Epidermolysis bullosa. A mucocutaneous disease

Epidermólisis ampollosa. Una enfermedad mucocutánea

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ABSTRACT

Epidermolysis bullosa corresponds to a term that encompasses a group of rare genodermatoses characterized by mechanical fragility of the skin and mucous membranes. It is characterized by the appearance of blisters and, subsecuently, erosions, scabs and scars on the skin and mucous membranes following minimal trauma. Stomatological manifestations are the most frequent after dermatological ones. Therefore, knowledge of its manifestations at both levels is essential to provide adequate treatment and follow-up. In this article, we report the findings described in the literature to date regarding the oral or stomatological manifestations in patients with epidermolysis bullosa, as well as the currently recommended interventions for their treatment and follow-up.

KEYWORDS: *epidermolysis bullosa, oral manifestations, blisters, dystrophic epidermolysis bullosa, junctional epidermolysis bullosa.*

RESUMEN

La epidermólisis ampollosa corresponde a un término que engloba un grupo raro de genodermatosis caracterizadas por una fragilidad mecánica de la piel y las mucosas. Se manifiesta por la aparición de ampollas y subsecuentes erosiones, costras y cicatrices en la piel y las mucosas luego de traumatismos mínimos. Las manifestaciones estomatológicas son las más frecuentes después de las dermatológicas. Por lo tanto, el conocimiento de sus manifestaciones en ambos niveles es esencial para proporcionar un tratamiento y seguimiento adecuados. En este artículo se presentan los hallazgos descritos en la literatura hasta la fecha sobre las manifestaciones orales o estomatológicas en pacientes con epidermólisis ampollosa, así como las intervenciones actualmente recomendadas para su tratamiento y seguimiento.

PALABRAS CLAVE: *epidermólisis ampollosa, manifestaciones orales, ampollas, epidermólisis ampollosa distrófica, epidermólisis ampollosa de unión.*

Introduction

Epidermolysis bullosa (EB) is a term used to classify a group of non-autoimmune genodermatoses characterized by the appearance of mucocutaneous blisters after minor trauma or traction.[1] The aim of this manuscript is to report the oral manifestations associated with EB and to raise awareness among all healthcare professionals involved in the care of these patients. This is intended to facilitate early detection, improve overall quality of life, and enable timely interventions that may prevent subsequent complications.

Epidemiology and pathophysiology

It is a rare disease, with incidence varying depending on the geographical area and subtype of epidermolysis. There have been no differences found between sex or ethnic groups. Generally, it is considered to have an incidence of 20 cases per million live births and a prevalence of 8-11 cases per million.[2]

EB occurs due to mutations in genes encoding structural proteins of the dermoepidermal junction. Those mutations alter adhesion and allow blister formation in both the skin and mucous membranes.[1] There are at least

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40 phenotypes of EB depending on the mutated protein.[3] However, it is divided into four main subtypes depending on the site of involvement:

- Simple epidermolysis bullosa (SEB): affects epidermal proteins and is further subdivided into suprabasal and basal. It is the most common subtype, accounting for around 70% of cases.
- Junctional epidermolysis bullosa (JEB): affects proteins of the dermoepidermal junction in the lamina lucida.
- Dystrophic epidermolysis bullosa (DEB): affects proteins in the upper papillary dermis in the sublamina densa. It can be subdivided in recessive (RDEB) or dominant (DDEB).
- Kindler syndrome (KS): affects more than one area within the basement membrane. It is characterized by the presence of acral blisters, photosensitivity, and poikiloderma.[2]

Oral mucosa also consists of stratified squamous epithelium, although non-keratinized, it possesses extracellular proteins similar to skin epithelium such as laminin 332 in the basement membrane, cellular structural proteins like kindlin 1, transmembrane proteins like collagen type VII in anchoring fibrils of the basement membrane, and collagen type XVII in hemidesmosomes. Thus, mutations leading to defects in such proteins are associated with blisters in both skin and oral mucosa.[4]

As a result, oral involvement is frequent in EB, occurring in 75% of patients, classified as the second in clinical manifestations after the skin.[5]

Oral manifestations

The presentation in the oral mucosa varies depending on the underlying type of EB, encompassing from few vesicles to large blisters with ulcerations and significant dental involvement.[6]

Blisters in simple EB tend to be mild, healing without scarring. Localized junctional EB is characterized by oral blister formation with minimal scarring, while patients with severe or widespread junctional EB may have blisters with extensive erosions and ulcerations of the oral mucosa and a tendency for scarring healing resulting in microstomia.[7]

