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Congenital Epidermolysis Bullosa, in Neonatal Intensive Care Unit: Case Report and State-of-the-Art

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Abstract: ***Epidermolysis bullosa (EB) is a rare hereditary disease, characterized by fragility in the skin and mucous membranes; This is a consequence of mutations in structural proteins of the skin. Reports indicate pathogenic variants in 16 different genes, with more than 1000 mutations. These can be de novo or follow an autosomal dominant or recessive inheritance pattern. There are approximately 30 clinical subtypes, grouped into four main types: Simple EB, Union EB, Dystrophic EB, and Kindler Syndrome. The clinical manifestation is characterized by the presence of lacerations, ulcers, blisters, trauma, abnormal wound healing, skin atrophy and depigmentation, the diagnosis is clinical, confirmed by biopsy by electron microscopy and indication of complete exomic sequencing. Treatment is always directed to the severity of the lesions and individualized. We detail a case identified in a tertiary institution in Barranquilla, Colombia, encompassing the clinical presentation, diagnosis, differential diagnoses, therapeutic approaches, underpinned by a bibliographic review covering EBs definition, classification, pathophysiology, and clinical picture. This report emphasizes the importance of a multidisciplinary approach in managing such complex cases.***

Keywords: Epidermolysis bullosa, mutations, hemidesmosomes, keratinocytes, biopsy.

1. Introduction

Epidermolysis bullosa(EB) is a hereditary disease, which can be either autosomal dominant or recessive, characterized by fragility in the skin and mucous membranes[1, 2, 3]. This fragility triggers a series of consequences, such as lacerations, ulcers, blisters, trauma, abnormal wound healing, skin atrophy, and depigmentation [4, 5, 6], with great clinical, genetic and histopathological variability and a series of complications that develop from neonatal stages to adult life [7, 8], where tissue alteration of the skin layers, mainly epidermis and dermis and mutations that affect the structural proteins of the skin play the pathophysiological role of the condition [9, 10, 11]. Clinical identification and subsequent diagnosis with biopsy and complete exomic sequencing are important to classify the pathology [5, 7, 11], which marks a therapeutic prognosis, where the complexity of the treatment will depend on the severity of the lesions, always requiring a multidisciplinary team, and individualizing each case [12, 13, 14]. This article is significant as it provides valuable insights into the clinical challenges and management strategies of congenital epidermolysis bullosa in neonatal care, contributing to the existing body of medical literature on rare hereditary diseases.

2. Methodology

The methodology of this case report involves a comprehensive review of clinical records, including diagnostic testing and therapeutic outcomes of a patient with Epidermolysis bullosa in a neonatal intensive care unit, combined with an extensive review of relevant literature to explain the findings in the patient and update of the topic.

3. Clinical Case

Newborn at 37 weeks by Ballard, product of a 21-year-old first-time mother, blood group O+, with a personal history of grade II obesity and urinary tract infection during pregnancy with in-hospital management for 1 week in her third trimester of gestation. The mother had a controlled pregnancy, denies consumption of medications or toxic substances, has a negative TORCH report. It was found right renal ectasia, adequate growth percentile and low risk of aneuploidies without detection of evident malformations in anatomically detailed ultrasonography.

He was born by vaginal delivery in cephalic presentation with APGAR of 6-9-10 respectively at 1, 5 and 10 minutes. Birth weight 2800 grams, height 50 cm and head circumference 34 cm, all appropriate for his gestational age. Dermatosis is evident, characterized by vesicular lesions predominantly in joint areas such as the elbow, disseminated blisters that affect the eyelids and forehead, including the palms and soles, predominance in the anterior thighs, back of the hands and feet, along with abrasions in the same places (See figure 1- A) later transferred to the neonatal intensive care unit due to the extent of the injuries.

After her admission, neonatal screening is received including VDRL (Negative), Blood group: O-; admission blood count without alteration of cell lines, given generalized compromise, it was decided to culture and start antibiotic coverage with ampicillin and gentamicin, an increased cardiothymic silhouette with an index of 0.65cm is evident on admission x-ray, screening of negative heart

disease and subsequent normal echocardiogram. Analgesia is started by schedule.

