De novo epidermolysis bullosa simplex in sasak Tribe
Newborn, East Lombok, Indonesia: A rare case

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Abstract

Introduction: Epidermolysis Bullosa Simplex (EBS) is one of the major forms of rare genodermatosis
EB characterized by non-scarring bulla on the skin or mucosa induced by minor trauma. The
worldwide prevalence of EBS is estimated 1 in 50,000 births. The most common etiology of EBS is
mutations gene KRT5 and KRT14 who were genetically inherited or de novo in sporadic case.
Case: A newborn from the Sasak tribe without a family history of blistering disease was referred to
emergency room with generalized multiple blisters with exfoliate skin at birth.
Discussion: The accurate diagnosis of EB types and subtypes is important for the management and
prognosis of the disease. Many developing countries have difficulty access for advanced laboratory
facilities to support the diagnosis of EB while clinically diagnoses are often inaccurate. Clinical
Diagnostic Matrix (CDM) is a simple clinical diagnostic tool that can used by the clinical practitioner
in limited resource conditions to diagnose type and subtype EB.
Conclusion: EBS is the most common type of EB with a generalized form in most sporadic cases.
CDM can be used as a diagnostic tool for diagnosis EB more accurately in developing countries such
as Indonesia.

Keywords: Epidermolysis bullosa simplex, blistering, de novo, sporadic

Introduction

Epidermolysis bullosa (EB) is a group of rare genodermatosis characterized by skin and
mucosa fragility causing blistering formation in response to mild trauma [1, 2]. The ratio of EB
in males and females is equal and is not influenced by race or ethnicity [3]. EB was first
described by Koebner in 1886 as an inherited bullous disease. In 1962, Pearson gave the
term mecanobullous to EB because the blister formation was preceded by mechanical
trauma [2-4]. It is estimated that there are 500,000 cases of EB in the world with a ratio of
1:17,000 live births. In Scotland, EB estimated 49 per 1 million population. The exact
prevalence of EB in Indonesia is unknow. Based on database from DEBRA Indonesia in
2018, there were around 31 cases of EB in Indonesia [2, 5] A case report from Indonesia
within 2013-2020 found 9 cases of EB on Javanese [6]. EB is classified into 4 major types
based on the level separation of the epidermis from the basal membrane zone (BMZ) or the
location of the blister to the dermo-epidermal junction, namely, epidermolysis bullosa
simplex (EBS-in basal cells of keratocytes), junctional bullous epidermolysis (EBJ-between
BMZ), epidermolysis bullosa dystrophic (EBD-underneath BMZ), and Kindler syndrome
(multiple levels of separation). EBS is the most common type of EB with an incidence of 75-
85% of EB cases in the Western country [7]. The worldwide prevalence of EBS is estimated
1:50,000 live births. EBS is usually caused by mutations in KRT5 and KRT14 genes which
are inherited in an autosomal dominant and rarely in autosomal recessive. In sporadic cases,
mutations in KRT5 and KRT14 gene due to de novo (new mutation) [2, 7-9]. We reported the
first case of EBS in East Lombok Regency, West Nusa Tenggara, Indonesia in a newborn
from Sasak tribe without a family history blistering.

Case

A newborn from the Sasak tribe was referred from the Public Health Center to the hospital
emergency room with generalized multiple blisters with exfoliative skin at birth. Based on
the history, the baby is the second child, 38 weeks of gestation, born spontaneously from
vaginal delivery at the Public Health Center.
The baby cried immediately with a birth weight 3000 g. No antenatal and natal complications. There was no family history of blistering disease. Systemic examination was within normal limits. On dermatology examination, revealed skin lesions with generalized distribution, multiple blistering which mainly were eroded and exfoliated with erythematous base. No involvement of the oral cavity, eyes, nails, scalp, and genitalia. Complete blood count was normal. Skin biopsy examination was not performed due to the parents did not give consent.

In our region, confirmatory diagnostic tools such as electron microscopy, immunofluorescent antigen mapping, and molecular genetic testing were difficult to access. Furthermore, there was also a refusal of the skin biopsy from the parents. Based on the clinical features and family history without blistering disease, a suspected de novo EBS diagnosis was made. Finally, we decided to use a feasible and simple diagnostic tool, namely CDM, to get a more accurate diagnostic of EB type and subtype. Based on the CDM, the final diagnosis of EBS was made with an intermediate generalized subtype. We also working together with pediatrics. The treatment is conservative and symptomatic. Baby are given soft and breathable clothing, erosion and exfoliate skin were cleaned with NaCl 0.9% solution once daily then covered with hydrocolloid wound dressing to prevent secondary infection. From pediatrics, the baby was received systemic antibiotics injection to prevent secondary infection and paracetamol infusion as pain relieved. During the treatment, the baby was stable and did not have any new lesions. The baby was discharged on day 5 of hospitalization. The parents are explained and educated about their child's condition and the proper way to skin management at home. The mother was provided with sterile gauze, NaCl 0.9% solution, wound dressing, moisturizer, and fusidic acid 2% cream which could later be applied in case having secondary infection of the skin. Skin lesions were healed without scarring on day 12.