Dominant dystrophic EB presents minimal oral blisters, but those with recessive dystrophic EB often have blister formation and scarring resulting in limitation of tongue mobility, loss of the vestibular sulcus, and microstomia.[6] This inhibits food and dental plaque removal, predisposing to severe dental caries and complications such as dentoalveolar infections; gingivitis and pulpitis being the most frequent. Patients with recessive dystrophic EB are the most severely affected.[8]

Oral blisters in kindler syndrome tend to decrease with age, but are unique because the junctional epithelium that attaches the gingival tissues (gums) to the dental enamel is defective, and patients experience severe and early-onset periodontal disease, involving progressive loss of alveolar bone and tooth loss if not treated early.[9]

Overall, oral manifestations should be intentionally sought in patients with epidermolysis bullosa including vesicles, blisters, oral mucosal ulceration, loss of the vestibular sulcus, papillary atrophy, microstomia, ankyloglossia, caries, and enamel defects. No alteration of the salivary glands has been demonstrated.[6] As for the site of involvement, gingival mucosa has been reported as the most common site in 80%, followed by buccal mucosa in 73%, lips in 64%, and palatal mucosa in 61%.[6,10,11]

A retrospective study conducted in pediatric patients with EB found that the oral cavity was affected in 75% of patients, with blisters and vesicles being the most frequent lesions in 48.5% (**figure 1**), followed by ulcers in 20%. Dental caries is found in 86.6% of patients and it is mainly due to an increase in food contact time since there is limitation in tongue mobility, loss of the vestibular sulcus, presence of dental pits, and poor oral hygiene to avoid injuring the mucosa.[5] The development of caries is not specific to any type of EB.[12]

Dental calculus has been reported in 80% of patients with EB and it is very similar in all subtypes, which is associated with periodontal disease. It is important to note that the presence of gingival bleeding cannot always be associated with periodontal disease since gingival bleeding may be due to inflammation from the underlying pathology.[13]

Gingivitis and periodontitis are more common in EB patients than in the general population (**figure 2**). They

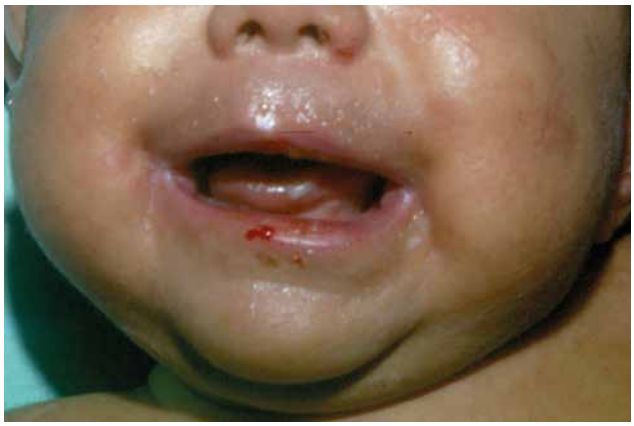

Figure 1. Blister on the tongue.

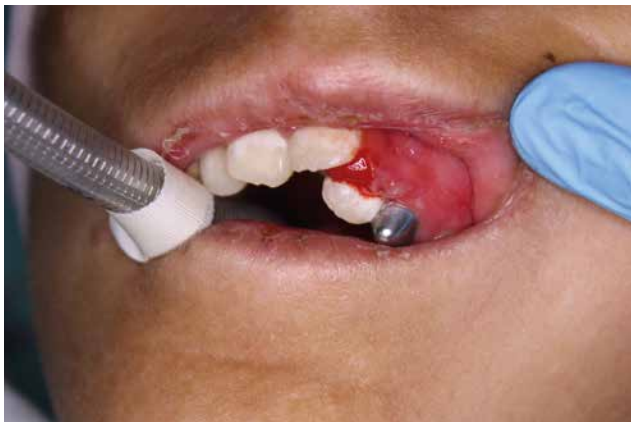

Figure 2. Gingival inflammation.

