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Case Report / Olgu Sunumu

Oral Manifestations of Dystrophic Epidermolysis Bullosa: Four Case Reports

Distrofik Epidermolizis Büllozanın Oral Bulguları: Dört Vaka Sunumu

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ABSTRACT

Background: This case report aims to contribute to the understanding of oral findings and dental approaches in dystrophic epidermolysis bullosa, a rare hereditary disease.

Cases: We reported four congenital dystrophic epidermolysis bullosa cases from two separate families with clinical and radiographic findings in this case report. Erosive-cicatrized lesions were observed on the skin in all cases. Pseudosyndactyly was present in two cases. In the intraoral examination, reduction in mouth opening, obliteration of the vestibule sulcus, ankyloglossia, and many decayed teeth were observed in all cases. There was no intraoral lesion in two cases, but loss of lingual papillae. Intraoral bullae and erosive lesion formation were observed in two cases.

Conclusions: Dystrophic epidermolysis bullosa is a rare hereditary disease. Lesions are usually seen on the skin, but mucosal involvement is also common. For this reason, dentists should know the oral manifestations of this disease and the dentist's approach in detail.

Keywords: Ankyloglosia; dental caries; dystrophic epidermolysis bullosa; epidermolysis bullosa; microstomia

ÖZ

Amaç: Bu vaka raporu, nadir görülen kalıtsal bir hastalık olan distrofik epidermolizis büllozanın ağız bulguları ve diş hekimliğine yaklaşımı hakkındaki bilgilere katkıda bulunmayı amaçlamaktadır.

Olgu Sunumu: Bu olgu sunumunda iki ayrı aileden dört konjenital distrofik epidermolizis bülloza olgusunu klinik ve radyografik bulgularıyla bildirdik. Tüm vakalarda ciltte eroziv skatrize lezyonlar gözlendi. İki olguda psödosindaktili mevcuttu. Ağız içi muayenede tüm vakalarda ağız açıklığında azalma, vestibül sulkusta obliterasyon, ankiloglossi ve çok sayıda dişte çürük gözlendi. İki olguda ağız içi lezyon yoktu ancak lingual papilla kaybı vardı. İki olguda ağız içi bül ve eroziv lezyon oluşumu gözlendi.

Sonuç: Distrofik epidermolizis bülloza nadir görülen kalıtsal bir hastalıktır. Lezyonlar genellikle deride görülmekle birlikte mukozal tutulum da sıktır. Bu nedenle diş hekimlerinin bu hastalığın ağızdaki belirtilerini ve diş hekiminin yaklaşımını detaylı olarak bilmesi gerekmektedir.

Anahtar Kelimeler: Ankyloglosia; diş çürüğü; distrofik epidermolizis bülloza; epidermolizis bülloza; mikrostomi

Introduction

Epidermolysis bullosa (EB) is a rare hereditary disease that can show autosomal dominant or recessive inheritance.[1] It is characterized by tissue fragility and the formation of bullae following minimal mechanical trauma to the skin and mucosal surfaces[2]. Bullae formation results from mutations in genes encoding proteins in the dermo-epithelial junction structure[3]. These bullae may progress into erosions and non-healing ulcers, and in some cases, lead to scar formation and transformation into squamous cell carcinoma.[2] Four main types and numerous subtypes of EB, caused by mutations in different genes, have been identified. The primary EB types are EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB). EBS is characterized by changes in the basal layer, JEB in the lamina lucida, and DEB in the lamina densa. Among these, EBS is the most prevalent subtype, while DEB rank as the second most common subtype.[4]

DEB, one of the four main EB types, exists in two forms: autosomal dominant and recessive. Clinical findings are typically mild in the autosomal dominant form, with patients generally maintaining good health and normalcy. Skin involvement manifests as hypopigmented papules. In contrast, autosomal recessive DEB represents a life-threatening form marked by extensive scarring, severe mucous membrane involvement, and deformities.[5]

