EPIDERMOLYSIS BULLOSA

Definition

Epidermolysis bullosa (EB) is a term used to describe a group of rare mainly hereditary, chronic, non-inflammatory diseases of skin and mucous membranes. EB is characterized by the development of bullae (blisters) as a result of mild to moderate trauma. Bullae easily break, causing ulcerative lesions which usually heal with atrophic scarring.

The inheritance may be either autosomal dominant or recessive but there is also an acquired form. The hereditary types of epidermolysis bullosa have their onset at or within a few weeks of birth, can affect all populations and racial groups and there is no apparent predilection for males or females.

EB is classified into three main types (simplex, dystrophic and junctional) and at least 23 subtypes. The classification is based upon mode of inheritance, anatomic location and distribution of lesions and associated morbidity. There is also a rare acquired form of disease. Ten distinct genes encoding key molecular components of hemidesmosome anchoring complex and associated keratin filament network are recognized as underlying the three major forms of EB, and several sub-types of Epidermolysis Bullosa Simplex.

Epıdermolysıs Bullosa Sımplex

Epidermolysis Bullosa Simplex (EBS) is usually autosomal dominant, but in some cases it can be autosomal recessive. The cleavage through basal keratinocytes, which is special for EBS, is caused by mutations of genes encoding keratins 5 and 14 and plectin. EBS is characterized by lysis of basal keratinocytes, leading to the formation of intraepidermal blisters. Mainly the suprabasal layers are not disturbed, so the terminal differentiation is normal. Vesicles and bullae usually form secondary to minor trauma, friction sweating or increased body temperature. Lesions typically heal without scaring. EBS presents most commonly in early infancy, and although usually not life threatening, sometimes can be fatal.

There are 3 major subtypes of EBS:

Dowling-Meara EBS

Weber-Cockayne EBS

Köbner EBS

Dowling-Meara Epidermolysis Bullosa (EBS-DM), is not usually immediately life-threatening, but is the most severe form of EBS and it can be fatal during infancy usually because of sepsis. Extreme blistering of the skin and mucous membranes is herpetiform with marginal spreading. Other features may include nail dystrophy, milia formation and progressive palmar-plantar hyperkeratosis.

Weber-Cockayne Epidermolysis Bullosa (EBS-WC) is the mildest and the most common form of EBS. Blistering usually begins between infancy and early childhood; but in rare cases it appears

during adolescence. Blistering is primarily restricted to the hands and feet, while oral involvement is uncommon.

Köbner Epidermolysis Bullosa is seasonal milder blistering of the palms and soles, and at other sites of friction.

Dystrophıc Epıdermolysıs Bullosa

Dystropic Epıdermolysıs Bullosa (DEB) is associated with mutations in the genes encoding type VII collagen. DEB has two subtypes - *recessive epidermolysis bullosa* and *dominant epidermolysis bullosa.* The incidence of recessive DEB is approximately 1 in 300.000 births and dominant DEB 1 in 50.000.

The recessive dystrophic subtype of EB with generalized involvement is a dermatological condition producing serious mucosal lesions with sub-lamina dura separation, due to blistering below the lamina densa of basement membrane zone. There are widespread blisters involving skin and mucosa, that heal with scarring, causing dysphagia, oesophageal strictures and ocular lesions. The lesions tend to heal with fibrosis. Macroscopically, the oral mucosa, including palate and gingiva, appears smooth, erythematous and edematous. Normal growth can be a problem in children with recessive DEB, mainly because of feeding difficulties. Children with recessive DEB can show retarded skeletal growth and development affecting also the cranio-facial bones, while teeth are relatively unaffected, although the reduced jaw size can lead to severe anterior crowding.

Junctıonal Epıdermolysıs Bullosa

The junctionalis form of EB (EBJ) is characterized by separation within the basement membrane. EBJ has been linked with mutations in genes encoding for laminin 5 (alternatively known as nicein or kalinin), $\alpha_6\beta_4$-integrin and type XVII collagen. Almost all patients with EBJ present with enamel defects (including pitting, furrowing and hypoplasia), whereas the prevalance of defects in simplex and dystrophic types is similar to that of control population (~27%).

Epıdermolysıs Bullosa Acquısıta

Epidermolysis bullosa acquisita (EBA) is an acquired chronic subepidermal blistering disease that occurs primarily in adults, though an increasing number of childhood EBA has been reported over the last few years.

