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Epidermolysis Bullosa Dystrophica in a Chinese Neonate

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Abstract Epidermolysis bullosa dystrophica (EBD) is a rare blistering disease that may present in the neonatal period. Diagnosis is based on clinical symptomatology, histopathology, electromicroscopy and genetic studies. Age of onset, symptomatology and prognosis of the various subtypes are varied. We describe a case of EBD diagnosed in the neonatal period and discuss the many issues associated with the disease. A multidisciplinary approach with inputs from the neonatologists, paediatricians, dermatologists, plastic surgeons, dietitians, physiotherapists, occupational therapists, and special nurses are required to assure optimal outcome.

Key words Epidermolysis bullosa dystrophica; Neonate

Introduction

Epidermolysis bullosa (EB) is one of the rare blistering diseases that may present in the neonatal period. Many subtypes are recognised. Most of them are associated with high morbidity and significant mortality. Diagnosis of EB is based on clinical signs, histopathology, electromicroscopy, and, if available, genetic studies. Age of onset, clinical presentation and prognosis of the various subtypes are varied. We describe a case of EB dystrophica (EBD) diagnosed in the neonatal period. The skin lesions, growth and psychosocial issues associated with the disease are described. A multidisciplinary approach with inputs from the neonatologists, paediatricians, dermatologists, plastic surgeons, dietitians, physiotherapists, occupational therapists, and special nurses are required to achieve optimal outcome.

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Case Report

A 2.95 kg-boy, delivered at term in March 2006 by elective Caesarean section at a private hospital, was noted to have multiple large bullous lesions over his buttocks and calves (Figure 1). The lesions contained clear fluid. When deroofed, the base of the lesions was erythematous. The lesions were well-demarcated with normal surrounding skin. His eyes, nails and oral mucosa were normal. There was no fever or systemic upset, making the differential diagnoses of bullous impetigo or neonatal herpes unlikely. He was transferred to the neonatal unit of a university teaching hospital for further management. There was no apparent history of skin diseases in the family. The Plastic Surgical team was involved for skin and dressing care. Skin

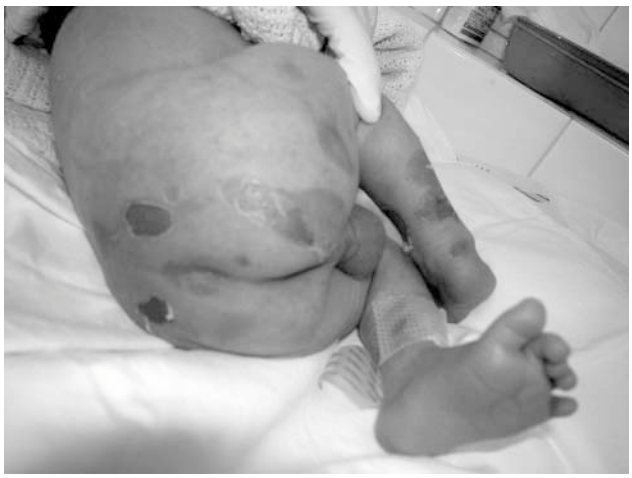

Figure 1 Multiple bullae with erosions involving the buttocks and lower limbs.

