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A rare genetic disorder encountered in dentistry: a case of lipoid proteinosis

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Abstract

Lipoid proteinosis disease is a rare autosomal recessive genodermatosis first described by Urbach and Wiethe in 1929. This disease occurs as a result of homozygous or compound heterozygous mutations in the ECM1 gene located in the 1q21 chromosome region. Approximately 400 cases have been encountered in the literature to date. Although it is seen worldwide, a higher prevalence of has been observed in Europe and South Africa. Although this disease can be seen anywhere in the body, the upper respiratory tract and mouth are affected in the majority of patients. The first clinical sign in Lipoid Proteinosis patients is a weak and muffled cry caused by laryngeal infiltration that develops shortly after birth or during infancy. Skin and mucosal changes develop during the first few years of life and later. Intraoral symptoms include macroglossia due to infiltration of waxy yellowish-white plaques and nodules, fissured macrocheilia, and nodular thickened mucosa. The prognosis of Lipoid Proteinosis disease is good and there is no specific treatment. Dentists are in the earliest position to diagnose Lipoid Proteinosis and help provide appropriate treatment to improve the quality of life impaired by the disease.

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Introduction

Lipoid proteinosis (LP) is a rare autosomal recessive disease that was first described by Urbach and Wiethe in 1929 (Khan *et al.*, 2023). It has been reported that LP develops as a result of mutation in the ECM1 gene located on chromosome 1q21 (Gonçalves *et al.*, 2010). The ECM1 gene is known to encode the structural element of the basement membrane and extracellular matrix (Ravi Prakash *et al.*, 2013). There are 3 types of glycoproteins in the ECM1 gene: ECM1a, ECM1b and ECM1c (Gonçalves *et al.*, 2010). The ECM1 gene is a glycoprotein that can contribute to scarring, skin adhesion, angiogenesis and wound healing. It has been reported that deficiency of the ECM1 gene leads to impaired protein-protein interactions, leading to the degradation of sphingolipids and glycolipids, as well as the accumulation of basement membrane collagen types and hyaline material (Shah & Shah, 2022). Histopathologically; The presence of irregular acanthosis, thickened dermis, epidermal hyperkeratosis, large periodic acid Schiff-positive and diastase-resistant extracellular amorphous hyaline tissue deposits has been reported (Mittal *et al.*, 2016).

This rare disease has approximately 400 cases reported in the medical literature to date (LeWitt *et al.*, 2023). Lipoid proteinosis is a disease that can be seen worldwide; however, it has been more frequently reported in Europe and South Africa. Although a significant number of cases in the

literature have been reported from Turkey, the true prevalence of the disease remains unclear (An *et al.*, 2021; Nanda *et al.*, 2001).

Lipoid proteinosis has been reported to present with hoarseness due to vocal cord infiltration, usually in early infancy. This is later followed by recurrent blood or pus-filled vesicles, bullae, macules, papules and skin-colored nodules; these are often described as being itchy. It has been reported that it can appear anywhere on the body (Kabre *et al.*, 2015). It has been reported that LP can cause calcification in the temporal lobes or hippocampus of the brain. This condition can manifest itself in some patients with epilepsy, memory problems, schizophrenia-like behaviors, mental retardation, emotional fluctuations and other mental problems (Shah & Shah, 2022). Oral manifestations of LP are usually described to occur before the development of cutaneous lesions. One of the most common findings is a "woody" or thickened tongue appearance due to hyaline deposition in both the lingual frenulum and the tongue tissue, along with restriction of tongue movement (Lee *et al.*, 2018). Gingival hypertrophy has also been reported to develop (Chan *et al.*, 2007). The salivary glands are also affected by this disease and it has been reported that the submandibular and parotid glands are usually involved, which can lead to poor oral hygiene by causing decreased saliva secretion or xerostomia. Ulcerations in the oral mucosa have also been detected (Kabre *et al.*, 2015).

There is no definitive and effective treatment for LP. It has been reported that the treatment generally aims to reduce morbidity and prevent complications. Although it is a progressive disease, the prognosis is good with a normal life expectancy (Deshpande *et al.*, 2015).

