

Epidermolysis Bullosa Simplex – Dowling Meara Variant

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problem was worse after trivial trauma or in the summer. Vesicles or erosions would heal up spontaneously without any scarring. All along, his skin condition improved with age but never subsided. On several occasions oral mucosa were also found to be involved.

CASE SUMMARY

History

A 15-year-old boy presented with a history of recurrent blisters and erosions over his limbs and trunk since birth. He was the only child in the family. His mother noticed he suffered from vesicles and erosions over his both heels since 3 days old. The vesicles and erosions gradually spread over to his limbs and trunk as he grew up and were more severe over his lower limbs and upper back. There was mild itchiness accompanied with the vesicles and his skin

He was a 3-kg full-term baby born with caesarian section because of low-lying placenta. There was no consanguineous marriage between parents and the pregnancy was uneventful.

He had normal developmental milestones both physically and mentally during his childhood. His body weight and height were within normal range.

His grandfather and three of his aunts also suffered from blistering skin disease since their childhood. In fact, one of his aunts died of skin disease at 10 years old. His family pedigree was shown in Figure 1.

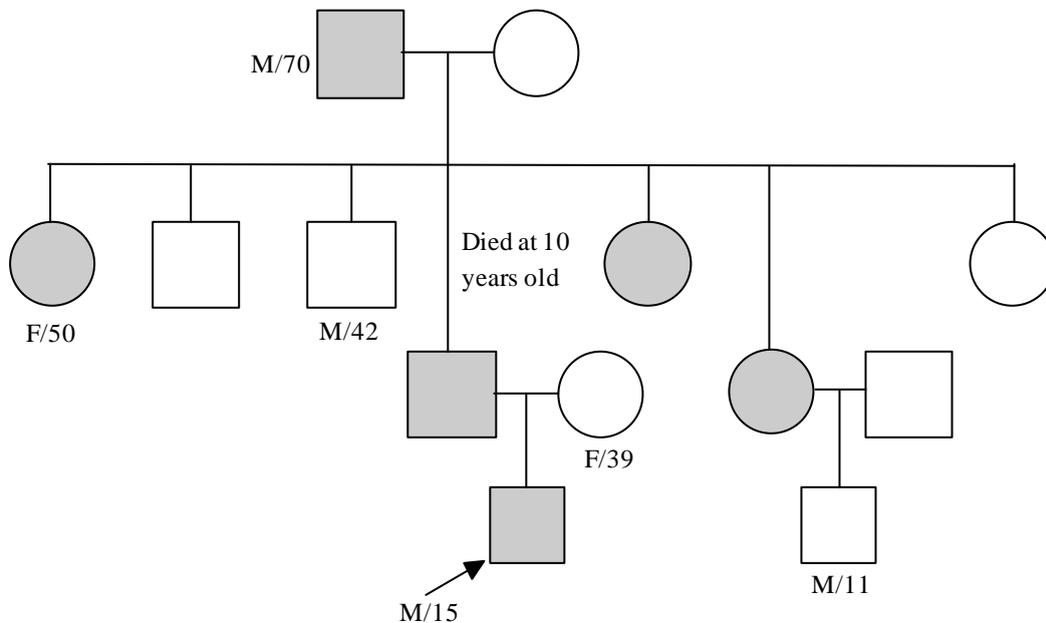


Figure 1: Family pedigree

Physical examination

Erosions were seen over his left upper back and both shins (Figure 2). There was no vesicle, milia or scarring seen. Post-inflammatory hyperpigmentation were noted. The erosions did not appear in cluster. Plantar keratoderma was also noted (Figure 3). His right thumb, index finger and left ring finger showed nail dystrophy. His face and flexural area were spared. No oral mucosa or teeth were involved.

Differential diagnosis

In view of the onset and nature of the disease, the likely diagnosis is mechano-bullous skin disease. Epidermolysis bullosa simplex is higher on the list of differential diagnosis, while dominant type dystrophic epidermolysis bullosa and junctional epidermolysis bullosa are the differential diagnoses.

Investigations

An incisional biopsy over his right upper back was taken for histology, immuno-flourescent and electron microscopy.

Histology

A piece of skin with hyperkeratosis, parakeratosis and accumulation of serum and neutrophils in the cornified layer was seen. There is subepidermal bulla formation with no acantholysis. Periodic-Acid-Schiff (PAS) stain shows basement membrane material only on the dermal side. Immuno-flourescence studies show no specific deposits.