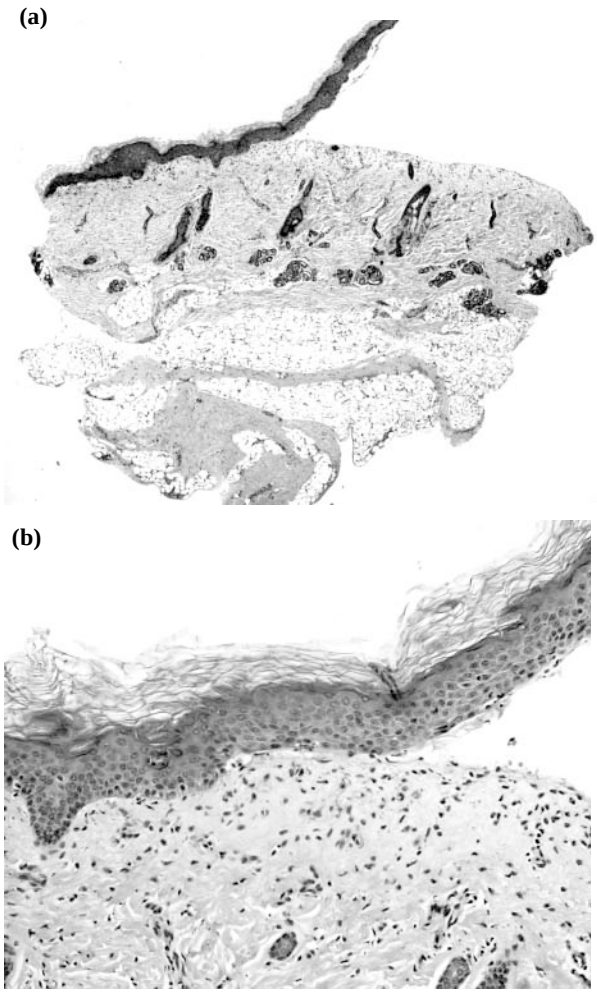

Figure 2 Histology at low and medium magnifications showing cell poor subepidermal bulla with scar-like granulation tissue at upper dermis.

biopsies from right thigh and right lower calf showed cell poor subepidermal blister formation (Figure 2). There was focal deficiency of type VII Collagen on immunostaining. Type VII collagen is normally present in anchoring fibrils which maintain attachment of the epidermis to the dermis at the dermo-epidermal junction. Electron microscopy showed presence of lamina densa at the roof of the blister (Figure 3). The findings of collagen VII deficiency and sublaminal split were consistent with EBD. The child remained stable and was discharged 12 days later. During his hospital stay, the family was counselled and issues of feeding, skin and dressing care taught and practiced to ensure familiarity with details of the procedures. This helped relieve the parents' anxiety and distress in handling an infant with a disabling disease. At 4-week of age, the baby developed a papulopustular rash over his chest and anterior abdomen. The lesions were swabbed and cultured and yielded heavy growth of *Staphylococcus aureus*, which improved with 2% fusidic acid cream, applied four times daily. At the 2-month, the mother reported that the boy was developing one blister approximately every 3 days in the ankle region. He also had severe seborrhoeic dermatitis of the scalp and mild facial eczema, which was treated with 0.1% mometasone furoate lotion as needed. Growth and development were satisfactory. At the 3-month, mother

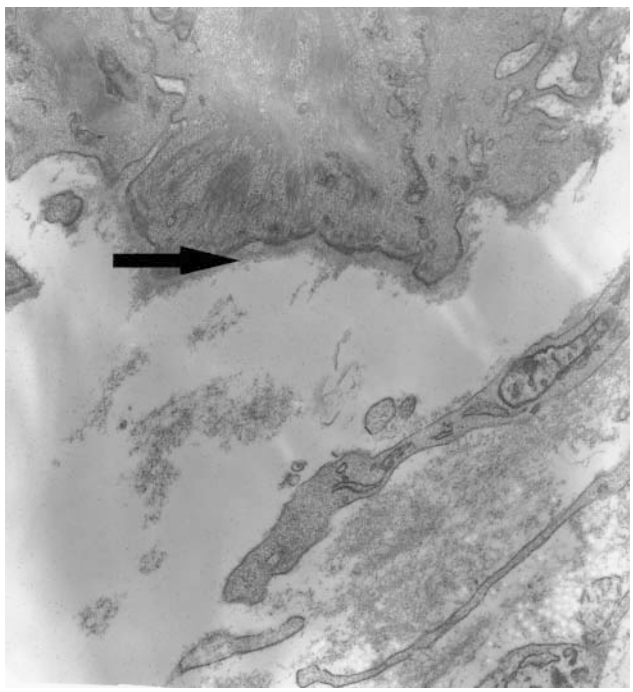

Figure 3 Electron microscopy showing presence of lamina densa (arrowed) at roof of the cleft.

