Epidermolysis Bullosa Pruriginosa in a 12-Year-Old Male: A Case Report*

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ABSTRACT

Introduction: Epidermolysis Bullosa Pruriginosa (EBP) is a rare subtype of the inherited Dystrophic Epidermolysis Bullosa spectrum of diseases and results from a gene mutation in COL7A1. Though predominantly an autosomal dominant disease, autosomal recessive and even sporadic mutations have been reported.

Case Summary: We report a case of a 12-year-old Filipino male presenting with a chronic history of numerous scratching-induced blisters predominantly distributed on the extensor aspect of his arms and legs without concomitant oral lesions, nail dystrophy, or hair findings, and without a family history of similar lesions. Histopathologic assessment, Direct Immunofluorescence (DIF), and Indirect Immunofluorescence (IIF) showed a subepidermal split with scant inflammatory infiltrates, no immunofluorescence, and absent u-serrated linear immunofluorescence at the dermal-side of the Salt Split Skin slide, respectively, which were all consistent with EBP. Enzyme-Linked Immunosorbent Assay (ELISA) for Anti-Collagen VII antibodies was slightly elevated, which may suggest an alternative diagnosis of Epidermolysis Bullosa Acquisita (EBA). This slight elevation may be due to the mutated Collagen VII protein becoming antigenic and therefore provoking an immune response. To conclusively distinguish EBP from EBA, a COL7A1 gene mutation analysis was recommended. With a diagnosis of EBP cannot totally rule out EBA, the patient was initially managed with dapsone monotherapy, counseled regarding behavioral modification to reduce scratching and trauma, advised wound care and close monitoring for the development of oropharyngeal lesions, and recommended for COL7A1 genetic mutation analysis.

Conclusion: This report demonstrates a case of EBP with elevated Anti-Collagen VII antibodies. The distinction between EBP and EBA is important because this changes the management: EBP is largely supportive, while EBA may benefit from immunosuppressive therapy.

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INTRODUCTION

Epidermolysis Bullosa Pruriginosa (EBP) is a subtype of the inherited Dystrophic Epidermolysis Bullosa spectrum of disease, resulting from a gene mutation in COL7A1 leading to a glycine substitution within the triple helical collagen domain of the type VII collagen, which is a component of the anchoring fibrils that attach the dermis to the epidermis, rendering it dysfunctional. This is in contrast to Epidermolysis Bullosa Acquisita (EBA), which is an acquired autoimmune blistering disease where a breakdown in immune tolerance results in the production of IgG antibodies against Collagen VII. Both diseases result in skin fragility, wherein tense blisters form in response to trauma. The distinction between both diseases is important in the management and prognosis: EBA benefits from immunosuppressive therapy while the management of EBP is largely supportive.

In this paper, we present a case of a 12-year-old Filipino male that that appeared as a straightforward case of EBP, but Anti-Collagen VII IgG antibodies were found to be elevated through ELISA, and may point towards a diagnosis of EBA.

CASE

A 12-year-old male, Filipino, from Quezon City, Philippines, consulted for multiple blisters on the legs and arms after scratching.

2 years prior to consult, the patient's family noted first-onset erythematous to purplish plaques with tense blister formation after the patient scratches his lower legs. The patient was noted to have a history of habitual scratching of his legs in response to his emotional state, as well as rubbing and pinching the lesions on his feet. Prior to the onset of the skin lesions, there was no drug, vitamin, or food supplement intake, without history of blister formation in response to insect bites, intake of gluten-containing food, or sun exposure.

At this time, consult with a dermatologist was sought. The patient was clinically assessed to have a probable blistering disease. Over the course of 2 years, the patient was managed with courses of topical corticosteroids ranging from hydrocortisone to mometasone, wound care with normal saline solution and sterile aspiration of the tense blisters, short courses each of betamethasone + loratadine (Claricort) and betamethasone + dexchlorpheniramine (Celestamine), and antibiotics as needed for wound infection. There was no noted improvement or worsening of the blisters.

In the interim, new blisters would continue to form on the patient's legs and feet after scratching, which were managed with steroids and sterile aspiration, leaving behind hyperpigmented patches once healed. There was no development of dysphagia, odynophagia, ocular complaints, lesions on the genital or oral mucosa, nail dystrophy or hair loss.

1 week prior to consult, the patient suffered a bicycle accident, with tense blister formation on his forearms. This prompted consult with their dermatologist, who urged the patient to undergo further investigation to identify the specific blistering disease, prompting consult at this institution. At the time of consult, the patient's father denies any topical application or oral intake of corticosteroids within 2 weeks of the consult.

