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Epidermolysis Bullosa

Melisa Hunis, Adrian Hunis*

School of Medicine, Universidad de Buenos Aires (UBA), Argentina

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***Corresponding author:** Adrian Hunis, School of Medicine, Universidad de Buenos Aires (UBA), Argentina

ABSTRACT

Epidermolysis Bullosa (EB) is a heterogeneous group of rare, inherited skin disorders characterized by extreme skin fragility and the formation of blisters and erosions following minimal trauma. EB is classified into four major types-simplex, junctional, dystrophic, and Kindler syndrome-based on the level of skin cleavage and the underlying genetic mutations. The clinical spectrum ranges from mild localized blistering to severe, life-threatening forms with widespread mucocutaneous involvement, scarring, and significant morbidity. Complications include chronic wounds, infections, nutritional deficiencies, and an increased risk of aggressive squamous cell carcinoma, particularly in severe subtypes. Diagnosis is based on clinical evaluation, histopathological analysis, immunofluorescence mapping, and genetic testing. Management is multidisciplinary, focusing on wound care, infection prevention, pain control, nutritional support, and surveillance for complications. Recent advances in molecular genetics and gene therapy offer hope for targeted treatments, but EB remains a challenging disease with a significant impact on quality of life. Ongoing research and international collaboration are essential to improve outcomes for affected individuals.

INTRODUCTION

Historical Context

Epidermolysis Bullosa (EB) has been recognized for over a century, with early descriptions dating back to the late 19th and early 20th centuries. The term "epidermolysis bullosa" was first coined in 1886 by Dr. Heinrich Koebner [1]. Over time, the understanding of EB has evolved from clinical observations to a molecular and genetic focus. The establishment of patient registries and international collaborations, such as DEBRA (Dystrophic Epidermolysis Bullosa Research Association), has been crucial in advancing research and improving patient care [2].

Definition and Classification

Epidermolysis Bullosa is a group of inherited disorders characterized by skin fragility leading to blister formation. The classification is based on the level of skin separation and genetic mutations:

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Table 1: Classification of Epidermolysis Bullosa

Type of EB	Subtypes	Key Characteristics
EB Simplex (EBS)	Localized, Generalized	Blistering within the epidermis, mutations in KRT5/KRT14 [3]
Junctional EB (JEB)	Herlitz, Non-Herlitz	Blistering at the lamina lucida, mutations in LAMA3/LAMB3/LAMC2 [4]
Dystrophic EB (DEB)	Dominant, Recessive	Blistering below the lamina densa, mutations in COL7A1 [5]
Kindler Syndrome	-	Mixed levels of blistering, photosensitivity, mutations in FERMT1 [6]

Etiology and Pathogenesis

EB is caused by mutations in genes encoding proteins essential for skin integrity. These mutations lead to structural weaknesses at various skin levels. In EBS, mutations in keratin genes disrupt the cytoskeletal network, causing cell fragility [7]. In JEB and DEB, mutations affect basement membrane components, compromising the dermal-epidermal junction [8]. Pathogenesis involves mechanical stress leading to blister formation, chronic wounds, and scarring.

Epidemiology

EB is a rare disorder with an incidence of approximately 1 in 50,000 live births. EBS is the most common form [9]. Epidemiological studies emphasize the importance of genetic counseling and comprehensive patient registries to understand EB's distribution and impact [10].

Clinical Features

The clinical presentation varies by subtype:

- Skin Blistering: Occurs with minor trauma.
- Scarring and Milia Formation: Especially in dystrophic forms (Photo 1)
- Nail Dystrophy: Common across all types.
- Mucosal Involvement: Includes oral, esophageal, and ocular lesions, leading to complications like dysphagia and vision problems [11].

