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Variable expressivity in dystrophic epidermolysis bullosa: A case study

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Abstract
Epidermolysis Bullosa (EB) is a rare group of genetic cutaneous disorders that lead to the formation of blisters and erosions upon minimal trauma or friction. This condition leads to skin weaknesses, resulting in intraepidermal or dermal-epidermal cleavage. Over 30 subtypes exist; however, they fit within four significant groups, which are EB simplex (EBS), junction EB (JEB), dystrophic EB (DEB), and Kindler syndrome, defined by the location of the split. EB has a heterogeneous expression that can vary from mild blister to life-threatening skin compromises depending on the inheritance pattern and mutation. There is currently no cure, and management is supportive by avoiding triggers, trauma, and infection. With the promising future of gene therapy, much more research is needed to develop a treatment for each mutation and subtype. The prognosis for those who have mild phenotypes is favorable, but those with severe symptoms can live a life with chronic pain and complications that potentially lead to death. Our patient with DEB, however, presented differently from the pathognomonic manifestations.

Keywords: Dystrophic, epidermolysis bullosa, expressivity, dermatology, pediatrics

Introduction
Epidermolysis bullosa (EB) is a rare inherited mechanobullous disorder identified by fragile mucocutaneous tissue prone to blister formation upon minimal trauma. This condition presents as a broad phenotypic spectrum, with potentially severe extracutaneous manifestations, morbidity, and mortality [1, 2]. Patients are typically diagnosed at birth or during the early stages of life due to unexplained lesions; however, there are instances where adults receive the diagnosis later in life. Given the multitude of subtypes of EB, accurate diagnosis is essential as management and prognosis vary significantly across subtypes. The genetic basis of EB involves mutations in several genes, with inheritance patterns ranging from autosomal dominant to autosomal recessive. The severity of the disease depends on the expressivity of affected genes, with the core of EB pathology lying in a defect in the attachment between or within the epidermis and dermis of the skin, leading to blister formation [1].

The four main types of EB include epidermolysis bullosa simplex, junctional epidermolysis bullosa, dystrophic epidermolysis bullosa, and Kindler syndrome. The disease is characterized by the layer in which the blister cleaves [3]. According to the National Epidermolysis Bullosa Registry (NEBR), the prevalence and incidence of all EB types was 11.1 per one million population and 19.6 per one million live births, respectively [4]. EB Simplex (EBS) is the most common variant of the disease, accounting for about 70% of EB patients, usually inheriting it in an autosomal dominant fashion [2]. Most simplex patients have defects in keratin, a protein that comprises the cytoskeleton in the basal keratinocytes where the split occurs [2]. This form typically involves the extremities, specifically areas of high friction, such as the palms and soles, while having little systemic involvement and not leading to scar formation. Newborn patients will typically have lesions in the hips due to diapers and lips due to bottle-feeding [5]. Patients with this form have favorable outcomes, with lesions mainly occurring in the palms and soles decreasing with age and do not affect longevity [1, 6]. Junctional EB (JEB) accounts for about 5% of EB cases and is typically inherited in an autosomal recessive pattern, with separation occurring through the lamina lucida [2].

Defects in type XVII collagen, laminin 332, and integrin alpha3 subunit are responsible for the condition with the degree of deficiency relating to the severity of the presentation [1]. Patients experience diffuse blistering of the body and mucus membrane, leading to scarring, granulation, and possibly fatal complications. Severe cases can develop webbing of the digits, contractures, esophageal strictures, and damage to the teeth and eye [5, 7].

Recently, Kindler syndrome was added to the spectrum as the rarest form of EB. It is inherited in an autosomal recessive manner with splits in variable layers and is accompanied by photosensitivity and poikiloderma [8]. Gingivitis and dental issues occur in many groups of EB due to a lack of awareness by providers on how to handle patients with patients and the barriers patients face in receiving care [5]. Dystrophic EB (DEB) has a mixed inheritance pattern occurring either in an autosomal dominant or recessive pattern; however, all cases are due to a mutation in COL7A1, collagen Type VII Alpha 1 Chain, which makes up the anchoring fibrils that connect the epidermis to the dermis. The separation is located at the upper dermis level below the lamina densa. Roughly 25% of all cases of EB are identified in this class [2]. Those with the recessive pattern have the greatest severity, presenting similarly to JEB with oral erosions, esophageal strictures, and ocular damage leading to inadequate nutrition. Patients can suffer from recurrent squamous cell carcinoma and pseudosyndactyly, unlike those with the dominant inheritance, which may improve over time or present with symptoms later in life with only milia, nail dystrophy, and pruritis [9].

