Oral-clinical findings and management of epidermolysis bullosa

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Epidermolysis bullosa (EB) is a diverse group of disorders that have as a common feature blister formation with tissue occuring at variable depths in the skin and/or mucosa. This article reports two cases of EB and review oral- clinical findings of the EB types and approaches for managing the oral- clinical manifestations. While systemic treatment remains primarily palliative, it is possible to prevent destruction and subsequent loss of the dentition through appropriate interventions and dental therapy.
J Clin Pediatr Dent 30(1): 59-66, 2005

INTRODUCTION

Epidermolysis Bullosa (EB) consists of a group of rare skin-related diseases which are acquired or genetically transmitted as autosomal dominant and recessive traits.[1] It is a multiracial disorder that is characterized by the formation of vesicles and bullae on the skin and mucous membranes. The vesicles may arise spontaneously or from minor trauma. In some varieties of EB, high room temperature may precipitate blisters.[2]

While the specific pathogenesis of these disorders remains unknown bullae formation has been associated with numerous basic defects including structural and/or biochemical abnormalities of keratin, hemidesmosomes, anchoring fibrils, anchoring filaments and physicochemically altered skin collagenase.[3-10]

More recently, molecular genetics studies have shown a variety of defects in different EB types. The genetic defects in the Weber-Cockayne, Koebner and Dowling Meara EB simplex subtypes are linked to defects of keratins 5 and 14.[4,10,11] Dominant dystrophic EB shows linkage to the type VII collagen gene located on chromosome 3.[12] Specific gene defects have not, however, as yet been identified for other major EB forms including recessive dystrophic and junctional EB (Table I).

Distinct types of EB have been identified, each of which is classified in to three major subgroups based on the level of tissue cleavage following mechanical trauma to the skin:

Epidermolytic (Simplex EB)
Lamina lucidolytic (Junctional EB)
Dermolytic (Dystrophic EB) (Table I).[6,7,13-15]

EB subtypes are further defined based on mode of inheritance, ultrastructural and phenotypic features and the expression of specific basement membrane antigens.[6,7,13,14,15]

During the 1980's, The National Institute of Health established four regional institutional centers that were designated as clinical sites for the National Epidermolysis Bullosa Registry (NEBR). These centers were charged on new developments, research and understanding the clinical, diagnostic and laboratory characteristics of EB. As a results of these and other investigations, knowledge concerning the different characteristics and oral manifestations of the 23 different EB subtypes has increased markedly[6] (Table II and III).

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Table I. Ultrastructural site of tissue separation and common morphologic features of the major EB types. [6, 13, 14, 15]

Major EB Type	Site of Tissue Separation	Common Morphologic Features of Tissue
EB Simplex	Within or just above the stratum basalis ("epidermolytic")	Cytolysis of basilar or suprabasilar keratinocytes
Junctional EB	Within dermoepidermal junction (intralamina lucida, "lamina lucidolytic")	Absence of or rudimentary appearing hemidesmosomes Reduced or absent subbasal dense plates
Dystrophic EB	Beneath the entire dermo-epidermal junction (sublamina densa; "dermolytic")	Reduced numbers of or absent anchoring fibrils

In this manuscript we will present two cases of EB and review oral- clinical findings of the different EB types and approaches for managing the oral- clinical manifestations.

CASE REPORT 1

A boy was born October 10, 1993. The first diagnosis of recessive dystrophic EB was determined through a skin biopsy at Istanbul University Faculty of Medicine in Department of Dermatology. There was no family history of EB. He had numerous blisterings on his hands, ears, knees, elbows, feet, trunk, scalp, face and anus following minor trauma (Figure 1, 2, 3).

At the age of 6 years, he was operated as he developed digital webbing with mitten-type deformities of his hands from continuous blistering and scarring.

The patient was bathed daily and patted dry to prevent trauma. An antibacterial ointment was used on the lesions and gauze wrapped around the affected areas.

