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Genetics Corner: Mild Expression of COL7A1-Associated Epidermolysis Bullosa in a Mother and Child

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"A 2-week-old male with small blisters on both hands presented to the Emergency Department of an outside children's hospital. His mother had noticed the bullous lesions on his hands on DOL 2. He was admitted for two days, during which he had a skin biopsy and was treated with topical and oral antibiotics."

Case Report:

A 2-week-old male with small blisters on both hands presented to the Emergency Department of an outside children's hospital. His mother had noticed the bullous lesions on his hands on DOL 2. He was admitted for two days, during which he had a skin biopsy and was treated with topical and oral antibiotics. His mother was instructed to follow up with a dermatologist. The blisters increased in number on his hands and feet. Due to insurance issues, he was seen at three months by an adult dermatologist, who did not provide a diagnosis. At around four months of age, he was evaluated by a pediatric dermatologist (Figures 1 and 2). The initial skin biopsy results were unavailable, so a second skin biopsy was performed. Based on his clinical presentation, a provisional epidermolysis bullosa (EB) diagnosis was made. He was referred to Clinical Genetics.

When evaluated in the Genetics clinic at five months and in follow-up at seven months of age, bullae were resolving, and the resolved lesions had healed well without scarring. There were no oral or mucosal lesions. The infant was thriving and was on target for his developmental milestones. No other health concerns were identified. The pregnancy was uneventful. Fetal ultrasound exams were normal. The baby was delivered by NSVD at term to a healthy 24-year-old primigravida mother. Birth weight (3.48 kg) and length (50.8 cm) were normal. There were no postnatal complications except for mild jaundice. The baby was discharged with the mother after receiving phototherapy for one day. No skin lesions were appreciated.

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The family history was significant for dystrophic thick great toenails in his mother and maternal grandfather. The mother also reported occasional blisters on her feet when she walked a lot. There was no other family history of skin lesions, birth defects, developmental delay, intellectual disability, early infant deaths, or multiple miscarriages. Parental consanguinity was denied.

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Gene testing with an epidermolysis bullosa gene panel was ordered while dermatohistopathology results were pending.

Histopathology on skin biopsy did not identify any definitive evidence of epidermolysis bullosa, but the clinical findings, preserved collagen VII staining, and intact lamina densa on electron microscopy supported a diagnosis of epidermolysis bullosa simplex. Molecular genetic testing detected a pathogenic variant in *COL7A1:* c.6007G>A (p.Gly2003Arg) associated with the dystrophic form of EB. This variant was maternally inherited.

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Assessment and counseling:

Epidermolysis bullosa (EB) is a genetic skin disorder characterized clinically by blister formation from mechanical trauma. The main types of epidermolysis bullosa are:

- Epidermolysis bullosa simplex: The most common type of EB affects mainly the palms of the hands and soles of the feet. Heat and friction increase the risk of blisters that occur in the basal keratinocytes and heal without scarring.
- Junctional epidermolysis bullosa: This type of EB is characterized by fragility of the skin and mucous membranes, and blisters form with little or no trauma. Blistering may be severe, and granulation tissue can form on the skin around the oral and nasal cavities, fingers and toes, and internally around the upper airway. Examination of the skin basement membrane on transmission electron microscopy can detect splitting in the lamina Lucida of the basement membrane of the epidermis or just above the basement membrane at the level of the hemidesmosomes in the lowest level of the keratinocytes layer.
- Dystrophic epidermolysis bullosa: EBD is divided into two major types based on the inheritance pattern: recessive dystrophic epidermolysis bullosa and dominant dystrophic epidermolysis bullosa. Each type is further divided into multiple clinical subtypes. The diagnosis is confirmed by molecular genetic testing or skin biopsy. Immunofluorescence staining on a skin biopsy specimen may help establish the broad category of EB type based on the level of clefting in the skin. Collagen VII staining using antibodies is diminished or absent but may be normal in milder types.
- Kindler syndrome: This type of EB can involve all layers of the skin with extreme fragility. The blisters tend present in infancy or early childhood. It increases sun sensitivity and can cause the skin to look thin, mottled, and wrinkly.