An evaluation is requested by pediatric dermatology, who evaluates on the third day of life (See figure 1 B and C), considering that it is very likely, due to clinical characteristics, that it is congenital epidermolysis bullosa, Dermatology service indicate a skin biopsy, evidence of lesions level of oral mucosa and request evaluation by gastroenterology to rule out lesions at that level, they consider rotating coverage to beta-lactam, reduced spectrum of the penicillin group (oxacillin), continuing aminoglycoside, completing biconjugate therapy and starting topical management with aluminum acetate, topical antibiotic and cleaning the oral cavity with topical antifungal.

During his stay in the ICU, there was a decrease of just over 20% of his initial weight on the seventh day of life, with clinical signs of respiratory distress, Silverman 4 points, arterial blood gases with decompensated metabolic acidemia, with compromised alertness. Therefore, it was decided to ensure an airway, blood was cultured again with positive isolation for *Elizabethkingia meningosepticum* in blood cultures and retrocultures, subsequently new born presented with extreme bradycardia, starting advanced cardiopulmonary resuscitation maneuvers without a satisfactory response, the necrotic appearance of the skin in the last hours after the death of the patient (See figure 1 D and E).

Days after her death, a skin biopsy report was received reporting a subdermal blister with vacuolization of the basal stratum, compatible with Epidermolysis bullosa simplex, confirming the initial diagnostic impression; it was not possible to perform a genetic sequence in the patient.

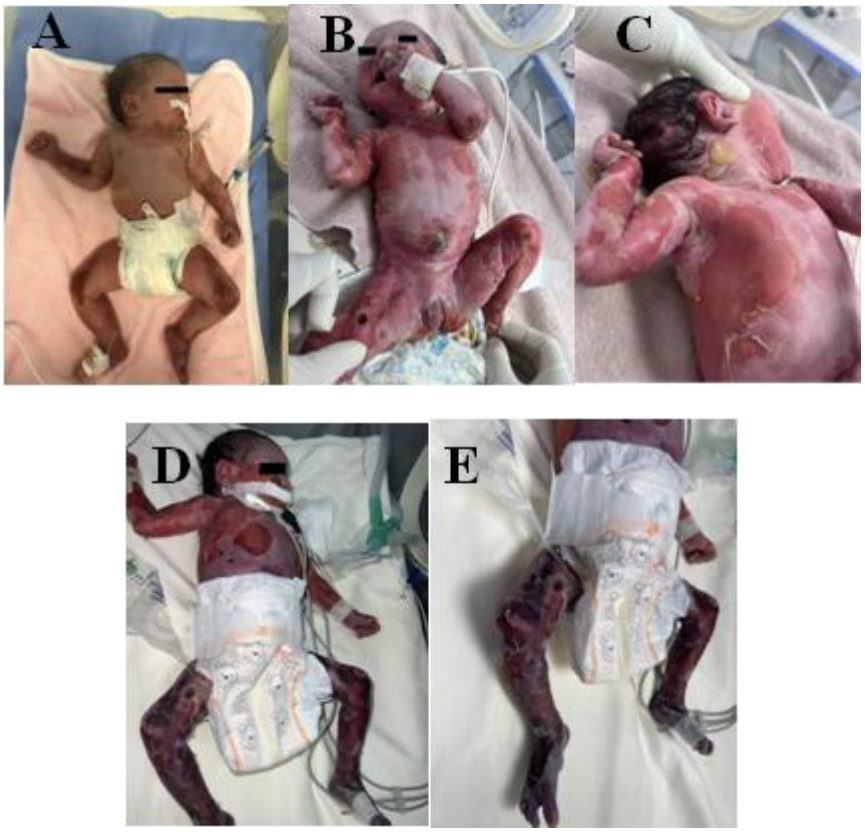

Figure 1: Images of patient with Epidermolysis Bullosa (EB) **A)** Large areas of denuded and erythematous skin is noted which appear during childbirth, these involve the face, neck and trunk, with a marked predominance in the upper and lower limbs in joint areas. **B)** Third day of life: Universal skin condition characterized by multiple areas of denuded skin on almost the entire skin surface including the genital area, leaving erythematous and dry areas; note the crust of blood on the anterior surface of the right thigh. **C)** Complement to // Complementing the previous image, an intact blister is observed on the neck, accompanied by large areas of bare skin. **D)** Post-mortem image of the patient, in which a universal skin pattern is observed, with multiple denuded areas, which leave erythematous areas interspersed with areas of skin with a purplish appearance. **E)** Multiple areas of necrosis in the skin of the lower limbs.

