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Lipoid Proteinosis: A Rare Disease In Pediatric Dentistry

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This report describes the diagnostic process of a rare disorder in a Brazilian female child. The patient presented initially as a 7-year-old with multiple whitish submucosal nodules of a fibrous consistency in the lower lip, but with an inconclusive pathology report. When she turned 9 years of age, she presented with exacerbation of the original clinical findings, which then involved the upper lip, buccal mucosa, tongue and lingual frenulum. In addition, dermatological lesions were noted on the child's limbs and face, as well as a hoarse voice. Histopathological examination of the buccal mucosa revealed dense connective tissue with hyaline foci, which were positive with periodic acid-Schiff (PAS) staining and resistant to diastase digestion. Clinical and histopathological findings led to the diagnosis of a rare genetic disease with fewer than 300 reported cases - lipoid proteinosis. Magnetic resonance imaging revealed calcium deposits in her amygdaloid region of the brain, and nasopharyngolaryngoscopy revealed lesions in her vocal cords. The patient currently is stable and under multidisciplinary follow-up, but no treatment has been recommended to date.

Key Words: Lipoid proteinosis, Urbach-Wiethe disease, cutaneous-mucosal hyalinosis.

Introduction

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis with approximately 300 reported cases. The first clinical manifestations may be congenital or occur in early childhood. This disease, first described by Erich Urbach and Camilo Wiethe in 1929, is characterized by the deposition of amorphous hyaline material within the skin, mucous membranes and viscera (1). LP is also known as Urbach-Wiethe disease or cutaneous-mucosal hyalinosis. According to several authors, LP is more common in countries with higher rates of inbreeding marriages (2,3).

LP is caused by mutation in the extracellular matrix gene 1 (ECM1), which acts on extracellular matrix formation, cell adhesion, signaling, and regulation of angiogenesis, as well as on tissue differentiation and maturation (4). The mutated ECM1 gene, however, generates abnormalities in the glycolipid or sphingolipid pathway, with underproduction of fibrous collagen and overproduction of basement membrane proteins (4), causing deposits of hyaline material in the mucous membranes of the upper aerodigestive tract and skin (2).

Clinical examination of LP patients reveals waxy papules grouped as beads along the eyelash line, known as moniliform blepharosis, and papules in the skin (5). There is gradual and diffuse infiltration of the skin that becomes thick with a yellowish appearance, including the formation of extensive scars, even to small, mild trauma (2).

An early clinical sign of LP is hoarseness due to hyaline deposition in the laryngeal mucosa that may manifest at birth or during childhood. Later features can include diffuse white or yellowish papules throughout the oral mucosa, which may present as nodules or flat areas that are rough on palpation (6). Histologically, LP is characterized by dense connective tissue with the presence of amorphous and extracellular eosinophilic hyaline material due to the deposition of non-collagenous proteins and glycoproteins. These deposits are positive with periodic acid-Schiff staining and resistant to diastase digestion. Amorphous hyaline deposition is a common finding around vessels. The diagnosis of LP is based on clinical findings and confirmed by histopathological examination (7).

The objective of this study is to report the diagnosis of this rare childhood disorder, highlighting the clinical findings and their evolution.

Case Report

In 2015, a 7-year-old black female was referred to the oral medicine clinic of a public health service in Louveira, SP, Brazil, for evaluation of asymptomatic submucosal nodules of unknown duration in the lower lip. The lesions were whitish in color, fibrous in consistency, and exhibited an irregular surface. The patient was extremely shy and

unable to converse with the dental surgeon. During history taking, her mother reported that the child had no systemic diseases and the family history was negative for chronic diseases or genetic abnormalities. The mother and the child consented to a biopsy, which was taken from the lesion in the lower lip. The histopathology report described moderately cellular dense connective tissue with focal remnants of mucosal epithelium (Fig. 3A). As the clinical manifestations and pathology report were not sufficient to fulfill the criteria of LP, periodic follow-up was agreed to monitor the progression of her condition. Regrettably, the patient was lost to follow-up for nearly 2 years.