The patient was noted to have a history of asthma, well-controlled, and allergic rhinitis, mild, intermittent. He has no history of gastrointestinal disease or intolerance to wheat, bread, or rice. There was no family history of blistering disease, nail dystrophy or discoloration, alopecia, or chronic pruritus.

During consult, the patient was noted to have multiple approximately 0.1 x 0.1 cm at the smallest, faintly erythematous to violaceous plaques with tense bullae showing confluence and erosions without active discharge, clustered on the extensor surface of the bilateral legs, with few blisters scattered across the bilateral arms, in the background of hyperpigmented patches, and no visible milia or scar formation. There was no observed nail dystrophy nor lesions on the oral mucosa.

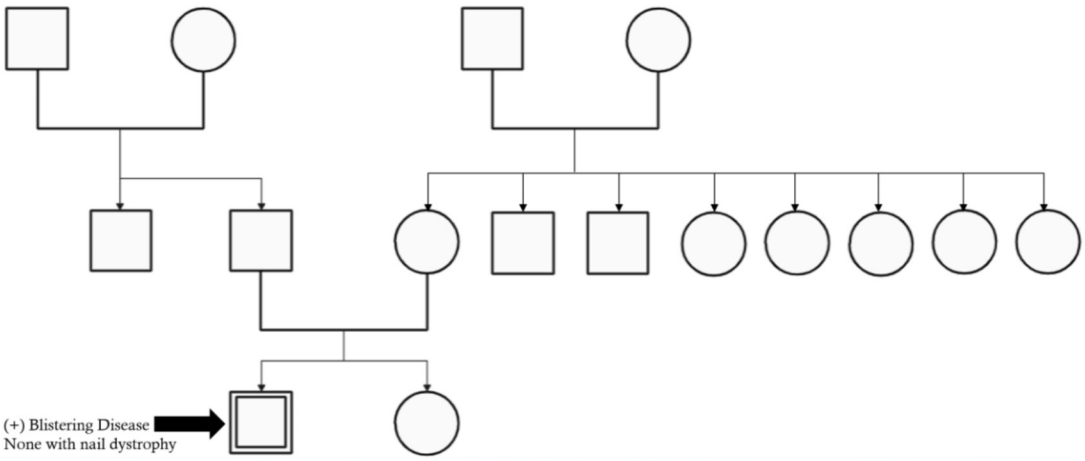
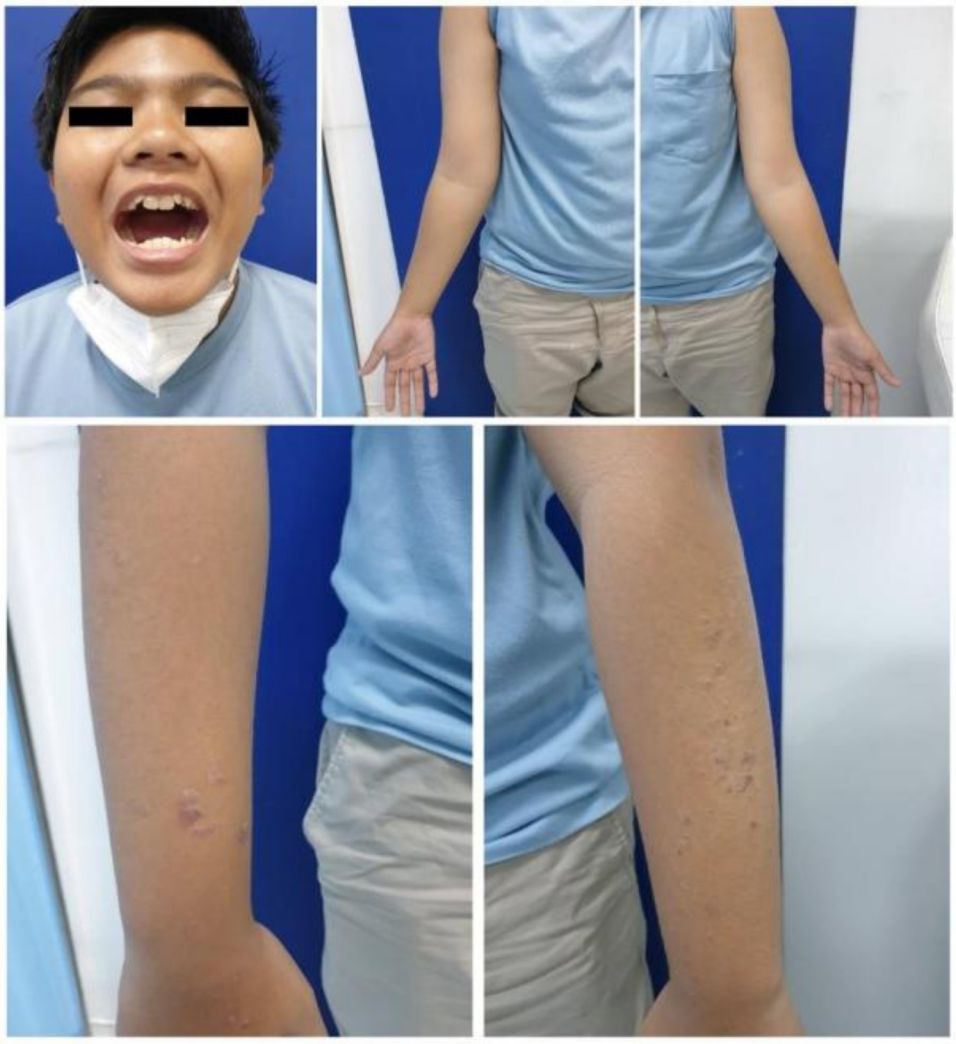