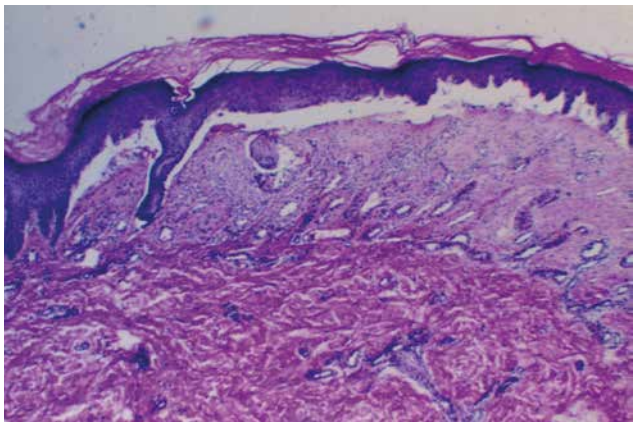

Figure 4. Subepidermal blister in a cutaneous lesion of RDBE.

are infectious and inflammatory diseases characterized by marked inflammation that can lead to progressive destruction of soft and hard tissues supporting the tooth, causing loss of alveolar bone and even tooth loss.[14]

Enamel lesions is reported in 66% of patients with EB.[11] It can range from pits to generalized hypoplasia resulting in a very thin layer of dental enamel[15] (**figure 3**). It is noteworthy to compare by subtypes as Joseph *et al.* distinguished that 75% of patients with UEB had enamel damage compared to 12% in patients with DEB and 8% in SEB.[11]

Dental malocclusion is reported in 75% of patients with EB. It is important an early to prevent recurrent trauma, and furthermore, dental treatment is more difficult later with the onset of microstomia.[16]

Patients with recessive dystrophic EB have been reported to have a higher frequency than the general population of oral mucosal changes suggestive of malignancy, and in most cases correspond to a carcinoma.[17] Isolated cases of trismus have been reported.[18]

Papillary atrophy is reported in only 19% of patients, all of them with DEB. Krämer *et al.* propose this finding as highly suggestive of DEB.[19]

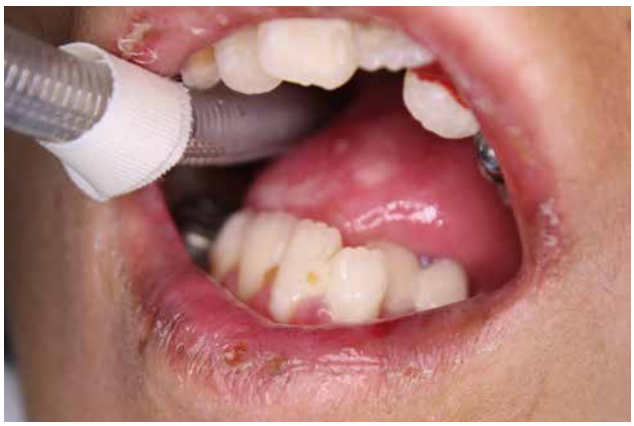

Figure 3. Dental enamel hypoplasia.

Microstomia is a decrease in mouth opening due to the formation of scar bands in the lining mucosa and skin of the lip region, mainly in the lip commissures. Ankyloglossia is a condition in which the lingual frenulum under the tongue is very thick, making its protrusion difficult and causing limited tongue movements.[20] Microstomia and ankyloglossia are mainly found in patients with DEB.[11]

Diagnosis

The clinical diagnosis of the subtype of EB is not simple, so we must rely mainly on complementary studies. Histopathologically, subepidermal blisters can be observed in all types of epidermolysis with minimal inflammation (**figure 4**). Although, in theory, simple EB presents with supraepidermal separation at the basal layer, it may not always be easily distinguishable from other subtypes using this method.[1] Electron microscopy allows visualization of the exact level of involvement, but it is a restricted study for certain centers, mainly research centers. Antigen mapping by immunofluorescence allows the use of antibodies to demonstrate the expression of a structural protein, but is scarce available. Genetic diagnosis, possibly the gold standard, requires complete genetic sequencing to identify the mutation because not all subtypes are associated with a point mutation, although commercially available panels with mutations known to date are already established.[21]

Fortuna *et al.* developed a severity score for oropharyngeal EB (EBOS) that can be used in all patients to establish the severity of oral involvement more objectively and monitor its evolution during subsequent consultations. It should be noted that the score is objective and does not include associated symptoms. Furthermore, it does not include parameters of caries, periodontal disease, or malignancy since it was considered that they are not directly related factors but rather secondary consequences. Up to

this moment, no studies have been conducted to establish the usefulness of this scoring system. In other words, a classification for these scores that could define a need for specific treatment or other recommendations is lacking. Nevertheless, it is a score that can guide the clinician in subsequent evaluations regarding the overall status and progression of oral lesions to decide to implement early therapeutic management.[22]

Treatment

Currently, there is no cure, and treatment is mainly symptomatic focusing on relieving symptoms and preventing complications. However, there are commercially available gene therapies, and multiple other gene, cellular, protein, and oligonucleotide therapies are in development.