In 2017, the patient was referred again to the oral medicine service of Louveira, SP, for evaluation of lesions located on both upper and lower lips (Fig. 1A), buccal mucosa (Fig. 1B) and tongue (Fig. 1C). The same clinical features observed in 2015 were present in 2017, though greater in number and extent. Thickening of the lingual frenulum was an additional feature (Fig. 1D), which was compromising tongue mobility. On that second occasion, the 9-year-old girl was still extremely shy, though the dental surgeon managed to establish a short conversation with her, when a hoarse voice was noticed. The mother reported that hoarseness had been present since the age of two years and that the child had already undergone speech-language therapy to no avail.

In 2017, the patient also presented with several scars on the upper and lower limbs (Fig. 2A) as well as on her forehead (Fig. 2B), accompanied by keratotic plaques on her elbows (Fig. 2C). The presence of moniliform blepharosis (Fig. 2D) was also noted, characterized by a line of waxy papules in the shape of beads along the edges of her eyelids.

Incisional biopsy from a nodular lesion in her buccal mucosa (Fig. 1B) revealed abundance of hyaline material within the connective tissue (Fig. 3B). Histologically, the hyaline material stained positively for PAS and was diastase resistant. Congo red staining, followed by polarized light microscopy, showed no amyloid material. The histopathology and histochemistry findings, combined with clinical data, favored the diagnosis of LP.

The patient was referred for speech therapy and nasopharyngolaryngoscopy, which revealed a round lesion in the middle third of her right vocal cord. The patient was referred to a neurologist, who requested magnetic resonance imaging (MRI) of her brain, which revealed two symmetrical oval foci of calcium deposits in her amygdala. All such lesions are compatible with LP.

Discussion

This is a clinical case report of LP in a 9-year-old Brazilian child. This rare disease mainly affects white individuals of South African descent, since mutation of the ECM1 gene is reported to have occurred in South Africa in the mid-seventeenth century (3). This disease is also more prevalent among eastern Mediterranean inhabitants where consanguine marriages are common (8). Inbreeding between parents of children with LP occurs in approximately 20% of cases (9), although no known consanguinity was

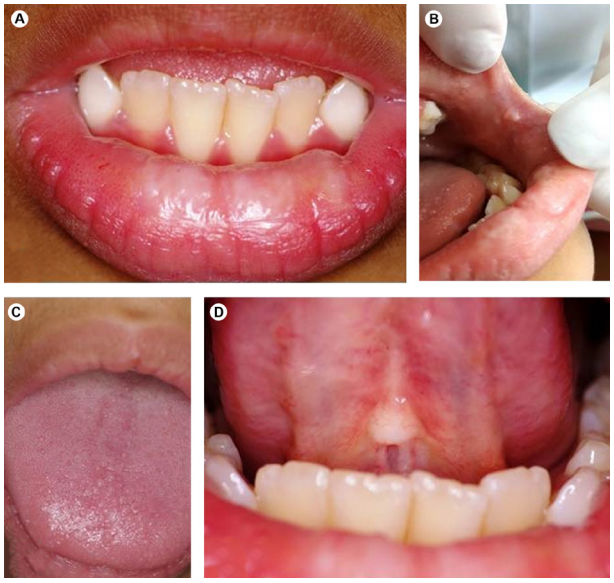

Figure 1. A: Yellowish-white thickening of the lower lip. B: Yellow nodular firm lesion on right buccal mucosa. C: Multiple normochromatic papules in anterior third of the tongue. D: Thickening and nodule on the lingual frenulum.

