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Case Report

Clinical diagnostic matrix (CDM) as a tool to diagnose subtypes of epidermolysis bullosa cases in children

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Abstract

Background: Epidermolysis bullosa (EB) is a rare genetic skin disease characterized by trauma-induced blisters, which appear shortly after birth. Immunofluorescence antigen mapping and mutational analysis are essential for establishing an accurate diagnosis of EB. However, in limited resource settings like in Indonesia, such techniques are not always readily available, forcing many clinicians to diagnose EB based on clinical features alone that is often inaccurate. Recently, a novel clinical diagnostic matrix (CDM) tool has been developed to improve the diagnostic accuracy of EB in such settings.
Case Illustration: We examined clinical photographs and medical records of patients registered at the Dr. Moewardi hospital with a provisional diagnosis of EB since 2013 to 2017 and completed the 19 clinical manifestations required for the CDM's electronic version.
Discussion: CDM provides a diagnosis of the EB subtype, which cannot be concluded in advance from the previous three cases, although histopathological examination have been carried out. Since immunofluorescence examination and genetic mapping are inaccessible in Indonesia, the CDM gave a brief possibility of diagnosing EB subtypes. Completing the CDM took less than five minutes and the result was available immediately after clinical features data input.
Conclusion: CDM appears to be practical, easy to be used and helpful in characterizing EB, especially in limited resource settings. Moreover, it helps in clear documentation of clinical features in an EB patient that could be useful for accurate phenotype-genotype correlations in the future.

Keywords*: clinical diagnostic matrix, epidermolysis bullosa*

Background

Inherited epidermolysis bullosa (EB) is a rare and debilitating disorder characterized by blister formation and fragility of the skin and other tissues. This detachment is based on the separation of the basal membrane and the bridging protein between the epidermis and the dermis.[1] The genes associated with EB mutations are varied, depending on the location of the separated intercellular bonds.[2] To define the accurate diagnosis of the type and sub-types of EB, laboratory examinations are required, such as skin biopsy with immunofluorescence antigen mapping and/or electron microscopy.[3]

EB occurs in one in every 17,000 live births and it is estimated that 500,000 cases have been found worldwide.[4] In the United States, EB arises in 19 per 1 million people, 32 per 1 million people in Northern Ireland, and it appears in 49 per 1 million people in Scotland.[5] The prevalence of EB in Indonesia remains unknown. Based on the case report, there were 5 cases in Surakarta between 2013 and 2017. This number is less than it is expected because based on the estimated number of cases worldwide, Surakarta with a population of 499,337 people in 2010 is estimated to have 29 EB patients. Diana reported around 31 EB cases in Indonesia (2018) based on DEBRA Indonesia.[6]

The small case finding in Indonesia is probably due to the lack of knowledge in diagnosing EB among health workers, deprived socio-economic EB parents to come to healthcare centres and hardly accessible health facilities, as well as the

parents' unawareness about their children's illness.

Fine et al.[2] updated the classification of EB in 2014 based on the major EB type present (based on the identification of the level of cleft formation in the skin), phenotypic characteristics due to the distribution and the severity of disease activity, specific extra cutaneous features, the mode of inheritance, target protein and its relative expression in skin, gene(s) involved and type(s) of mutation present, and when possible specific mutation(s) and their location(s). EB is divided into 4 major types, which are EB simplex (EBS), junctional (JEB), dystrophic EB (DEB), and Kindler syndrome.[2] The clinical features of EB vary widely, ranging from as mild as localized EBS, to a severe type, namely the generalized recessive DEB, but overlapping phenotypes are often found between one subtype with another subtype. This considerable variation influences the therapy and prognosis. Thus, an accurate diagnosis needs to be obtained, as it affects the management and counselling[6]. Hence, to overcome these difficulties, we adopt CDM to be used as one of the diagnostic tools of EB cases in Surakarta.