Figure 1: Genogram showing the patient's family tree. The black arrow points towards the patient. There were no relatives within three degrees of relations with blistering disease or nail dystrophy.



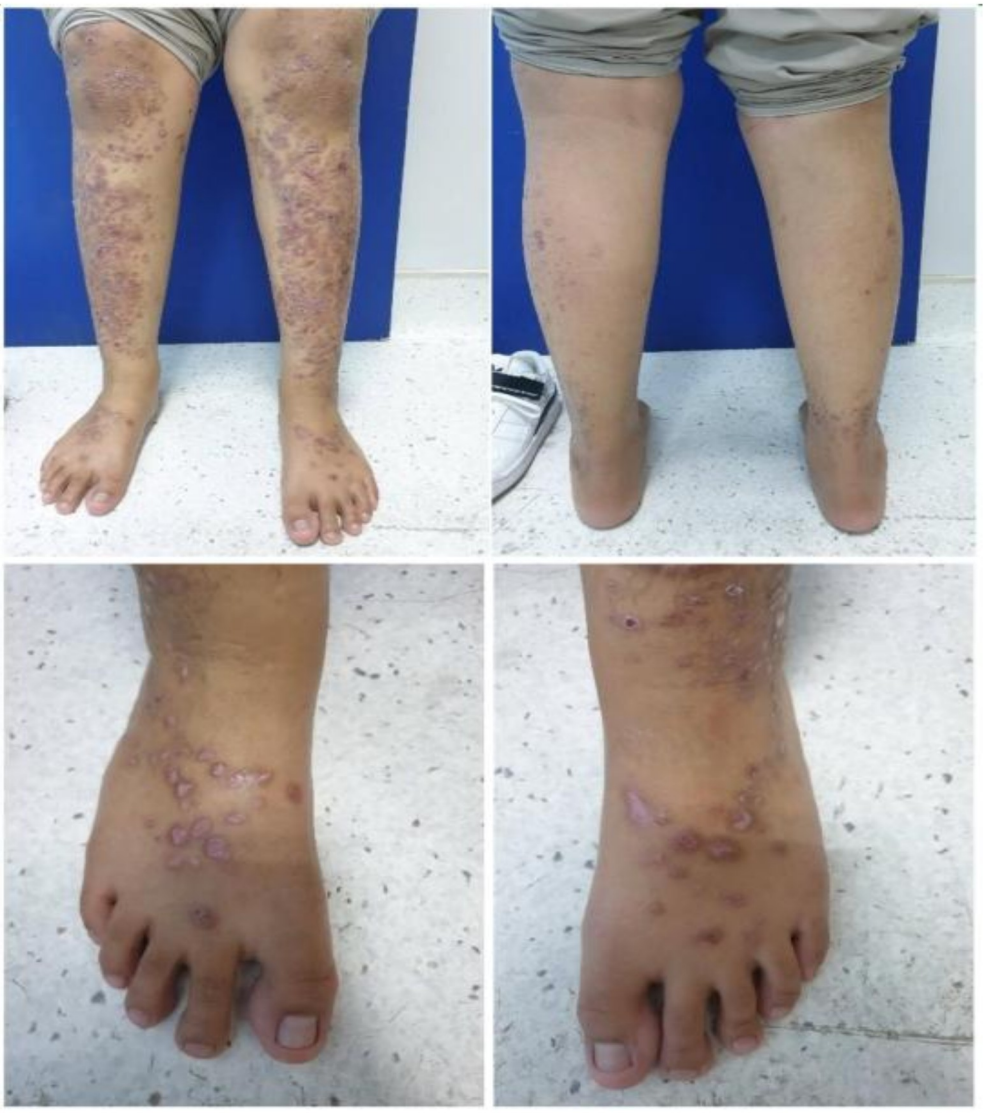


Figure 2: The patient's lesions. Note the numerous blisters, some with confluence, in the background of hyperpigmentation. No obvious milia-like scarring, oral mucosa involvement or nail dystrophy were present.

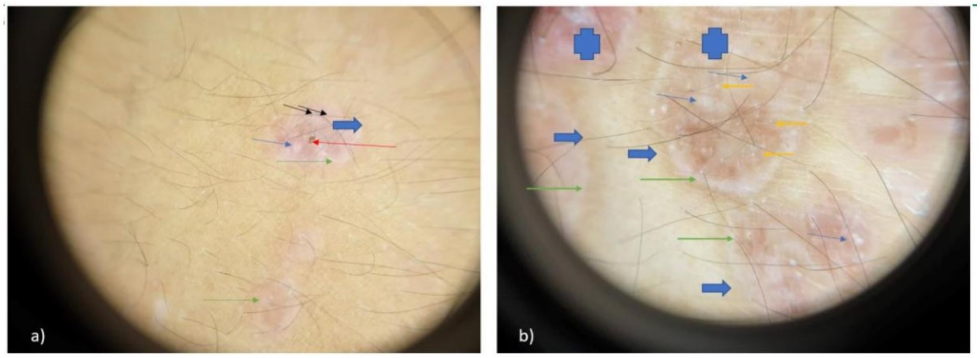


Figure 3: Dermoscopic findings of the a) arm and b) leg lesions, showing an erythematous to pink structureless background (blue cross) suggestive of an inflammatory process, with white globules (thin blue arrows), perilesional halo (thin green arrow), and white streaks (thin black arrow) suggestive of a vesiculation. Several lesions show prominent perilesional brown zone (thick blue arrow) akin to post-inflammatory pigment deposition. White dot-like areas (thin yellow arrow) can be seen, that may either be milia-like cysts or perifollicular openings. Some areas also show erosions (red arrow).

Three skin punch biopsy specimens were taken: one lesional biopsy each from the arm and leg for histopathologic examination and one perilesional biopsy for Direct Immunofluorescence (DIF) examination. In both lesional skin specimens, a subepidermal split in the background of scant inflammatory infiltrates was observed. DIF examination, however, showed no fluorescence for IgG, IgA, IgM, C3, and Fibrinogen. Indirect Immunofluorescence (IIF) using EUORIMMUN BIOCHIP MOSAIC showed inconclusive – to – negative results, owing to a negative result in the positive control. Enzyme-Linked Immunosorbent Assay (ELISA) showed normal ranged Anti-BP180 and Anti-BP230, but a slightly elevated Anti-Collagen VII with a result of 30.8 IU and a normal range of < 20 IU.

Due to these laboratory findings, the patient was assessed as a case of Epidermolysis Pruriginosa cannot totally rule out Epidermolysis Bullosa Acquisita. The patient was then worked up for baseline laboratory parameters to initiate oral dapsone monotherapy, advised wound care and to avoid trauma to the skin, strongly advised for regular monitoring for flares of the disease, and advised to undergo *COL7A1* gene mutation analysis.