Epidermolysis bullosa (EB) presents a spectrum of skin lesions, encompassing blister formation, erosions, ulcers, cicatrization, alopecia, pigmentation anomalies, nail dystrophy, fusion of limb folds, and limitation of movement due to pseudosyndactyly[3]. Beyond cutaneous manifestations, numerous types of EB entail extracutaneous complications that can lead to morbidity and, in severe cases, mortality. These complications include issues with the oral mucosa, nail dystrophy, gastrointestinal and upper respiratory tract complications, ocular complications, musculoskeletal complications, malnutrition, anemia, growth retardation, delayed puberty, osteopenia/osteoporosis, cardiomyopathy, squamous cell carcinoma, and malignant melanoma. Especially in dystrophic type EB, the risk of squamous cell carcinoma development in areas of chronic cicatrix is high.[6] In EB, lesions are usually seen on the skin, but mucosal involvement is also common. Oral manifestations of EB include vestibule sulcus obliteration, ankyloglossia, microstomia, maxillary atrophy, enamel hypoplasia, extensive caries, susceptibility to candida infections, and squamous cell carcinoma.[3]

There is currently no definitive cure for this devastating disease group, but new therapeutic options are being developed.[2,7] The primary goal of treatment is to alleviate trauma, thereby preventing the formation of new bullae, averting secondary infections, expediting the healing process of wounds, and ensuring adequate nutritional support[8]. Symptomatic treatments include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antihistamines, antibiotics, and phenytoin. The use of topical or systemic corticosteroids has not provided a permanent cure.[3,8] Oral side effects; NSAIDs cause fixed drug eruptions, oral ulceration, aphthous ulceration, pemphigoid-like lesions and erythema multiforme, antihistamines cause dry mouth, antibiotics cause oral candidiasis, ptyalism, black hairy tongue, taste changes, phenytonin causes taste disturbance, gingival hyperplasia, salivary gland swelling, oral ulceration and lichenoid-like reaction.[9] In current approaches, pre-clinical or clinical testing of gene therapies (gene replacement, gene editing, RNA-based therapy, natural gene therapy), cell-based therapies (fibroblasts, bone marrow transplantation, mesenchymal stromal cells, induced pluripotential stem cells), recombinant protein therapies, and small molecule and drug repurposing approaches, have generated new hope for better patient care.[10]

Patients with mild forms of EB usually do not need a special approach to dental treatment. However, these patients should be approached

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with caution due to their susceptibility to oral tissue lesions. Especially in severe forms of EB, it is necessary to minimize soft tissue trauma[4]. Dentist visits should be recommended from the first months of life for patients with EB who are diagnosed early.[11]

We reported four DEB cases from two separate families (case 1 and case 2; case 3 and case 4) in this paper. This case report aims to contribute to the knowledge about the oral findings of epidermolysis bullosa (EB), a rare hereditary disease.

Case Reports

In cases 1 and 2, the findings of two siblings who were referred to the clinic for dental complaints and were diagnosed with congenital DEB in their medical history are presented. It was revealed that the parents and the third child of the family were healthy.

In cases 3 and 4, the findings of two siblings with congenital DEB who were admitted to the clinic for dental reasons are presented. It was revealed that their parents were healthy.

After dental examinations, patients were referred for various dental procedures, including tooth extraction, root canal treatment, dental fillings, periodontal treatment, and prosthetic treatment. They were advised to schedule regular follow-up visits to the dentist after the completion of their dental treatments.

Case 1

A 20-year-old female patient presented to the clinic with dental caries and missing teeth. Extraoral examination revealed erosive lesions and scarred healed wounds on her arms and neck. In the medical history, it was learned that the patient has a congenital diagnosis of DEB. She also stated that she was receiving nutritional support due to malnutrition and was using eye drops for dry eye.

In the intraoral examination, numerous carious lesions and dental calculus were identified. No enamel hypoplasia lesion was detected. Additionally, the patient had the loss of lingual papillae. The patient's mouth opening was measured as 30 mm, and there were signs of obliteration and ankylosis in the vestibular sulcus. The patient was unable to raise and protrude her tongue when it was asked to her. Panoramic radiography showed multiple decayed teeth, bone destruction due to periodontal disease, and tooth loss (**Figure 1**).