A diagnosis can require up to three skin biopsies: one for histology, one for immunophenotypic, and electron microscopy [5]. The current gold standard for diagnosis is electron microscopy [10]. The biopsy will eliminate other differential diagnoses and evaluate the level of the split. Venous blood can be drawn to conduct mutational analysis, and prenatal diagnosis can be done through chorionic villus sampling [1]. While there is no cure for EB, management primarily revolves around symptomatic management and prevention of new injuries and infections. Treatment requires a multidisciplinary approach from a dermatologist, wound care specialist, dentist, occupational therapist, and dietician to mitigate pain and minimize the risk of blistering and infection to provide optimal healing. Wound care practices are implemented, such as using padded bandages and wearing loose-fitting clothing to prevent new wounds; however, wound care can be time-consuming, with patients typically requiring daily or alternate-day bandage changes carrying an increased disease burden that can have psychosocial implications. Extracutaneous manifestations of EB, such as gastroesophageal reflux disease, anemia, osteoporosis, blepharitis, and corneal erosion, commonly require the management of professionals knowledgeable about the nuances of EB. Novel translational therapy and gene therapy has emerged to modify disease course. Despite ongoing efforts to improve treatments, the management of EB remains challenging, highlighting the urgent need for tailored therapeutic approaches. This case report aims to raise awareness about EB among healthcare professionals, emphasizing recognizing its signs, symptoms, and high patient variability. Additionally, it underscores continued research's need to develop more effective and personalized treatments for this debilitating condition. Furthermore, the development of validated quality-of-life measurements is needed to capture the burden of disease, with those who have the dystrophic variant having been linked to a greater risk of depression.

Case Report

Ethical Statement

Written informed consent was obtained and signed by the patient to have the case details and any accompanying images published.

A 16-month-old female presented to the pediatric clinic with her mother due to excessive mucus and cough. Past medical history includes atopic dermatitis treated with triamcinolone and dystrophic epidermolysis bullosa (DEB) diagnosed at birth. Prior family history was unremarkable. The patient's mothers state that her mouth ulcers have worsened due to sickness, decreasing her appetite and ability to eat. She was experiencing regular bowel movements three times per day. The patient's DEB typically manifests in the tongue, gums, beneath the nails, hands, feet, and parts of the legs since birth. Mother denies seeing her scratch intertriginous areas. She had a history of ocular involvement, requiring tobramycin drops and occasional steroid use to manage symptoms and prevent corneal complications (Image 1). The patient's mother reported a meticulous care regimen, including using Mepitel silicone bandages and mupirocin ointment to cover and avoid infection of lesions, along with padding to protect the affected areas. The patient also demonstrated brittle toenails and a lesion around the eye but no photosensitivity.

A review of birth history revealed the patient was born at 39 weeks through repeat cesarean section due to spontaneous rupture of membrane. The patient received prenatal care for all vertically transmitted diseases, which were negative, including the day of birth (Table 1, Table 2). The mother had lesions in her mouth suspicious of HSV, which was treated with Acyclovir. After a successful c-section, the patient had an APGAR score of 9 at 1 minute and nine at 5 minutes. An unincarcerated moderate umbilical hernia was observed. Per neonatology, no lesions were observed at birth, but over 12 hours, she had an increasing number of bullae where she was handled. Areas included her oral mucosa, lips, and feet (Image 1, 2, 3, 4, 5, 6) due to her sucking on gloved hands, which then led to her poor feeding.