Discussion
EBS is one of the major types of EB characterized by skin and mucosa fragility leading to the formation non-scarring blister after minor trauma (mechanical or temperature). Ultrastructurally, EBS has a separation level in intraepidermal basal cells. The etiology of EBS in many cases is a mutation of interfilamentous proteins keratin II (KRT5) and keratin I (KRT14), both were attached to the hemidesmosome and formed basal cell skeleton structure. Keratin 5 and 14 were maintaining the architecture and function of the hemidesmosome as junctional structure in basal cells keratocytes to BMZ [1, 2]. Mutations are usually inherited as autosomal dominant and rarely in autosomal recessive, in many sporadic cases are de novo mutation. It has been reported in the literature that de novo variant usually causes generalized form in mild to severe EBS type [7-9]. Pfendner et al., [8], reported in a cohort study of 18 EBS patients that 15 patients showed de novo mutations in KRT5 and KRT14. The same thing was also reported by Chong et al. [7] where 37% of de novo EBS cases were pathogenic variants of KRT5 and KRT14. Meanwhile, Hachem et al. [10] found the new de novo KLHL24 gene mutation caused
EBS cases in Italy. The pathogenesis of de novo EBS is still unknown. A study in Hong Kong have been reported that highly mutation CpG dinucleotide in several codons in multiple families of de novo EBS [7]. Another study showed that pathogenic variants were found in the proband (the first family member who has been affected with the medical genetic disorder) but were not detected in one of parent's leukocyte DNA was caused by germline mosaicism [3]. In our case, the patient was the second child with no family history of blistering disease so we suspected that the patient had sporadic cases with clinical features of generalized EBS.

A new consensus in 2014 was classified EB into 4 major types with the “Onion Skin” approach based expands of histologic features and molecular level (DNA and protein) in Figures 3 and 4. [1, 2].

**Fig 3:** Mutation in molecular level (DNA and protein) and comparison of 2008 nomenclature with 2014 “Onion Skin” terminology.

| Old Name (per 2008 recommendations) | 2014 Nomenclature |
|-----------------------------------|-------------------|
| EBS, localized                     | EBS localized, normal keratin 5 and 14 staining, KRT5 or KRT14 pathogenic variant (specify type) |
| EBS, Dowling-Meara                | EBS generalized severe, normal keratin 5 and 14 staining, KRT5 or KRT14 pathogenic variant (specify type) |
| EBS, generalized other            | EBS generalized intermediate, normal keratin 5 and 14 staining, KRT5 or KRT14 pathogenic variant (specify type) |
| EB-MP                             | EB-MP, normal keratin 5 staining, KRT5 pathogenic variant (specify type) |

| EBS Subtype | Localized | Generalized Intermediate | Mottled Pigmentation | Generalized Severe |
|-------------|-----------|--------------------------|----------------------|-------------------|
| Age of onset| Infant can present at birth, usually by 12-18 months | Birth/infancy | Birth/infancy | Birth |
| Clinical features | Blister Distribution | Usually limited to hands, feet; can occur at sites of repetitive trauma | Generalized | Generalized | Generalized |
| Herpetiform | No | No | Sometimes | Yes |
| Hemorrhagic | No | No | No | Common |
| Micral | Rare | Occasionally | Occasionally | Often |
| Hyperkeratosis of palms and soles (keratoderma) | Occasionally | Occasionally | Common, focal | Common, progressive |
| Nail involvement | Occasionally | Occasionally | Occasionally | Common |
| Milia | Rare | Occasionally | Unknown | Common |
| Hyper/hyppigmentation | No | Can occur | Always | Can occur, laryngeal |
| Extracutaneous | No | No | No | Common |

