Case 12

A 14-year-old Thai girl from Pathumthani.

Chief complaint: Tense bullae and vesicles at trunk, both hands and soles for 8 years.

Present illness: The patient developed tense bullae at her soles since 5 years old associated with excessive walking which rarely clear of symptoms. After resolved, lesions turn to be hypo pigmented macules. 1 year later lesions progress to both hands and trunk. She lacks other systemic symptom. Her teeth, hair and nails are normal.

Past history

No underlying disease.

No history of collodion baby at birth.

Family history

Her sister also has tense bullae at her soles associated with excessive walking, but less severity. Normally,she has no symptom.

Other family members are normal.

No family history of consanguinity.

She denied history of photosensitivity.

Skin examination

Tense bullae and vesicles at trunk, both hands and soles.

Hyper- hypopigmented macules at trunk and extremities.

Mild thickening of palms and soles.

Normal oral mucosa. No milia. No scar. No hypertrichosis.

Histopathology (S10-15553)

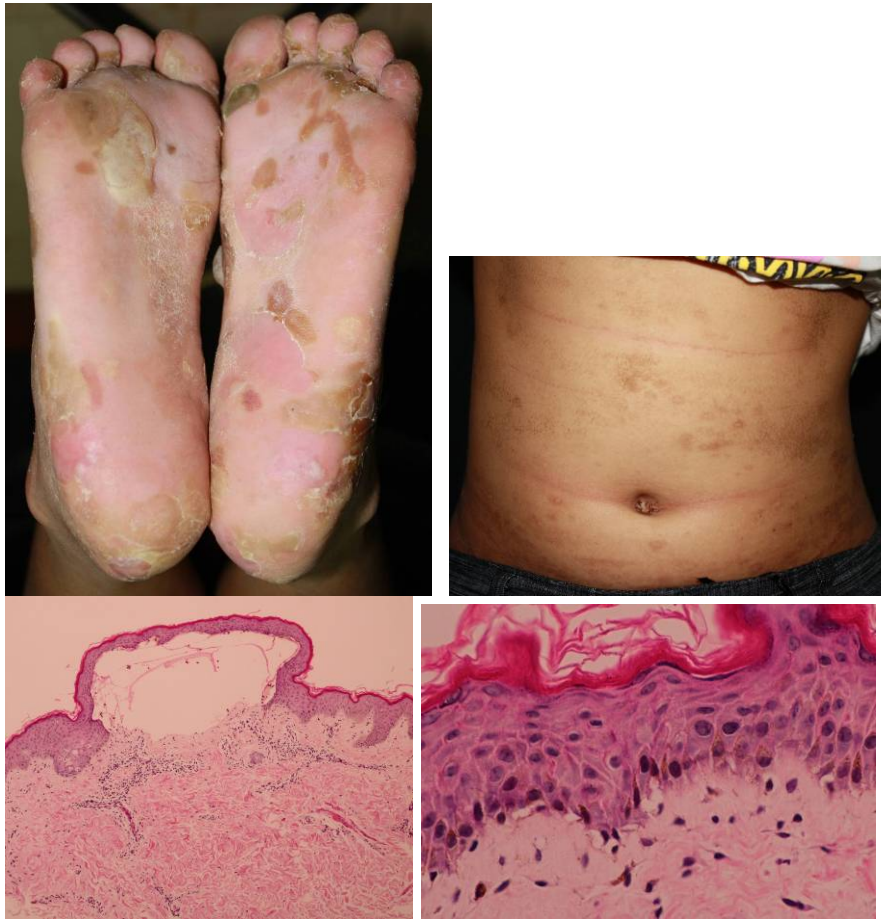
subepidermal vesicle with mild to moderate inflammatory-cell infiltrate of lymphocytes admixed with eosinophils and melanophages

well-preserved dermal-paillae pattern

vacuolar alteration of basal cells in perilesional skin

Electron microscope

Intrabasal separation compatible with epidermolysis bullosa simplex.



Diagnosis: Epidermolysis bullosa simplex (generalized type)

Treatment: Wet dressing. Oral and topical antibiotics.

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Discussion:

Epidermolysis bullosa simplex (EBS) is one major type of interited epidermolysis bullosa (EB) characterized by intraepidermal blistering in respond to mild trauma.[1]

The etiology and pathogenesis of EB has not been well defined but many reports suggest that EB is genodermotoses disease which resulting from gene mutations (keratins 5 and 14; plectin; α6β4 integrin; plakophillin-1; desmoplakin).[1]

According to the third international consensus meeting on diagnosis and classification of EB in 2007, interited epidermolysis bullosa generally classified into 4 major types-epidermolytic (Epidermolysis bullosa simplex;EBS), lucidolytic (Junctional epidermolytic bullosa;JEB), dermolytic (Dystrophic epidermolytic bullosa;DEB) and mixed (Kindler syndrome) which based on the level of BMZ separation.[1, 2]

Recently EBS was separated into 2 major subtypes (Suprabasal and basal subtypes.[1] (Table I)

The mose common EBS types include generalized (Koebner), localized (Weber-Cockayne), and herpetiform (Dowling-Meara;DM).