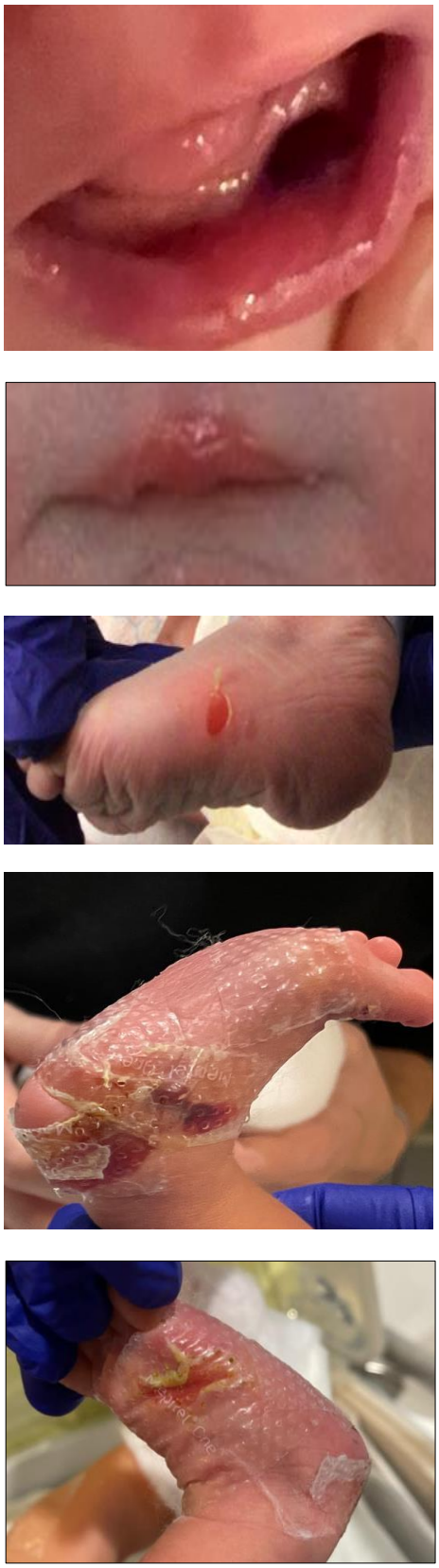

Image 1-6: Per neonatology, no lesions were observed at birth, but over 12 hours, she had an increasing number of bullae where she was handled. Areas included her oral mucosa, lips, and feet (Image 1, 2, 3, 4, 5, 6) due to her sucking on gloved hands, which then led to her poor feeding

HSV was ruled out due to the increasing size and quantity of lesions, which is inconsistent with the disease. On hospital day two, a skin biopsy was sent for hematoxylin and eosin staining (HE) (Image 7) and direct immunofluorescence (DIF) (Table 3). The baby was able to feed with Haberman nipple, and by the fourth day, lesions were healing with the placement of mittens for protection. A central line was initiated due to skin fragility concerns, with a bulla culture sent for gram staining, which showed no neutrophils or organisms present. Complete blood count (CBC) was drawn multiple times during her stay, with her hemoglobin (HGB) and hematocrit (HCT) being decreased and white blood cells (WBC) fluctuating from normal ranges to leukopenia (Table 3). We theorize that this may be due to anemia of chronic disease secondary to chronic inflammation from her wounds, but this information is not substantiated.

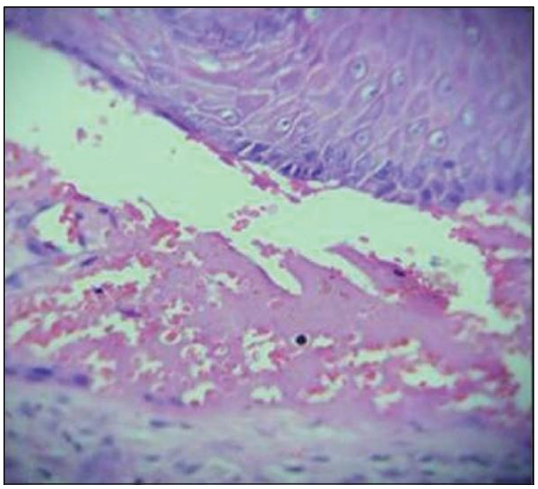

Image 7: Epidermal biopsy with H&E staining showing subepithelial split [10]

Pathology reported, “Contiguous dermis with sparse superficial lymphocytic infiltrate and absence of the epidermis. This may be due to a subepidermal blister; therefore, epidermolysis bullosa is a diagnostic possibility (although the findings are inconclusive).” The initial set of newborn screening results was inaccurate and demonstrated acidemia due to contamination of total parenteral nutrition (TPN). DIF report showed the absence of immunoglobulins in any layers of the tissue, demonstrating no evidence of immunobullous etiology supporting the diagnosis of EB (Table 4). The mother did not do prenatal screening, such as extraction and examination of fetal DNA derived via chorionic villus sampling. Upon follow-up appointment, no resolution of symptoms was reported, with slight worsening of oral lesions.

