Epidermolysis Bullosa Simplex in a 13-year-old Filipina

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Introduction: Epidermolysis Bullosa (EB) is a rare genodermatosis characterized by fragility of the skin and mucous membranes, manifested by blistering with little or no trauma. There are three subtypes: EB Simplex, Junctional EB, and Dystrophic EB. Each type of EB has its own specific genetic defect. We report a case of a 13-year-old girl who presented with multiple tense blisters and eroded plaques since birth on the entire body.

Case summary: This is a 13-year-old-girl who presented with solitary tense blister on her right thigh three days after birth, which gradually affected the scalp, trunk, and upper and lower extremities, particularly on the trauma prone areas. There was nail dystrophy and multiple brownish dental pits at three years of age. A 4 mm lesional skin punch biopsy showed subepidermal blisters containing fibrin, lymphocytes and few red blood cells. PAS showed basement membrane zone beneath the blister, compatible with EB. Immunofluorescence mapping showed decreased immunofluorescence (+1) on keratin 5/6, (+2) on keratin 14, and absence of immunofluorescence on alpha 6 / beta 4 integrins. Final diagnosis is EB Simplex.

Conclusion: Early detection is important in managing this case, to detect systemic involvement and provide palliative care. Genetic counseling is recommended for prospective parents who have a family history of any form of epidermolysis bullosa. The prognosis of Inherited EB is very variable and the mortality is usually due to complications of systemic involvement. A multidisciplinary approach in the supportive management of this case is necessary as there is still no cure for this condition.

Keywords: *inherited epidermolysis bullosa, alpha 6 and beta 4 integrin, immunofluorescence mapping*

INTRODUCTION

Epidermolysis Bullosa (EB) is a heterogeneous group of hereditary disorders characterized by extreme fragility of the skin and mucous membranes, which gives rise to the formation of blisters and erosions following minor trauma.[6] The areas of the body most often affected are sites subject to frequent pressure or friction. EB may be diagnosed by immunofluorescence antigenic mapping, transmission electron microscopy and genetic analysis. The two diagnostic tests that are routinely employed are transmission electron microscopy and immunofluorescence antigenic mapping.[5]

Discrepancies between these two techniques arise in only about 3% of all specimens, suggesting that either approach may serve as the gold standard for the diagnosis of inherited EB.[2]

CASE REPORT

This is a case of a fourteen year old girl who presented with a solitary bullae on the right thigh three days after birth. Few days after, bullae were noted to easily appear on sites of trauma. The patient was treated as a case of impetigo and was given a topical antibiotic with minimal improvement. The symptoms were recurrent. At three years of age, nail dystrophy and multiple brownish dental pits were noted.Patient sought consult with a private dermatologist and was assessed to have a blistering disorder, and was given unrecalled oral and topical medications providing minimal improvement of the

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lesions. In the interim, the lesions increased in size and number now affecting the scalp, trunk, upper and lower extremities. Persistence of lesions, prompted consult in our institution. Upon consultation, examination revealed multiple tense bullae and eroded plaques on the scalp, face, trunk and extremities. Multiple dystrophic nails on the hands, toes as well as enamel hypoplasia on all teeth were noted. Patient was underweight with a body mass index of 13.08. Patient denies any problem with appetite.