Table I.EBS subtypes[1]

Major subtypes	EBS subtypes	Targeted proteins
Suprabasal	Lethal acantholytic EB	Desmoplakin
	Plakophillin deficiency	Plakophillin-1
	EBS superficialis (EBSS)	Keratin 5,Keratin 14
Basal	EBS, locailized	Keratin 5,Keratin 14
	EBS, Dowling-Meara	Keratin 5,Keratin 14
	EBS, generalized (Koebner)	Keratin 5,Keratin 14
	EBS with mottled pigmentation	Keratin 5
	EBS, migratory circinate	Keratin 5
	EBS autosomal recessive	Keratin 14
	EBS, Ogna	Plectin
	EBS with muscular dystrophy	Plectin
	EBS with pyloric atresia	Plectin;α6β4 integrin

EBS, Epidermolysis bullosa simplex

The phenotypes of diseases could range from mild to severe among each variants.

Localized form EBS, Weber-Cockayne subtype, The blistering is restricted to the hands and feet.[3] This is most common and regards as the mildest form of EBS subtype while Dowling-Meara is regards as the most severe form of EBS. Usually it presents during infancy and childhood, occasionally presents in early adulthood after excessive mechanical trauma, such as it develop blistering on the feet after marching during military service. Common association is hyperhidrosis of palms and soles. When lesion resolved, post-inflammatory pigmentary abnormalities often occur. Milia and scarring are absent in this type. Oral erosions are rarely present and resolve with increasing age. Nail involvement is rare.

Koebner subtype is more generalized than Weber-Cockayne subtype, showns an onset of blister at birth or during early infancy. Usually involved hands, feet and extremities. Lesions often heal with hyper- or hypopigmentation, and occasionally atrophy and milia can develop but less frequent than Dowling-Meara type. Thickening of the soles is common but often present in later childhood. The oral mucosa sometimes shows mild erosion but usually improves with increasing age.

While Dowling-Meara EBS has generalized distribution and also present at birth similar to koebner varient. But oral mucosa is more often involved, sometimes showing extensive erosions. Milium formation occasionally occurs in infancy but usually resolves later in childhood. Sometimes, clinical is shown as grouped or "herpetiform" blisters which usually occur on the trunk and extremities and heal without scarring. This subtypes often shows nail dystrophy. Heat can exacerbates the blistering in other EBS subtypes but does not have a major impact in this type. Hyperkeratosis of palms and soles often develops in early childhood and can eternally progress to painful confluent keratoderma of the palms and soles. These

sometimes interfere with ambulation has led to flexural contractures.

Tables 2 shows clinical summary of most common EBS subtypes; localized EBS, generalized EBS, Dowling-Meara EBS.

Table 2. EBS subtypes: Clinical summary[1]

	EBS, Localized	**EBS, Generalized**	**EBS,Dowling-Meara**
Transmission	AD	AD	AD
Onset	Early childhood	Birth	Birth
Skin distribution	Palms and soles	Generalized	Generalized
Skin findings (Frequency*)			
-Blisters	4+	4+	4+
-Milia	Rare	1+	1-2+
-Atrophic scaring	Rare	1+	2+
-Dystrophic nails	Uncommon	1-2+	2+
-Granulation tissue	Absent	Absent	Absent
-Scalp lesion	Absent	Absent	Absent
-Keratoderma (Palms and soles)	Focal (by adulthood)	Focal	Usually diffused
-Other	None	None	Herpetiform
Extracutaneous			
-Anemia	Absent	Absent	Variable
-Growth retardation	Absent	Absent	Common
-Oral cavity			
Soft tissue defect	Erosion(25%)	Variable	Common
Enamel hypoplasia	Absent	Absent	Absent
Caries	Normal frequency	Normal frequency	Normal frequency
GI tract	Absent	Absent	2+ (constipation)
GU tract	Absent	Absent	Absent
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Absent	Uncommon
Risk by age 30 of:			
SCC, MM, BCC	None	None	None
Death related to EB	None	None	Uncommon

AD, Autosomal dominant;GI tract, Gastrointestinal tract; GU tract, Genitourinary tract; SCC, squamouse cell carcinoma; MM, Malignant melanoma; BCC, Basal cell carcinoma
*Scale: absent or none, 1+,2+,3+,4+.

Additional varients of EBS are EBS of Ogna, EBS superficialis and EBS with mottled pigmentation

EBS of Ogna characterized by seasonal blistering (summer) that heal without scar. All patients in this subtype have come from Norway and also show a characteristic of onychogryphosis of the great toenails.[4]

EBS superficialis is uncommon form, characterized by intraepidermal cleavage just beneath subcorneal level. Therefore, its develop erosions and crusts rather than intact bullae and heal with post-inflammatory pigmentary changes. Oral erosions, nail dystrophy, milia and atophic scaring are also seen in this subtype.[5, 6]

EBS with mottled pigmentation, is characterized by intraepidermal blisters after minimal trauma, the mottled pigmentation of limbs and trunk, nail dystrophy and punctuate palmoplantar hyperkeratosis. Blistering begins at birth or early infancy and improve with increasing age. The net-like reticular hyper- and hypopigmentation usually begins in the infancy and spreads from the extremities to the trunk.

