Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.65, No.2(2025). p.xxx ; DOI: https://doi.org/10.14238/pi65.2.2024.XXX

Case Report

Neonates with epidermolysis bullosa: a case series

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Epidermolysis bullosa is a rare and currently incurable inherited disorder characterized by mechanical fragility of affected tissues which can be fatal. We describe two cases of neonatal epidermolysis bullosa followed in the high-risk neonates ward. The first case presented with bulla one day after birth with amniotic band syndrome, and the second case presented with bulla right after birth. **[Paediatr Indones. 2025;65:XXX; DOI: https://doi.org/10.14238/pi65.6.2025.XXX**].

Keywords: *epidermolysis bullosa simplex; neonates*

Epidermolysis bullosa (EB) is one of the rare blistering diseases that may present in the neonatal period. According to information from the *National Epidermolysis Bullosa Registry*, the prevalence and incidence of EB are 11.07 and 19.57, respectively, per 1 million live births.[1] Due to the shear force trauma, it results in mucocutaneous blistering, erosions, and ulceration. The severity can be mild to severe potentially being disabling or fatal.[2] Epidermolysis bullosa encompasses many clinically distinctive phenotypes, all of which have skin blistering and risk of extracutaneous manifestations and premature death.[3] The intricacy and rarity of EB make proper treatment challenging. The diagnosis criteria for EB is based on anamnesis, physical examination, skin biopsy, immunofluorescence, transmission electron microscopy (TEM), or DNA analysis. This case series covers aspects of skin pathology, clinical presentation, diagnosis, and treatment of epidermolysis bullosa,with the aim o improving the care for affected patients.

The cases

The first case was a 2-day-old male newborn hospitalized due to generalized bullae one day after spontaneous birth. Bulla found all over the body, and when ruptured, they produced yellow clear fluid. There were no clinical findings that support infection etiologic, no family history of the same disease, and no history of using drugs such as penicillamineor captopril which can induce bullae. Physical examination showed some bullae on the face, buccal mucous, lower lip, palate, and tongue. On the chest, abdomen, and both legs, there were ruptured bullae with erythema and yellow liquid, crusts, and reddish blisters around both ankles with the former coiling of the umbilical cord (amniotic band syndrome) (**Figure 1**). Skin culture was performed and showed *Enterobacter cloacae* (*E. cloacae*), and a skin biopsy revealed skin lesions with a vesiculobullous reaction showed pieces of thigh skin tissue lined with stratified squamous epithelium and

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Submitted January 17, 2023. Accepted April 22, 2025.

keratin, accompanied by bullae in the subepidermal layer. The lumen of the bulla contains erythrocytes and some inflammatory cells of lymphocytes. The dermis layer was composed of a stroma of moist fibro-collagenous connective tissue containing skin adnexa with the distribution of inflammatory cells of lymphocytes, PMN leukocytes, and histiocytes in the superficial dermis (**Figure 2**). The blood laboratory examination (haemoglobin, white blood, and platelet count) was normal and the blood culture was sterile. Based on the clinical and biopsy examination, the baby was diagnosed with the EB simplex (EBS). The baby was treated conservatively with topical antibiotic including fusidic acid and silver sulfadiazine twice daily. Ampicillin were also administered. The wound was managed without dressing with normal saline to prevent secondary infection. The baby was discharged after 16 days of hospitalization because of clinical improvement such as no other new bulla, dried out lesion, no sign of secondary skin infection At 2 years follow-up, there were conjoint foot fingers due to amnion band syndrome (ABS), but it does not affect walking activity.