4. Discussion

Epidermolysis bullosa (EB) is a hereditary disease, with data reported since the 19th century, described by Fernidand Ritter von Hebra, a dermatologist of the time who made advances in skin diseases with anatomopathological criteria [6, 7, 8], characterized by fragility. On skin and mucous membranes that trigger a series of consequences such as lacerations, ulcers, blisters, trauma, abnormal wound healing, skin atrophy and skin depigmentation [1, 2, 3]. The skin can be affected in its entirety, with greater focus on sites exposed to friction (4), as well as there may be extra-cutaneous manifestations, such as in the gastrointestinal, vesico-urinary, and pulmonary epithelium [5].

This incidence is between 1 case per 17, 000 live births, with

an estimate of 500, 000 cases annually worldwide [5]. It does not show predilection by race, ethnicity and sex, [1].To date, pathogenic variants have been identified in 16 different genes that are associated with EB [3], with more than 1000 mutations, which can be de novo or follow an autosomal dominant or recessive inheritance pattern [9].

The skin is the largest organ in the body and the barrier between the body and the external environment, with a protective function against physical and chemical agents, ultraviolet radiation and dehydration; it is composed of the epidermis made of stratified epithelium and the dermis formed by fibroblasts [10].

The tissue division of the skin as an organ begins with the epidermis composed of multiple layers of keratinocytes, the broader dermis as a whole, is composed of greater cellular differentiation and greater extracellular matrix [11], a structure in the known dermo-epidermal junction. As an epidermal basement membrane, it fulfills an anchoring function between the two tissues [12].

Keratinocytes express a cytoskeleton made up of keratin 5 and keratin 14 filaments, important for maintaining the morphological integrity of the epidermis by connecting to monosomes and hemidesmosomes, The complex desmosomes being highly specialized in the formation of intercellular junctions with main components such as the cadherins desmocholin, desmoglein, plakoglobin, pacophylline and desmoplakin [13, 14, 15]. In the formation of the dermo-epidermal junction, hemidesmosomes play an important role as the main unit of adhesion, molecularly constituted by keratin filaments, plakin: plectin and the 230kDa ampoule perphygoid antigen (BP230), associated with transmembrane proteins such as alpha6b64 integrin, bullous pemphigoid antigen 180kDa (BP180), laminin 332, collagen type I, III, IV, VII [11, 15].

The genetic role in EB has evolved in recent years, Kotalevskaya et al. [3] In his review article on the molecular genetic basis of epidermolysis bullosa, shows that there are currently pathogenic variants associated with EB in 16 different genes and they encode proteins that are part of the anchoring structures of the skin or are proteins of signaling, causing dysfunction of the narrow cells, differentiation, ploriferation and apoptosis of the cells that causes mechanical instability of the skin.

30 clinical subtypes have been identified, grouped into four main types of epidermiolysis bullosa (Simple EB, Union EB, Dystrophic EB and Kindler syndrome) [16]. Table 1 shows the classification of epidermolysis bullosa, its main pathogenesis mechanisms and the affected genetic profile.