reported that more blisters developed daily on his hands and ankles as the boy became more active. Occupational therapy was consulted to design barrier splintage to reduce frictional injuries. The seborrhoeic dermatitis of his scalp and facial eczema both improved. By 4-month of age, he was developing one bulla per week on his limb. In order to reduce rubbing and scratching triggering the formation of bullae, skin dryness and mild facial eczema were treated with aqueous cream, 10% urea cream, 1% hydrocortisone acetate cream, and occasional use of oral chlorpheniramine maleate. The mother reported that the combination treatment helped relieve the itch and rubbing. By eight months, the family was handling the child's skin and general health well. The boy was only having one new bulla on the face or earlobe per month. At 11 months, his growth and development remained satisfactory with weight and height along the 50% percentile on the standard growth chart. The relatively mild clinical course in this case and the lack of family history of similar disease suggest that the patient probably had the dominant form of the disease that was inherited sporadically. The family continued to receive multidisciplinary support from the paediatricians, dermatologists, plastic surgeons, dietitians, physiotherapists, occupational therapists, and special nurses to ensure optimal outcome. The pediatricians monitor his growth and development, and any medical or psychosocial problems that may arise with time. The plastic surgeons evaluate his skin condition and hand mobility, and special nurses provide ongoing age-appropriate dressing and skincare advice. The physiotherapists and occupational therapists give age-appropriate handling and splintage advice, whereas the dietitians give pivotal advice on optimal nutrition for growth. EBD is a lifelong disease but the form inherited in this child appears to be relatively mild and his skin condition may improve with age.

Discussion

Epidermolysis bullosa (EB) is a heterogeneous group of rare inherited bullous disorders characterised by blister formation in response to rubbing or frictional trauma.[1,2] Congenital EB is classified into 3 major categories, each with many subtypes, including: (1) EB simplex (EBS; intraepidermal skin separation); (2) junctional EB (JEB; skin separation in lamina lucida or central basement membrane zone BMZ); and (3) dystrophic EB or EB dystrophica (EBD; sublamina densa BMZ separation) (Table 1).[3] EB Simplex occurs in the epidermis of skin; whereas junctional EB and Dystrophic EB occur in the basement membrane zone. Researchers recently have proposed a new category termed hemidesmosomal EB (HEB), which exhibits splitting at either the intracellular or extracellular domains of the hemidesmosome. EBS usually is associated with little or no extracutaneous involvement, while the more severe hemidesmosomal, junctional, and dystrophic forms of EB may produce significant multiorgan system involvement, involving the mucosal surface of the mouth, esophagus, stomach, intestines, upper airway, bladder, and the genitals.[4]

According to a National Epidermolysis Bullosa Registry report, 50 EB cases occur per 1 million live births. Of these cases, approximately 92% are EBS, 5% are EBD, 1% is JEB, and 2% are unclassified.[5] It occurs in all racial and ethnic groups and affects males and females equally. As in our case, onset of EB is at birth or shortly after. The exception occurs in mild cases of EBS, which may remain undetected or undiagnosed even in adulthood. Infancy is an especially difficult time for EB patients. Generalised blistering caused by any subtype may be complicated by infection, sepsis, and death. Severe forms of EB increase the mortality risk during infancy. Patients with the Herlitz or letalis form of JEB have the highest risk with an estimated mortality rate of 87% during the first year of life.

When assessing an infant with EB, a thorough physical examination of skin, nails, hair, teeth, conjunctival, oral, and genital mucosae must be performed. It is important to evaluate the size, location, character of blisters, and to estimate the level of split. Usually, subcorneal blisters manifest as crusted erosions, intraepidermal blisters are flaccid and may expand under pressure (i.e. Nikolsky's sign), and intralamina lucida blisters are tense and heal with atrophy but no scarring. Sublamina densa blisters heal with scarring and milia formation.