The second case was an 8-day-old female newborn referred to our hospital with a complaint of bullae on all extremities and abdomen, along with a plaque in the mouth that appeared immediately right after birth. There were no clinical findings that support infection etiologic, no family history of the same disease, using drugs such as penicillamine and captopril that can induced drug induce bullae. Physical examination showed bullae with erythema on the face, mouth ulcer, ruptured bullae with erythema and yellowish liquid, and crusts on the chest, abdomen, and four extremities, especially in both legs (**Figure 3**). Skin culture was performed and showed *Staphylococcus aureus* (*S. aureus*), while skin biopsy showed skin lesions with a vesico-bullosa reaction and skin tissue

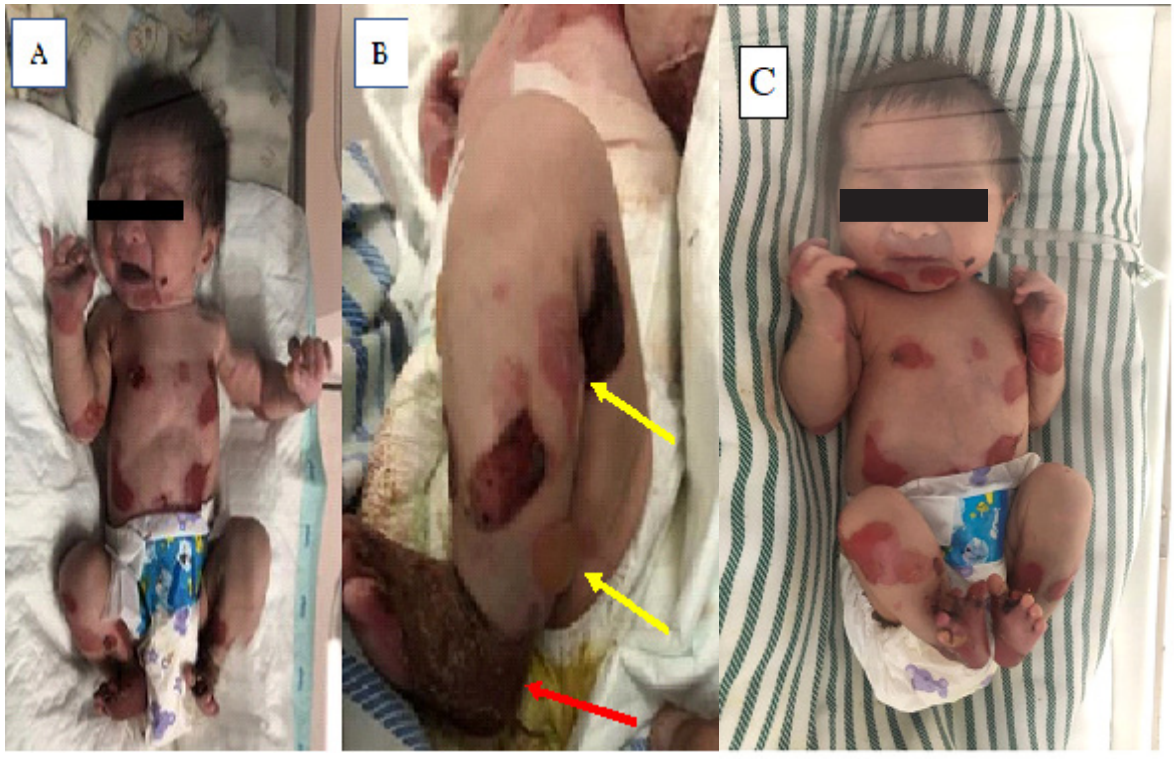

Figure 1. Clinical presentation on 1st case.
A: several bullae, erythema, and erosion on face, chest, abdomen, and all extremities.
B: tense bullae (yellow arrow) and reddish blister around both of ankles of the former coiling of the umbilical cord (red arrow).
C. Improvement of skin lesion after 16 days, there are no new bulla and no secondary infection.