Table II. Clinical findings of inherited epidermolysis bullosa variant.[6]

EB Type	Subtype	Inheritance	Age of Onset	Distribution	Scarring	Medical Fragility	Retardation
Simplex	Localized (Weber-Cockayne)	AD	0-4 yr	Palms/Soles	Rare	Rare	Absent
	Generalized (Koebner)	AD	0-2 yr	Extremities > elsewhere	Rare	Rare	Absent
	Herpetiformis (Dowling-Meara)	AD	Birth	Generalized	Variable	Variable	May be delayed
	Localized with Hypodontia (Kallin)	AR	3mo-1 yr	Hands/feet	Absent	?	Absent
Junctional	Generalized (Herlitz;Gravis)	AR	Birth	Generalized	Common	Moderate or severe	Severe
	Generalized (Mitis; Non-Herlitz)	AR	Birth	Generalized	Common but focal	Moderate	Absent or mild
	Localized (Minimus)	AR	Birth	Hands,feet, pretibial	Absent	Absent	Absent
Dystrophic	Generalized (Pasini; Cockayne-Touraine)	AD	Birth	Generalized	Common	Variable	Absent
	Localized (Minimus)	AD	Early childhood	Acral	Absent	?	Absent
	Generalized (Gravis; Hallopeau-Siemens)	AR	Birth	Generalized	Common	Severe	Severe
	Generalized (Mitis)	AR	Birth	Generalized	Present	Moderate	Absent

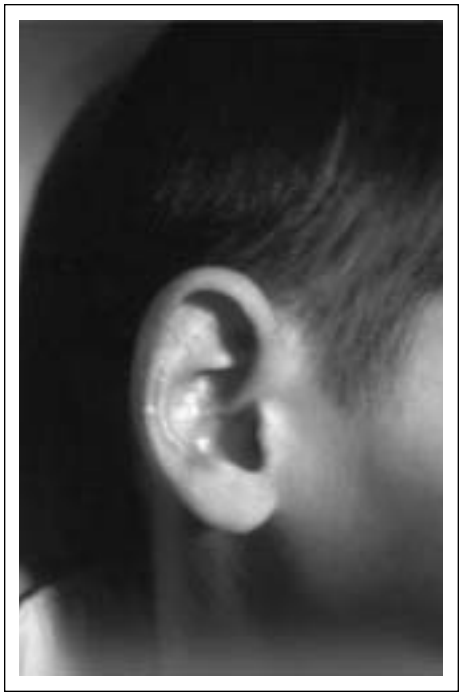

Figure 1. Blistering and scarring on ear in this 10 year-old with recessive dystrophic EB.

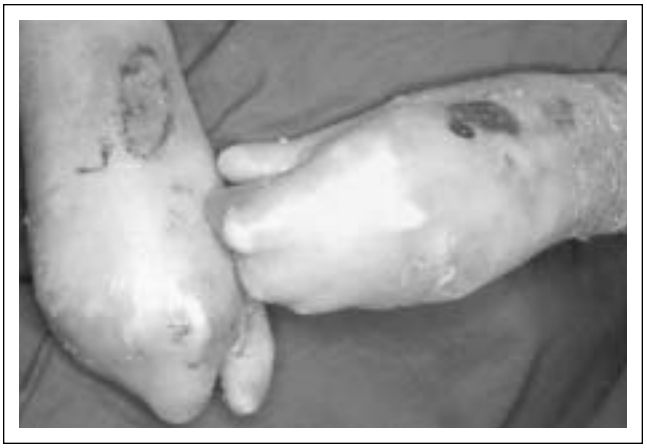

Figure 2. Severe mitten-hand deformities result from the continual process of blistering and scarring around the digits.

Intraorally, lesions can be found at any site. White lesions of various size were seen on the tongue, gingiva and buccal mucosa. Because of the repeated scarring with subsequent contracture, he presented vestibular obliteration of the palatal rugae, lingual papillae and microstomia. Intraorally, we observed rampant dental caries, especially in the anterior teeth (Figures 4,5).

He showed eating difficulties from severe blistering. He also presented serious problems with tooth-

Table III. Oral manifestations of inherited EB subtypes6.

EB Type	Subtype	Mucosal Erosions	Oral Scarring	Ankyloglossia	Microstomia	Enamel Hypoplasia	Hypodontia anodontia	Rampant caries
Simplex	Localized (Weber-Cockayne)	Occasional	Absent	Absent	Absent	Absent	Absent	Absent
	Generalized (Koebner)	Occasional	Absent	Absent	Absent	Absent	Absent	Absent
	Herpetiformis (Dowling-Meara)	Common	Absent	Absent	Absent	Absent	Reported	Absent
	Localized with Hypodontia (Kallin)	Present?	Absent	Absent	Absent	Absent	Present	Absent
Junctional	Generalized (Herlitz; Gravis)	Common	Mild/ Variable	Absent/ Mild	Moderate	Severe	Absent	Severe
	Generalized (Mitis; Non-Herlitz)	Common	Absent/ Mild	Absent/ Mild	Absent	Moderate/ Severe	Absent	Moderate
	Localized (Minimus	Common	Absent	Absent	Absent	Mild/ Moderate	Absent	?
Dystrophic	Generalized (Cockayne-Touraine)	Mild/ Moderate	Absent	Absent	Absent	Absent	Absent	Absent
	Generalized (Gravis& Pasini Hallopeau-Siemens)	Severe	Severe	Severe	Severe	Absent	Absent	Severe

