

# Junctional Epidermolysis Bullosa

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Epidermolysis bullosa (EB) encompasses a heterogeneous group of genodermatoses, characterized by fragility and blistering of the skin, often associated with extracutaneous manifestations. The level of vesiculation within the skin defines 3 major subtypes of EB: EB simplex, junctional EB, and dystrophic EB. We present the case of a male neonate of 36 weeks' gestation, who was born with a few blisters with erosions and who rapidly developed extensive blistering of the skin. Histopathology revealed subepidermal blistering. Electron microscopy confirmed the cleavage of epidermis from dermis within the lamina lucida. Junctional EB was the diagnosis. The patient was discharged after hospitalization for 28 days. The development of new blisters with erosions were gradually improved after AQUACEL® Ag dressing, and the general condition was much better than at admission. The patient likely has a subtype of junctional EB termed generalized atrophic benign EB that clinically improves with age. He has the potential to father children and has a normal life expectancy. [*J Chin Med Assoc* 2006;69(10):503–506]

**Key Words:** epidermolysis bullosa, junctional epidermolysis bullosa, subepidermal blistering

## Introduction

Epidermolysis bullosa (EB) encompasses a group of heterogeneous diseases of the skin and mucous membranes, which share the common feature of the formation of blisters and erosions in response to minor mechanical trauma. Most cases of EB are inherited.<sup>1,2</sup> A comprehensive classification based on clinical presentation, genetic pattern of inheritance and electron microscopic features was proposed in 1991 by the Subcommittee of the National EB Registry.<sup>3</sup> EB is classified into 3 groups by the level at which the separation occurs: EB simplex (EBS; intraepidermal skin separation); junctional EB (JEB; skin separation in lamina lucida); and dystrophic EB (DEB; sublamina densa separation). EB is easily misdiagnosed as infectious bullous disease. The management of the former is primarily supportive and preventive, and that of the latter is with antibiotics. It is certainly important to distinguish between EB and infectious bullous diseases because skin biopsies are required for appropriate diagnosis and classification of EB.<sup>2</sup>

The incidence of EB estimated by a National EB Registry report is 50 EB cases occurring per 1 million

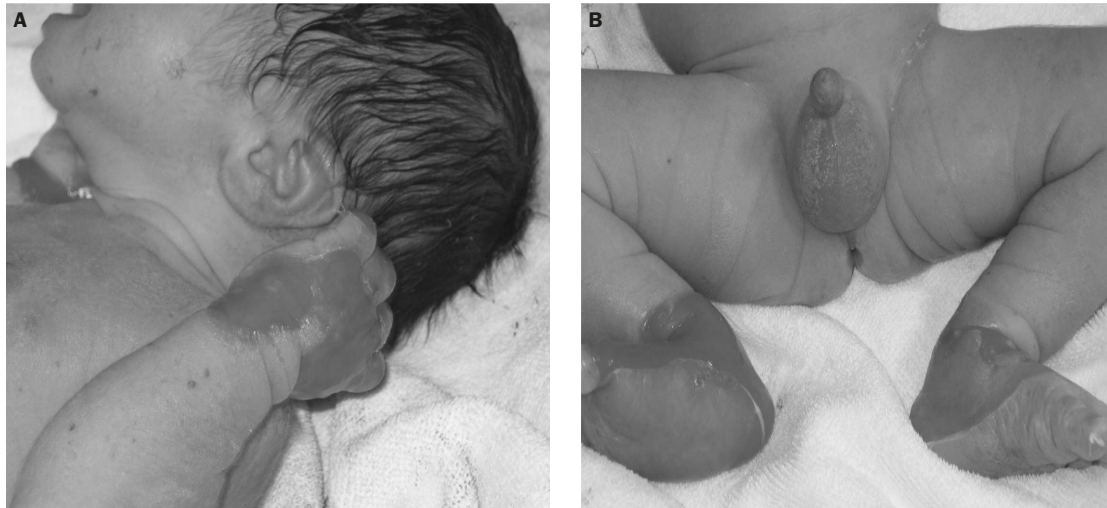
live births; of these cases, approximately 92% will be EBS, 5% DEB, 1% JEB, and 2% unclassified.<sup>1</sup> We describe a patient with JEB (which has an incidence of 0.5 per million<sup>1</sup>) who was managed initially with AQUACEL® Ag dressing.