Table 1: Classification of epidermolysis bullosa (EB) and main mechanisms of pathogenesis

Subtype	Type	Gene affected	Mechanism
Simplex EB – intraepidermal			
Localized	AD	*KRT5*	Abnormal keratin cytoskeletal network and basal cytolysis
Intermediate		*KRT14*	
Severe	AD	*KRT5* *KRT14*	Abnormal keratin cytoskeletal network, clumping of keratin tonofilaments leading to basal cytolysis
With mottled pigmentation	AD	Predominantly: *KRT5* Less frequently: *KRT14*	Rupture of keratin filaments, basal cytolysis, and additional aggregation of densely packed complex melanosomes in the perinuclear cytoplasm of basal keratinocytes
Migratory circinate	AD	*KRT5*	Keratin 5 elongation due to late termination codon generation leads to T-cell mediated inflammation
Intermediate with cardiomyopathy	AD	*KLHL24*	Pathogenic variants result in a truncated and more stable KLHL24 protein, followed by increased degradation of KRT14
Intermediate with *PLEC* mutations	AD, AR	*PLEC*	Reduced HD due to disruption of the internal plaque to which the keratin cytoskeleton attaches, followed by basal cytolysis
Intermediate with muscular dystrophy	AR	*PLEC*	The cleavage is as close as possible to the BMZ; HD is significantly reduced in size; breaking of the interaction of sarcomeres due to the rodless isoform of plectin inside the Z-disks; defective attachment between assembled desmin filaments triggers the formation of desmin protein aggregates, as well as secondary mitochondrial failure
Severe with pyloric atresia	AR	*PLEC*	Absent plectin
EB simplex	AR	*KRT5, KRT14*	Absence or significant reduction of bundles of tonofilaments in basal keratinocytes
Localized or intermediate with BP230 deficiency	AR	*DST*	Absence of inner HD plaques, compensatory increase in KRT14 and plectin, which may explain the mild phenotype
Localized or intermediate with exophilin 5 deficiency	AR	*EXPH5*	Disruption of intracellular vesicles transport along actin and tubulin networks; an increase in perinuclear vesicles with abnormal keratin; loss of basal keratinocyte adhesion
Localized with nephropathy (CD151 deficiency)	AR	*CD151*	Pathogenic variants lead to reduced adhesion of keratinocytes mediated by laminin-332-integrin α3ß1 complexes in the epidermis and podocytes
Junctional EB – Intralamina lucida			
Severe	AR	*LAMA3, LAMAB3 LAMC2*	Laminin 332 is usually absent; reduced HD; abnormal or absent sub-basal lamina densa; reduction of anchoring filaments
Intermediate	AR	*LAMA3,*	Reduced laminin-332; absent or reduced collagen of type XVII

		LAMAB3 LAMC2, COL17A	
With pyloric atresia	AR	*ITGA6, ITGB4*	Absent or markedly reduced α6β4 integrin; Pathogenic variants in the *ITGB4* gene leading to partial expression of integrin β4 may cause a milder phenotype
Localized	AR	*LAMA3, LAMAB3 LAMC2, COL17A, ITGB4, ITGA3*	Variable abnormalities and expression levels in defective proteins
Inversa	AR	*LAMA3, LAMAB3 LAMC2*	Reduced expression of laminin-332
Late onset	AR	*COL17A*	Reduced or abnormal expression of type XVII collagen
Laryngo-onycho-cutaneous índrome	AR	*LAMA3*	Abnormally truncated α3A subunit of laminin-332
With interstitial lung disease and nephrotic syndrome	AR	*IGTA3*	Variants with loss of function of the α3 integrin subunit are common; missense variants may cause milder disease and improve survival
Dystrophic EB – sublaminadensa			
DDEB, intermediate	AD	*COL7A1*	Reduced or abnormal type VII collagen; usually due to missense mutations causing glycine replacement at the hinge region of the type VII collagen triple helix
DDEB, localized	AD	*COL7A1*	Reduced or abnormal type VII collagen resulting from monoallelic deletions, missense variants, or splice site mutations
DDEB, pruriginosa	AD	*COL7A1*	Pathogenic mechanism is unknown
DDEB, self-improving	AD	*COL7A1*	Intracellular accumulation of unsecreted procollagen VII; retention of type VII collagen in basal keratinocytes; gradual improvement in the formation of type VII collagen and anchoring fibrils for unknown reasons
RDEB, intermediate	AR	*COL7A1*	Combinations of biallelic pathogenic variants in *COL7A1* (missense, nonsense, insertions, deletions, and splice site variants) result in reduced or abnormal production of type VII collagen
RDEB, severe	AR	*COL7A1*	Biallelic null variants in *COL7A1* that result in a markedly reduced or absent type VII collagen and, therefore, in a lack of functional anchoring fibrils
RDEB, inversa	AR	*COL7A1*	It is assumed that specific mutations of arginine and glycine in the triple helix of type VII collagen reduce the thermal stability of the protein, causing clinical manifestations in areas of the body with a higher temperature, incl. on mucous membranes
RDEB, localized	AR	*COL7A1*	Reduced or abnormal type VII collagen
RDEB, pruriginosa	AR	*COL7A1*	As in DDEB, pruriginosa
RDEB, self-improving	AR	*COL7A1*	As in DDEB, self-improving
DEB, severe	AD, AR	*COL7A1*	Pathogenetic mechanisms are unknown, the phenotype occurs in compound heterozygotes for a dominant mutation of glycine in *COL7A1* in one allele and a recessive variant in the second allele, which changes the protein microenvironment in the BMZ area, increasing the severity of clinical manifestations
Kindler syndrome – variable and mixed			
Kindler syndrome	AR	*FERMT1*	Pathogenic variants promote disruption of keratinocyte cytoskeletal networks, abnormal integrin activation, and loss of keratinocyte adhesion to the underlying basement membrane

