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CASE REPORT

Treatment conundrum: A case of recalcitrant Epidermolysis Bullosa Acquisita (EBA) in a 50-year-old Filipino male

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ABSTRACT

INTRODUCTION Epidermolysis Bullosa Acquisita (EBA) is a rare autoimmune blistering disease which presents in the skin and mucous membranes. The decrease in anchoring fibrils in the basement membrane zone causes separation of the epidermis from the dermis, resulting in its blistering presentation. The treatment plan will depend on the severity of the disease. The first-line treatment for mild EBA includes topical corticosteroids and immunomodulators such as dapsone and colchicine; while severe cases of EBA may be given intravenous immunoglobulins, systemic steroids, and immunosuppressants such as azathioprine and cyclophosphamide.

CASE REPORT This is a case of a 50-year-old Filipino male who presented with a 2-year history of vesicles and tense bullae which evolved into papules, plaques and erosions with scarring and milia formation on the scalp and trauma-prone areas of the trunk and extremities. Clinical examination revealed multiple, well-defined, irregularly shaped erythematous papules and plaques with crusts, scales, erosions, pearl-like milia and scarring on the chest, back, upper, and lower extremities. The oral mucosa was moist with some ulcers on the tongue. Histopathologic examination using Hematoxylin and Eosin (H&E) stain revealed the absence of the epidermis with retention of dermal papillae suggestive of subepidermal clefting. Further examination with direct immunofluorescence (DIF) revealed monoclonal immunoglobulin (IgG) deposits demonstrating an intense linear fluorescent band at the dermoepidermal junction, consistent with Epidermolysis Bullosa Acquisita. Overall, the combined administration of prednisone, azathioprine, and colchicine resulted only in transient and incomplete resolution of lesions in this case of EBA.

CONCLUSION The management of EBA is mostly supportive with the goal of minimizing complications. Combination treatments using steroids, colchicine, and azathioprine have been reported with various results. Its management remains challenging as most cases are refractory to treatment.

KEYWORDS Epidermolysis Bullosa Acquisita, blistering disease, bullous disease, azathioprine, colchicine, prednisone, direct immunofluorescence study

INTRODUCTION

Epidermolysis Bullosa Acquisita (EBA) is a rare autoimmune blistering disease which presents in the skin and mucous membranes. Long-term remission in EBA patients is difficult to achieve. The combined administration of prednisone, azathioprine, and colchicine resulted only in transient and incomplete resolution of lesions in this case of EBA.

CASE SUMMARY

A 50-year-old Filipino male was initially seen via teledermatology with a 2-year history of vesicles and tense bullae which evolved into papules, plaques and erosions with scarring and milia formation on the scalp and trauma-prone areas of the trunk and extremities. The patient also experienced occasional constipation, for which no consult was sought. He was previously seen and managed by a private dermatologist who advised skin biopsy, but it was not done due to insufficient funds. He was then managed clinically as a case of pustular psoriasis and was prescribed bilastine 20 mg once a day for seven (7) days, amoxicillin + clavulanic acid 625 mg/capsule twice a day for 7 days, and isotretinoin 10 mg once a day for three (3) months. He was also prescribed clobetasol propionate ointment twice a day for two (2) weeks and mupirocin ointment twice a day for seven (7) days with minimal improvement; hence, consultation at our institution.