## Case Report

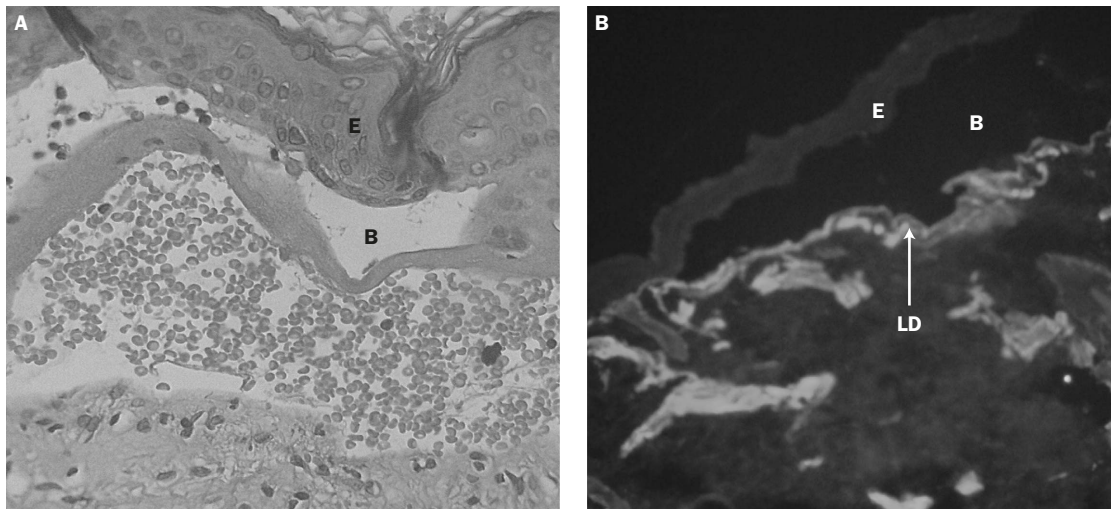
This was a male neonate of 36 weeks' gestation, birth weight of 2,846 g, Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, and normal spontaneous delivery. The mother had developed urinary tract infection 11 days before delivery, and she had been given cefazolin for 1 week. There was no consanguinity or family history of any bullous disease. The patient was noted at birth to have blisters with erosions on the face, scrotum and four extremities, especially at the wrists and ankles (Figure 1).

He was then referred to a tertiary teaching hospital where physical examination on admission revealed a tympanic temperature of 37°C, pulse of 140 beats/minute, respiratory rate of 40/minute, and blood pressure of 65/41 mmHg. Breath sounds were clear, and

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**Figure 1.** A neonate with junctional epidermolysis bullosa has blisters with erosions on the face, scrotum and 4 extremities.



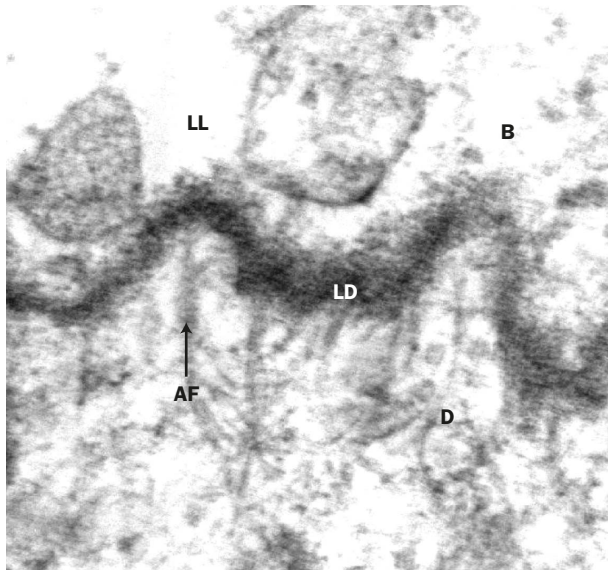
**Figure 2.** (A) Histopathology shows subepidermal blistering without inflammatory cells. The roof of the blister consists of full-thickness epidermis. The picture is compatible with epidermolysis bullosa (original magnification, 400 $\times$ ). (B) Immunofluorescence mapping with fluorescing antisera against type IV collagen (localized on the lamina densa) shows a positive linear immunofluorescence (arrow) at the base of the blister. This allocation of collagen type IV in the blister indicates a junctional cleavage. E = epidermis; B = blister; LD = lamina densa.

