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Two-Days Old Newborn with Epidermolysis Bullosa Simplex: Severe Subtype.

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Abstract:
This case report details a rare instance of severe epidermolysis bullosa simplex (EBS) in a two-day-old neonate with distinctive clinical features. The patient exhibited extensive blistering on the hands, tongue, face, and ears, prompting admission to the Neonatal Intensive Care Unit. Genetic testing confirmed a heterozygous dominant negative mutation on the KRT14 gene, confirming the diagnosis of severe EBS. Laboratory findings revealed leukocytosis and electrolyte abnormalities, while biopsy examination showcased subepidermal blisters. The neonate received supportive management, including nasogastric tube feeding and wound care, resulting in improvement and subsequent discharge with a follow-up plan. Discussion delves into EB classification, emphasizing the unique features of severe EBS. A succinct comparison table outlines clinical distinctions among localized, intermediate, severe, and mottled pigmentation EBS. This case highlights the complexities in diagnosing and managing severe EBS in neonates and advocates for further research to establish comprehensive treatment guidelines, especially in newborns, and explore emerging therapies for epidermolysis bullosa.

Keywords: newborn epidermolysis bullosa, blistering skin disorder, epidermolysis bullosa simplex, fragile skin.

1. Introduction

Epidermolysis bullosa (EB) is a group of rare inherited connective tissue disorders that come in forms of blister formation on the skin. The incidence rate is 20 per million births in the United States [1]. The onset of appearance of the lesion can vary in each type of epidermolysis bullosa. Blisters usually occur at the sites of trauma or pressure, which are primarily the hands, feet, and diaper area in children, but may also present in the mouth, gastrointestinal tract, or genitalia [2].

EB is generally classified into four types as follows: 1) simplex EB with blisters within the epidermis, 2) dystrophic epidermolysis bullosa (DEB), 3) junctional EB with blisters in the epidermal dermal junction, and 4) Kindler syndrome with blisters at multiple levels of the skin [3,4].

Epidermolysis bullosa simplex is characterized by blisters caused by mechanical trauma and irritation on the skin. The blister usually resolves leaving no scars. Epidermolysis bullosa simplex is differentiated from other causes of epidermolysis theoretically by the location of the blisters in the skin. Epidermolysis bullosa simplex has blisters that is shown within the epidermal layer of the skin [5].

2. Case Presentation Section

A two-day old female full-term newborn was shifted to the NICU duo to severe blistering of the multiple areas on the skin.

2.1. Patient Presentation

On NICU admission, history of one day blistering of the skin, starting from the right palm then left palm and sole were not affected at the time of admission. Three blisters over the right palm with the largest being less than 1 cm. one blister was present on the left palm. Sudden forming of blisters was noticed by the father and a pediatrician was consulted immediately. Lesion not associated with injury. No associated symptoms were reported at the time of admission. Used to eat well and pass normal stool in the first day of her life but starting from the second day of her life she refused to feed. No fever or chills. No history of vomiting. No history of cough or shortness of breath. Not on any current medication with unremarkable past medical and surgical histories.

Birth history, Prenatal: gravida 7 para 5 mother with gestational diabetes mellites on insulin. Mother is positive to Group B Streptococcus. The mother also had oligohydramnios. During the second trimester there was high alpha fetoprotein with normal anomaly screening test. No history of contact with someone with chickenpox or herpes.

Natal: Delivered at the hospital by normal delivery. The delivery was at term. The gestational age was 38+4 weeks. The APGAR score was 9, 10 at first and fifth minutes respectively. The birth weight was 3 kg. She has clear blisters on her skin and with peeling of skin noticed from the first day of her life but when she became ill and refused feeding NICU admission was advised to the parents.

Feeding history, she was on breast milk on her first day of life but refused feeding on the second day. The patient is not yet immunized due to family refusal. Negative family history of any similar blistering disorder.