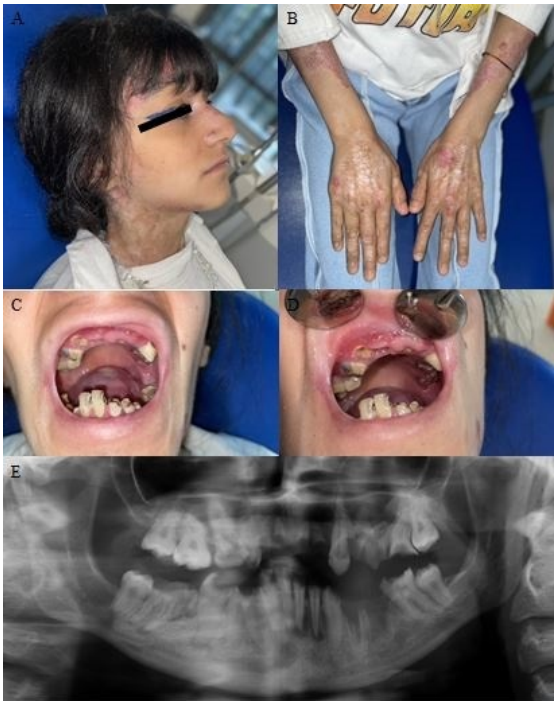

Figure 1. Case 1 (A) Scar lesions on the neck (B) Erosive lesions and scar lesions on the arms, (C) Multiple carious lesions, and loss of lingual papillae, (D) Obliteration of the vestibule sulcus, (E) Multiple carious teeth, bone destruction caused by periodontal disease, and tooth loss on panoramic radiograph.

Case 2

A 17-year-old male patient presented to the clinic with pain in his right upper molar for dental reasons. Extraoral examination revealed erosive lesions on his arms. In medical history, it was learned that the patient had a congenital diagnosis of DEB. He also mentioned receiving nutritional supplements due to malnutrition.

The intraoral examination revealed the presence of multiple carious lesions and dental calculus, but no enamel hypoplasia. Additionally, the loss of lingual papillae and rugae was observed. The patient was noted to have a decreased mouth opening, measured at 20 mm. Signs of obliteration and ankylosis were present in the vestibular sulcus. When the patient was asked to lift his tongue up and bring it to forward, he was unable to perform these functions. His panoramic radiography showed multiple decayed teeth and an impacted supernumerary teeth in the right mandibular premolar region (**Figure 2**).

Figure 2. Case 2 (A) Erosive lesions on the arm, (B) Limitation in mouth opening, (C) Obliteration of the vestibule sulcus, loss of palatal rugae, and multiple caries lesions, (D) Multiple caries lesions and obliteration of the vestibule sulcus, (E) Many caries lesions, along with an impacted supernumerary tooth in the right mandibular premolar region on panoramic radiograph.

Case 3

A 25-year-old female patient presented at the clinic with dental caries. During the extraoral examination, erosive and cicatrizing lesions on the skin and pseudo-syndactyly in her hands were observed. In the medical history, it was discovered that the patient had a congenital diagnosis of DEB. Additionally, the patient mentioned that she was using nutritional supplements due to malnutrition and taking medication for dry eye and asthma.

The intraoral examination revealed multiple carious lesions and dental calculus without enamel hypoplasia. Maxillary atrophy, space stenosis, and dental crowding were also identified. The patient exhibited restricted mouth opening, bullae and erosive lesions on the lips, obliteration of the vestibular sulcus, and ankylosis. When asked to raise and protrude her tongue, she was unable to do these movements. Her panoramic radiography displayed multiple carious teeth with advanced coronal destruction (**Figure 3**).

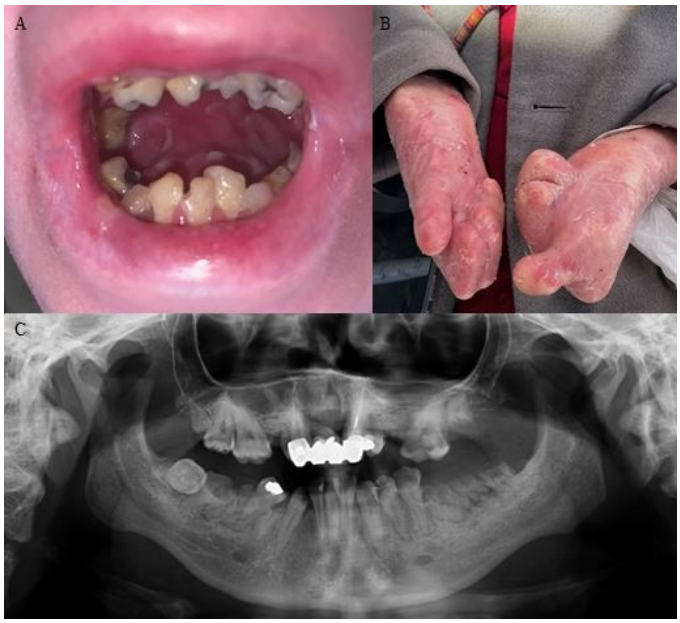

Figure 3. Case 3 (A) Erosive lesions on the lips, bulla on the tongue, multiple carious lesions, limitation in mouth opening, maxillary atrophy, narrowness of space, and crowding, (B) Erosive-cicatrized lesions on the skin and pseudo-syndactyly, (C) A large number of carious lesions, along with multiple carious lesions showing coronal destruction, observed on panoramic radiograph.

Case 4

A 17-year-old female patient presented at the clinic with dental caries and gingival bleeding. During the extraoral examination, erosive and cicatrizing lesions on the skin and pseudo-syndactyly in her hands were observed. In the medical history, it was discovered that the patient had a congenital diagnosis of DEB. She also mentioned using nutritional supplements due to malnutrition and eye drops for dry eye.

Intraoral examination revealed multiple caries lesions and dental calculus deposits as well as bullae and erosive-ulcerated lesions. However, no enamel hypoplasia was detected. The patient exhibited restricted mouth opening with obliteration of the vestibular sulcus and ankylosis. When asked to raise and protrude her tongue, she was unable to perform these functions. Her panoramic radiography displayed multiple decayed teeth and inadequate root canal treatment (**Figure 4**).

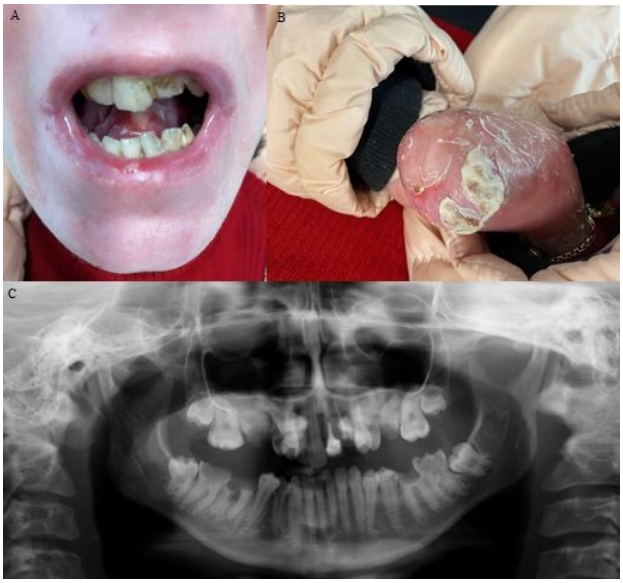

Figure 4. Case 4 (A) Limitation in mouth opening, multiple carious lesions, erosive-ulcerated lesion on the tongue, (B) Erosive-cicatrized lesions on the skin and pseudo-syndactyly, (C) Multiple decayed teeth and inadequate root canal treatment on panoramic radiograph.