Diagnosis of EB during the neonatal period is by skin biopsy, immunofluorescence and electromicroscopy following a thorough history and physical examination. The usual approach is to obtain 2 biopsy specimens for analysis, one specimen using electron microscopy (EM) and the other using immunofluorescent microscopy. Biopsy specimens from a fresh blister are obtained by gently rotating a pencil eraser back and forth over an area of skin until epidermal separation is achieved, sampling both unblistered and blistered skin, and immediately sending it for transmission EM. EM is important for determining the level of blistering and provides essential information on BMZ morphology. Other investigations should be performed if indicated. Anemia may be present in the severe EBD and should be

evaluated using complete blood count with iron studies. Bacterial cultures should be performed from poorly healing wounds or wounds that appear infected. Esophageal strictures associated with JEB, EBD, or the pyloric atresia associated with a rare form of JEB can be visualised by an upper GI series or endoscopy.

Neonatal EBD is a distressing disease to parents and physicians alike. This neonate had two of the frequently encountered issues associated with the disease, namely recurrent blister formation and infection with *S. aureus*. Many other issues of management may accompany the disease (Table 2). Infants with mild forms of EB may not require extensive treatment. Individuals with moderate and severe forms may have many complications and the family will require psychological support. Doctors, nurses, social workers, clergy members, psychologists, dietitians, patient and parent support groups can assist with care and provide information and emotional support. It is important that parents, or care providers should not feel that they must deal with all the complicated aspects of EB care alone.

Handling blisters.[5] This is the most essential element in the care of EB patients. Parents should be taught to handle the child's condition right from the neonatal period. They should attempt to minimise blister formation and prevent

Table 1 Major types of epidermolysis bullosa[1-3,11]

Types	**EB simplex[12]**	**Junctional EB[13-15]**	**EB dystrophica[1,15-19]**
Incidence[3,5]	10.7-34.4 cases/million live births	2.0-3.2 cases/million live births	26.4 cases/million live births
Cleavage plane of EBM	Cytolysis of infranuclear portion of basal keratinocytes	Within lamina lucida of dermo-epidermal junction	Beneath lamina densa of dermo-epidermal junction
Pathophysiology	Genes encoding keratins 5 or 14, or HD1/plectin	Genes *LAMA3, LAMb3, LAMC2* encoding the polypeptide chains of laminin 5; *COL17A1* encoding type 17 collagen; *ITGA6* and *ITGB4* encoding $\alpha 6\beta 4$ integrin	Gene (*COL7A1*) encoding type VII collagen on chromosome 3p21
Inheritance	AD, AR (rare)	AR	AD (common and mild), AR (rare and severe), AD/AR heterozygote
Features	May involve hands, feet, extremities, nails, teeth, mucous membranes. Nonscarring, milia	Usually severe, involving buttocks, trunk and scalp. Also fingertips, nails, mucosae, and perioral involvement with sparing of lips. May be life threatening. Bullae non scarring.	Milia, nail dystrophy. Cockayne-Touraine variant: acral distribution. Mucosae not involved. Pasini variant: more extensive blistering, scarlike papules on the trunk (albopapuloid lesions), and involvement of the oral mucosa and teeth. AR subtype: scarring.
Prognosis	Normal lifespan, usually improves by puberty Weber-Cockayne: mild and localised Koebner: Palmoplantar hyperkeratosis and erosions common Dowling-Meara: severe, involves oral mucosa and manifests with grouped herpetiform blisters	JEB-Herlitz lethal Severe growth retardation, recalcitrant anaemia. Other types compatible with survival into adulthood	Cutaneous malignancies[20] Normal life expectancy in dominant form Risk of early death in recessive form

AD: autosomal dominant; EBM: epidermal basement membrane

Table 2 General principles in management of EB patients[1,2,5]

Multidisciplinary support:

1. Involvement of neonatologists, paediatricians, dermatologists, plastic surgeons, dietitians, physiotherapists, occupational therapists, and special nurses to assure optimal outcome.
2. Prevention of trauma, with padding of limbs, reduces blistering. A soft diet helps reduce oral and esophageal erosions.
3. Trained home health care providers to aid with skin care, nutrition, and physical therapy.