The aetiology of EBA is unknown, but evidence suggests the presence of autoantibodies to type VII collagen, localized to anchoring fibrils within the dermoepidermal junction of skin. Patients with EBA have IgG deposits within the dermal-epidermal junction of their skin.

EBA has two variants - *mechanobullous* and *inflammatory.* The mechanobullous variant, or *classical* EBA, is characterized by skin fragility, blisters and erosions localized to mechanically stressed surfaces, which heal with scarring and milia formation. Inflammatory variants mimic cicatricial pemphigoid, bullous pemphigoid or linear IgA disease.

Clinically, the oral lesions of EBA are similar to those seen in hereditary EBD. The most characteristic feature is soft tissue fragility with subsequent development of blistering. Blisters,

erosions, ulcerations and scarring have been described on buccal mucosa, tongue, gingival, palate and lips and it has been suggested that either perioral or intraoral blistering can lead to microstomia, ankyloglossia, scar formation and obliteration of the oral vestibular area. Patients usually have erosions and scars of the mouth, conjunctiva, upper oeosophagus, anus and urogenital tract.
The presence of scars secondary to blistering is a major diagnostic feature to distinguish EBA from bullous pemphigoid

Clınıcal presentations of EB

Bullae can be initiated on skin or mucous membranes at sites of trauma or pressure (Nikolsky's sign) and on rupturing they leave a painful erosion which heals with scar formation. Bullae can occasionally develop spontaneously. Fingers are destroyed with resorption of phalanges, and hands become unsightly and club-shaped (Fig. 1). This disorder is often associated with extracutaneus complications such as nutritional deficiencies, recurrent infections and motor disabilities. Nutritional problems are the consequence of restricted nutritional intake, chronic constipation and increased whole-body protein turnover, probably caused by chronic non-healing wounds and infections.
Oral mucosal scarring and contracture due to minor trauma such as toothbrushing, can lead to tongue-tie, obliteration of the sulci, limited opening, lingual depapillation and atrophy of the palatal folds (Fig. 3-5). During blistering and subsequent cicatrization, epithelial cells become entrapped and give rise to milium cysts, particularly in the hard palatal mucosa. Areas of leukoplakia and oral squamous cell carcinoma (OSCC) have also been reported, affecting mainly the lingual mucosa.
All three main types of EB produce oral defects. Abnormal enamel development is a common feature, including thin enamel and localized or generalized hypoplasia. Structural abnormalities include fine or coarse pitting defects, or thin or uneven enamel which may also lack prismatic structure. The amelodentinal junction may also be smooth. The mineral and chemical composition of dental enamel in EB however, is no different from normal and does not predispose the teeth to caries, although the prevalance of dental caries is significantly increased in individuals with junctional EB and recessive EB, probably due to lack of oral cleansing. There is no direct relationship between the extent of oral blistering and caries experience. The salivary flow rate has been investigated and no difference found between EB individuals and controls.

Dıagnosıs

The evaluation of any patient suspected of having EB should begin with a detailed history, including mapping of the family pedigree. A typical history includes spontaneous blister formation in areas of frequent trauma from birth or early infancy. Nonmolecular laboratory tests for the diagnosis include transmission electron microscopy (TEM), immunofluorescence antigen mapping

and immunohistochemical staining with EB-specific monoclonal antibodies. With advances in molecular biology, the underlying gene defects and linkage of various forms of EB with certain genes provide a basis for direct mutation detection and indirect linkage analysis in affected families. First-trimester prenatal diagnosis using DNA from chorionic villi and amniotic fluid can provide the diagnosis as early as 10 weeks gestation. Direct methods include Southern blotting and restriction enzyme analysis, allele-specific hybridization and polymerase chain reaction amplification. Indirect methods include DNA polymorphism.

Treatment

There is no specific therapy for EB. Traditionally, treatment has been both supportive and preventive. Common strategies include wound management, nutritional support, infection control and patient education. Topical steroids, and topical antibiotics frequently are used to promote healing and prevent secondary infection of blisters. Oral tetracycline therapy may be beneficial for patients with EBS. Dapsone and low-dose prednisolone appear to be very effective in EBA.
Performing oral hygiene is difficult because of the poor ability to grip and hold a toothbrush. Children with EB should be actively encouraged to use fluoride supplements and 0.2% chlorhexidine gluconate either as a mouth rinse or a spray.
Retention of the teeth by preventive measures is essential as dentures cannot be tolerated or even retained. Patients with EB should be seen on a regular basis to reduce bacterial plaque accumulation. Periodic follow-ups are also necessary due to the potential for malignant transformation.