This case report discusses the clinical findings of a patient with Lipoid proteinosis. It is aimed to evaluate the general and oral findings of Lipoid proteinosis by emphasizing them.

Case report

A 13-year-old male patient applied to our Harran University Faculty of Dentistry Pedodontics clinic due to oral and dental problems. In the anamnesis, it was learned that the patient had Lipoid Proteinosis. It was also learned that the patient had affected relatives and that the patient's parents were in a consanguineous marriage. Intraoral examination revealed that the patient had missing teeth, anomalous shape in the upper canines, thickening and hardness of the tongue, and thickening of the lower lip. Clinical examination revealed the presence of numerous beaded papules (moniliform blepharosis) on the patient's eyelid margins (Figure 1-4). At the same time, the patient was observed to have hoarseness.

Discussion

Lipoid proteinosis (LP) disease has been reported to be a rare autosomal recessive genodermatosis (Alfahaad *et al.*, 2023). Amorphous hyaline deposits in the glycoprotein structure have been reported to affect various organs including the skin, oral mucosa, larynx, lymph nodes, small intestine, and brain. The etiopathogenesis of LP is still not fully elucidated, but it has been suggested that it may be associated with abnormalities in collagen synthesis and metabolism (An, 2025; Kabre *et al.*, 2015). It has been reported that mutations in the Extracellular Matrix Protein 1 (ECM1) gene located on chromosome 1q21 play a role in the etiology of the disease. At the same time, it has been shown that the ECM1 gene encodes an important component that ensures the structural integrity of the basement membrane and the extracellular matrix (Shah & Shah, 2022).

The first signs and symptoms of LP are reported to appear more frequently in the first year of life and include a hoarse and low-pitched cry due to the involvement of the vocal cords. Apart from vocal cord symptoms, skin lesions have also been reported to tend to appear later in childhood

(Lourenço *et al.*, 2020). The disease has been reported to commonly affect the oral mucosa. The mucosal membranes of the pharynx, tongue, and lips are usually reported to be infiltrated with firm, yellow-white papular lesions.

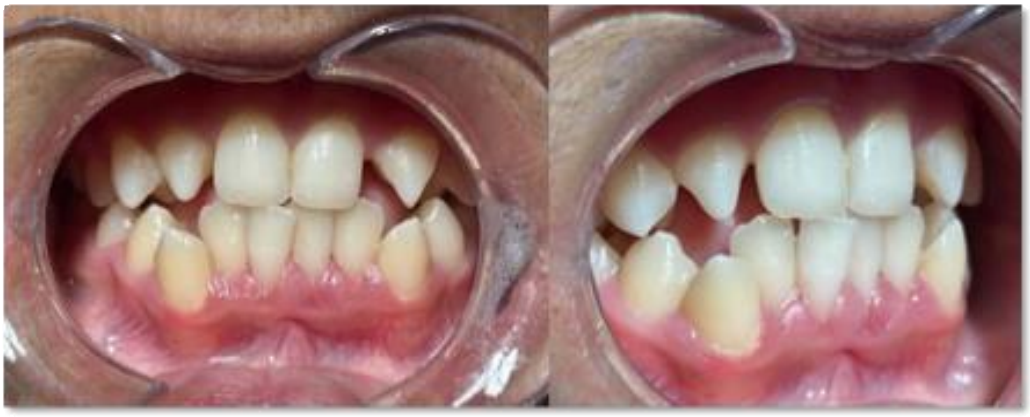

Figure 1. The patient's lateral teeth are missing, microdontia is seen in the canine teeth.