Genetic testing revealed a dystrophic subtype of EB with a unique expression of genes, resembling simplex but with dystrophic characteristics on histology. Despite the severity of the dystrophic type, the patient exhibited milder symptoms and superficial lesions attributed to variable expressivity. The mother decided to delay the child’s vaccination schedule due to her symptomatic intolerance after each vaccine dose. The patient’s diet primarily consisted of organic pureed and cold foods, alleviating her symptoms. Overall, the prognosis is favorable, with the condition remaining localized to the areas of initial presentation without worsening or spreading. Psychosocial impacts on the family have been significant, with overall maternal anxiety about the patient’s future health and ability to have a healthy life without being significantly impacted by her condition. Treatment strategies to optimize skin integrity and minimize complications to ensure the best quality of life for the patient are of the highest priority.

Treatment focused on skin protection and wound healing, focusing on blistering areas. Steroid creams for eczema were used on the unaffected EB regions without exacerbating EB symptoms. Her symptomatic treatment approach should focus on mouth sores and nutrition; however, the patient has not followed up with a dentist over concerns that the provider would not be equipped to handle her delicate condition.

Discussion

EB is a condition that has variable presentation due to the large gamut of gene mutations associated with the disease. Even those with the same mutation or class of EB can have different symptoms. This inconsistency in presentation is attributed mainly to variable expressivity, a phenomenon where individuals with the same genotypic variant exhibit different phenotypes [11]. In some cases, it is easier to understand this disease as a spectrum that can vary significantly from one another, classifying it as a complex disease to diagnose even by an experienced dermatologist. Irregular inheritance patterns, nuances in gene mutations, and lack of family history create obstacles for clinicians to arrive at a diagnosis, as all other causes must be excluded [1]. Those with milder types can be more symptomatic than those with worse types due to differences in the level of functional gene expressivity. The genetic defect identified in most cases of DEB is COL7A1. A common manifestation of DEB that differentiates from simplex includes mitten deformities, scarring, corneal erosions, esophageal strictures, nail and tooth involvement [12]. There are two types of DEB: dominant dystrophic epidermolysis bullosa (DDEB) and recessive dystrophic epidermolysis bullosa (RDEB). The dominant variant presents with generalized blistering at birth that becomes localized to the hands, feet, elbows, or knees as they age. RDEB is the more severe form of the disease with scarring and debilitating deformities, such as fused fingers and toes, due to severe blistering, internal blisters, and increased risk of squamous cell carcinoma in chronic lesions. In contrast, DBEB has nail hypoplasia, minimal scarring, and fewer lesions. The patient's symptoms seem to correlate with the DDEB phenotype, though she has RDEB, as evidenced by her lack of family history of the disease.

One interesting factor to consider is epigenetics. The patient consumed an organic diet devoid of processed foods. We speculate that her conscientious lifestyle and dietary choices might have played a role in alleviating the severity of her symptoms. This could be attributed to the reduced inflammation resulting from the avoidance of triggering foods, emphasizing that DNA methylation can be altered by diet through foods rich in cofactors that help cellular processes [13]. DNA, histone, and chromatin methylators also affect epidermal stem cell homeostasis, proliferation, and wound healing [14]. Similar logic can be applied to explain how inflammation, provoked by viral illnesses, may exacerbate her lesions and potentially modulate gene expression. Maternal diet may play a role in utero embryogenesis, with the mother ingesting folate and sulforaphanes, which can affect keratin 14 mutation in EBS [15]. However, further investigation regarding this subject is warranted.