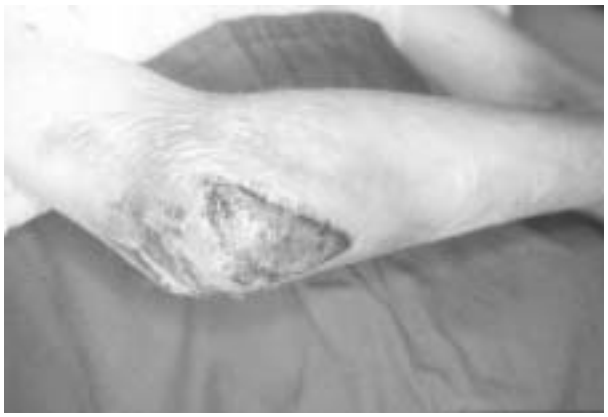

Figure 3. Blistering, scarring and erosions are seen on elbow in this 10 year-old with recessive dystrophic EB.

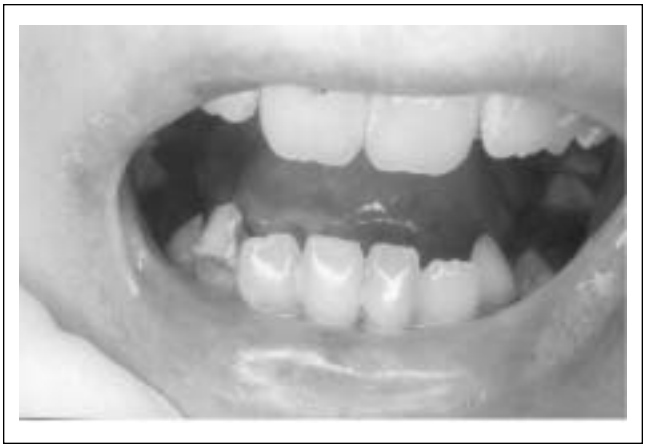

Figure 4. Severe generalized recessive dystrophic EB has lost all the papillae on the tongue which is ankylosed . Microstomia and rampant dental caries are clearly evident.

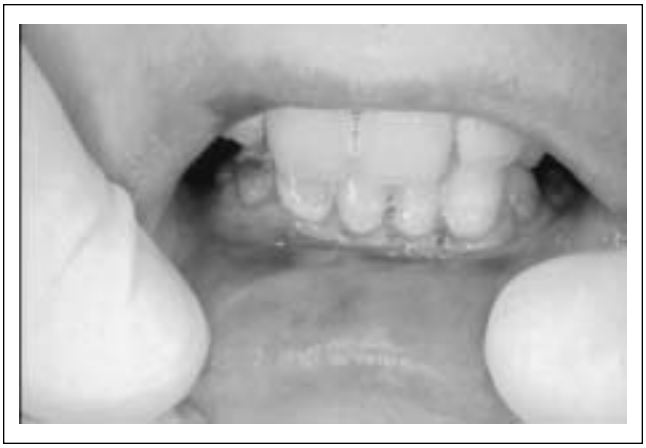

Figure 5. Rampant dental caries and vestibular obliteration are seen in this 10 year-old with recessive dystrophic EB.

brushing due to his insufficient manipulation ability and oral discomfort caused by the painful lesions.

CASE REPORT 2

A boy was born March, 2003. The first diagnosis of recessive dystrophic EB was determined through a skin biopsy at Marmara University Faculty of Medicine in Department of Dermatology. There was no family history of EB and his sister was healthy. Lesions were found on the hands, feet, ear, nails, face (Figure 6, 7, 8).

Intraorally, we observed blistering on lips, palate and tongue. At 3 month, his first primary tooth erupted, producing blisters on the palate mucosa and limiting feeding from repeated scarring (Figure 9). We beveled his erupted tooth to prevent greater traumatic effects on mucosa.