Note. AD – autosomal dominant type of inheritance; AR – autosomal recessive type of inheritance; BMZ – basement membrane zone; HD – hemidesmosome; DDEB – dominant dystrophic epidermolysis bullosa; RDEB – recessive dystrophic epidermolysis bullosa.

Source: Kotalevskaya YY, Stepanov VA. Molecular genetic basis of epidermolysis bullosa. VavilovskiiZhurnal Genet Selektsii. 2023 Mar;27(1):18-27. PMID: 36923479; PMCID: PMC10009482 [3].

The degree of clinical manifestations is linked to the different types of Epidermolysis:

Epidermolysis bullosa simplex (ESB): It is the most common, with greater skin involvement, in a mild form with painful blisters. Blisters affect the outer layer of the skin and are classified by their distribution, severity and frequency into: a) Localized EBS that present limited blisters, b) Generalized EBS with involvement throughout the body, 3) Dowling-Meara or EBS-DM presence of generalized vesicles with herpetic distribution, 4) EBS with optical pigmentation or EBS-MP also present skin pigmentation, 5) EBS with muscular dystrophy or EBS-MD with weakness of extremities and 6) Acantholytic EBS accompanied by loss of nails and alopecia [10].

Junctional epidermolysis bullosa (JEB): It is subdivided into Herlitz which is lethal, non-Herlitz or non-lethal and JEB with pyloric atresia; they are characterized by blisters and erosions on the face and neck with involvement of the upper respiratory tract, nail involvement, enamel hypoplasia and granulation [10].

Dystrophic epidermolysis bullosa (DEB): The autosomal dominant form (DDEB) is characterized by blisters predominantly on the hands, esophagus, elbows, and knees; They cause scars that can generate contracture in the joints or mouth, stenosis or narrowing of the esophageal diameter. Autosomal recessive has 3 subtypes: a) severe generalized autosomal recessive: generalized blisters at birth with subsequent scars, deformities in hands and feet, growth retardation, anemia and esophageal stricture; it can cause serious kidney complications or aggressive squamous cell carcinoma with a poor prognosis for life, b) non-Hallopeau-Siemens autosomal recessive: it presents less skin involvement, is less severe, is also known as intermediate generalized and there is a risk of squamous cell carcinoma when the risk of metastasis is minimal in the severe generalized form and c) reverse EBDR [10].

Kindler syndrome or mixed epidermolysis: Generalized acral blisters at birth or secondary to photosensitivity, diffuse palmo-plantar hyperkeratosis, poikiloderma and pseudosyndactyly, which can cause esophagitis, severe colitis and urethral stricture [3, 10].

The diagnosis is initially clinical and should be suspected in newborns or infants with frequent blisters in regions of friction or skin fragility associated or not with extracutaneous anomalies. It is important to ask about a family history of BE, age of parents, consanguinity and origin of relatives [3].