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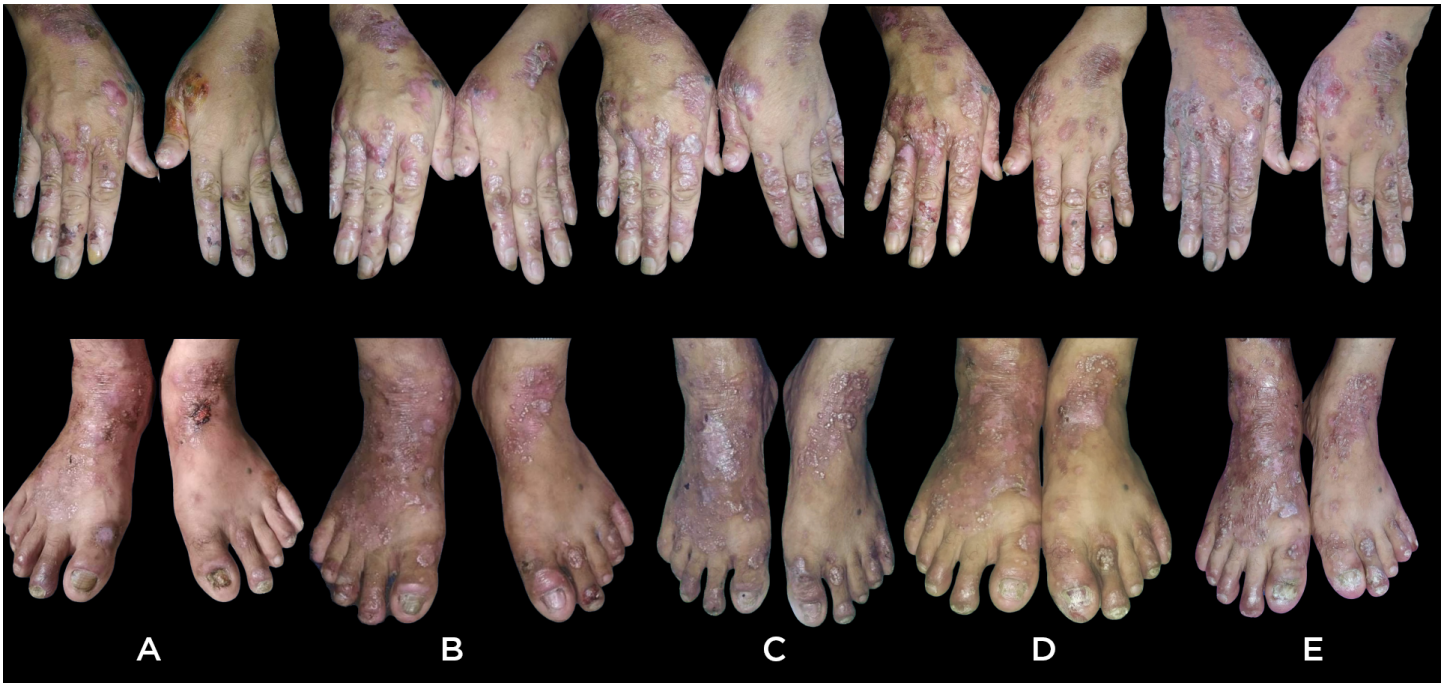

Figure 1. Baseline and follow-up photos while on medications. A. Initial consult. B. Week 4 of treatment on prednisone 30 mg/day. C. Week 12 of treatment on colchicine 1000 mcg/day and prednisone 30 mg/day. D. Week 20 of treatment on azathioprine 50 mg/day and prednisone 30 mg/day. E. Week 28 of treatment on azathioprine 150 mg/day and prednisone 20 mg/day.

On initial consultation, clinical examination revealed multiple, well-defined, irregularly shaped erythematous papules and plaques with crusts, scales, erosions, pearl-like milia, and scarring on the chest, back, upper, and lower extremities. The oral mucosa was moist with some ulcers on the tongue. Onycholysis and subungual hyperkeratosis were appreciated on the nails of the hands and feet, as well as onychomadesis on the first digit of the left foot (Figure 1). A 4-mm skin punch biopsy was taken from a fresh bulla for routine histologic examination and another specimen on perilesional skin for direct immunofluorescence (DIF). The histopathologic examination using Hematoxylin and Eosin (H&E) stain revealed the absence of the epidermis with retention of dermal papillae suggestive of subepidermal clefting. On high power view, sparse superficial perivascular infiltrates consisting of lymphocytes and eosinophils were also identified. The DIF revealed monoclonal immunoglobulin (IgG) deposits which demonstrated an intense linear fluorescent band at the dermoepidermal junction (Figure 2). Other diagnostic tests such as complete blood count, urinalysis, fasting blood sugar, lipid profile, kidney and liver function tests were all normal.

With the clinical, histopathologic, and immunofluorescence findings, a diagnosis of epidermolysis bullosa acquisita was made. The patient was started on clindamycin 300 mg capsule every 6 hours for one (1) week to address an ongoing secondary bacterial infection, prednisone 40 mg once a day (0.6 mg/kg/day) and topical corticosteroids. Supportive management such as cetirizine, mupirocin 2% ointment and an oral gargle of sucralfate 4mg + aluminum hydroxide + magnesium hydroxide 60ml + diphenhydramine hydrochloride 12.5/5ml 30ml were also prescribed. For wound cleaning, mild soap and the use of normal saline solution (NSS) were advised. After the first two (2) weeks of medications with good compliance, there was minimal improvement, noted as flattening and drying of the lesions with no development of new bullae.