heart examination was normal. In addition to the skin lesions, 1 blister was found in the oral cavity. Antibiotics (oxacillin and gentamicin) were initially prescribed on the presumption that the bullae were secondary to bacterial infection. Laboratory investigations showed: white blood cell count, 4,200/mm<sup>3</sup> (with neutrophils 22.6%, lymphocytes 69.5%, monocytes 3.2%); hemoglobin, 16.7 g/dL; platelets, 313,000/mm<sup>3</sup>; C-reactive protein, 0.15 mg/dL. Antibiotics were discontinued on the 2<sup>nd</sup> day of admission due to no obvious focus of bacterial infection. Wound culture and blood culture were subsequently found to be negative.

Over the subsequent few days, new blisters developed on the trunk, buttocks and thighs, especially at friction points. Areas of re-epithelialization and

remnants of blister roofs were seen at the periphery of fresh erosions. The whole skin was very fragile, and handling the baby caused new blisters. The wounds were covered with AQUACEL<sup>®</sup> Ag dressing (ConvaTec, A Bristol-Myers Squibb Company, Princeton, NJ, USA) followed by gauze padding and elastic bandage.

Skin biopsy was performed when he was 6 days old. Histopathology revealed subepidermal blistering without inflammatory cells. The roof of the blister consisted of full-thickness epidermis. The picture was compatible with EB (Figure 2A). Direct immunofluorescence of lesional skin was negative for IgG, IgA, IgM and C3. Immunofluorescence mapping with fluorescing antisera against collagen type IV (localized in the lamina densa) showed a positive linear



**Figure 3.** Electron microscopy shows that the cleavage plane of the blister is in the lamina lucida. The lamina densa, measuring about 30–46 nm, is on the floor of the blister. There are no cytoplasmic remnants of basal keratinocytes above the lamina densa. Well-preserved anchoring fibrils in the dermis are present, but no hemidesmosomes are noted at the lamina densa. Junctional epidermolysis bullosa was diagnosed. LL = lamina lucida; B = blister; LD = lamina densa; AF = anchoring fibrils; D = dermis.

immunofluorescence at the base of the blister (Figure 2B). In turn, collagen type IV was present in the lamina densa. This allocation of collagen type IV in the blister indicated a junctional cleavage.<sup>4,5</sup>

Electron microscopy demonstrated that the cleavage plane of the blister was in the lamina lucida. The lamina densa was on the floor of the blister. There were no cytoplasmic remnants of basal keratinocytes above the lamina densa. In addition, well-preserved anchoring fibrils (collagen type VII) in the dermis were present, but no hemidesmosomes were noted at the basal lamina (Figure 3). JEB was the diagnosis.

The patient was discharged after hospitalization for 28 days. The wounds were covered with AQUACEL<sup>®</sup> Ag dressing after discharge home. He was regularly followed-up at our outpatient department. At the age of 3 months, his body weight was 5.6 kg, and his general condition was much improved. The previous blisters with erosions were healing gradually, and the development of new blisters was gradually being reduced with the use of AQUACEL<sup>®</sup> Ag dressing.

## Discussion

A neonate presenting with blisters opens a broad spectrum of differential diagnoses which include infectious

diseases such as bullous impetigo, staphylococcal scalded skin syndrome, or toxic epidermal necrolysis, and immunologic diseases such as pemphigus or bullous pemphigoid, and hereditary diseases such as EB. Differential diagnosis is based on clinical examination, histopathology, direct immunofluorescence and bacterial culture. The initial presentation of this case included a few blisters with erosions on the skin after birth, a picture that is difficult to differentiate from staphylococcal scalded skin syndrome. However, there was no obvious focus of infection. Subsequent laboratory studies including blood and wound cultures were negative.