Nutrition:[7]

1. Regular assessment of growth parameters.
2. Dietitians to review caloric and protein intake.
3. Watch out for gastrointestinal complications which include oral blistering, abnormal esophageal motility, strictures, dysphagia, diarrhoea, malabsorption, and dental problems.

Skin care:[21]

1. Regular whirlpool therapy by physiotherapists may help with gentle cleansing and debridement of wounds.
2. Patients with severe EB require significant amounts of wound-care supplies (plain petroleum gauze, nonadhering gauze such as adaptic or Telfa, petroleum jelly, antibiotic ointment, and self-adhering gauze). Sufficient quantities of these materials must be prescribed.
3. Human keratinocytes cultured atop dermal equivalents are now available as skin equivalents. These allografts facilitate the wound healing process and stimulate reepithelialization of the patients' wounds.

Surgical, orthopaedic and plastic surgery input:[22]

1. Individuals with the severe forms of autosomal recessive EBD whose esophagus has been narrowed by scarring may require esophageal dilatation or gastrostomy feeding tube.
2. Pseudosyndactyly (mitten-hand deformity) is a frequent complication in patients with recessive EBD and surgery may be required to release them.

Dental care:

1. The patient should be educated to avoid harsh mouthwashes containing alcohol.
2. Regular visits to the dentist familiar with EB are recommended.

Squamous cell cancer:

1. Careful surveillance of non-healing areas is important to enable early detection.

Gene and protein therapy:[2]

1. Type VII collagen and laminin-5 gene therapy have been proven effective through in vivo models. Type VII collagen protein therapy has similarly been shown to be effective in an in vivo model. Currently, these therapies are being extensively studied at the preclinical stage, in animal models.

Genetic counseling and prenatal diagnosis:[18,23]

1. Prenatal diagnosis can now be accomplished by amniocentesis or sampling the chorionic villus for DNA analysis as early as the 8-10 week of gestation. Mutational studies make it possible to identify defective genes in EB patients and their family members in major centres overseas.
2. Mutation screening is performed by restriction fragment-length polymorphism analysis, hotspot analysis, and finally, direct DNA sequencing.

An international EB forum exists where professionals can share information in a secure manner. (www.internationalebforum.org)

More information and a parent self-help group can be found at www.debra.org.uk.

infection when blisters occur.[6] Detailed instructions and support must be provided to the parents prior to discharge of the patient. As blisters may form with minimal pressure or friction, parents are often hesitant to pick up and embrace the fragile young babies. Providing a gentle human touch with affection and a sense of security is particularly important in these patients. Our parents were taught to lift the baby by placing him on a soft material (such as a folded towel inside a pillowcase) and supporting him under the buttocks and behind the neck. The patient must not be picked up under the arms. A number of maneuvers can be done to protect the skin from injury, such as keeping rooms at an even temperature to avoid overheating, applying lubricants to the skin to reduce friction and dehydration, using simple, soft clothing that requires minimal handling when dressing a child, using sheepskin on car seats and other hard surfaces, and wearing mittens at bedtime to help prevent scratching. When blisters appear, the goals of care are to reduce pain or discomfort, prevent excessive loss of body fluid, promote healing, and prevent infection. Dressings that are sticking to the skin may be removed by soaking them off in warm water. It may be more comfortable to bathe the child in stages where small areas are cleaned at a time. Instructions on how to aspirate a blister in its early stages while still leaving the top skin intact to cover the underlying area should be provided. After puncturing and draining, an antibiotic ointment should be applied to the area of the blister before covering it with a sterile, non-sticking bandage. To prevent irritation of the skin from tape, a bandage can be secured with a strip of gauze that is tied around it. Self-adhering gauze or tape is a preferred choice for keeping dressings in place. Adhesive tape must not be applied directly to the skin. Non-adherent mesh dressings should be applied directly to wounds and overlaid with absorbent gauze to allow for exudate control. Gauze or bandages that are impregnated with petroleum jelly, glycerin, or emollients may be used.