Oral rehabilitation depends on the clinical manifestations and type of epidermolysis of the patient. The main objective is the preservation of teeth and preventing oral complications.[23] Treatment may include non-surgical approaches, such as scaling and root planning and antibiotics, or surgical measures such as reduction of the periodontal pocket or soft tissue and bone grafts.[2]

Patients with mild forms do not need major changes from the usual recommended oral hygiene except to be careful not to damage the mucosa.[24] General hygiene is recommended with toothbrushes with soft and short bristles. For caries control, the use of mouth rinses with chlorhexidine can be added, although its effectiveness compared to placebo has not shown substantial changes.[25,26] Some experts recommend the use of fluorides every three months to decrease the risk of caries or periodontal disease.[27] When a blister is found, it should be punctured with a sterile needle to drain its contents and prevent its expansion.[18] In the case of frequent blisters and ulcers, the utility of sucralfate has been reported.[28,29]

Some authors recommend sealing fissures and pits since oral hygiene and other preventive measures can be difficult to perform in those areas. However, some experts prefer to avoid it since the technique is very sensitive and may not be an option for some patients due to lack of cooperation and difficulty in follow-up. Patients with microstomia should perform daily exercises for 30 minutes to improve and maintain the best possible oral opening.[24]

Extractions and surgical interventions are the treatment of choice in the most severe cases (**figure 5**). It should be noted that intraoral local anesthesia can cause tissue damage; it should be injected more deeply to avoid blister formation. Care should be taken in these patients, avoiding the use of suction equipment if possible, and covering the material with rubber and/or petrolatum.

Figure 5. Dental extractions in a patient with RDBE.

Oral rehabilitation under general anesthesia is the preferred method for treatment, especially in patients with severe involvement.[17]

In the anesthetic management, consideration should be given to the limitation of oral opening and cervical flexion. It is recommended that all equipment in the upper airway be lubricated with petrolatum to minimize friction, as well as gauze with petrolatum beneath the anesthesiologist's hands to avoid damaging the skin during mask ventilation. An alternative if available is to use transnasal humidified rapid insufflation ventilatory exchange (THRIVE) with the use of a high-flow nasal oxygen cannula placed over a petrolatum gauze, which reduces the risk of facial trauma due to mask ventilation and prolongs breathing time and safe apnea time during difficult intubation.[17]

Careful fiberoptic-guided intubation by an expert with a well-lubricated small endotracheal tube is the recommended technique to minimize trauma to the airways. Another alternative when mouth opening is sufficient is the use of a laryngeal mask, but it can be complicated by the formation of lingual blisters. It should also be noted that intubating a patient under general anesthesia can complicate the posterior airway after extubation with blister formation. The skin and oral mucosa where the endotracheal tube is fixed and passed should also be protected. For both the endotracheal tube and securing intravenous access, it is recommended to secure with non-adhesive dressing strips or soft silicone tape like Mepitac® and then wrap with self-adhesive wrap or gauze to secure it in place[30] (**figure 6**).

Management is multidisciplinary, and patients require close follow-up by stomatology, dermatology, gastroenterology, nutrition, ophthalmology, and psychology. Dental check-ups are individualized depending on each patient, but generally, it is recommended to attend every three to six months for review.[24]

Conclusions

The stomatological manifestations of EA are very frequent and, in many cases, treatable to prevent later complications.

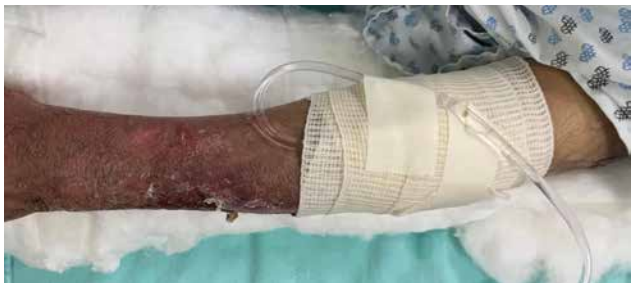

Figure 6. Avoid placing adhesives directly on any part of the skin.

It is necessary to know the basic care that these patients require, provide and instruct parents and other healthcare professionals in their management, and have adequate multidisciplinary follow-up to optimize the quality of life of these patients. The dermatologist plays a key role in referring and promoting the evaluation of these patients.

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