The skin histopathology that suggested a diagnosis of EB simplex and the molecular genetic testing results that supported a dystrophic type of EB were discrepant in our patient. This may have been due to the site from which the skin sample was obtained. Pathogenic variants in *COL7A1* cause a wide variety of dystrophic EB (EBD) phenotypes. The significant family history of dystrophic toenails in the mother and maternal grandfather, and occasional blisters on the feet in the mother, without other significant skin lesions, supported an autosomal dominant inheritance pattern with variable expression.

"The COL7A1 variant in our patient was located in a hotspot region of the gene associated with dominant EBD, at amino acid residues 2000-2080, in the triple helical domain of the protein. This same variant was reported as being causative in the original family described by Bart et al. in 1966 (1, 2). "

The *COL7A1* variant in our patient was located in a hotspot region of the gene associated with dominant EBD, at amino acid residues 2000-2080, in the triple helical domain of the protein. This same variant was reported as being causative in the original family described by Bart et al. in 1966 (1, 2). Bart subtype of EBD (EBD, Bart, MIM #132000) is a more severe phenotype than expressed in our patient, characterized by congenital absence of skin on the lower extremities, blistering of the skin and mucous membranes, and congenital absence or deformity of nails.

Clinical, ultrastructural, and immunohistologic findings were reported on 37 family members from the original Bart kindred (3). There was a wide variability of clinical symptoms in affected family members ranging from nail involvement only to congenital absence of skin on the lower extremities. Twenty-one family members had a congenital localized absence of skin (CLAS) with blistering of the skin or mucous membranes and nail abnormalities. Ten had blistering and nail involvement without CLAS, 3 had nail involvement only, and two had blistering only. While there was complete penetrance, there was variable expressivity. Importantly, at least two mildly affected family members (with nail involvement only) had offspring with blistering or CLAS. The same variant was also reported in a family from China with Bart syndrome in which three members presented with congenital absence of skin at birth, and one had blisters on the mucous membranes. There was complete healing with minimal scarring on follow-up (4).

These reports of severe EBD in patients with the same COL7A1 variant as this family led us to counsel the family that future affected offspring could have a severe presentation with congenital localized loss of skin. We counseled the family that the infant's presentation appears mild, with decreasing frequency and resolution of blisters without scarring. While we do not expect him to have severe symptoms, as the mother is heterozygous for the pathogenic *COL7A1* variant, she has a 50% chance of having off-

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Practical applications:

1. Dystrophic epidermolysis bullosa presents with a variable phenotype with wide intrafamilial variability. The significance of the mother's dystrophic toenails was only appreciated after the return of the genetic test results.
2. EBD can present with mild blisters, in this case, on day of life 2. Any blisters in a newborn warrant genetic and dermatologic evaluations. The consequences of a late diagnosis could be a second and perhaps more severely affected child born to these parents.
3. Believe the clinical presentation when the presentation conflicts with dermatopathology and use genetic testing early in the evaluation. A recent retrospective review of EB by Saunderson *et al.* (2019)(5)suggested that "rapid molecular diagnostic testing can provide the precise diagnosis of EB in many cases, negating the need for skin biopsy… for less severe cases."
4. Clinical correlation of the pathogenic variants requires a careful review of the published literature review, which is crucial in providing a recurrence risk for the family.

Figure 1: Bullous lesion on the palm of our patient:

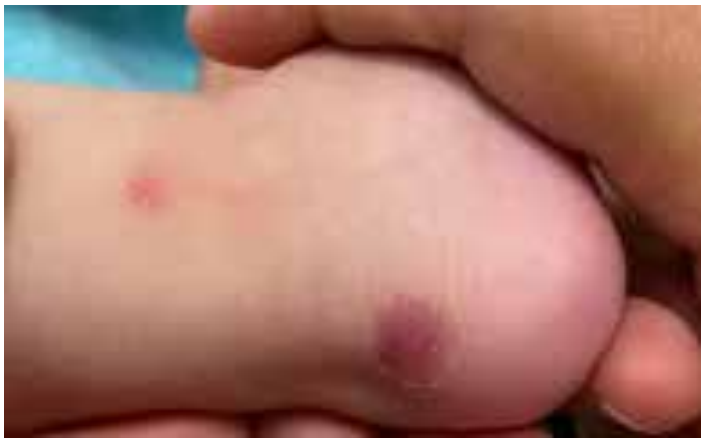

Figure 2: Healing lesions on ankle and heel.

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Disclosures: The authors have no disclosures

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