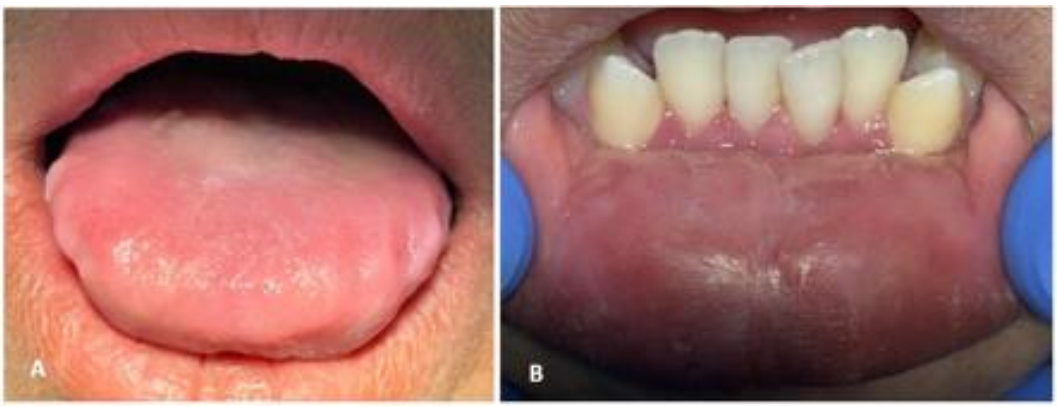

Figure 2. Hard and thick tongue view (A), and lip involvement view(B).

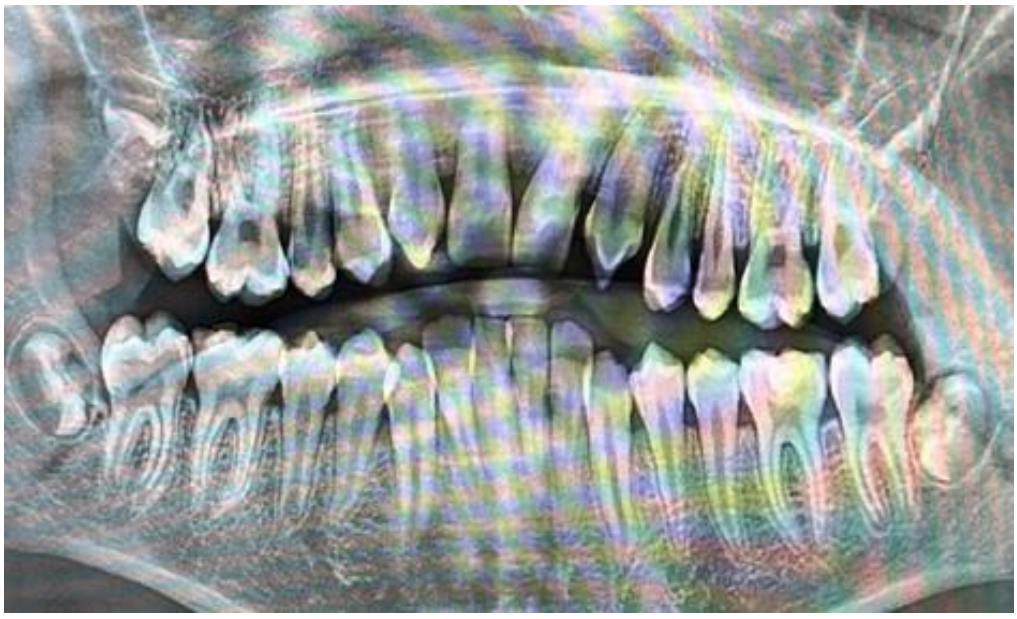

Figure 3. Panoramic image of the patient.