**Gambar 4:** Clinical features of the four most common subtype of EBS.

EBS suspected should be made in an individual with the following disorders: skin and mucosal fragility with blisters forming in response to mild trauma which the blister usually heal without scarring; blisters may be present in the neonatal period to childhood especially on the hands and feet but may affect the entire body; blisters may cause hyperpigmentation or hypopigmented spots on trunk and extremities; symptoms usually improve or disappear with age; focal or severe keratoderma on palm and plantar; milia; nail dystrophy; exuberant granulation tissue in the periorificial, axillary folds, nape of the neck, lumbosacral spine, periungual and proximal nail folds. Symptoms were worsened by heat weather or sweat. Excrucutaneous features are usually found in severe generalized EBS. Hoarseness is the hallmark of larynx involvement but not life-threatening. The absence of a family history of blistering disease does not exclude the diagnosis of EBS. In general, generalized intermediate EBS was distinguished from localized EBS based on the extent of skin lesion distribution. Generalized intermediate EBS is usually milder than generalized severe EBS due to the blistering can be severe enough to cause death. Meanwhile, mottled pigmentation EBS is clinically indistinguishable from the generalized forms of EBS [2, 3, 5].

The diagnosis of EB can made clinically and established by genetic molecular testing to identify specific gene or protein mutations in EB. In newborns with extensive blisters and erosions, skin biopsy is necessary for evaluate, especially if genetic testing is not available and the family history is unknown. Histopathological examination can be used to rule out the differential diagnosis of other blistering diseases although does not enough for made an accurate diagnosis of EB. The gold standard for diagnosis of EB is electron microscopy for detection blister formation at the dermo-epidermal junction ultrastructurally. However, some literature states that immunofluorescent antigen mapping is more often used due to rapid turnover time results with high sensitivity and specificity compared to electron microscopy [1, 2]. Unfortunately, in this case the patient’s parents refused to perform a skin biopsy on their child. Currently, many developing countries do not have or having...
a difficult access to advanced laboratory facilities for diagnosis EB, so mainly diagnosis was made clinically. On the other hand, many clinical features of EB were overlap and leading an inaccurate diagnosis. To overcome this problem, in 2016 a team from India, Abu Dhabi, dan UK were developed a simple diagnostic tool that is easier to determine the diagnosis and subtype of EB. It also can be used for all clinical practitioner not just a dermatologist, namely Clinical Diagnostic Matrix (CDM) [11]. CDM is available in electronic version and can be downloaded free from the eb-clinet website. The address can be found at https://www.eb-clinet.org/resources/tools-links-further-information/clinical-diagnostic-matrix/. CDM has an accuracy of 92.5% and a sensitivity of 97% in distinguishing 4 types of EB. A study reported a concordance between matrix and molecular diagnosis for major types of EB was 91.1% and 75.7% for classifying subtypes of EB [5, 6, 11]. Yenamandra et al. [11] reported that CDM is very helpful in making a diagnosis type and subtype of EB more accurate, especially in limited resources countries. The diagnosis of EB plays an important role in determining prognosis and disease management. The patient in our case was initially suspected EBS based on clinically and family history. The patient showed clinical manifestations that lead to generalized EBS feature, where the patient was born spontaneously by normal vaginal delivery having blisters and exfoliate skin on almost all of his body at birth. Blisters occur due to trauma during vaginal delivery. No involvement of nails and mucosa and also absence of keratoderma and milia. The patient was no family history of the blistering disease. The lesions healed without leaving hyperpigmentation and scarring within 12 days of treatment. Based on CDM, the diagnosis of EBS was obtained with generalized intermediate subtype.

The differential diagnosis of EBS such as bullous ichthyosiform erythroderma, staphylococcal scaled skin syndrome, neonatal varicella, neonatal pemphigus, bullous impetigo, bullous pemphigoid, linear immunoglobulin A disease [1, 9].

There is no definitive treatment for EBS until now. Treatment is based on symptomatic and supportive and also requires a multidisciplinary approach. Psychological support for patients and family members is important. Skin management is focused on preventing blisters and secondary infectious complications. Prevention by minimizing traumatic conditions such as wearing soft cotton clothes that can absorb sweat; always wear appropriate-sized and comfortable footwear; used moisturizer to reduce friction, dryness, and promote wound healing; taking a bath with gentle soap and drying it by tapping with a soft towel; maintain room temperature. If the blister forms, aspiration the blister fluid with a sterile needle while leaving the roof of the blister for prevent blister expansion. Meanwhile, if the bulla eroded, the surface was clean with NaCl 0.9% solution and covered with a suitable wound dressing to prevent infection and promote healing. Do not use adhesive tapes to cover wounds. Topical antibiotics are given if secondary infection occurs. Nutrition must also be considered to support growth development and increase wound healing. EB is not a contraindication to vaccination [1-4, 9, 12].

The prognosis of EBS is generally good than other types of EB. The blister will improve and disappear with age [1, 2]. Recurrence in family is varies, but a study was reported the risk of recurrence in families with one affected offspring is approximately 2-5% so genetic counseling is needed in families with EB [8]. Complications that often occur are secondary infections and some cases of EBS generalized severe can lead to sepsis. Squamous cell carcinoma risk is not always associated to EBS [2, 3, 12].

**Conclusion**

EBS is the most common type of EB. De novo causes in sporadic cases usually have a generalized form due to mutations in KRT5 and KRT14 genes. CDM is a simple diagnostic tool that can help more accurately diagnose EB types and subtypes in limited resources countries.

**References**

1. Marinkovich MP. Inherited epidermolysis bullosa. In: Kang S, Amagai M, Bruckner AL, Enk AH, Morgolis DJ, McMichael AJ, et al., editors. Fitzpatrick’s Dermatology 9th Ed: McGraw-Hill Education; 2019, 1011-1030.
2. Pfender EG, Bruckner AL. Epidermolysis bullosa simplex [Updated Oct 13]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReview [Internet]. Seattle (WA): University of Washington; Seattle; 1993-2016. Available form: https://www.ncbi.nlm.nih.gov/books/NBK1369/
3. Mahato SK, Lama S, Agarwal N, Chaudhary N. Inherited epidermolysis bullosa: a case report. Journal of Universal Collage of Medical Science [Internet]. 2015;3(11):39-42. Available from https://www.researchgate.net/publication/333391620_Inherited_Epidermolysis_Bullosa_A_case_report
4. Aisah S. Epidermolysis bullosa. In: Menaldi SL, Bramono K, Indriatmi W, et al., editors. Ilmu Penyakit Kulit dan Kelamin Edisi Ketujuh; Badan Penerbit FK UI 2016, 248-58
5. Widiati S, Marcella B, Dewi SR, Paramitasari AR, Ellistari EY, Julianto I. Clinical diagnostic matrix (CDM) as a tool to diagnose subtype of epidermolysis bullosa cases in children. J Gen Proc Dermatol Venereol Indones [Internet] 2019;3(2);1-7. Available form: http://jgenprodvi.ui.ac.id/index.php/jdvi/article/view/115
6. Widiati S, Danarti R, Trisnowati N, Purnomosari D, Wirawata T, Soebono H. Novel mutations of epidermolysis bullosa identified using whole-exome sequencing in Indonesia Javanese patients. Intractable & Rare Diseases Research [Internet] 2021;10(2):88-94. Available form: https://pubmed.ncbi.nlm.nih.gov/33996353/
7. Chong SC, Hon KL, Scaglia F, Chow CM, Fu YM, Chiu TW, et al. Severe generalized epidermolysis bullosa simplex in two Hong Kong children due to de novo variants in KRT14 and KRT5. Case Rep Pediatr [Internet], 2020;17:4206348. Available form: https://pubmed.ncbi.nlm.nih.gov/32351751/
8. Pfendner EG, Sadowski SG, Uitto J. Epidermolysis bullosa simplex: recurrent and de novo mutations in the KRT5 and KRT14 genes, phenotype/genotype correlations, and implications for genetic counseling and prenatal diagnosis. J Invest Dermatol [Internet] 2005;125(2):239-43. Available form: https://pubmed.ncbi.nlm.nih.gov/16098032/
9. Yordanova I, Vassileva S, Demerjieva Z, Gospodinov D, Tsankov N. Epidermolysis bullosa simplex dowling-meara - a case report. JofIMAB [Internet] 2008;14(1):59-62. Available form: https://www.researchgate.net/publication/228767060_Epidermolysis_Bullosa_Simplex_Dowling-Meara_-A_case_report

10. Hachem ME, Barresi S, Diociaiuti A, Boldrini R, Condorelli AG, Capoluongo E, et al. Phenotypic features of epidermolysis bullosa simplex due to KLHL24 mutations in 3 Italian cases. Acta Derm Venereol [Internet] 2019;99(2):238-239. Available form: https://pubmed.ncbi.nlm.nih.gov/30226531/

11. Yenamandra VK, Moss C, Sreenivas V, Khan M, Sivasubbu S, Sharma VK, et al. Developing of a clinical diagnostic matrix for characterizing inherited epidermolysis bullosa. Br J Dermatol [Internet] 2017;176(6):1624-1632. Available form: https://pubmed.ncbi.nlm.nih.gov/27925151/

12. Peterside O, Kunle-Olowu OE, Adeyemi OO, Akinbami FO, Omene J. Epidermolysis bullosa simplex: a case report. Niger J Paed [Internet] 2012;39(4):194-196. Available form: https://www.ajol.info/index.php/njp/article/view/80132