CLINICAL FINDINGS

Cutaneous findings vary considerably and may include blisters, crusted erosions, milia, scarring, granulation tissue, pigmentation changes, cicatricial alopecia, and absence or dystrophy of nails.[4] Extracutaneous involvement may include eyes, teeth, oral mucosa, oesophagus, intestinal tract, anus, genitourinary tract, and/or mucoloskeletal system. Extracutaneous involvement can be so severe that it significantly alters an individual's lifestyle.[16]

EB Simplex is the least serious form of the disease. In simplex EB, blister formation occurs within basal keratinocytes due to mutations in the keratin 5 and 14 genes. In most patients, blisters are mild and do not scar after they heal. Some forms of EB simplex affect just the hands and feet (Simplex localized with hypodontia "Kallin"), other forms of EB, simplex can lead to more widespread blistering, as well as hair loss and missing teeth (Simplex herpetiformis "Dowlıng-Meara"). Recurrent blistering is annoying but not life threatening.[1,6,7]

The second form of EB, Junctional EB, blisters arise within the lamina lucida of the basement membrane and several mutations have been described in the 3 genes that encode the anchoring filament protein lamin 5. In most patients it does not lead to scarring. However, skin an the areas prone to blistering, such as the elbows and knees, often shrinks. In one variation of junctional EB, called Gravis Junctional EB of Herlitz, the blistering can be so severe that affected infants may not survive due to massive infection and dehydration.[1,6,7]

The third form of EB, Dystrophic EB causes blisters to form on the superficial papillary dermis as a consequence of mutations in the type VII collagen gene. It varies greatly in terms of severity, but more typically affects the arm and legs. In one variation, called Hallopeau-Siemens EB, repeated blistering and scarring of the hands and feet causes the fingers and toes to fuse, leaving them mitten-like and dysfunctional. The disease is also observed at birth or shortly after.[1,6,7]

Figure 6. Scars, blisters and erosions are seen on his hands and nails with recessive dystrophic EB.

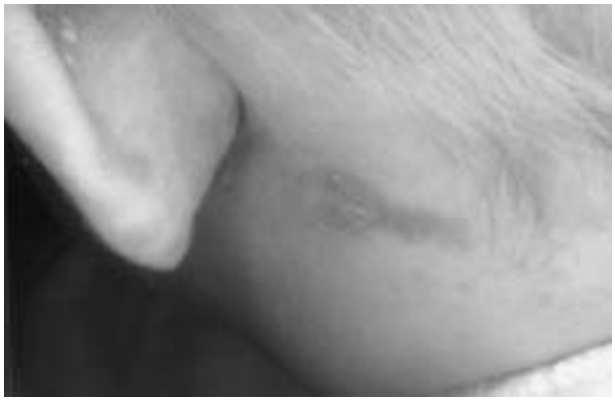

Figure 7. Scarring on ear and retroauricular region in this 10 month-old with recessive dystrophic EB.

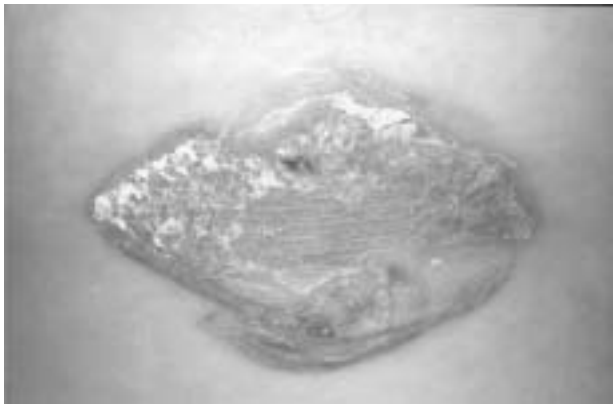

Figure 8. Scarring on the breast in this 10 moth-old recessive dystrophic EB.

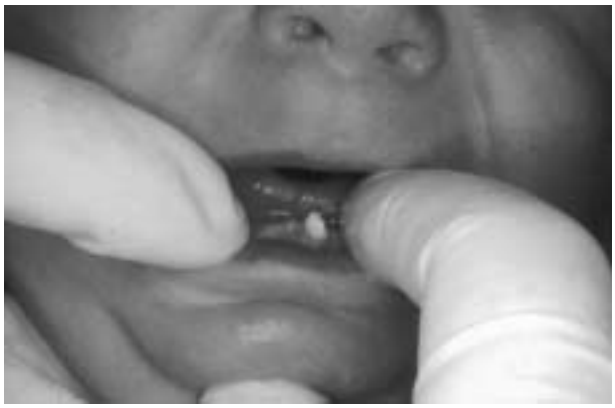

Figure 9. Blistering on the tongue result from the eruption of his first tooth.