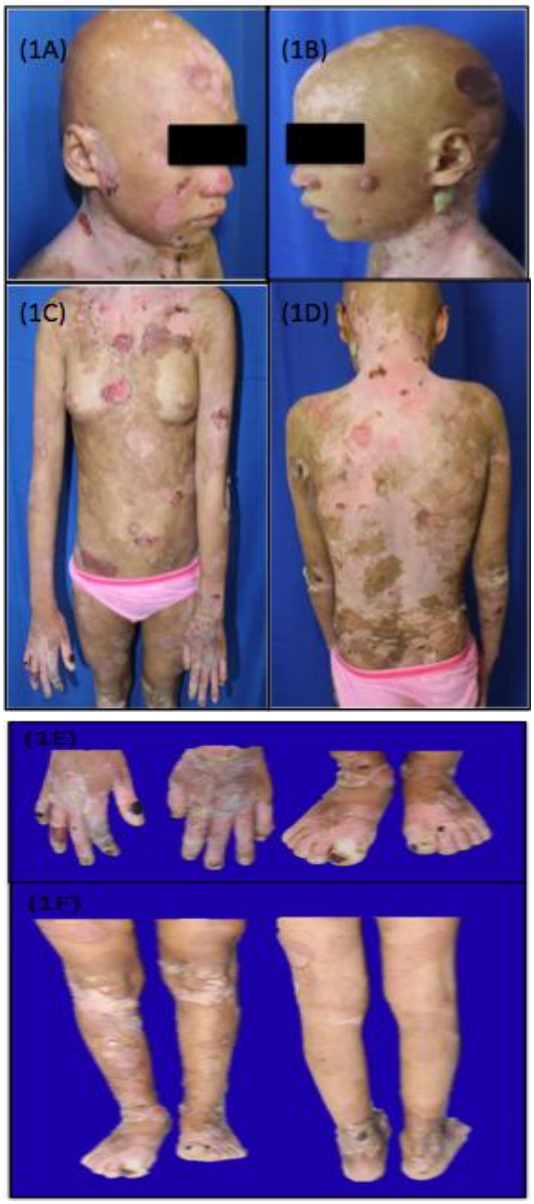

Figure 1. Clinical findings, multiple tense bullae and eroded plaques on the scalp, face trunk and extremities, with dystrophic nails on the digits of both hands and feet (A-F)

A 4 mm skin punch biopsy of the lesion was done and sent for H&E. Results showed intra-epidermal vesicle with sparse inflammatory infiltrate on the dermis, confirming the diagnosis of Epidermolysis Bullosa. Electron microscopy findings showed ultrastructural observations of the skin with separation between the epidermis and dermis. The roof consisted of the epidermis which showed lysis of the basal layer. The floor consisted of the dermis with an intact attached basement membrane. Immunofluorescence mapping showed the following: Positive results below the blister for alpha 6 integrin (CD 49f), Laminin V beta 3 chain, Laminin V alpha 3 chain, Laminin V gamma 2 chain, type IV collagen and type VII collagen. Positive results above and below the blister were Keratin 5/6, LAD1, Beta 4 integrin (CD 104). It was however negative with Keratin 14. These findings were consistent with Epidermolysis Bullosa Simplex.

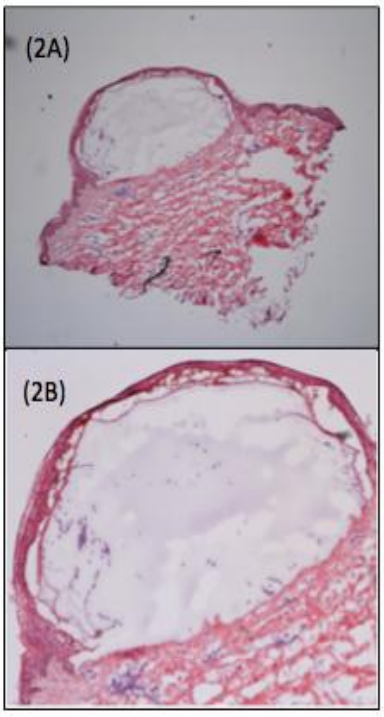

Figure 2.Histopathological findings, intra-epidermal vesicle with sparse inflammatory infiltrate on the dermis (H&E, 4x-40x, A-B).

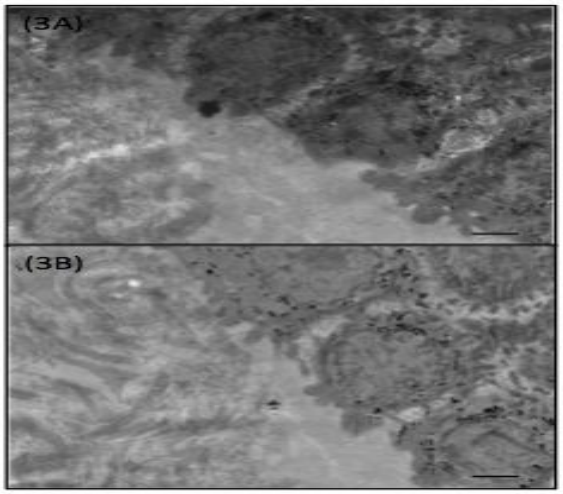

Figure 3.Electron microscopy findings, the roof consists of the epidermis which show lysis of the basal layer. The roof consists of the dermis with intact attached basement membrane (EM, A-B).