However, upon the decrease of prednisone dose to 30 mg/day on week 4, new bullae developed and he was started on colchicine 500 mcg/day. The colchicine dose was gradually increased up to 2500 mcg/day by week 18. On week 20, the patient noted the appearance of new bullae on areas previously clear of lesions such as the trunk and back, despite being on colchicine 2500 mcg/day and prednisone 30 mg/day. Colchicine was shifted to azathioprine by week 21, initially at 50 mg/day then gradually increased to 150 mg/day. Around this time, the patient complained of increased frequency and severity of his constipation,

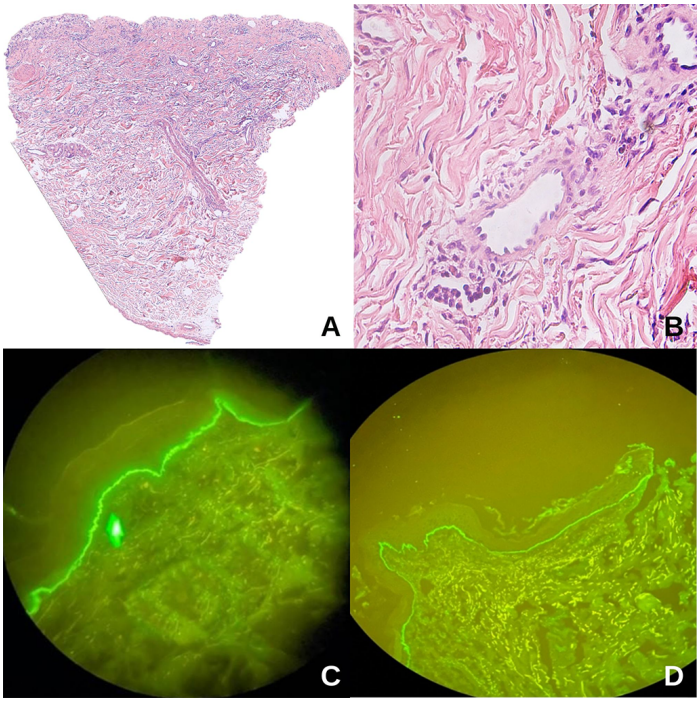

Figure 2. A. Absence of the epidermis with retention of dermal papillae suggestive of subepidermal clefting (H&E, 4x); B. Sparse superficial perivascular infiltrates consisting of lymphocytes and eosinophils (H&E, 40x); C. Direct immunofluorescence studies showed (+) Linear IgG; D. Grade 3 and (+) Linear C3, Grade 2.

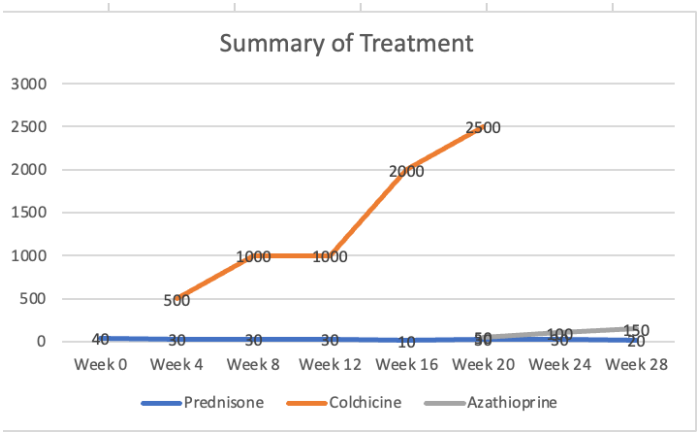

Figure 3. Summary of medications given from weeks 0 to 28.

with pain on defecation. Colonoscopy was requested but it was not done due to financial constraints. Instead, supportive management such as fiber supplementation was advised. Skin care was also recommended which included avoidance of trauma and infection; as well as the use of the following topical corticosteroids on affected areas to facilitate healing: mometasone furoate 0.1% cream and hydrocortisone 1% cream for the face, and betamethasone valerate cream, halobetasol propionate 0.05% ointment, clobetasol propionate 0.05% ointment, and betamethasone dipropionate 0.05% ointment for the body. These topical corticosteroids were prescribed to be used alternately, every two (2) weeks to prevent tachyphylaxis and minimize unfavorable side effects. The patient was managed for a total of 32 weeks with minimal improvement, until he was lost to follow-up.