ORAL FINDINGS

Oral manifestations of EB vary in frequency and severity. The lesions may range from small discrete vesicles to large bullae that rupture leaving denuded, eroded areas. These lesions may appear at any site in the oral cavity for the different EB categories or subtypes. Table III reviews the predominant oral features of the major EB subtypes.[6] In addition to blister formation, scarring, microstomia, and the tendency for oral malignant transformations are all possible manifestations of EB. Occasionally, oral manifestations may precede those of the skin[2].

Dental involvement also varies according to different subtypes. In the simplex form, the teeth are not affected, however, the dystrophic forms often display malformed teeth with early caries development. The enamel changes observed resemble those seen in amelogenesis imperfecta.[17] Because of the repeated scarring with subsequent contracture, the patients with recessive dystrophic forms will exhibit vestibular obliteration of the palatal rugae and lingual papillae and microstomia. Continuous oral blistering may produce tissue changes with malignant potential. Carcinomas are often associated with the generalized recessive dystrophic form.[2,18,19]

Rampant dental caries is frequently seen in patients with severe generalized recessive dystrophic EB despite appearing to have normal dentition development.[20] It has been hypothesized that excessive dental caries is a result of the presence and severity of the soft tissue involvement, which leads to alterations in the diet (soft and frequently high carbohydrate consumption), increase oral clearance time (secondary to limited tongue mobility and vestibular constriction), and creates an abnormal tooth/soft tissue relationship (buccal and lingual mucosa) which is firmly positioned against the tooth.[21]

Examination of salivary flow rates and salivary antibody titres in a large EB population indicates there is no diminution in salivary function that predisposes these individuals to dental caries.[22]

CLINICAL MANAGEMENT

There are no known cures and most systemic therapeutic approaches have proved to be ineffective.

Eroded skin surfaces are best covered with nonadherent dressings after applying a topical antibiotic such as bacitracin or mupirocin.[23] Oral nutritional supplements including iron and zinc may be partially beneficial in managing individuals suffering from anemia and liquid preparations high in protein and broths may help patients with growth retardation.[24,25]

Nutritional counseling should stress the control of refined carbohydrate consumption since individuals with severely affected oral mucosa and oesophageal structures usually consume soft and pureed foods high in calories.[8]

Surgical intervention helps to correct mitten deformities and digit webbing.[26]

ORAL MANAGEMENT

Dental rehabilitation and anesthetic management of EB patients are dependent on the specific manifestations and type of the disease.[27] The goal of dental therapy is preservation of the dentition.[28]

Extraction and surgical intervention have been the treatment of choice, especially in the more severe cases, because of the fragility of the oral mucosa, presence of bullae, microstomia, extensive caries and periodontal breakdown.[18]

Comprehensive dental care for pre-cooperative children and for patients with severe soft tissue involvement are best managed with general anesthesia.[29,30]

When administering intraoral local anesthesia, the anesthetic solution should be injected deeply in to the tissues slowly enough to prevent tissue distortion, which may cause mechanical tissue separation and blistering.[31]

Clinicians have approached anesthetic management with great caution; their concern is the possibility of developing airway obstruction due to blister formation and tissue damage. Anesthetic management for dental care has therefore varied greatly and included such techniques as IV ketamine, insufflation and orotracheal and nasotracheal intubations.[32,33]

During these procedures, every precaution is taken to protect the skin and oral mucosa from trauma. Pre-operative and post operative antibiotic therapy is used to prevent infection of the bullae.[2] A dietitian should be consulted due to the presence of severe oral and oesophageal involvement.[31,34]

Heavily flavored or alcohol-based fluoride rinses and topical applications are often not well accepted in patients with substantial oral involvement.[31]

Neutral sodium fluoride topical applications and nonalcohol based rinses may prove to be effective.[34]

In patients prone to oral blistering oral hygiene may best be accomplished with a soft-bristled, small-headed toothbrush. Chlorhexidine mouth rinses may also help control dental caries.[21,31]

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Oral-clinical findings and management of epidermolysis bullosa: