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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 mechanobullous 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 exfoliating 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.

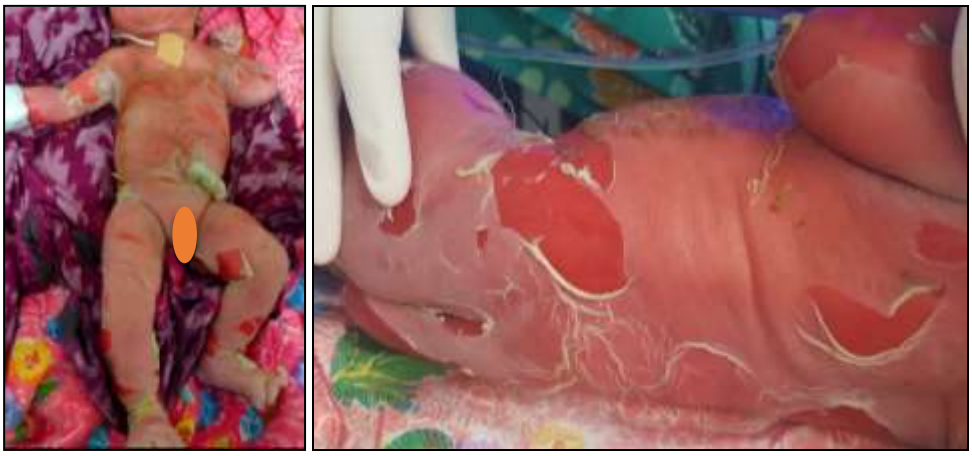

Fig 1: Generalized bullous who mainly eroded and exfoliate skin with erythematous base

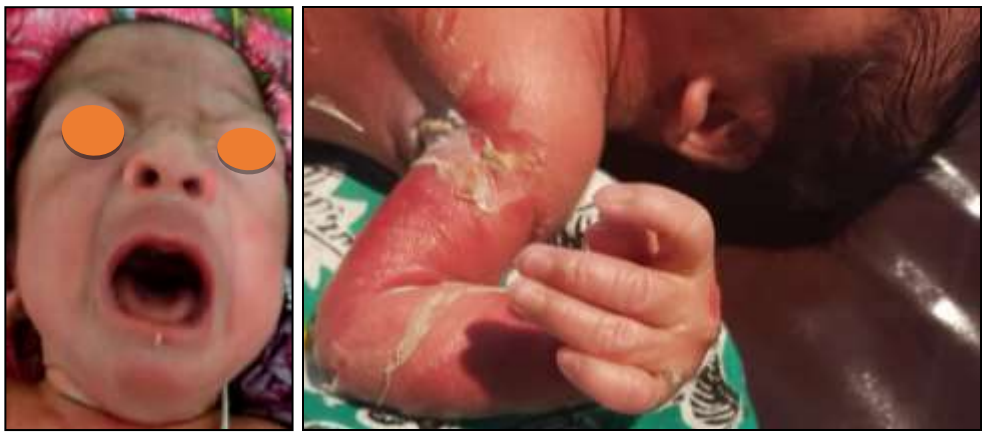

Fig 2: No involvement of mucosa, eyes, nails, and scalp

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 [2]. 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].

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)
EBM-MP	EBS-MP, normal keratin 5 staining, *KRT5* pathogenic variant (specify type)

EBS = epidermolysis bullosa simplex; MP = mottled pigmentation

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

EBS Subtype			Localized	Generalized Intermediate	Mottled Pigmentation	Generalized Severe
Age of onset			Infancy 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 repeated trauma	Generalized	Generalized	Generalized
		Herpetiform	No	No	Sometimes	Yes
		Hemorrhagic	No	No	No	Common
		Mucosal	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/hypopigmentation		No	Can occur	Always	Common
	Extracutaneous		No	No	No	Can occur, laryngeal

Fig 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 palmar 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. Extracutaneous 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 erythrodermia, staphylococcal scalded 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.

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