Infections. S aureus colonisation occurred in our neonate. Patients with severe EB may be immunologically compromised and prone to infections by *Staphylococcus aureus, Streptococcus pyogenes*, or *Pseudomonas aeruginosa*. The risks of skin infection can be reduced by good nutrition and by careful observation of strict antiseptic skincare regimen. Antiseptic soaking solution for whirlpool therapy, an antibiotic ointment, or an oral antibiotic may be used to reduce bacterial growth. Non-healing wounds should be treated by biologically developed skin or semi-occlusive non-adherent dressings.

Nutrition.[7] Oral and esophageal blisters may cause difficulty in feeding in some patients with EB.[4] The infant may be fed using a soft nipple with large holes, a cleft palate nipple, a Habermann feeder, or a syringe. When the baby becomes old enough to take in food, adding extra liquid to finely mashed food makes it easier to swallow. Food must not be over-heated. The majority of patients with EBD have inadequate intake of a wide spectrum of nutrients. Persisting substantial improvements in dietary intake despite thorough counselling may be unsecured.[7] It is important to involve dietitians to prepare easy-to-consume recipes, identify high-caloric and protein-fortified foods and beverages to replace protein lost in draining blisters, suggest vitamin and mineral nutritional supplements, and recommend adjustments in the diet to prevent gastrointestinal problems, such as constipation, diarrhoea, or painful elimination. The most disabling complication is esophageal lesions, which may be found in some of the EB subtypes. Phenytoin and oral steroid elixirs may reduce the symptoms of dysphagia, and anticandidal is helpful if oral candidiasis is present. Esophageal dilation and removal of esophageal strictures by colonic interposition has proved effective in cases of advanced disease. Gastrostomy tube insertion has been effective in providing nutrition to individuals with esophageal strictures.

Eye care. Although not present in our patient, some patients with EB may develop recurrent blepharitis, bullous lesions of the conjunctivae, corneal ulcerations, corneal scarring, obliteration of tear ducts, eyelid lesions, and cicatricial conjunctivitis.[8] Corneal erosions are treated with application of antibiotic ointment and use of cycloplegic agents to reduce ciliary spasm. Tape to patch the eye must be avoided because of frequent blistering of the skin under the adhesive. Chronic blepharitis can result in cicatricial ectropion and exposure keratitis. Moisture chambers and ocular lubricants are used commonly for management. Regular ophthalmology assessments are indicated if the eyes are involved.

Skin cancer. In patients with EB that survive childhood, the most common cause of death is metastatic squamous cell carcinoma (SCC).[9] This skin cancer primarily occurs on the hands and feet and may begin as early as the teenage years in patients with the recessively inherited EBD. It tends to grow and spread faster in people with EB than in those without the disease. Importantly, failure to diagnose EB or its complications such as skin cancer can incur litigation. In contrast, dominantly inherited EBS and EBD and milder forms of JEB are not associated with risk of skin cancer and may not affect a patient's life expectancy adversely.

Many countries have established National EB Registers

to collect information from patients with EB, characterise the many different forms of EB and determine risks of various symptoms associated with the disease. The information is used for research to improve understanding and provide better treatment of EB. The National Epidermolysis Bullosa Registry (NEBR) and the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) are organisations that provide valuable support and medical information to physicians, patients and their families.[10] The number of severe cases is small and there has not been any registry in Hong Kong. Definitive genetic diagnosis is reliant on overseas connections. These patients should preferably be followed in larger regional centres where multidisciplinary care can be delivered.

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