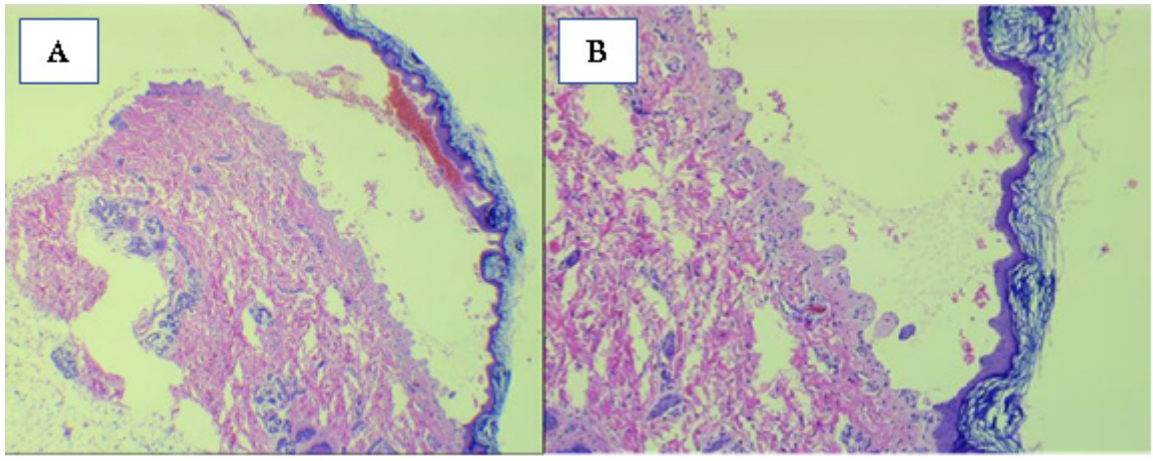

Figure 2. Microscopic skin biopsy on 1st case.
Bullae in the subepidermal layer, the lumen of the bulla contains erythrocytes and some inflammatory cells of lymphocytes. HE stained 100x (A), and 400x (B) magnification.

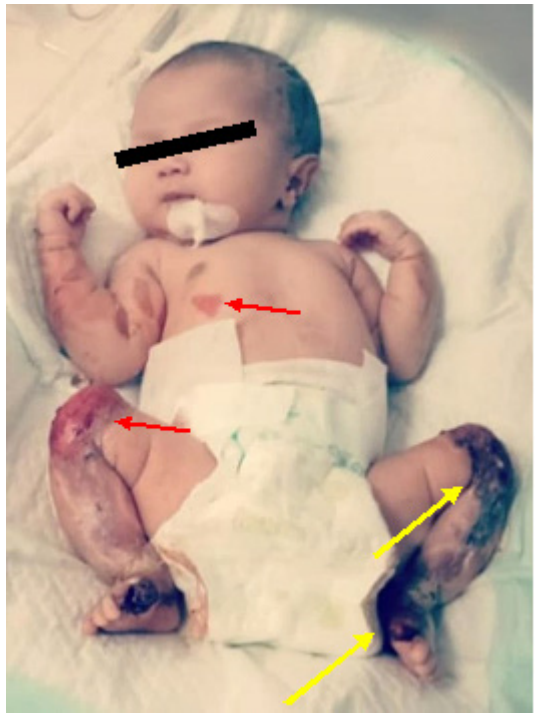

Figure 3. Clinical presentation on 2nd case.
Several ruptured bullae, erythema, and yellow liquid around the mouth, chest, and four extremities (red arrows), along with crusts in both legs (yellow arrows).

lined with stratified keratinized squamous epithelium consisting of sub-epidermal bullae formation filled with erythrocytes and some leukocytes. The dermis layer is composed of fibrocollagenous stroma and containskin adnexa, with infiltration of lymphocytes, PMN leukocytes, and histiocytes in the superficial dermis (**Figure 4**). The blood laboratory examination (haemoglobin, white blood and platelet count) was normal, and the blood culture was sterile. By clinical and biopsy examination the baby was diagnosed with the EBS. The baby was treated conservatively with topical antibiotics containing fusidic acid and silver

sulfadiazine twice daily, along with erythromycin. The wound was managed properly with normal saline to prevent secondary infection. The baby was discharged after ten days of hospitalization because of clinical improvement.