2.2. Physical Examination

Looks ill and in distress, attached to a cardiac monitor. Stable in room air. Vitally stable with temperature was 36.7. Pulse rate:130 Bpm. Respiratory rate: 56 Bpm. Blood pressure was stable (61/41). Oxygen saturation: 98%. Hands show blisters on both palms and full loss of fingernails. Erythroderma is also visible. Skin peeling of face and lower lip. Blistering and erythroderma are also visible mainly on cheeks. There were severe blisters on the tongue. Peeling of the ears. The chest examination revealed good air entry bilaterally with vesicular breathing and no added sounds. S1 and S2 normal, no murmur. Soft. Non-distended abdomen, bowel sounds were present, the umbilical is normal in both position and shape. No hernia, no organomegaly. Genitalia normal. Clear soles with no blistering on them. Loss toenails. Hip joint bilaterally stable. Calcaneus-valgus of right foot with sandal gap of both feet. No jaundice, no cyanosis. No hyperkeratosis of the soles. Mild hyperkeratosis of the right palm. No milia or area of hypopigmentation nor hyperpigmentation. Neurological examination showed normal tone, movement, and reflexes. The anterior fontanelle is soft. The growth chart is attached in Table 1 and in Figure 1.

Table 1. Growth Chart

Parameter	Value	Percentile
Weight	3 KG	15th percentile
Length	48 cm	15th percentile

Head circumference	33.5 cm	15th percentile

2.3. Investigation

Complete blood count is shown in Table 2. Showing leukocytosis with acceptable predominant Neutrophils 70%.

Abnormal biochemical analysis results: potassium 5.9 mmol/L (normal: 3.5–5.5 mmol/L), chloride 119 mmol/L (normal: 99–109 mmol/L), phosphorus 1.69 mmol/L (normal: 0.81–1.45 mmol/L), iron 4.9 mmol/L (normal: 9.0– 30.4 mmol/L).

Immunological study results: C-reactive protein 4.30 mg/dL (normal: 0–0.8 mg/dL), and rheumatoid factor 12.9 IU/mL (normal: 0–20 IU/mL).

Genetic test shows heterozygote dominant negative mutation on gene *KRT14*

Biopsy examination result: subepidermal blisters with variable inflammation; blistering around the dermal-epidermal junction in the keratinocytes.

Based on the clinical picture and the investigation a diagnosis of severe epidermolysis bullosa simplex was made and the patient was treated accordingly.

Table 2. This table shows the complete blood count of the patient.

Category	Parameter	Value	Normal range
CBC	RBC	4.6	4.00–6.60 (x10 *6/µL)
	Hemoglobin	15.7	14.5-22.5 (g/dL)
	Hematocrit	49	45-67 (%)
	MCV	99	95- 121 (fl)
	MCH	36	31-37 (pg)
	MCHC	32	29-37 (%)
	RDW	17	13.0–18.0 (%)
	Platelets	188	150 – 450 (x10*3/µL)
CBC	WBC	22	9.0–35.0 (X10*3/µL)
	Differentials	Normal differentials percentages and absolute counts	Normal

2.4. Progress Through Admission

Day 1 of admission: Nasogastric tube was inserted in the NICU for continuous feeds 10 ml/hr formula. Orogastric tube was avoided due to blisters in the mouth. PICC line, silver-impregnated dressings, and paracetamol every 6 hours. IV fluid 90ml/kg/day dextrose 10% was given. Wound care with moist exposed burn ointment (MEBO) and non-sticky dressing.

Day 2 of admission: same management showed improvement of the existing blisters with no new blisters' formation.

Day 7 of admission: patient has no new blister formation. Genetic counseling for the parent was done and advised for further genetic testing. The nasogastric tube was removed, and the baby tolerated oral feeding.

Day 8 of admission: discharged from the NICU to the ward.

Day 10 of admission: discharged from the hospital with a follow up appointment after one week in the outpatient clinic (OPD).

Follow up in OPD after 1 week of discharge: new blister over the left sole but resolving of the palm blisters on both sides. To apply moist exposed burn ointment (MEBO) and non-sticky dressing.