In neonates, this anomaly should be suspected in the presence of findings such as skin fragility with blisters in the absence of or minimal trauma involving mucous membranes. Other common findings are aplasia cutis congenita or extensive skin lesions involvement on the head and extremities. Finding congenital pyloric atresia with abdominal distension and vomiting that shows a distended stomach on the x-ray [5] associated with mentioned clinical manifestations should be taken into account, also when there are kidney disorders such as obstructive uropathy, acute renal tubular necrosis or interstitial nephritis. It is transmitted in an autosomal recessive manner and the absence of a family history should not exclude or delay the diagnosis [17].

It is necessary to perform a skin biopsy by transmission electron microscopy (TEM) or mapping of antibodies or immunofluorescent antigens, taken at the anterior edge of a blister < 12 hours of appearance, to histologically localize EB [16, 17], however biopsies where the blister tissue obtained is stained with hematoxylin and eosin could be observed in light microscopy, however the definitive diagnosis is performed with [18].

The multigene panel helps us identify the cause with greater probability, but it can limit detecting variants that do not match the phenotype or are uncertain, comprehensive genomic tests do not precisely determine affected genes and exome sequencing is the one most used in the laboratory [17].

Differential Diagnosis: It is important to rule out Pemphigus vulgaris in neonates, benign mucosal pemphigoid, bullous pemphigoid, herpes virus lesions, bacterial skin infections due to *Pseudomona aeruginosa*, congenital syphilis [19]. In epidermolysis bullosa acquisita, bullous systemic lupus erythematosus must be ruled out. When they are tense blisters on sun-exposed areas in girls with photosensitivity [20].

There is currently no single effective treatment for EB; based on symptomatic management and prevention of complications. Given the great variability of symptoms that EB presents, it requires a multidisciplinary approach and management [16]. Skin care begins with the prevention of trauma and blistering, especially in newborns where greater care must be taken with umbilical clamps or plastic identification bands. If tension blisters form, they must be punctured.

If tension blisters form, they should be pierced at the base with a sterile needle, drain their contents and keep the roof of the blisters intact to reduce pain and the risk of infections [5, 16, 17].

Colonization and infection of wounds in EB occur frequently, so regular baths are recommended along with the use of antibacterial soaps. The use of topical antibiotics is only recommended in short courses to reduce the increase in bacterial resistance. In the event that topical management fails to remedy critical colonization in the wound, healing is not achieved or there are systemic manifestations of infection, the use of systemic antibiotics is indicated, always guided by an antibiogram of a sample taken from the wound [16, 18].

Estrada et al. [18] in their presentation of a case of epidermolysis bullosa in a 4-year-old patient, show similar findings in the biopsy to those reported in our patient, even with a variable course of antibiotics used, linked to the differential diagnoses that were documented in their case. Patient, a fact that to a certain extent agrees with our antibiotic management, due to the simultaneous modifications that were made to the proposed antibiotic therapy as the days passed.

Recently, studies related to EB have focused on finding new therapies that can modify the course of the disease; for example, protein therapy, cellular therapy with fibroblasts, mesangial stromal cells and hematopoietic cells, and gene therapy [16].

The prognosis of this disease varies depending on the subtype of the disease and the comorbidities present in the patient; having a better prognosis and a normal life expectancy, those patients with the simple localized BE subtype; while those with more severe manifestations usually occur in the first years of life [5, 16, 20].

5. Conclusions

Epidermolysis bulbosa (EB), a rare disease, with an autosomal dominant or recessive inheritance pattern, it is important to recognize it from birth for the therapeutic individualization that patients require, always with a multidisciplinary team; Although the diagnosis is clinical, a

histopathological and genetic report is necessary to help classify the type of EB in progress, as well as prepare hospital services, mainly neonatal intensive care units, with elements and personnel trained to care for these patients.

6. Future Scope

With our case report on congenital epidermolysis bullosa we seek to underline the complexity of managing such rare hereditary diseases in neonatal intensive care. Highlighting the need for a multidisciplinary approach and emphasizing the importance of early recognition and personalized therapeutic strategies. This contributes significantly to the body of knowledge on the treatment of rare skin diseases in newborns and to prepare better equipment in future cases, in addition to encouraging research on these medical conditions.

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