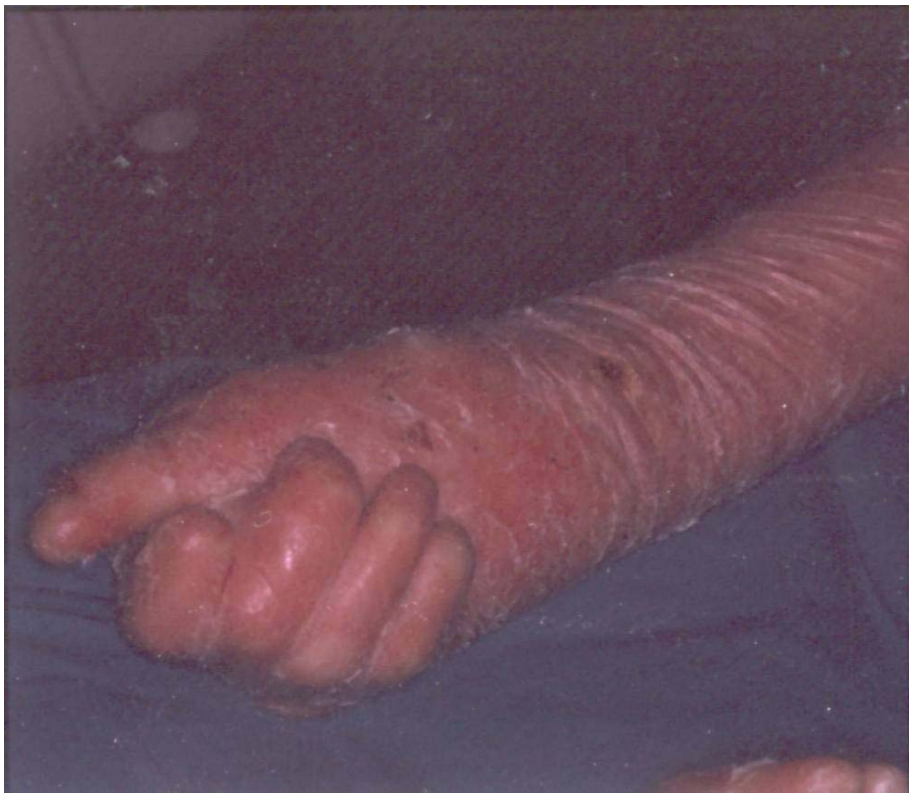

Figure 1. Epidermolysis bullosa. Cutaneous lesions

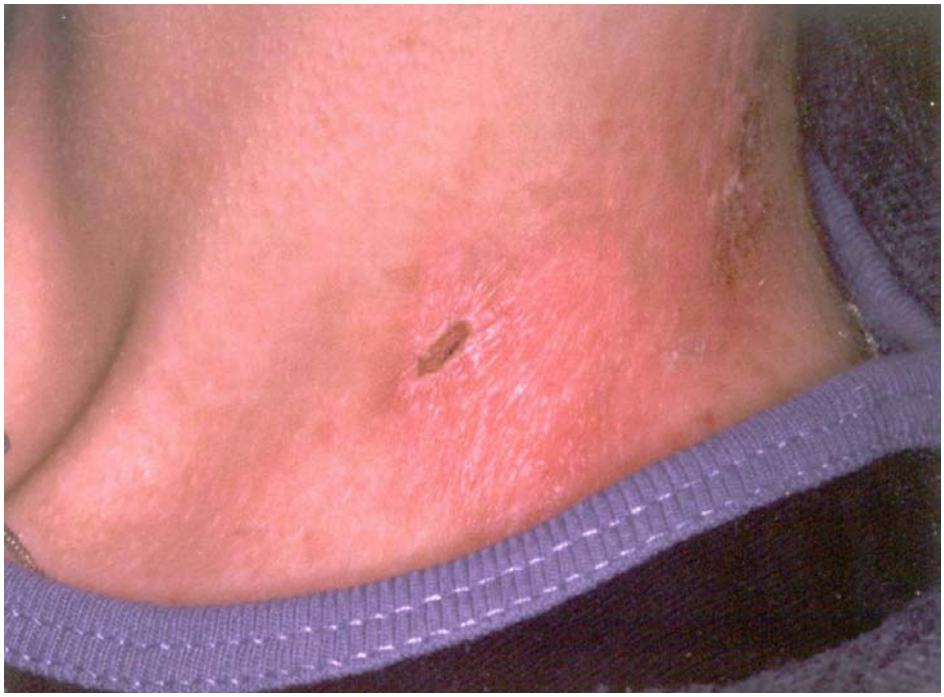

Figure 2. Epidermolysis bullosa. Cutaneous lesions

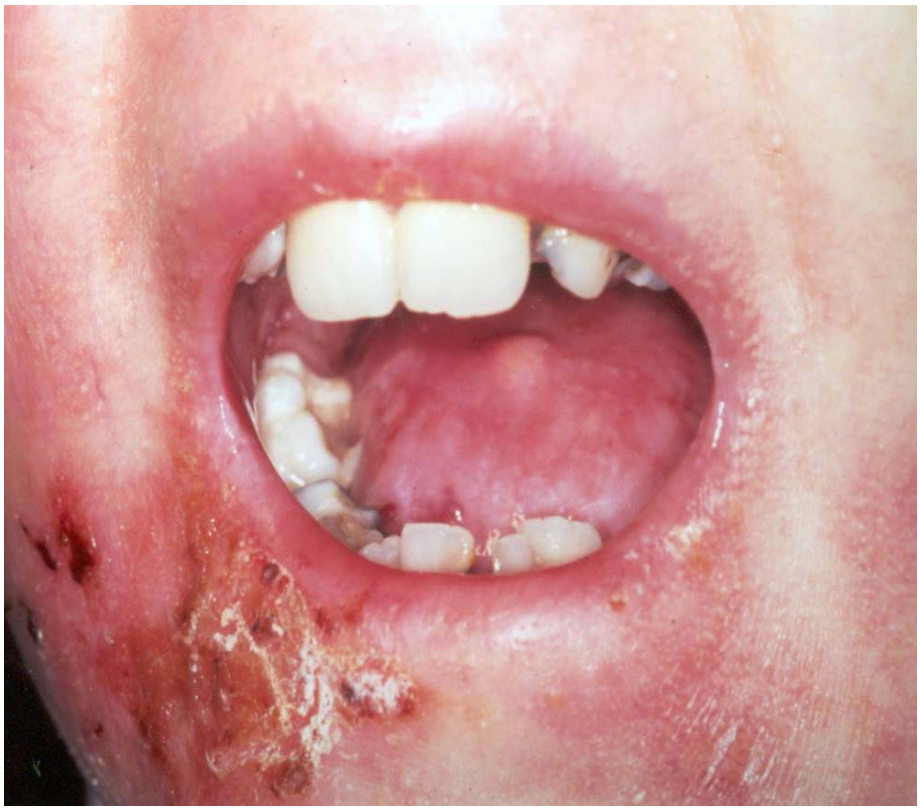

Figure 3. Epidermolysis bullosa. Oral lesions

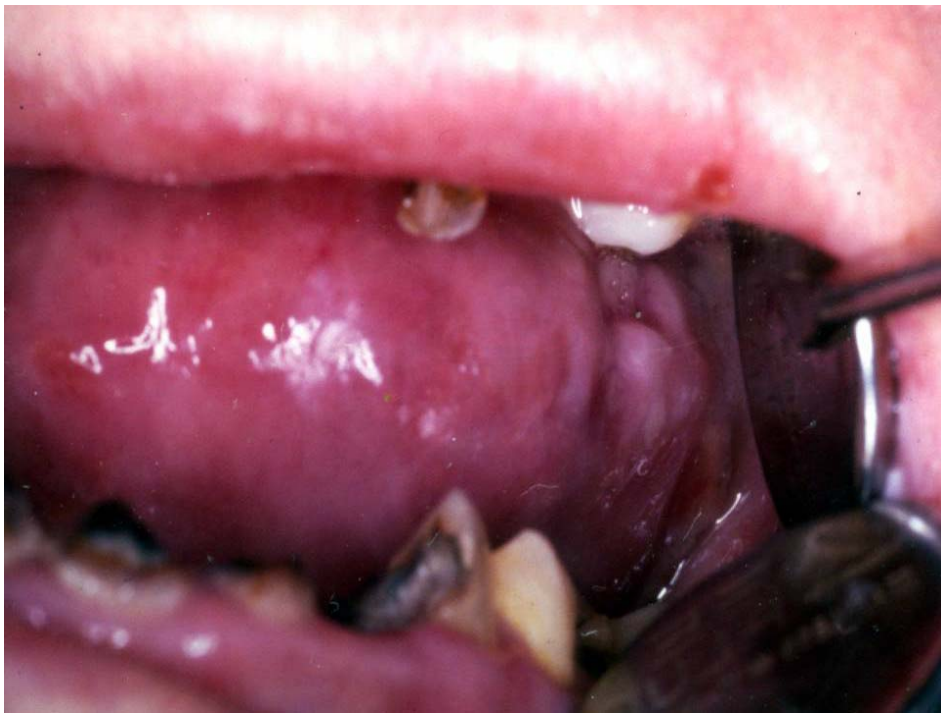

Figure 4. Epidermolysis bullosa. Oral lesions