3. Discussion

Epidermolysis bullosa (EB) is a group of rare inherited connective tissue disorders that come in the form of blister formation on the skin. It can be divided into four main categories according to the location of the blisters. Epidermolysis bullosa simplex is a common type where the blister will occur in the epidermal layer. Epidermolysis bullosa simplex can be further divided into four main subtypes where the main difference will be in the age of onset, the location of the blisters on the body with some differences in the associated signs and symptoms (Hyperkeratosis of palms and soles, Nail involvement, Milia and/or Hyper/Hypopigmentation) **[2]**. The main part of this discussion will be to finalize the main pathway to differentiate the provisional diagnosis of epidermolysis bullosa simplex into its four subtypes and to highlight the differences between each one. The four main subtypes are: 1) localized EBS, 2) intermediate EBS, 3) Severe EBS, and 4) With mottled pigmentation EBS **[5]**. A simple comparison including the mentioned criteria of differentiation can be found in Table 3.

Table 3. This table shows a comparison of all types of epidermolysis bullosa simplex.

Clinical Features	**Localized EBS**	**Intermediate EBS**	**Severe EBS**	**W/mottled pigmentation EBS**
Age of onset	Infancy, usually by 12-18 mo	Birth/infancy	Birth	Birth/infancy
Blisters	Blisters are usually limited to hands, feet; can occur at sites of repeated trauma. Rare mucosal blisters	Generalized Occasional mucosal blisters	Generalized Grouped (herpetiform) blisters. Mucosal blisters	Generalized ± grouped (herpetiform) blisters. ± mucosal blisters
Hyperkeratosis of palms & soles	Occasionally	Occasionally	Common, progressive, & diffuse	Common, focal
Nail involvement	Occasionally	Occasionally	Common	Occasionally
Milia	Rare	Occasionally	Common	Unknown
Hyper-/ hypopigmentation	No	Can occur	Common	Always

Localized epidermolysis bullosa simplex is characterized by infancy age of onset, with 12-18 years being the most common age. Blisters are usually limited to hands and feet; can occur at sites of repeated trauma with rare mucosal blisters. In the associated signs and symptoms occasionally nail involvement and hyperkeratosis of palms and soles can be found in patients with localized epidermolysis bullosa simplex. while Milia is rarely seen in these patients. Absence of hyper or hypopigmentation in these patients is an Important differentiating point in localized epidermolysis bullosa simplex **[6]**.

Intermediate epidermolysis bullosa simplex is characterized by infancy age of onset, but also can happen in less prevalence during birth. Blisters are usually generalized in pattern with occasional mucosal involvement. All the associated signs and symptoms of epidermolysis bullosa simplex can be found occasionally in intermediate epidermolysis bullosa simplex subtype even hyper or hypopigmentation can occur **[6]**.

Severe epidermolysis bullosa simplex is characterized by birth age of onset. Blisters are usually generalized in grouped patterns also called herpetiform blisters, with mucosal involvement. All the associated signs and symptoms of epidermolysis bullosa simplex are commonly found occasionally in severe epidermolysis bullosa simplex subtype. Which makes this subtype the most appropriate diagnosis of our patient discussed in this case report **[1,2,6]**.

Finally, the mottled pigmentation epidermolysis bullosa simplex is not well known nor well studied but it's always characterized by having hyper or hypopigmentation associated signs with generalized blisters that can come in all patterns and with focal hyperkeratosis of the palms and soles. birth age of onset but can come with infancy age on less common occasions. **[6]**.

4. Conclusions

For future research, it's advised to dig deep into the treatment plan and formulate a guideline for managing a patient with epidermolysis bullosa simplex and how management could differ in newborn patients in comparison to adult patients. With new gene therapy also knocking on all genetic disorder doors it's still a wide space for research to find a cure for epidermolysis bullosa that can allow the patients to have near-normal quality of life.

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