To establish the EB types and subtypes in the limited resource country is quite challenging, especially for conducting immunofluorescence (IFM) examinations or electron microscopes. Yenamandra et al[7] developed a simple matrix to help diagnose EB types and subtypes clinically. Matrix is formed based on clinical lesion found and it included nine most commonly found EB subtypes of 33 subtypes. There are 19 distinctive clinical findings according to EB subtype, which will then be scored using a computer application. This matrix is called clinical diagnostic matrix (CDM).[7]

The CDM has 92.5% accuracy in distinguishing four major types of EB, this result has similar sensitivity (97%) of IFM reported by Yiasemides et al. The concordance between the matrix and molecular diagnosis for the major types of EB was 91.1% with 75.7% agreement in classifying EB into its nine subtypes[7].

The use of CDM in Indonesia has never been done before. Applying CDM is expected to help clinicians to diagnose EB subtypes more readily in in daily practice, so that the therapy and counselling related to the patient's need can be optimized and comprehensive.

Case Illustration

The medical records from 2013-2017 with EB as a working diagnosis were reconciled in term of the clinical manifestation from the photograph and matched the finding with the electronic version of CDM.

CDM was downloaded from the eb-clinet website for free and the address can be found in http://www.eb-clinet.org/about-eb-clinet/media-center/eb-clinical-diagnostic-matrix.html. CDM is an electronic version with clear illustrative images, which make it easier for clinicians to match the image with the present clinical findings. Yenamandra et al[7] developed this system in 2016, and included nine commonly found EB subtypes in the matrix, which are EBS-localization (EBS-L0; EBS-intermediated generalized (EBS-GI); EBS-generalized severe (EBS-GS); JEB-generalized intermediate (JEB-GI); dominant DEB (DDEB); recessive DEB-generalized severe (RDEB-GS); DEB recessive-generalized intermediate (RDEB-GI) and Kindler syndrome (KS).[6]

Table 1. Characteristics of the Patients and CDM Scoring

Cases, Age	Gender	Diagnosis in MR	CDM Score	Diagnosis with CDM (FOR)
A. A 7-year-old	Male	EB	17	RDEB-GS
B. A 2-year-old	Male	Junctional EB	13	JEB-GI
C. A 4-year-old	Male	EB	15	RDEB-GS
D. Neonate	Female	EB	-	Ectodermal dysplasia left palate cleft
E. Neonate	Female	EB	-	Epidermolytic hyperkeratosis

CDM = Clinical Diagnostic Matrix, EB = Epidermolysis Bullosa, JEB-GI = Junctional Epidermolysis Bullosa-Generalized Intermediate, MR = Medical Record, RDEB-GS = Recessive Dystrophic Epidemolysis Bullosa-Generalized Severe.

After re-evaluation with CDM, of the five patients who were previously diagnosed with EB, three of them matched with CDM and fulfilled the EB criteria, with subtypes of each are generalized recessive EB and EB junctional generalized intermediate. Two other patients were incompatible with CDM, and thought as ectodermal dysplasia and ichthyosis disorder (**Table 1).** All EB patients were males, aged 2 to 7-year-old, and one EB patient died of sepsis. The non-EB patients were neonatal/ new born, who unfortunately died within days of treatments.

Case 1

A 7-year-old boy was diagnosed with EB with no specific type and subtype. The clinical features were generalized skin lesions, with milieu and scar, without excessive granulation tissue or nail dystrophy, but some nails were partially disappeared on syndactyly fingers. The dental enamel was poor, apthous ulcer and some chronic wounds were seen on his lower extremities (**Figure 1**). He appeared to be stunted. There was no abnormality or similar disorder in neither his parents nor family. A CDM score of 17 was obtained which supported the diagnosis of RDEB-GS.

Case 2

A 2-year-old boy was diagnosed with JEB based on the histopathological examination. Clinical findings showed generalized skin lesions, with excessive granulation tissue on the buttocks. Some milia appeared on the face accompanied by old wound scar. Nail dystrophy, syndactyly and oral mucosal lesion made him difficult to eat (**Figure 2**). His mother reported that sometimes there was eye discharge. His palm and soles were thickened and chronic wound on his chest appeared painful. There was no history of the same illness in his parent or family. Unfortunately, patient died six months after hospitalization because of sepsis. The CDM score was 13 and revealed to be JEB generalized-intermediated.