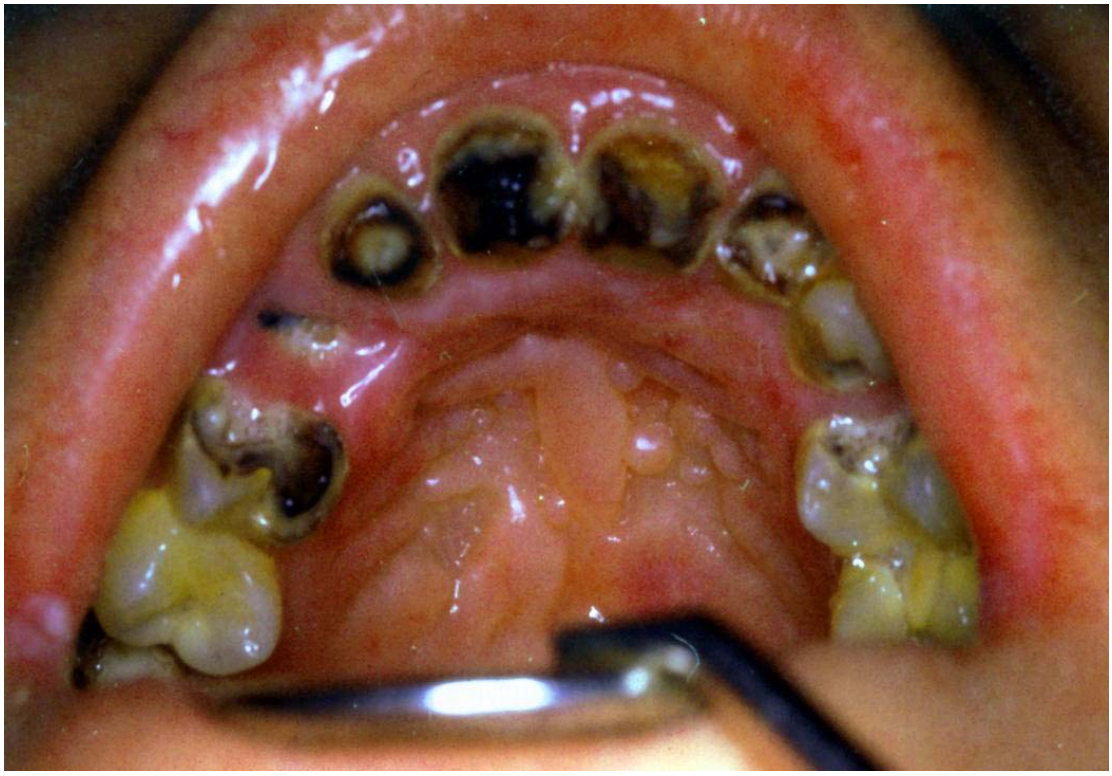

Figure 3. Epidermolysis bullosa. Palatal lesions and neglected mouth

Further reading

1 Das B.B, Sahoo S. Dystrophic Epidermolysis Bullosa. Journal of Perinatology 2004; 24:41-7

2 Shah H, McDonald F, Lucas V, Ashley P, Roberts G. A cephalometric analysis of patients with recessive dystrophic epidermolysis bullosa. Angle Orthod 2002; 72:55-60

3 Horn HM, Tidman MJ. The clinical spectrum of epidermolysis bullosa simplex. British Journal of Dermatology 2000; 142:468-72

4 Okulicz JF, Kihiczak N, Janniger CK. Epidermolysis bullosa simplex. Pediatric Dermatology 2002; 70:19-21

5 Retief CR, Malkinson FD, Pearson RW. Two familial cases of epidermolysis bullosa simplex successfully treated with tetracycline. Arch dermatol. 1999; 135:997-8