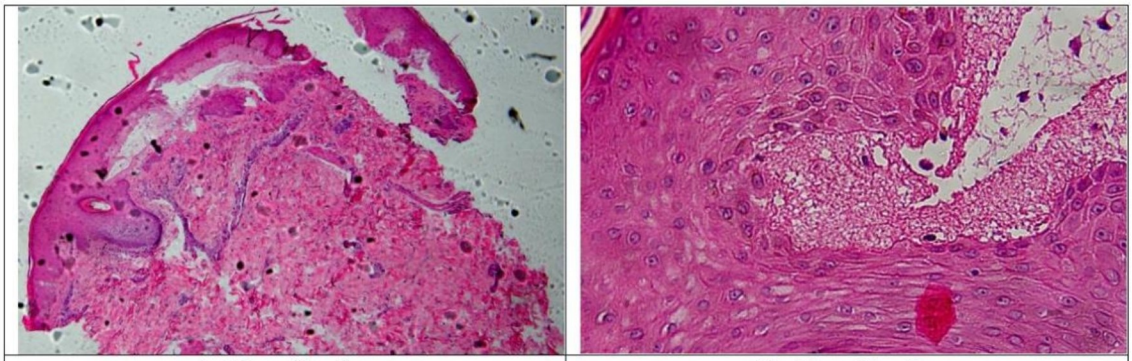


Figure 4. Histopathologic examination of lesional skin on the leg shows a subepidermal split with scant to almost absent inflammatory infiltrates composed of lymphocytes, neutrophils, eosinophils, and prominent subepidermal edema. Acantholysis is seen at the split.

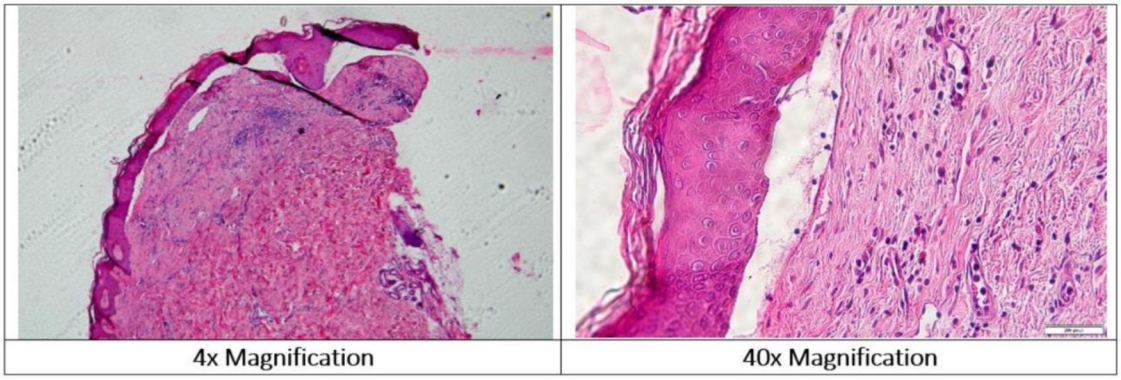


Figure 5. Histopathologic examination of lesional skin on the arm likewise shows a subepidermal split with scant to mild superficial infiltrates of lymphocytes, neutrophils, and eosinophils, with few to almost absent eosinophils and neutrophils within the blister.

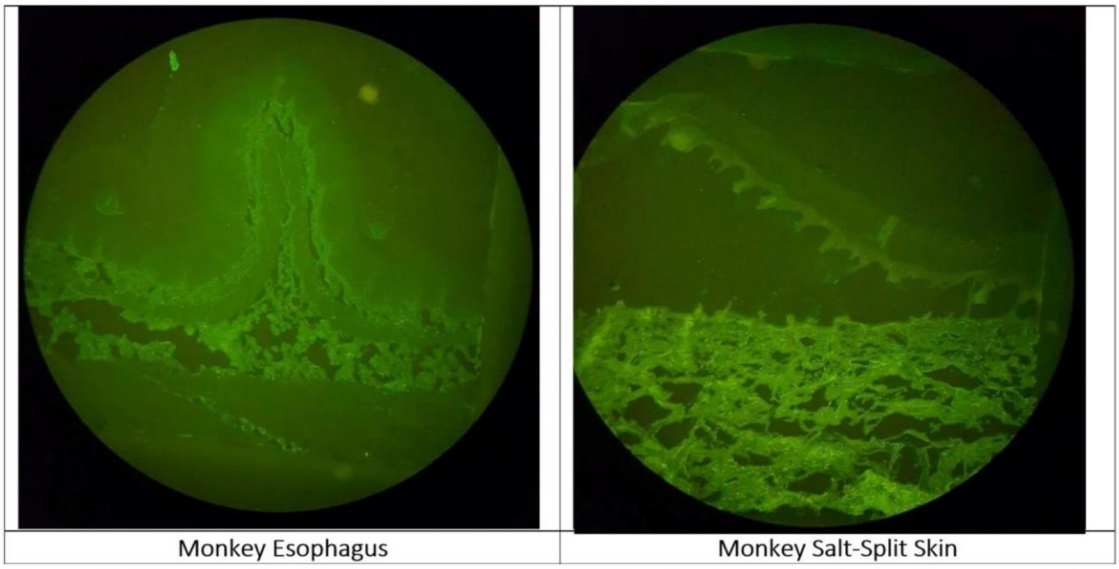


Figure 6. IIF using the EUROIMMUN BIOCHIP Mosaic does not display the expected fluorescence at the level of the basement membrane on the Monkey Esophagus slide, nor an n-serrated or u-serrated pattern expected of Bullous Pemphigoid or Epidermolysis Bullosa Acquisita, respectively, on the Monkey Salt-Split Skin slide.