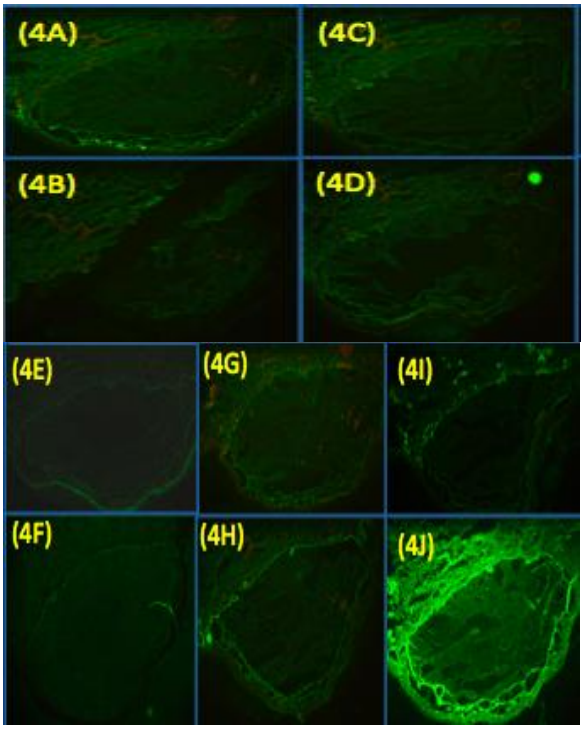

Figure 4.Immunofluorescence Mapping findings: positive in Keratin 5/6 (4A), negative in Keratin 14 (4B), positive alpha 6 integrin (4C) and beta 4 integrin (4D), normal expression of Laminin V alpha 3 chain (4E), reduced expression of Laminin V beta 3 (4F), Laminin V gamma 2 chain (4G), positive above and below the split in LAD1 (4H), type IV collagen (4I), and Type VII Collagen (4J). (IFM, A-B-C-D-E-F-G-H-I-J)

Patient was advised wound care with saline compresses, topical antibiotics, bleach baths and non stick dressings. The patient was also referred to a multidisciplinary team of experts such as a pediatrician, ophthalmologist, nutritionist, and dentist as supportive management. The patient was asked to follow up monthly as an outpatient, however, the patient was lost to follow up.

DISCUSSION

The term epidermolysis bullosa (EB) encompasses a number of non-inflammatory disorders characterized by the development of blisters or erosions following minor trauma of the skin, which is caused by mutations in various skin structural proteins.[2] The reported incidence of this disorder varies from one geographical zone to another, affecting approximately 1 in 17,000 live births with an estimated 500,000 cases worldwide.[3] Incidence is not affected by race or ethnic group, and the disease affects both sexes equally. At the Research Institute for Tropical Medicine, there were total of 8 cases out of the 289,250 new patients seen from the year 2006-2019. Of the 8 cases, only 3 cases were diagnosed to have the simplex type of Epidermolysis Bullosa. According to the Philippine Dermatological Society Health Information System, there were 51 cases of epidermolysis Bullosa from 2011-2019. Of the 51 cases, there were 30 cases of females and 21 cases in males, with 2 unspecified cases.

Inherited EB is caused by mutations within the genes that encode structural proteins that reside within epidermis (EB simplex), dermo-epidermal junction (junctional EB), or uppermost papillary dermis (dystrophic EB).[8] The site within which each of these proteins reside determines the ultrastructural location where the blisters arise. EB simplex is the most common form (92%) and dystrophic EB has the second highest incidence (5%), followed by junctional EB (1%).[2] In a study from Scotland, 259 individuals with epidermolysis bullosa were identified. Of these 149 had the simplex form, 108 the dystrophic form and 2 the junctional form.[4]

All forms of inherited EB are characterized by mechanically fragile skin, erosions and macroscopic blisters. In most forms of EB, minimal lateral and rotary traction on the skin leads to shearing within ultrastructurally uniform cleavage planes, resulting in

blister formation.[6] Scarring can occur in any type or subtype of EB. Other cutaneous findings include dystrophic or absent nails, milia, scarring alopecia of the scalp, and also extracutaneous finding such as dental enamel hypoplasia.[9] These findings were present in our patient. Extracutaneous findings such as defects that may be present in other tissues, including the eye, gastrointestinal, genitourinary tracts were not evaluated because the patient was lost follow up.

The first step towards making the diagnosis of EB begins with a thorough history and physical examination, including the age of onset and the presence of blistering in other family members.[4] A review of gastrointestinal, respiratory, ocular, dental, bone, and genitourinary systems are equally important as well as the evaluation of the general growth and development. Physical examination requires a complete skin examination and evaluation of mucosal tissues, hair, nails and teeth. Laboratory measurement include evaluation for urea and electrolytes, liver function, bone profile, iron, zinc, selenium, hemoglobin, urine culture for infection, echocardiogram, renal ultrasound, and radiographs for bone evaluation.[5]

Since the diagnosis depends on establishing the level of cleavage in the skin, care must be taken to select an appropriate site for biopsy. The best site would be the edge of a fresh blister.[7] The histological picture will be difficult to interpret and even misleading if the blister is more than 12 hours old, when healing had already begun. In our patient, the biopsy specimens were all taken from new spontaneous blisters by gently rotating a pencil eraser over an intact area of patient's skin. In EB simplex, the blister may appear to be a cell-poor subepidermal blister, because the cleavage is below the epidermis. Fragments of basal keratinocytes may be observed in the blister base. A PAS-positive basement membrane also can be found.[5] In our patient, histopathology on H&E stain showed a subepidermal blister and PAS staining highlighted the basement membrane zone (BMZ) just beneath the blister. However, routine histologic analysis can not be used to diagnose EB, but can be useful for excluding other causes of blistering. This is due to the fact that dermal-epidermal BMZ is simply too small to be visualized by light microscopy.