Electromicroscopy

No blister is seen in the tissue block. There are

clumps of dense tonofilaments and electron dense amorphous materials present in prickle cell layer, and in one area there is lysis of keratinocytes at the basal cell layer. In some areas, electron dense amorphous materials are surrounded by dense tonofilaments. There is increase in tonofilaments bundle in basal cell adjacent to basement membrane. The granular and superficial cell layers are unremarkable (Figures 4 and 5).

Diagnosis

The diagnosis was epidermolysis bullosa simplex-Dowling Meara variant

REVIEW ON EPIDERMOLYSIS BULLOSA SIMPLEX

In 1886, Koebner first used the term epidermolysis bullosa to describe a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. In 1962, Pearson and collaborators applied the techniques of electron microscopy to epidermolysis bullosa as a gold standard in distinguishing three major types of epidermolysis bullosa with reference of different level of splitting in anchoring complex. In epidermolysis bullosa simplex (EBS), the plane of cleavage is through the basal keratinocyte; in junctional epidermolysis bullosa (JEB) the splitting is at the level of lamina lucida; and in dystrophic epidermolysis bullosa (DEB) the splitting is just beneath the lamina densa.

Different phenotypic variants of EBS are recognized, three commonest variants are EBS-Weber



Figure 2: Erosions on shins



Figure 3: Planter keratoderma

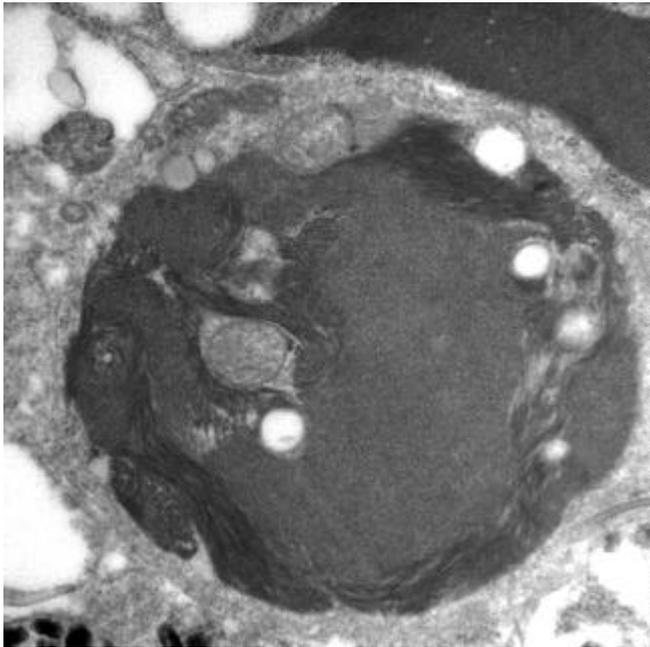


Figure 4

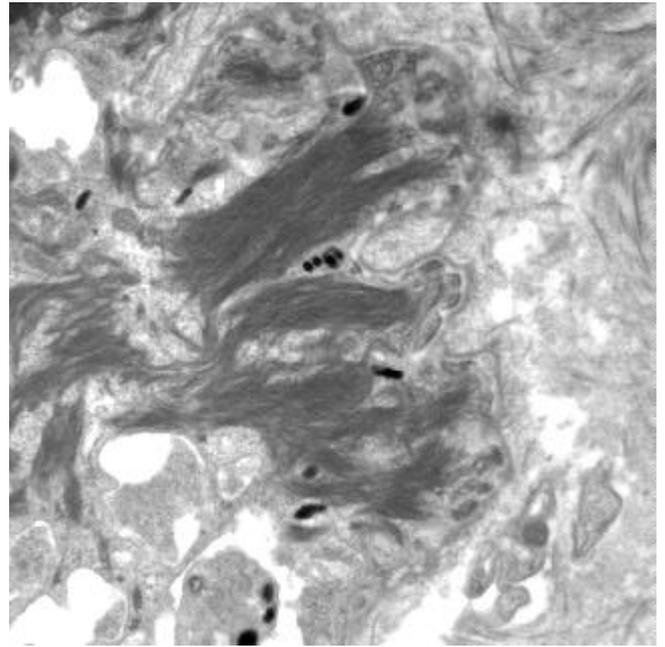


Figure 5

Figures 4 and 5: Electron micrographs of epidermolysis bullosa simplex (By courtesy of Dr. K. C. Lee, Department of Pathology, PMH)

Cockayne variant with the blistering predominantly on the volar surface; EBS-Kobner variant with more widespread involvement and EBS-Dowling Meara variant with generalized herpetiform blistering and focal palmoplantar keratoderma.