Discussion

Bullae was formed by fluid accumulation between cells in the epidermis or between the epidermal and dermal skin layers. Generalized bullous and skin erosions in the neonatal period with mucous membrane involvement can be suspected as inherited epidermolysis bullosa Inherited epidermolysis bullosa (IEB) is a group of genetic skin disorders characterized by spontaneous blistering or blistering caused by minor trauma.[4] Three classic types of inherited EB are simplex, junctional, and dystrophic. They are differentiated by the level of blister cleavage and subdivided according to the pattern of genetic inheritance, morphology/ topography of lesions, and genetic mutation involved.[5] Three hundred mutations have been identified until today.[6] These disorders represent heterogenous phenotypes and cause complications from localized skin fragility to neonatal death. Most of the cases are because of dominantly acting mutations in either keratin 14 (K14) or K5, which are type I and II intermediate filament (IF) proteins, tasked with forming a pancytoplasmic network of 10-nm filaments in basal keratinocytes to become fragile and account for their trauma-induced rupture.[7]

Specific diagnostic clues for EBS include blistering and keratoderma only affecting the palms and soles, indicative of a localized EB type. A sign of severe EBS is confluent palmoplantar keratoderma and cluster, arcuate herpetiform blisters. The newborn may cry hoarsely upon birth, and the perioral, axillary, and neck regions may later develop exuberant granulation tissue. There may also be dental enamel defects with or without patulous nail beds,microstomia, pseudo-syndactyly, contractures, and scarring with milia formation. Finally, photosensitivity and poikiloderma are also signs of severe form of EB dystrophic (EBD).[2] In our case series, the two patients showed bullae present since birth with spontaneous and minimal trauma, no family history of the same diseases, especially mother, and no history of using drugs such as penicillamine and captopril that can induce bullae. Physical examination showed the lesion appeared in areas that were often exposed to friction and there was involvement of the oral mucosa, but no conjunctival nor urogenital abnormalities were seen. The blister occurs in an annular pattern leading to progressive hyperpigmentation, and gradually disappears. Both cases showed no nail dystrophy, milia, or natal teeth. In the first patient, no extra-cutaneous involvement appeared, there was no atresia pyloric, no ureteral or renal anomalies, just involvement of the oral

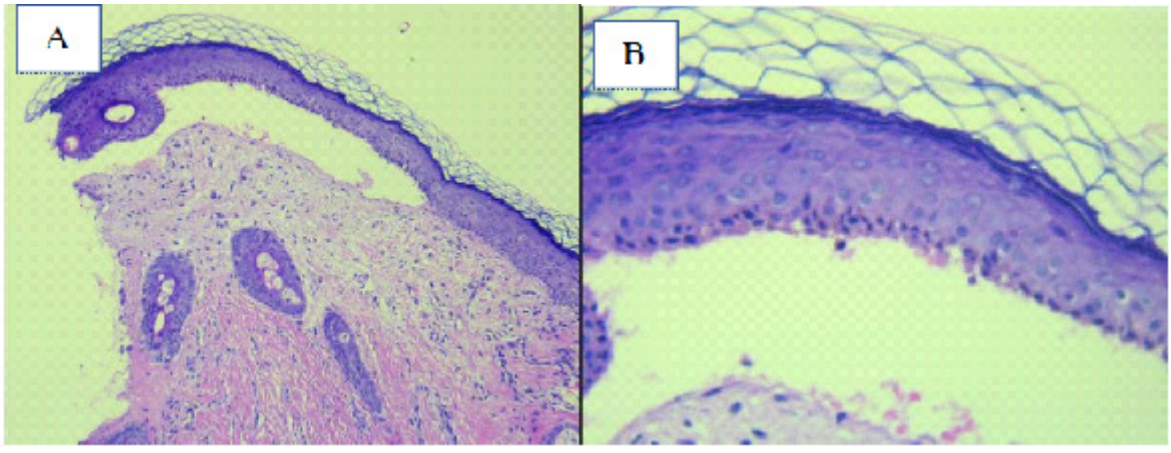

Figure 4. Microscopic skin biopsy on 2nd case.
Bullae in the subepidermal layer, the lumen of the bulla contains no inflammatory cells.
HE stained 100x (A), and 400x (B) magnification.