To differentiate levels of BMZ separation in skin biopsies, transmission electron microscopy (TEM) must be used. The use of TEM was the gold standard in the diagnosis of EB because it allowed visualization of the skin ultrastructure, in particular, the proteins of the basement membrane zone (BMZ), which are reduced or absent in certain EB types. It also has the advantage of identifying microsplits and subtle changes in the dermo–epidermal junction in mild forms of EB.[5]

Immunofluorescence mapping (IFM) allows detection and localization of the level of blistering as well as normal, reduced, or absent protein expression. Antibodies for most target proteins are available with this technique reported to be more sensitive (97% vs 71%) and specific (100% vs 81%) than EM.[3]

To identify the classification of EB, it is important to know the ultrastructure of the BMZ and the target proteins.[1] Most forms of EB simplex (EBS) are transmitted in an autosomal dominant manner. There are two main subgroups of EBS, suprabasal and basal, which differ in the ultrastructural level of the intraepidermal blister. Most of the target proteins involved in EB are found in the BMZ; within the desmosomes, which anchor keratinocytes to one another. The vast majority of EBS cases are in the basal group, most often resulting from a dominant-negative mutation within keratin 5 (K5) or 14 (K14) genes, expression of which is primarily within the basal layer of the epidermis. Suprabasal forms of EBS caused by mutations in the genes encoding the desmosomal proteins plakophilin-1, plakoglobin and desmoplakin.[3]

There are currently no specific therapies for any form of inherited EB. In the future, effective gene therapy may become a reality for at least some forms of EB.[7] For now, management of EB revolves around the prevention mechanical trauma and infections. Bathing and soaking with 0.005% sodium hypochlorite or 0.25% acetic acid may help to reduce bacterial colonization. Antibiotic should be used wisely, with avoidance of chronic treatment with topical mupirocin and oral antibiotics. Multidisciplanary clinics can provide care and support for the wide range of needs that patients with EB and their families have.[2] Regular skin checks are imperative to assess potential premalignant or malignant lesions. Dermatologists recommend regular skin checks every 3-6 months from the age of 10 years and every 3 months from 16 years onwards.

CONCLUSION

Early detection is important in managing this case in order to detect systemic involvement and provide palliative care. Genetic counseling is recommended for prospective parents who have a

family history of any form of epidermolysis bullosa. The prognosis of Inherited EB is very variable and the mortality is usually due to complications of systemic involvement. A multidisciplinary approach in the supportive management of this case is necessary as there is still no cure for this condition.

REFERENCES

1. Chan, Lawrence. *Blistering Skin Diseases*. 1st ed. London: Manson Pub., 2009.
2. Fine, Jo David, et al. "The Classification ofInherited Epidermolysis Bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis andClassification of EB." *The Classification of Inherited Epidermolysis Bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB*. Jaad, June 2008.
3. Fine, Jo-David. "Inherited epidermolysis bullosa." *Orphanet journal of rare diseases* 5.1 (2010): 12.
4. Gilliam, Anita C and Neil J. Korman *Subepidermal Vesiculobullous Dermatitis*. 1st ed. Cleveland,Ohio,USA: Department of Dermatology, Case Western ReserveUniversity/University Hospitals of Cleveland, 2015.
5. Haber, Richard M,et al. *Hereditary Epidermolysis Bullosa*. 1st ed. Toronto, Ontario, Canada: Journal of the American Academy of Dermatology, 1985.
6. Intong, Lizbeth RA, and Dédée F. Murrell. "Inherited epidermolysis bullosa: new diagnostic criteria and classification." *Clinics in dermatology* 30.1 (2012): 70-77.
7. Murrell, Dédée F. *Blistering Diseases*. 1st ed. Berlin: Springler, 2015.
8. Pfendner EG, Bruckner AL. Epidermolysis Bullosa Simplex. Seattle (WA): University of Washington, Seattle; 1993-2016.
9. Siañez-González, C. *Congenital Epidermolysis Bullosa: A Review*. 1st ed. Mexico: Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey, 2009.