EB can be differentiated from immunologic bullous dermatoses through histologic and immunofluorescent methods. In EB, the histologic picture is subepidermal bulla without inflammatory cells, while the direct immunofluorescence of both lesional and non-lesional skin is negative for IgA, IgG, IgM and C3.<sup>5</sup> Histopathology is generally not very helpful in delineating a specific subtype of EB, since all subtypes appear as subepidermal splits on light microscopy.<sup>5</sup> Ultrastructurally, EBS shows an intraepidermal separation at the level of basal cells; JEB and DEB show a subepidermal split through the lamina lucida, or beneath the lamina densa, respectively.<sup>6</sup> The level of tissue separation can be rapidly and reliably detected using immunofluorescence mapping.<sup>7</sup> Based on immunofluorescence staining, this method relates the level of cleavage to specific markers for structural proteins, which are strongly expressed in both normal skin and skin from EB patients. In JEB, anti-BP180 (anti-collagen type XVII) antibody will be located on the roof of the blister, whereas collagen type IV antibodies stain the floor.<sup>4,5</sup> In this patient, immunofluorescence mapping with antisera against collagen type IV showed a positive linear immunofluorescence at the base of the blister. This allocation of collagen type IV in the blister indicated a junctional cleavage.

There are more than 25 subtypes of EB, and they often become manifest at birth or during the 1<sup>st</sup> year of life.<sup>1</sup> The more severe the involvement, the earlier the blisters will occur, usually from mild trauma such as that encountered when a baby crawls or lifts objects or during teething.<sup>8</sup> Each type of EB has several variants based on inheritance, prognosis and clinical features. EBS is usually associated with little or no extracutaneous involvement, while the more severe junctional and dystrophic forms of EB may produce significant multiorgan involvement.<sup>9</sup> EBS, mostly an autosomal dominant disorder, comprises 92% of EB. There is an intraepidermal cleavage at the lower portion, owing to cytolytic alterations of basal keratinocytes with defects in cytokeratins 5 (*KRT5* gene) and 14 (*KRT14* gene).<sup>10</sup>

JEB is an autosomal recessive disorder characterized by cleavage at the lamina lucida. JEB mutations have been described in the 3 genes (*LAMA3*, *LAMB3*, *LAMC2*) that encode the anchoring filament protein, laminin 5, and the 2 transmembrane components of the hemidesmosome, collagen type XVII and integrin  $\alpha6\beta4$ .<sup>10</sup> DEB includes autosomal recessive and dominant forms. The mechanism of the disorder is a mutation in the gene encoding collagen type VII, leading to defective anchoring fibrils and causing sublamina densa separation.<sup>11,12</sup> Skin biopsies are required for appropriate diagnosis and classification in affected patients.<sup>2</sup>

The management of EB is primarily preventive and supportive, consisting of prevention of trauma, careful wound care, nutritional support and infection control. Surgical procedures are indicated when deformities are caused by the blistering and scarring.<sup>13</sup> Steroid therapy is controversial for EB; since EB are genetic disorders, no drug is capable of correcting the molecular defect.<sup>14</sup> Gene therapy is, potentially, a future therapy. Recently, researchers have reported sustainable genetic correction of JEB patient skin tissue with laminin 5 gene delivery.<sup>15</sup> Clinical physicians should provide genetic counseling for families at risk for EB.

The prognosis of EB depends on the severity of the illness. Primary subtypes of JEB include a lethal subtype (usually resulting in death in infancy) termed Herlitz or JEB letalis, a nonlethal subtype (with apparent scalp, nail and tooth abnormalities) termed JEB mitis, and a generalized benign type termed generalized atrophic benign EB (GABEB).<sup>9</sup> These varieties are distinguished clinically, although molecular studies may be useful. Our patient likely has the GABEB subtype that clinically improves with age. He has the potential to father children and has a normal life expectancy.<sup>9</sup>

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