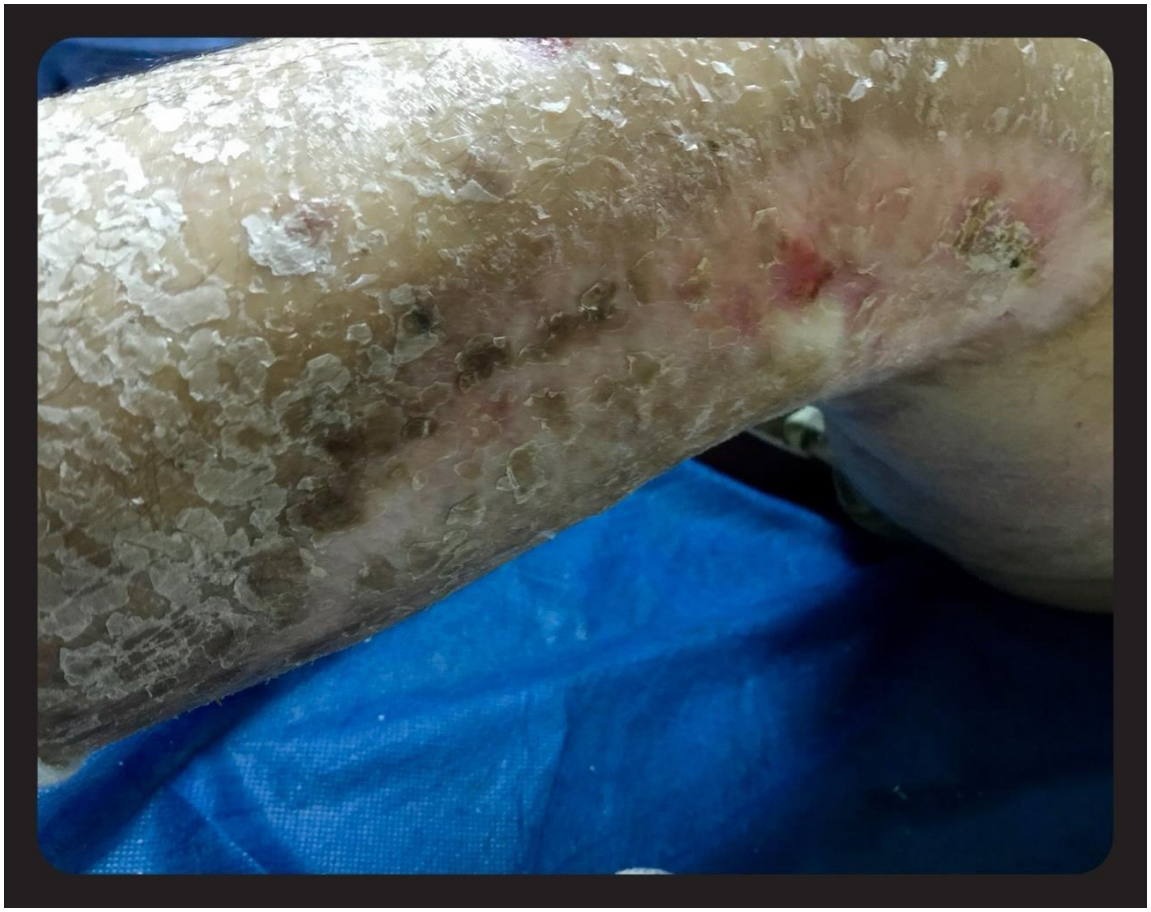

Photo 1: Scarring and Milia Formation: Especially in dystrophic forms (Coutersy, Adrian Hunis MD)

Signs and Symptoms

Patients with EB may experience:

- Pain and Pruritus: Due to chronic wounds.
- Secondary Infections: From open blisters.
- Growth and Nutritional Issues: Especially in severe forms.
- Psychosocial Impact: Anxiety, depression, and social isolation due to visible lesions [12].

Localization of Lesions

- Lesions typically occur at friction sites:
- Hands and Feet: Common in EBS and DEB.
- Elbows and Knees: Frequent in all forms due to mechanical stress. (Photo 2, courtesy, Adrian Hunis MD)
- Mucosal Surfaces: Oral cavity, oesophagus, and conjunctiva, especially in JEB and severe DEB [13].