Discussion

Systemic and oral manifestations in epidermolysis bullosa (EB) vary according to the subtype. In mild EB subtypes, the patient's life is not significantly affected. Oral findings are generally vesiculobullous lesions that occur occasionally, heal rapidly, and do not leave scarring. However, in severe EB cases, the entire oral mucosa may be affected, leading to scar formation. Microstomia, obliteration of the vestibule sulcus, and ankyloglossia may be observed after scar formation. Patients are fed up with a soft diet and may experience difficulties in oral hygiene. Enamel hypoplasia in patients with the EB subtype may cause a large number of decayed teeth in these patients.[4]

DEB resulting from changes in the lamina densa is the second most common form of EB. It can show autosomal dominant or recessive inheritance. The clinical manifestations are more severe in the recessive form[5]. The main feature of DEB is scarring following blistering, both on the skin and on the mucous membranes.[12] Mutations in genes encoding type VII collagen have been identified in DEB. This collagen is found in the basement membrane region of the oral mucosa and the early stages of tooth formation.[3]

In the dominant form of DEB, the soft tissue lesions in oral manifestations usually include fragile tissues without swelling. In its recessive form, diffuse ulcerations and scarring in soft tissue, microstomia, ankyloglossia, loss of lingual papilla and palatal rugae, and obliteration of the vestibule sulcus are seen. In hard tissue, there is no change in enamel, but the risk of caries is increased due to a soft diet and poor oral hygiene.[4]

Localized bullae occurring in the oral cavity are a common characteristic finding in all types of EB.[13] The frequency and severity of oral manifestations of EB vary according to the type of disease. Mucosal lesions usually include vesiculobullous lesions ranging from small vesicles to large bullae. These lesions can spread to all mucosal surfaces.[3] In our cases, we observed multiple bullae and erosive lesions in the intraoral region in cases 3 and 4. The presence of multiple lesions in the mouth in these patients was one of the reasons affecting the nutritional function of these patients.

Morphologically, ankyloglossia is characterized by a lingual frenulum of varying thickness, extending from the floor of the mouth to the tip of the tongue. Functionally, it is observed that the tongue movements are restricted and the tongue cannot be brought out.[3] Also, it can cause problems such as the inability to remove residues from the tooth surfaces through free movements of the tongue, the inability of the tongue to trigger the development of dental arches, difficulty in swallowing, and speech disorders.[3,14] Ankyloglossia was observed in all cases we presented, and patients reported varying degrees of feeding and speech disorders. The inability to remove debris with tongue function was one of the factors for the high number of caries and calculus in the cases. Patients were informed in detail about the importance of oral hygiene.

Microstomia is a condition in which the mouth opening is reduced as a result of the healing of the lesions in the oral mucosa, the skin around the lips, and the vestibular sulcus by leaving a scar.[13] It is defined as an interincisal distance of less than 40 mm or an interlabial distance of less than 45 mm.[15] Limited mouth opening; causes difficulties in chewing, phonation, and oral hygiene.[3] Due to the formation of intraoral cicatrization, maxillary atrophy is frequently seen, especially in patients with DEB. As a result, severe space narrowing and crowding of the teeth occur.[13] All cases exhibited varying degrees of maxillary atrophy and associated dental crowding. Nevertheless, in cases 3 and 4, maxillary atrophy and associated crowding were more pronounced. Restricted mouth opening was observed in all cases, posing challenges for patients in maintaining oral hygiene and complicating the administration of dental treatments.

Vestibular sulcus obliteration may occur as a result of the healing of lesions, which are usually caused by traumas to the jaw and teeth region at young ages, with cicatrized tissue.[3,16] The presence of the buccal sulcus is necessary not only for prosthetic applications but also for the normal function of the lip.[3] Vestibular sulcus obliteration was evident in all cases we presented. This condition posed challenge for speech problems and difficulties in maintaining oral hygiene. Cases with coronal destruction and missing teeth were referred for fixed prosthesis. Comprehensive information was provided regarding the

significance of preserving existing teeth.

Enamel hypoplasia is a surface defect of the dental crown, result from the disruption of enamel matrix secretion.[3,17] Extracellular matrix proteins such as laminin-332 and collagen-XVII play an important role in proliferation control during epithelial remodelling.[18] In addition, they are effective in ameloblast differentiation and enamel formation. In the case of mutations in the genes encoding these proteins, enamel defects and diffuse enamel hypoplasia are seen.[3,4] Depending on the type of EB, pathologies in dental hard tissues show different involvement. JEB is the most common type of EB with generalized enamel hypoplasia.[3]

Common dental caries in various forms of EB may develop due to factors such as tooth enamel involvement, soft tissue changes, and diet.[19] For this reason, oral hygiene is very important in patients with EB. In our cases, no evidence of enamel hypoplasia was observed because the DEB form of EB was observed. However, all of our patients experienced extensive dental caries. This situation caused the patients to have more mouth sores and more nutritional problems.