DISCUSSION

Being a rare disease entity, EBA is estimated to occur in only 0.08 to 0.5 cases per million individuals which only accounts for 5% of the total cases of autoimmune diseases affecting the basement membrane.[1] The exact etiology of EBA is unknown, although it is largely associated with the presence of autoantibodies against type VII collagen, which is the major component of anchoring fibrils. The decrease in anchoring fibrils in the basement membrane zone causes separation of the epidermis from the dermis, resulting in the blistering presentation of the disease.[2]

As it is rarely seen, EBA may be misdiagnosed as other cutaneous diseases that present with vesicles and bullae. In this case, the patient was previously managed as a case of pustular psoriasis before being diagnosed with EBA at our institution. Another pitfall in the diagnosis of EBA is that clinical presentation may change over time. Vesicles and bullae may evolve into erosions and ulcerations, and one may fail to diagnose the patient as a blistering disease if the patient no longer presents with vesicles or bullae at the time of consultation. Thus, good history taking and clinical eye are of utmost importance in clinching the diagnosis. However, there are some cases where EBA may not present with blisters. Non-mechanobullous forms comprise the majority of EBA cases at 55%, while mechanobullous forms comprise only 38% and those with features of both, comprise 7%.[3] The classical or mechanobullous form is characterized by the appearance of skin fragility and tense vesicles or bullae with scarring and milia formation; usually noted on the extensor surfaces and trauma-prone areas of the skin.[3,4] In contrast, the non-classical or non-mechanobullous form lacks the appearance of blisters but may present with inflammation and urticaria which resolve without scarring and milia formation. This particular patient presented with the classical or mechanobullous form.

The management of EBA is mostly supportive with the goal of minimizing complications. The treatment plan will depend on the severity of the disease. The first-line treatment for mild EBA includes topical corticosteroids and immunomodulators, such as dapsone and colchicine. In severe cases of EBA, patients may be given intravenous immunoglobulins, systemic steroids, and immunosuppressants such as azathioprine and cyclophosphamide.[1]

Colchicine is usually the first immunomodulator of choice due to its relatively good safety profile and is initiated at dosages between 0.5 and 2.0 mg/day and then increased gradually.[4,5] Colchicine acts by modifying collagen synthesis, resulting in structural alterations rendering EBA antigens unrecognizable by autoantibodies.[6] In most studies, the therapeutic response was noted as early as 2 weeks.[3,6,7] There were two (2) EBA cases reported, in which colchicine was administered initially at 2 mg/day, with total clearance of the lesions achieved at 8-12 weeks.[7] However, caution must be taken when administering colchicine as it may lead to diarrhea and abdominal pain.[3] Due to partial response, azathioprine was eventually prescribed in our patient, as immunosuppressants are recommended for severe and refractory cases. Azathioprine is usually given at doses between 50-150 mg/day. Its side effects include pancreatitis, fever, rash, malaise, nausea, diarrhea, leukopenia, and hepatitis.[1,4] In one retrospective clinical analysis of 30 cases of EBA, one (1) patient was prescribed azathioprine 100 mg after being on a combination of methylprednisolone, dapsone, and colchicine for one (1) month with no remission.[8] Combination treatments using steroids, colchicine, and azathioprine have been reported with various results.

Pressing forward, the plan for this patient was to find the optimal dose of azathioprine. Moreover, a more in-depth gastrointestinal investigation may be warranted in this case, given the association of EBA and inflammatory bowel diseases (IBD) and the patient's history of constipation. A review of literature from 1969 to 2013 showed a total of 42 recorded cases of EBA co-existing with IBD; most were cases of Crohn's disease due in part to the presence of type VII collagen autoimmunity in Crohn's disease.[9]

CONCLUSION

EBA is a rare bullous disease that is very difficult to manage, as exemplified in this particular case. The management of EBA remains challenging, as most cases are refractory to treatment and there are very few randomized controlled trials, given the rarity of the disease. Thus, proper documentation of cases with its corresponding treatment may help guide dermatologists in managing such a rare disease and eventually lead to the development of proper treatment guidelines and algorithms.

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