EBS-Dowling Meara variant or epidermolysis bullosa herpetiformis was first described by Dowling and Meara in 1954. Although sporadic cases occurred, most of the reported cases were transmitted in autosomal dominant trait.

In 1991, Vassar et al showed that mutant keratin 14 expression in transgenic mice causes cutaneous abnormalities resembling EBS-Dowling Meara type. In the same year, human molecular genetic studies demonstrated that point mutations in genes for keratin 5 and 14 accounted for the pathophysiology of EBS.¹

In ultrastructural study, keratin 5 and 14 contain a central alpha-helical domain flanked at either end by globular domains. The boundary region between the alpha-helical domain and its adjoining globular domains contains highly conserved sequences. Dowling Meara variant of EBS is caused by alteration of that highly

conserved region, which produce the most severe phenotypic effects.² EBS-Dowling Meara variant is characterized ultrastructurally by aggregation of tonofilaments. Clumping of keratins in the basal cells of the epidermis in form of compact round aggregations, whisklike clumps or both.³

Fifteen dermatologists active in the field of inherited EB met and reviewed the collective clinical, epidemiological, and laboratory data on inherited EB from National Epidermolysis Bullosa Registry (NEBR), which included a cohort of more than 3000 EB patients, in second international consensus meeting in May 1999. A new revised classification system for inherited epidermolysis bullosa was published,⁴ which tried to simplify and clarify this group of disease. It included the targeted proteins in subtyping inherited epidermolysis bullosa. At the same time the designation of localized versus generalized disease activity and genetic mode of transmission were omitted. The revised classification system for EBS was shown in Table 1.

In the past, the prenatal diagnosis of inherited EB was based on combination of ultrastructural and immunohistochemical staining techniques on fetal skin

Table 1. Revised classification system of EBS⁴

Major EB type	Major EB subtype	Protein/gene systems involved
EBS (epidermolytic EB)	EBS-Weber Cockayne	K5, K14
	EBS-Koebner	K5, K14
	EBS-Dowling Meara	K5, K14
	EBS-Muscular dystrophy	Plectin

biopsy specimens which cannot be performed until 16 to 18 gestational weeks and it carries the risk of fetal mortality. With the advance in molecular biological testing, chorionic villi or amniocentesis fluid samples can be used for prenatal diagnosis at 10-12 gestational weeks.

Management

As there is no effective curative therapy for EBS, most of the management plan would depend on preventing, monitoring and correcting complications and most important is to improve patient and their family's quality of life.

Preventing any trauma is the main objective as mechanical trauma induced blister or erosion. Wound care is also important to prevent any infection, scarring, syndactyly and other rare but important complications such as squamous cell carcinoma. Squamous cell carcinoma is usually presented with non-healing wound in dystrophic and junctional EB.

Oral blistering, abnormal esophageal motility, strictures, dysphagia, diarrhoea, malabsorption and dental problems all impair nutritional uptake, this may affect patient's healing ability and normal growth particularly in infant and early childhood. Team approach including paediatrician, paediatric surgeon, nutritionist, speech therapist and occupational therapist is the best way to managing nutritional deficiency.

The last, but not the least is genetic counseling service as most of the EBS is inherited as autosomal dominant trait.

In the future, the application of gene therapy may offer the new hope in correcting the absence or defective gene in inherited bullous dermatoses.

Learning points:

For epidermolysis bullosa, prenatal diagnosis, genetic counseling, preventing and managing complications to improve quality of life of patients and their family are important. Gene therapy may offer new hope in the future.

References

1. Bonidas JM, Rothman AL, Spstein EH. Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities. *Science* 1991;254:1202-5.
2. Fuchs E. Genetic skin disorders of keratin. *J Invest Dermatol* 1992;99:671-4.
3. Puddu P, Angelo C, Faraggiana T. Epidermolysis bullosa of the dowling-meara type: clinical and ultrastructural findings in five patients. *Pediatr Dermatol* 1996;13:207-11.
4. Fine JD, Eady RAJ, Bauer EA, et al. Revised classification system for inherited epidermolysis bullosa. Report of the second international consensus meeting on diagnosis and classification of epidermolysis bullosa. *J Am Acad Dermatol* 2000;42:1051-66.