The risk of squamous cell carcinoma in EB patients increases with age. It is most commonly seen in the recessive form of DEB but can also be seen in JEB, and the dominant form of DEB[3]. None of our patients had squamous cell carcinoma. Routine dental check-ups are also critical for the follow-up of the possibility of conversion of lesions to squamous cell carcinoma.

Dental treatments have to be done carefully with regular oral mucosal follow-up because the oral mucosa of these patients is prone to develop squamous cell carcinoma. Panoramic radiography should be preferred in EB patients because periapical radiography is difficult to place and the pressure that may occur during placement may trigger lesion formation.[4]Before starting the treatment, a lubricant such as petroleum jelly should be applied to the patient's lips. Soft and careful techniques should be used in all applications in order not to trigger the formation of bullae[4]. Local anaesthetic application should be done more deeply and slowly, saliva ejectors should be used at the lowest level and kept on the tooth surfaces, avoiding contact with soft tissue as much as possible.[8] When prosthesis is required, fixed prostheses should be preferred. In patients with enamel hypoplasia, teeth can be restored with veneers. Surgical extractions should be performed with minimal trauma and excessive pressure should not be applied while ensuring hemostasis. Since these patients are anaemic, the patient's physician should be consulted if serial extractions are necessary.[8] Mouthwashes and oral gels are generally preferred in the treatment of oral bullae and ulcerations. Topical fluoride should be applied to patients with high caries risk. Patients with microstomia should be given daily mouth opening and closing exercises. In addition, small-headed and soft-bristled toothbrushes may be recommended for oral hygiene in patients with microstomia and severe oral blisters.[4] In all our cases, the recommended dental procedures were followed to prevent the formation of lesions.

Various intraoral findings were observed in all of our cases. Restricted mouth opening and limited tongue movements, extensive dental caries, and intraoral lesions contribute to causing problems in feeding for patients. All cases received nutritional supplementation due to malnutrition. Dental procedures were performed carefully to avoid mucosal lesion formation. Common dental caries and periodontal diseases can be reduced with oral hygiene education in patients with DEB. In this way, fewer interventional procedures and less exposure to trauma will hinder more lesion formation. In addition, follow-up is critical in these patients due to the possibility of transformation of existing lesions into squamous cell carcinoma. The presence of the lesion for a prolonged duration and suspicious alterations in size, shape, color, and surface characteristics necessitate evaluation through biopsy. Early diagnosis presents a significant opportunity for treatment intervention.

Conclusions

EB is a rare inherited disorder. Lesions are usually seen on the skin but mucosal involvement is also common. Many intraoral findings are seen with mucosal involvement in the DEB form. Given the varied manifestations, it is imperative for dentists to be well-versed in the oral aspects of this disease and its specific dental approach. Regular follow-up of oral mucosa and teeth will make sure these patients to have healthy oral hygiene, to feed in a healthy way for their good physical condition and to be safe for missing potential malign lesions.

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Etik Beyan / Ethical statement

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It is declared that during the preparation process of this study, scientific and ethical principles were followed and all the studies benefited are stated in the bibliography.

Benzerlik Taraması / Similarity scan

Yapıldı – ithenticate

Etik Bildirim / Ethical statement

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Yazar Katkıları / Author Contributions

Çalışmanın Tasarlanması | Design of Study: RDT (%40), MTY (%25), HCK (%35)
Veri Toplanması | Data Acquisition: RDT (%40), MTF (%40), HCK (%20)
Veri Analizi | Data Analysis: RDT (%40), MTY (%25), HCK (%35)
Makalenin Yazımı | Writing up: RDT (%65), MTF (%10), HCK (%25)
Makale Gönderimi ve Revizyonu | Submission and Revision: RDT (%60), MTY (%10), HCK (%30)

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