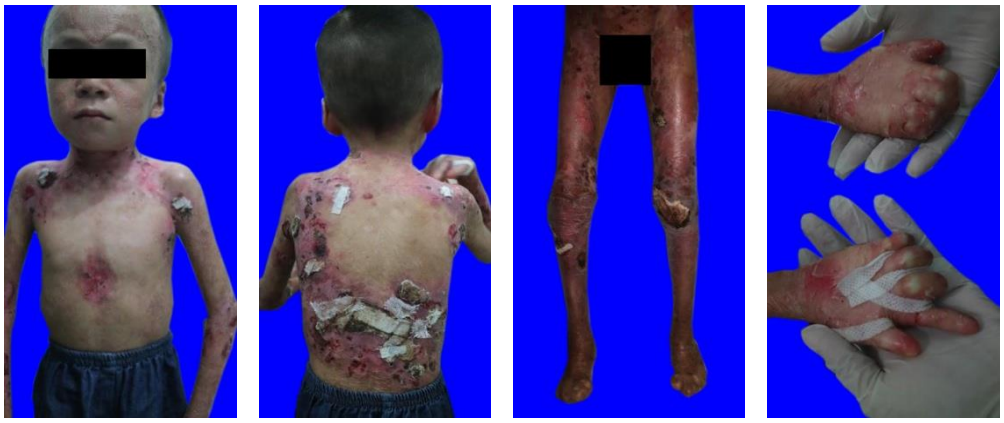

Figure 1. A 7-year old boy with RDEB-GS. Note the syndactyly of the fingers and case.

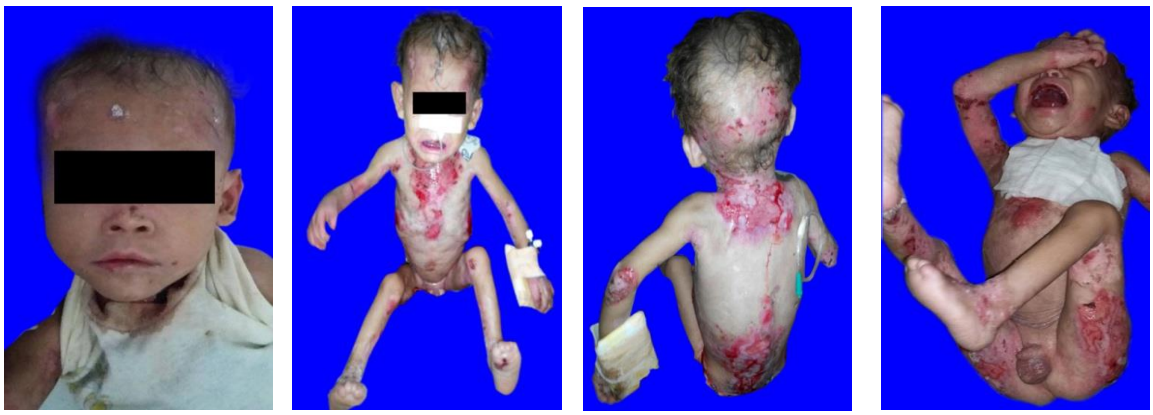

Figure 2. A 2-year old boy diagnosed with JEB-GI. The chronic wound appeared on his chest and thigh. Note the syndactyly and nail dystrophy.

Case 3
A 4-year-old boy was diagnosed with generalized skin lesions without extensive granulation tissue. Milia and eutrophic scars were observed on his face. The nails were dystrophic and some nails disappeared. Erosion was seen on his mouth with poor dental enamel. Patient had syndactyly fingers. On his extremities, there were chronic wound (**Figure 3**). His growth and development were poor. The CDM score was 15 favouring the RDEB-GS subtype.

Case 4
A new born girl was diagnosed with EB without histopathological examination. There were several erosions on her eyelids, shoulder, and extremities. The patient also had cleft lips and palate, as well as ectrodactyly. Therefore, the clinical features did not support diagnosis of EB (**Figure 4**). Thus, the diagnosis of EB was not fulfilled. The working diagnosis was ectodermal dysplasia with left cleft palate. Unfortunately, after twelve days of age, the patient died because of suspected choking.