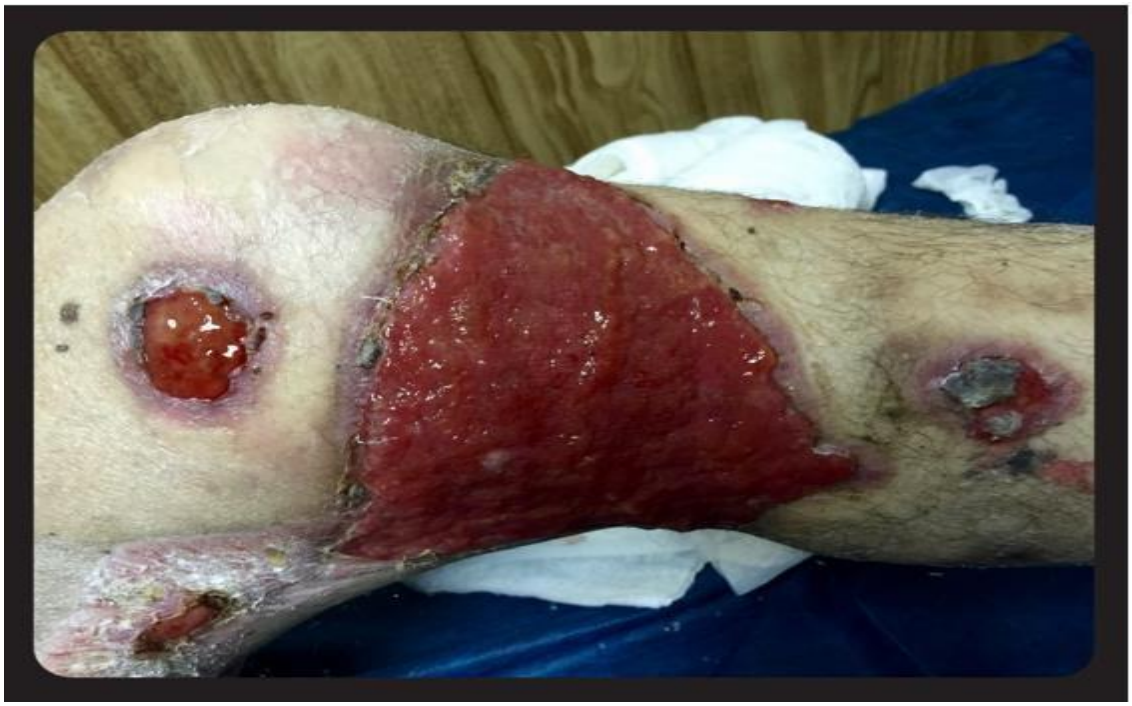

Photo 2: Courtesy, Adrian Hunis MD)

Diagnosis relies on:

- Skin Biopsy: To assess skin separation level.
- Immunofluorescence Mapping: To localize structural protein expression.
- Electron Microscopy: For ultrastructural visualization.
- Genetic Testing: Confirms diagnosis by identifying mutations [14].
- **Histopathology and Diagnostic Techniques** (Figure 1)

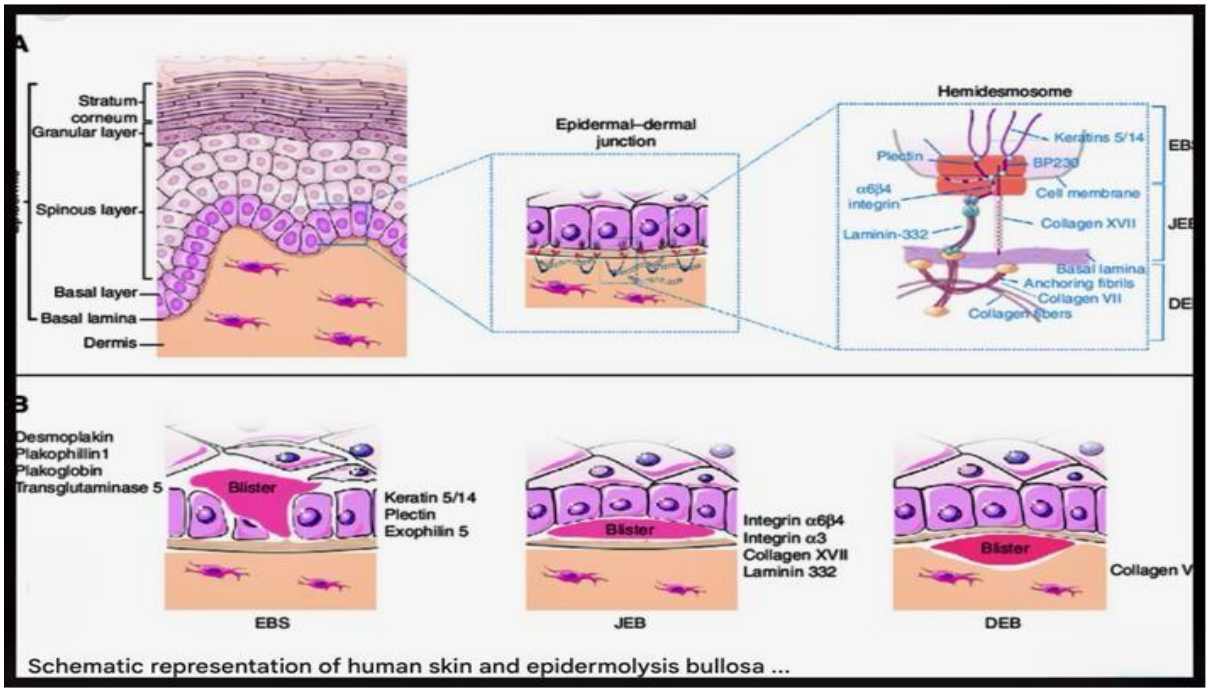

Figure 1:

Genetic and Molecular Basis

EB results from mutations in at least 16 genes. Key genes include:

Table 2: Genetic Mutations Associated with Epidermolysis Bullosa.