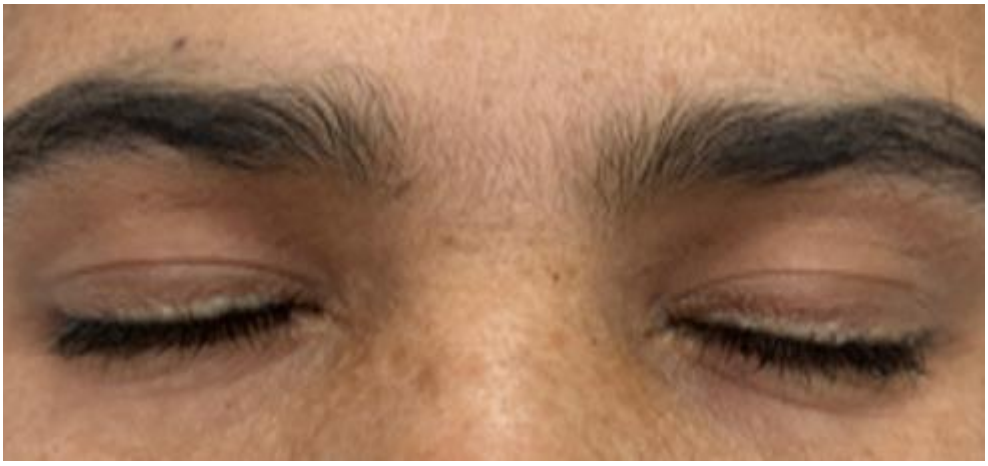

Figure 4. The view of bead-like papules at the eyelid margins (moniliform blepharosis).

Tongue enlargement and hardness on palpation have been reported. It has been reported that widespread infiltration of the larynx and pharynx can lead to dysphagia and respiratory distress (Dogru *et al.*, 2008). In the study conducted by Frenkel et al., the primary sites of oral involvement in patients with LP were reported as tongue (68%), palate (25%), lips (43%), floor of mouth (55.8%), buccal mucosa (40%) and gingiva (5.8%) (Frenkel *et al.*, 2017). In a case report conducted by Mainali et al., it was reported that during the intraoral examination of a 12-year-old female patient, the mouth opening was limited, the tongue was completely devoid of papillae, shiny, hard and had a woody consistency. And the patient's lingual frenulum was reported to be thick, short and hardened. The patient was reported to have both lateral incisors congenitally missing (Mainali *et al.*, 2011). In our case, the intraoral examination revealed that the patient's lateral teeth were congenitally missing, the tongue was hard and the lower lip was thickened.

It has been reported that the beaded papules extending along the eyelid margins, called moniliform blepharosis, are the most characteristic features of LP in LP patients (Lee *et al.*, 2018). In a study by Jahanimoghadam et al., moniliform blepharosis (multiple, beaded papules along the eyelash line) was reported in the eye findings of a 10-year-old boy (Jahanimoghadam & Hasheminejad, 2022). In our case, the patient's eye findings also revealed the presence of beaded papules on the eyelid margins.

Bilateral calcifications in the medial temporal lobes are a characteristic feature of LP and have been reported to occur in 52% of cases. When intracranial calcifications are prominent, epilepsy, mental dysfunction, and neuropsychiatric abnormalities have been reported (Jahanimoghadam & Hasheminejad, 2022).

It has been reported as a differential diagnosis of erythropoietic protoporphyria and systemic amyloidosis. Histopathologically, in erythropoietic protoporphyria, the accumulation of periodic acid-Schiff positive material was reported to be less dense around blood vessels and was not seen around sweat gland coils (Rao & Koppada, 2015).

It has been reported that there is no definitive treatment for this disease, and that treatment is symptomatic in most cases. Several drugs have been reported for the treatment of skin lesions, including dimethyl sulfoxide, its active metabolite acitretin, etretinate, D-penicillamine, and intralesional heparin. However, none of these drugs have consistently shown good results. It has been reported that dermabrasion can be recommended for patients whose skin lesions do not heal with routine oral medications. Carbon dioxide laser has also been reported as an option to consider for eyelid and aerogastrointestinal system

lesions. Removal of airway lesions using microlaryngoscopy has been described to improve airway and voice quality. It has been reported that anticonvulsants can be prescribed for patients with frequent seizures (Deshpande *et al.*, 2015; Jahanimoghadam & Hasheminejad, 2022). Dental treatment has been reported to be difficult due to limited mouth opening and mucosal irritation. Gingivectomy treatment has been reported to be an effective treatment option to reduce periodontal pocket formation and facilitate dental care (Lee *et al.*, 2018).

Conclusion

Lipoid proteinosis is a rare genetic disorder with systemic involvement, and it can significantly affect oral mucosa and dental structures. Therefore, it is essential for dental professionals to be aware of its clinical manifestations to ensure early diagnosis and appropriate referral. Given the multisystemic nature of the disease, a multidisciplinary approach involving close collaboration between dental and medical professionals is crucial for effective management. This case highlights the importance of awareness in recognizing and managing lipoid proteinosis within dental practice.

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