Case 5
A new born girl was diagnosed without histopathological examination as EB. Physical examination revealed erythematous and scaly skin throughout the body, erosion in the prominent area, some bullae on the left thigh, arms, peri-umbilicus and gluteus. The clinical features of EB in CDM were not found (**Figure 5**). Thus the diagnosis of EB was ruled out. The working diagnosis was clinically suitable for epidermolytic hyperkeratosis.

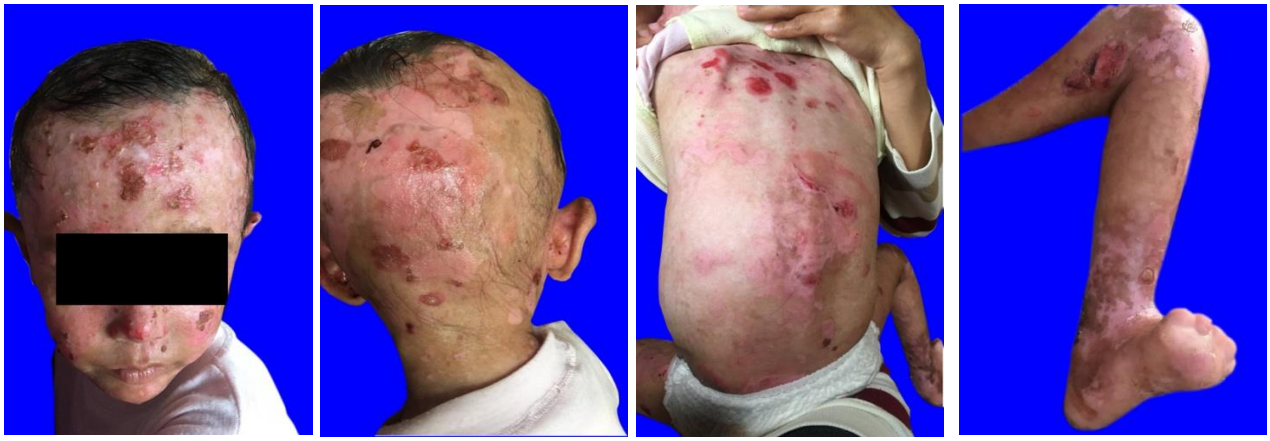

Figure 3. A 4-year old boy with RDEB-GS. Note the features of syndactyly and scarring**.**

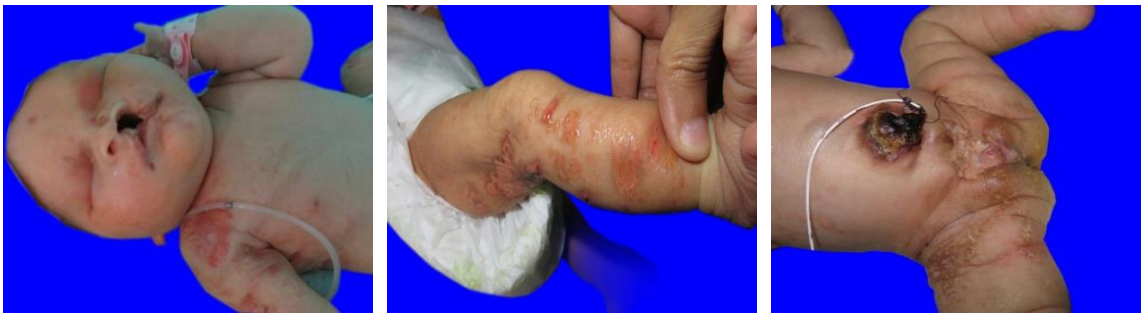

Figure 4. A new born girl with cleft lips and palate and also electrodatyl. Clinical features tend to support the diagnosis of ectodermal dysplasia with left cleft palate.