The self-reported disease burden is highest in those with RDEB, followed by JEB, DDEB, and EBS, sequentially decreasing [16]. Those with RDEB report consistently higher complications, ER visits, affected body area, and time spent managing wounds [17]. As much as this disease can be debilitating for patients, it also impacts caregivers, with most reporting that they choose to work less or not at all to care for the patients. Those with EB report that it significantly affects their quality of life and increases their financial burden. The psychosocial implications of EB include issues with mental health, self-image, and autonomy, with children feeling isolated from peers [18]. Though treatments remain supportive and palliative, DEB has advanced with novel agents such as Vyjuvek, a gene therapy gel that delivers a healthy copy of the gene, encoding the protein type VII collagen to targeted skin cells. The protein anchors the layers of skin together to promote healing. Oleogel-S10, which contains birch triterpenes or birch bark extract, has accelerated the healing of chronic wounds in junctional and recessive and dominant dystrophic epidermolysis bullosa [19].

Table 1: The patient received prenatal care for all vertically transmitted diseases, which were negative, including the day of birth

2nd Trimester		
Lab	Value	Reference Range
Blood Type	B+	N/A
RPR	Negative	Negative
Rubella (IgG)	Immune	Immune
HBsAg	Negative	Negative

Table 2: The patient received prenatal care for all vertically transmitted diseases, which were negative, including the day of birth

3rd Trimester		
Lab	Value	Reference Range
HIV	Negative	Negative
GC/Chlamydia	Negative	Negative
GBS	Positive Clindamycin resistant	Negative

Table 3: Labs at the hospital

Lab	Day 2	Day 3	Day 4	Day 6	Day 9	Day 10	Day 11	Day 13	Reference Range
WBC	--	8.67	4.27*	--	6.17	--	--	--	8.2-14.6 x 10^9/L
HGB	--	14.3	13.0	15.0	12.2	12.0*	12.0*	11.8*	13.4-20.0 g/dL
HCT	--	41.5	40.5	44.8	35.7*	35.5*	35.7*	34.7*	39.6-57.2%
PLT	--	329	267	--	507*	--	--	--	144-449 x 10^9/L
Seg Abs Neutrophils	--	53	40*	--	38*	--	--	--	47-55%
Lymphocytes		31	47*	--	--	--	--	--	1.75-8.00 x 10^9/L
Monocyte	--	10	7	--	15*	--	--	--	0.52-1.77 x 10^9/L
Eosino	--	5	5	--	4	--	--	--	0.09-0.64 x 10^9/L
Absolute Neutrophil count	--	4.6	1.71*	--	2.34	--	--	--	1.73-6.75 x 10^9/L
CRP	<2.90	--	--	--	--	--	--	--	<10 mg/L

Table 4: Direct immunofluorescence (DIF)

Location	Findings	Reference
Intracellular	IgG, IgA, IgM, C3, and fibrinogen are negative	IgG, IgA, IgM, C3, and fibrinogen are negative
Basement membrane	IgG, IgA, IgM, C3, and fibrinogen are negative	IgG, IgA, IgM, C3, and fibrinogen are negative
Vessels	IgG, IgA, IgM, C3, and fibrinogen are negative	IgG, IgA, IgM, C3, and fibrinogen are negative
Superficial Dermis	IgG, IgA, IgM, C3, and fibrinogen are negative	IgG, IgA, IgM, C3, and fibrinogen are negative
Comment	The above-described findings are not consistent with an immunobullous disease.	N/A

Conclusion

Spreading awareness of EB and its variable presentation to health professionals is part of the solution to managing EB. Many patients, like the one in this case, face barriers to receiving health care from professionals due to the gap in knowledge and hesitation in developing new lesions. Highlighting the facts about the pathogenesis of EB and the existing spectrum allows for tailored therapeutic approaches that tackle the patient's needs based on the level of expressivity they experience rather than just a diagnosis. This case reinforces the concept of treating the patient rather than a disease; though she experiences a rarer form of EB, her prognosis remains favorable due to her phenotype. Acknowledging EB as a spectrum of disease presentations allows individuals to understand that their diagnosis, though it may have a poor prognosis for some, may not affect their longevity similarly. This is important to minimize the psychosocial impact on caregivers and patients.

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