mucosa. This patient had amniotic band syndrome at both ankles. In the second patient, there was mucosal involvement but no other extracutaneous involvement appeared. After obtaining the history, a complete physical examination and careful assessment of the morphology and distribution of the lesions were performed. Our patient leads to the diagnosis of EBS and we have to prove it with further investigations.

In the case of EB, various diagnostic techniques are used to determine the extent of the disease and the specific location where it is located. These techniques include skin biopsy, transmission electron microscopy (TEM), and immunofluorescence antigen mapping (IAM). DNA analysis is also used to determine the cause of the disease.[2]

The histology images of the EBS revealed intact of the stratum corneum and upper epidermis, with vesicle formation in the lower epidermis in the basal layer caused by epidermal cell degeneration. The EB types can be identified based on the degree of blister formation in the cutaneous basement membrane zone as shown by diagnostic electron microscopy and/or immune epitope mapping: 1) Tissue separation in the EBS is intraepidermal, 2) The dermal-epidermal basement membrane, particularly the lamina lucida, is where the junctional EB (JEB) tissue cleavage occurs, 3) In the DEB, blistering occurs in the upper papillary dermis at the level of the anchoring fibrils below the lamina densa, 4) Mixed Kindler syndrome, in which the skin's tissue separates at various degrees.[5]

Our case series were diagnosed using history, physical examination, and a skin biopsy. However, we did not perform immunofluorescence, TEM, or DNA analysis due to its unavailability in our center. We only used skin biopsies to diagnose, so we did not know the type of EB and the affecting gene. The skin biopsy in both cases shows skin lesions with a vesiculobullous reaction. The biopsy revealed pieces of thigh skin tissue lined with stratified squamous epithelium and keratin, accompanied by bullae in the subepidermal layer. The lumen of the bullae contains erythrocytes and some inflammatory cells of lymphocytes. The dermis layer was composed of a stroma of moist fibro-collagenous connective tissue containing skin adnexa with the distribution of inflammatory cells of lymphocytes, PMN leukocytes, and histiocytes in the superficial dermis. There were no signs of malignancy. While routine light microscopy can identify the level of the split as intraepidermal versus subepidermal and the location of the bullae in the epidermis, subdermal, or dermal layers of the skin, it is not very helpful in identifying the specific subtype of EB as both junctional and dystrophic subtypes will exhibit subepidermal blistering.[8]

The congenital defects known as amniotic band syndrome (ABS) involve the disruption, distortion, and deformity of organs that were supposed to develop normally. The exact cause of amniotic band syndrome is unknown. However, it is believed that amnion rupture occurs early in pregnancy and causes the growth of many lost strands (amniotic bands), which stick to and entangle the fetus. Rarely does the literature refer to ABS and EB occurring simultaneously. Three out of 10 newborns hospitalized for EB who also had abnormalities as a result of ABS were described by a study in 1984. The authors proposed that membrane fragility, which results in early membrane rupture and ABS, may be caused by structural flaws in membrane connective tissue.[9] An ultrasound result suggestive of an amniotic band was described at 4- and 24 weeks of gestation in a more recent case report. The right leg of the newborn boy was found to be narrowed and constricted above the ankle, and his torso was covered in numerous blisters. Junctional EB was confirmed by histologic analysis.[10] Congenital constricting bands were infrequently reported in patients with all major types of hereditary EB as part of the *National Epidermolysis Bullosa Registry*.[5] These examples add to the scant reports of EB and ABS occurring simultaneously in the literature. According to a recent study, the amniotic epithelium's rivets, which are substantial anchoring structures, are made of type VII collagen. The integrity and anchoring capacity of the amniotic membrane may be hampered by abnormalities in type VII collagen of the amniotic epithelium in fetuses with DEB. As a result, the fetus may become entangled in loose amnion strands and develop constricting bands known as ABS in newborns with DEB.[11]