2 variants of EBS that caused by mutation in the plectin gene resulted in lethal EBS with muscular dystrophy or pyloric atresia (mutation in PLEC1 gene), but recently describes as new subtypes called Hemidesmosomal EB) due to forming a distinct level of skin separation.That is intermediate between that of EBS and junctional EB (JEB).[7]

There are also new described entities of EBS which are lethal acantolytic EBS[8] ,migratory circinate erythema[9] and plakophillin deficiency were reported.[1]

In our case, she developed generalized blistering since early childhood period, lesions mainly involved hands, feet, and extremities and healed with hyper- and hypopigmentation. No milia formation and scar. She also have mild palmo-plantar hyperkeratosis of palms and soles. Normal oral mucosa, hair and

teeth. No mental retardation. So in this case could be the most compatible with generalized form EBS (Koebner type).

Indirect immunofluorescence (IDIF) and Transmission electron microscope (TEM) is important diagnostic tool.[1] These tools allow determination of the level of skin cleavage in EB skin. That is intraepidermal, intra-lamina lucida, or sub-lamina densa. TEM has been regarded as the gold standard diagnostic tool of EB.[10] By providing visualization and semiquantitative assessment of specific structures which could be altered in number and/or appearance in each EB subtypes.[1] While IDIF can provide additional information on the level of blistering and clues for underlying molecular defects.

Prenatal diagnosis can be done by analysis of chorionic villus sampling at 8-10 weeks gestational age or amniocentesis in the second trimester.[2]

According to EB is monogenetic disease so corrective gene therapy is the most ideal therapy for EB.[11] But nowsaday there is still no curative treatment due to has no currently available therapies that can correct the underlying molecular defect yet. So therapy is by necessity supportive.

Treatment is usually a combination of wound care, infection control, prevention of repeated trauma, surgical management and nutritional support.[12]

Comprehensive topical therapy is mainstay of treatment with avoidance of trauma. Wound healing is impaired by endogenous factors such as foreign bodies, bacteria, nutritional deficiencies, anemia. Therefore,controlling of these factors can optimizing wound healing.

So in our case,we did wet dressing and provide topical and oral antibiotic treatment. Furthermore, we remained closely periodic follow up this patient.

References

1. Fine JD, Eady RA, Bauer EA, Bauer JW, Bruckner-Tuderman L, Heagerty A et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol 2008;58:931-50.
2. Fassihi H, Eady RA, Mellerio JE, Ashton GH, Dopping-Hepenstal PJ, Denyer JE et al. Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. Br J Dermatol 2006;154:106-13.
3. Yasukawa K, Sawamura D, Goto M, Nakamura H, Jung SY, Kim SC et al. Epidermolysis bullosa simplex in Japanese and Korean patients: genetic studies in 19 cases. Br J Dermatol 2006;155:313-7.
4. Koss-Harnes D, Hoyheim B, Anton-Lamprecht I, Gjesti A, Jorgensen RS, Jahnsen FL et al. A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical de novo mutations. J Invest Dermatol 2002;118:87-93.
5. Martinez-Mir A, Liu J, Gordon D, Weiner MS, Ahmad W, Fine JD et al. EB simplex superficialis resulting from a mutation in the type VII collagen gene. J Invest Dermatol 2002;118:547-9.
6. Fine JD, Johnson L , Wright T. Epidermolysis bullosa simplex superficialis. A new variant of epidermolysis bullosa characterized by subcorneal skin cleavage mimicking peeling skin syndrome. Arch Dermatol 1989;125:633-8.
7. Pulkkinen L , Uitto J. Hemidesmosomal variants of epidermolysis bullosa. Mutations in the alpha6beta4 integrin and the 180-kD bullous pemphigoid antigen/type XVII collagen genes. Exp Dermatol 1998;7:46-64.
8. Jonkman MF, Pasmooij AM, Pasmans SG, van den Berg MP, Ter Horst HJ, Timmer A et al. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. Am J Hum Genet 2005;77:653-60.
9. Gu LH, Kim SC, Ichiki Y, Park J, Nagai M , Kitajima Y. A usual frameshift and delayed termination codon mutation in keratin 5 causes a novel type of epidermolysis bullosa simplex with migratory circinate erythema. J Invest Dermatol 2003;121:482-5.
10. Shinkuma S, McMillan JR , Shimizu H. Ultrastructure and molecular pathogenesis of epidermolysis bullosa. Clin Dermatol 2011;29:412-9.
11. Sawamura D, Nakano H , Matsuzaki Y. Overview of epidermolysis bullosa. J Dermatol 2010;37:214-9.
12. Langan SM , Williams HC. A systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa. Clin Exp Dermatol 2009;34:20-5.