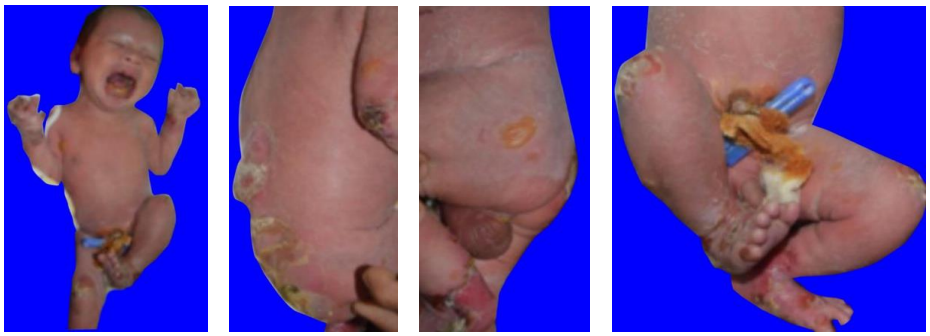

Figure 5. A new born girl with erythematous and scaly skin diagnosed with epidermolytic hyperkeratosis.

Clinical Diagnostic Matrix

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions	Hands & Feet	Generalised/ Limited	Herpetiform/ Generalised	Generalised	Generalised	Generalised/ Limited	Generalised	Generalised	Generalised/ limited
Excess Granulation tissue	-	-	-	+	- or +	-	-	-	-
Scarring	-	-	-	-	- or +	+ or ++	+ or ++	+ or ++	- or +
Milia	-	-	- or +	-	-	+ or ++	+ or ++	+ or ++	-
Nail Dystrophy	-	-	- or + or ++	+ or ++	- or + or ++	- or + or ++	- or + or ++	- or + or ++	- or +
Nail loss	-	-	-	+ or ++	- or + or ++	- or +	+ or ++	- or + or ++	-
Mucosal erosions	-	-	- or +	+ or ++	- or +	- or +	+ or ++	- or +	- or +
Eye involvement	-	-	-	- or + or ++	- or + or ++	-	- or + or ++	- or + or ++	-
Hoarseness	-	-	-	+ or ++	- or +	-	- or +	- or +	-
Microstomia/Ankyloglossia	-	-	-	-	-	-	- or +	- or +	-
Poor Dental Enamel	- or NA	- or NA	- or NA	+ or NA	+ or NA	- or NA	- or NA	- or NA	- or NA
Keratoderma	- or +	- or +	- or + or ++	-	-	-	-	-	- or +
Chronic Wounds	-	-	-	- or +	- or +	- or +	- or + or ++	- or +	- or +
Syndactyly	-	-	-	-	-	-	+ or ++	- or +	- or +
Alopecia	-	-	-	-	+ or ++	-	- or +	- or +	-
Poikiloderma	-	-	-	-	-	-	-	-	+
Relative Growth Failure	-	-	-	+ or ++	- or +	-	+ or ++	- or +	- or +
Survival after 2 yrs	+ or NA	+ or NA	+ or NA	- or NA	+ or NA	+ or NA	+ or NA	+ or NA	+ or NA
Parents affected	+ or NA	+ or NA	- or + or NA	- or NA	- or NA	+ or NA	- or NA	- or NA	- or NA
Total number of boxes ticked									

Figure 6. CDM to describe each type of EB and its clinical features.[7]

Discussion

EB was first proposed by Koebner in 1886 as hereditary epidermolysis bullosa, even though von Hebra mentioned this disorder and differentiated it with pemphigus and called it inherited blistering.[8,9] This genetic disorder affects skin and other epithelia attached to underlying connective tissue. Painful bullae and vesicle often develop after mild friction or trauma.[8]

EB is classified and sub-classified based on ultra-structural level within the blisters, which develop within the skin, mode of inheritance, and the combinations of clinical, electron microscopic, immunohistochemical, and genotypic features.[10] Since the publication in 2008, there are several new targeted genes and clinical subtypes identified. And a newer consensus on the classification of EB subtypes was published in 2014. Based on the clinical and molecular IFM and/or transmission electron microscopy, preferably newly induced blisters can identify the location of the cleft in the skin layer, which are important in diagnostic testing and classification in EB.[2] However, this examination are difficult to be

performed in limited resources country. Furthermore, diagnosis in this country remains clinical and often inaccurate, resulting in the inappropriate management and counseling.[7]

There is remarkable variability in the phenotypic spectrum of EB, from very mild blistering, localized to the hands and feet, to severe generalized and mucocutaneous blistering which can lead to death of severe individuals within the first days to year of life.[11] The cutaneous features are hallmark of inherited EB, easily inducible blister following minor trauma to mechanically fragile skin. In addition, it includes some or all of the following: milia, nail dystrophy or the absence of fingers and scarring.