Epidermolysis bullosa management is based on a number of fundamental ideas: (1) avoiding skin trauma to prevent the development of new blisters; (2) diligent wound care with suitable wound dressings to ensure prompt wound healing and infection prevention; (3) upholding good nutrition to promote growth and wound healing; (4) monitoring

for extracutaneous complications; and (5) ongoing psychosocial support.[3] The most crucial components of treatment in the neonatal period are preventing new blisters and wound care. New blister prevention involves gentle handling of the infant, wearing loose-fitting clothing, padding bony prominences, avoiding adhesives, and patting the skin instead of direct rubbing. Vaseline or another mild ointment should be used to keep the skin well-lubricated, and infants should be kept in cold, air-conditioned environments because excessive heat can weaken the skin. To reduce friction and blister development in this area, lift babies with EB by placing one hand behind the neck and the other beneath the child's bottom rather than from under the arms. Prophylactic wrapping is frequently used as the infant ages to stop new blisters.[3,12]

In EB wounds, colonization, critical colonization, and infection are common. Regular bathing, especially when combined with an antibacterial wash, as well as topical antimicrobial ointments or gels, can be beneficial. In general, due to issues with bacterial resistance, which are common in EB, the use of topical antibiotics should be restricted to brief and irregular periods. Systemic antibiotics should only be used when topical methods are ineffective at treating serious colonization in a site that is not healing or when an infection has caused systemic disturbance.[2] In accordance with the literature, the most frequent pathogen found in EB infection was *S. aureus*.[13] Similar to the second patient who had *S. aureus* detected in the wound swab examination, the first patient had *E. cloacae*. Based on the sensitivity test results, both patients were treated with erythromycin as the antibiotic.

Nutritional support is important for adequate growth and development and to help in optimal wound healing.[14] Parents should be advised about the prevention of trauma and occurrences of new lesions. When the baby's overall health is stable, and the parents are competent and secure in their ability to take care of their child, the infant should be sent home. The dermatologist, neonatologist, and pediatrician collaboratively make this decision.[8] In our case, both patients wre stable and the parents can take care the baby at home.

Most cases of the EBS are inherited in an autosomal dominant pattern and are caused by a defect in genes encoding keratin 5 and keratin 14, although the mode of transmission is recessive in some subtypes.[7] According to reports, people with EBS have a de novo mutation incidence that ranges from 37 to 58%.[15,16] In both cases, no parents were affected. The subtype of the disease has a significant impact on the prognosis of EB. The majority of EB patients, especially those with EBS and dominant dystrophic epidermolysis bullosa (DDEB), have normal life expectancies. However, severe morbidity can occur in some patients. Outcome of patient with mild EBS is generally good, and in some cases, it getting better with age. The significant difference between EBS and other forms of EBS is the non-scarring healing bullae. In both cases, they had mild forms of EBS. Based on the literature and the previous cases, the prognosis of this EBS are as follows: quo ad vitam dubia ad bonam, quo ad sanationam dubia ad malam, and quo ad functionam dubia ad bonam.

Declaration of consent

The authors certify that all necessary patient consent documents have been received by the parents. In the form, the parents have given their consent for their images and other clinical information to be reported in the journal. The parents are aware that although every attempt will be made to keep the patients' identities hidden, their names and initials will not be published. However, anonymity cannot be guaranteed.

Acknowledgment

We were very grateful to the Department of Pathology Anatomy and Dermato-venerology Faculty of Medicine, Diponegoro University, dr Kariadi General Hospital Semarang Indonesia for its contribution in completing this case series.

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