLE and EBA. Notably, the patient did not have

systemic symptoms of SLE, and complete blood count, liver function tests, creatinine, urinalysis, and chest X-ray, were normal. Additionally, antinuclear antibody testing (ANA) was negative, further corroborating the diagnosis of EBA.

Discussion

Epidermolysis bullosa acquisita (EBA) is uncommon. The estimated prevalence is less than 0.5 cases per million people[1,2]. The onset typically peaks in the second and seventh decades of life[1,2]. EBA is an exceptionally rare condition in the pediatric population[3,4]. From our literature review, fewer than 90 cases of pediatric EBA were identified.

In EBA, the autoantibodies target type VII collagen (COL7), which is a component of anchoring fibrils that connect the lamina densa to the papillary dermis within the basement membrane of the skin and mucosal tissues[2]. It is composed of a 145 kDa N-terminal non-collagenous (NC1) domain, a 34 kDa carboxyl-terminal non-collagenous (NC2) domain, and a 145 kDa triple-helical collagenous domain[2]. In most patients, the autoantigen identified is NC1[1,2]. The autoantibody against COL7 binds to the DEJ and promotes complement activation, inflammatory cascade and leukocyte chemotaxis[1]. Upon activation by skin-bound immune complexes via Fc receptors, neutrophils release reactive oxygen species and matrix metalloproteases, causing tissue damage[1]. While macrophages and T lymphocytes may contribute to the pathogenesis, neutrophils play an essential role in blister formation[1]. In the resolution phase, overexpression of Flightless I, an actin remodeling protein, impairs tight junction protein expression, causing delayed recovery[1].

Clinical presentation of EBA is categorized into the classical and the non-classical form[1,5]. In the classical or mechanobullous form, the skin is fragile, and bullae typically appear on non-inflamed skin in trauma-prone areas, healed by scars and milia[5]. Conversely, in non-classical form, bullous lesions are on inflammatory and non-inflammatory areas[2]. Subtypes of the non-classical form include bullous pemphigoid-like EBA (BP-like EBA), mucous membrane-EBA (MM-EBA), Brunsting-Perry-type EBA, and linear IgA bullous disease-like EBA[5]. Mucosal involvement varies among subtypes, with MM-EBA showing predominant involvement[1]. The classical form is more common in Europe, whereas the inflammatory subtype is more prevalent in Asia[5]. Clinical presentations of EBA in children differ from those in adults[3, 4]. While the classic mechanobullous form is common in adults, most pediatric cases, as highlighted in a case series by Zhang et al. from China, exhibit inflammatory phenotypes[3,4]. In this series, all seven pediatric patients showed BP-like or inflammatory characteristics[4]. Likewise, our patient exhibits mixed phenotypes, with predominantly BP-like EBA and minor features of the mechanobullous form.

Biopsy findings in EBA typically reveal subepidermal separation[2]. In the mechanobullous form, the infiltration is sparse, while inflammatory EBA exhibits inflammatory cell infiltration, including neutrophils, eosinophils, and lymphocytes[1,2]. Histopathology alone is insufficient to distinguish EBA from other autoimmune bullous disease, and definite diagnosis requires immunofluorescent analysis, circulating autoantibodies detection, or immunoelectron microscopy[1,2]. Circulating antibodies against COL7 can be detected through several methods: IgG deposition on the blister floor using salt-split IIF, IgG interacting with the 290-kDa antigen on immunoblotting, or ELISA, where concentrations of anti-COL7 antibodies are associated with disease severity[1,2]. A sensitivity of 50% is achieved using salt-split IIF combined with ELISA; therefore, EBA could not be excluded based on a negative serological test, and DIF might be helpful in diagnosis[1]. In DIF,

linear deposits of immunoglobulin or complement are present at the DEJ with a u-serrated pattern[2]. IgG and C3 staining is commonly observed in more than 90% of cases, while IgA and IgM staining may also occur[2,6,7].

In our case, clinical presentation and laboratory findings narrowed the differential diagnosis to either EBA or bullous SLE, both exhibiting anti-COL7 autoantibodies. In bullous SLE, patients typically manifest widespread tense vesicles, often on sun-exposed areas, along with other clinical features of SLE[8]. Notably, the healing process is characterized by post-inflammatory dyspigmentation rather than the scar observed in EBA[8]. Additionally, serum markers such as ANA are positive in most cases[8]. Although the DIF of the patient showed linear and granular immunoglobulin deposition at DEJ, which could suggest bullous SLE, our patient was diagnosed with EBA due to widespread milia and scarring, absence of other SLE features, and negative ANA.

Since EBA is rare, no randomized control trial for treatment was conducted[1]. Systemic corticosteroids are regarded as the primary treatment option[1,2]. Steroid-sparing treatments include colchicine, dapsone, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil[1,2]. In pediatric patients, systemic corticosteroids combined with dapsone are the most commonly used regimen. Monotherapy with dapsone was reported to achieve complete remission in 4 cases[4,6,9,10]. To our knowledge, there is no data on the use of colchicine in childhood-onset EBA. However, we considered using colchicine monotherapy because of the mild disease activity, the patient's concerns about systemic corticosteroids' side effects, and the safety profile of colchicine. After two months of treatment with 1.2 mg/day of colchicine, no new lesions developed. The same dosage was continued for the following three months, during which no spontaneous lesions appeared, although a few bullae formed after trauma. Subsequently, she was lost to follow-up.

In conclusion, we reported a rare childhood-onset EBA case. Our patient is successfully treated with topical corticosteroids with colchicine, which some experts consider the first-line treatment for EBA, especially in milder cases, owing to comparatively milder side effects than other therapeutic alternatives.[1]

Statements

Statement of Ethics

Prior to publication, informed consent was received from the patient. According to our local ethics committees, ethical approval is not required.

According to institutional guidelines, ethical approval was not required.

Conflict of Interest Statement

There are no conflicts of interest to declare.

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