Others finding, if present include exuberant granulation tissue (periorificial; axillary vaults; nape of the neck; lumbosacral spine; periungual and proximal nail folds), localized or confluent keratoderma of the palms and soles, and dyspigmentation; mottle or reticulate hyperpigmentation. Extremely nonspecific cutaneous findings and infrequently seen include decreased or absence of hair, albopapuloid lesions (flesh-colored or hypopigmented papules, usually arising on the lower trunk), and hypo or hyperhidrosis.[10] This broad spectrum of clinical findings in EB is often unfamiliar by dermatologist to address. Therefore, the diagnosis of EB is often inaccurate. To assess this pitfall, a formulated distinctive clinical features called CDM could help non-experts to make more accurate diagnoses of EB.[12]

CDM is used in this case series helped the clinicians to diagnose subtypes of EB accurately. Even though single clinical feature might not be pathognomonic for any particular form of EB, the 19 different recordable metrics which are derived from history and examination, can help drive the clinician to choose the most likely diagnosis. Vamsi et al. also tested the metrices to 74 genetically EB patients, applied the diagnostic matrix blindly and then compared with genetic diagnostic with 92.5% accuracy.[7]

The use of CDM in this study made it easier for clinicians to diagnose EB types and subtypes. The electronic version of CDM will minimize the time to 5 minutes to assess. Three cases previously diagnosed without EB subtypes can now have its subtypes to be estimated. Two cases which were suspected with EB in neonates were dropped from EB and diagnosed with other genodermatoses, which are ectodermal dysplasia with left palate cleft and epidermolytic hyperkeratosis eventually. Furthermore, the immunofluorescence antigen mapping examination is still required to confirm the EB subtypes.[13]

The subtype of EB in this case, are the generalized severe form is understandable because the wound healing in severe form can lead to progressive scarring which causes contractures in both hands and limbs to pseudo-syndactyly. Also, profound growth retardation, anemia, retrieve of growth, and esophageal stricture can also be found in recessive dystrophic epidermolysis bullosa. This manifestation also called “the most devastating genetically transmitted multi organ disease in mankind”.[10] Even though the most common form of EB subtype found is localized EB simplex, which is the mild form of EB, this disorder is often under diagnosed or neglected by their parent or caregiver. This explained why there is no localized EB simplex subtype found in our hospital.

Several disorders may complicate the diagnosis of EB by their overlapping phenotypes, which should be considered when evaluating an EB patient.[11] Ectodermal dysplasia cleft palate (EEC) and epidermolytic hyperkeratosis, a group of ichthyosis that are considered to be EB-like disorders. Both disorders have the same manifestation as EB based on their skin fragility and by varying degrees of blistering.

EEC syndrome, a genetic developmental disorder that features distinct ectrodactyly, ectodermal dysplasia and facial clefts may also be noticed with characteristics like recurrent urinary tract infections, vesiculoureteral reflux, photophobia, anomalies of kidney, hearing loss and speech impairment.[14] In this case, the left cleft lip and palate, erosion and ectrodactyly clinically support the diagnosis of EEC syndrome.

Epidermolytic hyperkeratosis or bullous congenital ichtyosiform erythroderma (BCIE) is present at birth with generalized erythema and epidermolysis, followed by the onset of hyperkeratosis. Localized blistering and skin fragility appear after trauma or infection and usually improve in adolescence.[15] The clinical manifestation in this case, similar to BCIE, with erythrodemic skin, and bullae and erosion in the traumatic area.

Conclusion

CDM is a helpful tool to diagnose the subtypes of EB, and it is easy to be used by the non-expert

clinicians. With this matrix, we can specify the subtypes of EB, as recessive dystrophic EB generalized and JEB generalized intermediate. We also excluded EB-like syndrome, which were ectodermal dysplasia and erythrodermic hyperkeratotic.

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