Gene	Protein Affected	EB Type(s) Affected
KRT5	Keratin 5	EB Simplex [3]
KRT14	Keratin 14	EB Simplex [3]
LAMA3	Laminin 332	Junctional EB [4]
COL7A1	Collagen VII	Dystrophic EB [5]
ITGB4	Integrin Beta 4	Junctional EB [4]
COL17A1	Collagen XVII	Junctional EB [4]
FERMT1	Kindlin-1	Kindler Syndrome [6]
PLEC	Plectin	EB Simplex, Junctional EB [7]
LAMB3	Laminin Beta 3	Junctional EB [4]
LAMC2	Laminin Gamma 2	Junctional EB [4]

Laboratory and Imaging Studies

Laboratory tests monitor complications like anemia and infection. Imaging, including endoscopy, assesses esophageal involvement and strictures in severe mucosal disease [16].

Natural History and Prognosis

The natural history varies by subtype:

- EBS: Mild with normal life expectancy.
- JEB: Life-threatening in infancy, especially Herlitz subtype.
- DEB: Chronic blistering, scarring, increased carcinoma risk. (Photo 3)
- Kindler Syndrome: Progressive photosensitivity and poikiloderma [17].

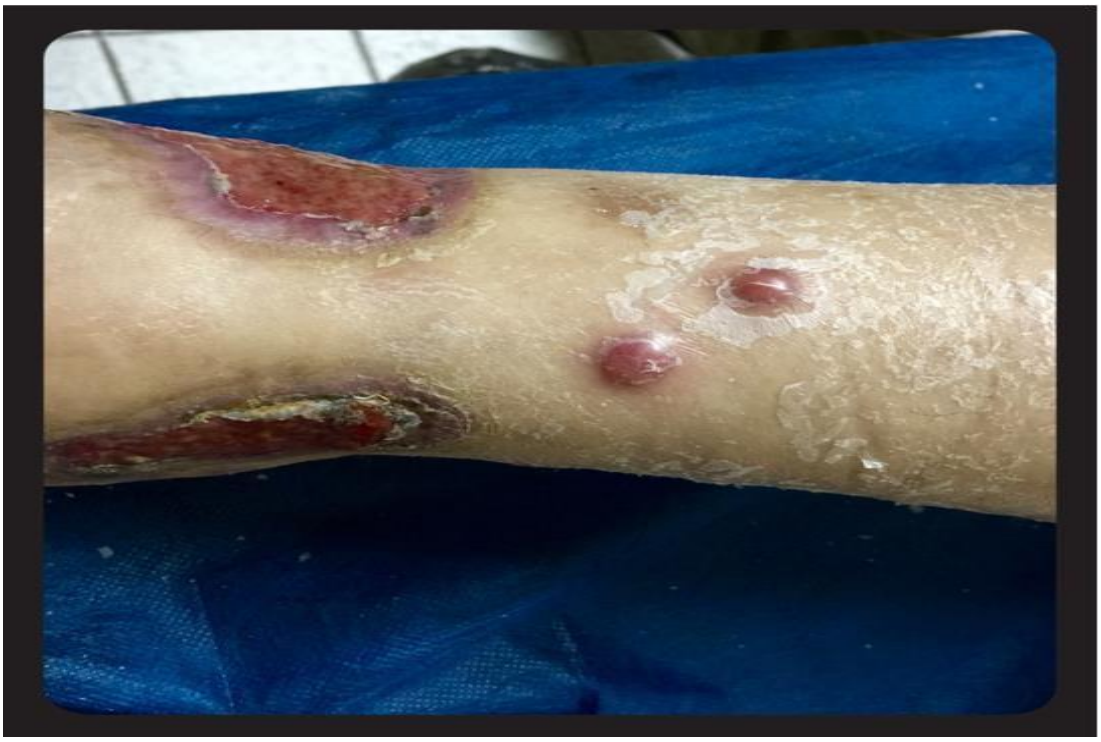

Photo 3: E. B. and two basal cell carcinomas (Coutersy, Adrian Hunis MD)

Association with Skin Carcinomas

Severe EB forms, particularly recessive DEB, have a significantly increased risk of squamous cell carcinoma due to chronic inflammation and scarring (Photo 3) [18].

Pretumoral Nature

EB is considered a pre-tumoralcondition due to the high risk of malignant transformation. Regular surveillance and early intervention are critical [19].

Current and Emerging Treatments

Management focuses on:

- Wound Care: To promote healing and prevent infection.
- Pain Management: Using topical and systemic analgesics.
- Nutritional Support: To address growth challenges.
- Emerging Therapies: Gene therapy, protein replacement, and cell-based therapies. Clinical trials are ongoing [20].

CONCLUSIONS

Epidermolysis Bullosa remains a complex condition with significant morbidity. Advances in molecular genetics and emerging therapies offer hope for improved outcomes. Ongoing research and international collaboration are essential for developing effective treatments and enhancing patient quality of life.

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