DISCUSSION

EBP is a rare disease that is typically autosomal dominant in inheritance, but reports of autosomal recessive and even sporadic mutations have been published. This is a subtype of inherited Dystrophic EB, where a mutation in COL7A1 occurs, leading to a glycine substitution within the triple helical collagen domain of the type VII collagen molecule. This disease is characterized by intense pruritus, excoriations, skin fragility, nail dystrophy, milia- like or violaceous linear scarring, and nodular prurigo-like lesions. While the exact cause of pruritus is unknown, it is suggested that the exposure of mutated Type VII collagen activates a kinin cascade, leading to bradykinin release. This pruritus then gives the clinical findings of prurigo-like lesions commonly associated with nail dystrophy.

This is in contrast to EBA. This is an acquired autoimmune blistering disease where a breakdown in immune tolerance results in the production of IgG antibodies against Collagen VII, which is a component of the anchoring fibrils that attach the dermis to the epidermis.

Simply, EBA is an autoimmune disease against Collagen VII while EBP is a mutation of collagen VII. Both diseases result in skin fragility, wherein tense blisters form in response to trauma. The distinction between both diseases is important in the management and prognosis: EBA benefits from immunosuppressive therapy while the management of EBP is largely supportive.

EBA exists as a spectrum of diseases divided into classical / mechanobullous / non-inflammatory and non-classical / non-mechanobullous / inflammatory subtypes. The non- classical subtype is further subdivided into Bullous Pemphigoid-Like EBA, Mucous Membrane-EBA, Brunsting-Perry-Type EBA, and IgA-EBA.

Should our patient be a case of EBA, the presence of skin-fragility, bullous lesions and erosions, encompassed by non-inflamed skin in trauma-prone sites and the extensor skin surface, as well as the scant inflammatory infiltrates in histology, point towards the Classic Subtype. However, scant inflammatory infiltrates associated

with a subepidermal blister have also been described in case reports of EBP.

Moving on to the DIF and IIF findings, it is first important to understand the mechanism behind each test. DIF subjects the patient tissue to fluorochromes bound to an antibody that attaches to the molecule under question. In our case, perilesional skin was assessed for IgG, IgA, IgM, C3, and Fibrinogen, yielding a negative result, thus showing no activity from the aforementioned molecules.

In a similar vein, IIF subjects the antibodies within patient sera to known tissue specimens. Thus, should patients have active Anti-Collagen VII antibodies such as in EBA, then IIF findings should show the characteristic linear basement membrane deposition on the Monkey Esophagus slide, and u-serrated dermal-side deposition in the Salt – Split Skin slide, both of which were not seen in our patient.

Thus, our patient presenting with negative DIF results and a possibly-negative IIF result raises the suspicion that an autoimmune process may not be involved as the underlying mechanism to his lesions. The normal-range Anti-BP180 and Anti-BP230 autoantibodies also rules out Bullous Pemphigoid as a diagnosis. In the background of an absent family history of blistering disease or nail dystrophy, our patient, therefore, is more likely to be a sporadic case of EBP.

However, for this to be a true case of EBP, the conundrum behind our patient's elevated IgG autoantibodies against Collagen VII, as documented by ELISA, is raised. A literature search revealed a case report published in 2012 of a 50-year-old woman with similar skin lesions to our patient, albeit with personal and family history of onychodystrophy, negative IIF studies, and elevated IgG antibodies against the NC1 domain of Collagen VII measured using immunoblot studies. This patient was managed with methylprednisolone and azathioprine, with her skin lesions healing after 15 months of maintenance therapy. However, the patient had unexpected flares of her blisters, prompting COL7A1 mutation search, showing the glycine substitution mutation in the triple helix domain of COL7A1, leading to the final diagnosis of EBP. The author of this case report explains that the presence of autoantibodies against Collagen VII in EBP can be as a result of an autoimmune reaction against Collagen VII.

CONCLUSION

In conclusion, given these clinical, laboratory, and literature evidence, our patient is therefore assessed as a case of EBP, and cannot totally rule out EBA. The one test that will be able to conclusively differentiate the former from the latter would be a COL7A1 assay.

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