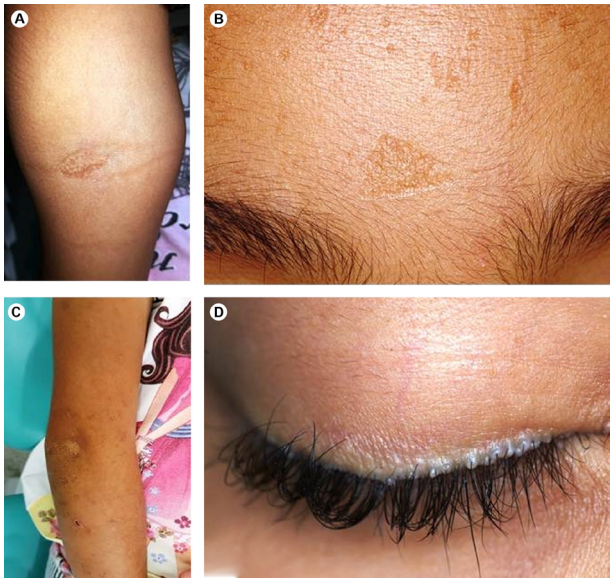

Figure 2. A: Scarring of the anterior region to the elbow. B: Atrophic scarring on the skin of the forehead. C: Thickening of the skin of the elbow. D: Beading papules along the margin of the eyelid.

identified between the parents of this particular patient. Her parents were unaware of any other family members being diagnosed with LP.

The first signs and symptoms of LP usually develop as early as the first year of life and may include hoarse crying due to infiltration of the vocal cords. Unlike vocal cord manifestations, skin lesions tend to appear later in childhood (10). The lack of awareness of such features by the parents and the difficulty in establishing a conversation with the patient in 2015 were relevant reasons for the delay in diagnosis. Oral lesions are often present in individuals with LP and may be the first manifestations of this syndrome, reinforcing the importance of the dental surgeon in early diagnosis. Frenkel et al. (2) verified that labial lesions may occur in the absence of dermatological manifestations, hence the great challenge in establishing a diagnosis at the first presentation in 2015.

The skin lesions on her upper and lower limbs in 2017, namely atrophic scarring to mild trauma, which the mother believed to have been sequelae of allergic reactions, were also important to establish a context of LP. Although the role of ECM1 in human skin has not been fully clarified, atrophic lesions have been attributed to underproduction of pro-collagen type I, which impairs tissue healing. Conversely, the papular or nodular lesions characteristic of LP have been attributed to overproduction of some structural proteins of the basement membrane, such as collagen type IV, perlecan and laminin (11). Such paradoxical scenarios may explain why dermatological manifestations vary considerably among LP patients. In addition to the atrophic scars, one must highlight beading of the eyelids and the presence of keratotic plaques on the elbows and knees (12). The presence of keratotic plaques has been related to the impact of ECM1 on keratinocyte differentiation and consequent hyperkeratosis (13). Also, thickening of the sublingual frenulum may be a frequent sign, leading to restriction of tongue movement (14).

Moniliform blepharosis was a key element in the diagnostic process. Callizo et al. (5) described this palpebral sign as a pathognomonic dermatological finding. Moniliform blepharosis is present in 50-70% of the cases and affects the Zeis, Moll, and Meibomian glands, causing loss of eyelashes or modification in their shape, which is accompanied by dry eye syndrome (13). In the patient reported herein, the authors observed time-dependent changes in the clinical severity of her moniliform blepharosis, which appeared less pronounced in subsequent follow-up visits, although this has not been reported in any previous studies reviewed for this manuscript.

Patients with LP may develop convulsions and neuropsychiatric symptoms as a result of amygdala calcifications located in the antero-inferior region of the temporal lobe (3). The amygdala plays an important role in controlling emotions and is an identifying center for danger. Some studies have shown that LP lesions may lead to alterations in the perception of fear, causing unresponsiveness to aversive stimuli (15,16). These findings were not detected in the patient reported herein, despite the presence of amygdala calcifications.

The patient is currently well and under periodic follow-up. Several treatments have been proposed for LP patients, most of which are aimed at the symptoms and signs, e.g. dermabrasion and chemical peeling for cutaneous lesions (17). Zhang et al. (18), in 2014, proposed local injection of betamethasone combined to oral hydrocortisone to reduce the symptoms caused by LP. Other studies have reported the use of oral dimethylsulfoxide, D-penicillamine, and oral retinoids (such as acitretin) with satisfactory results,

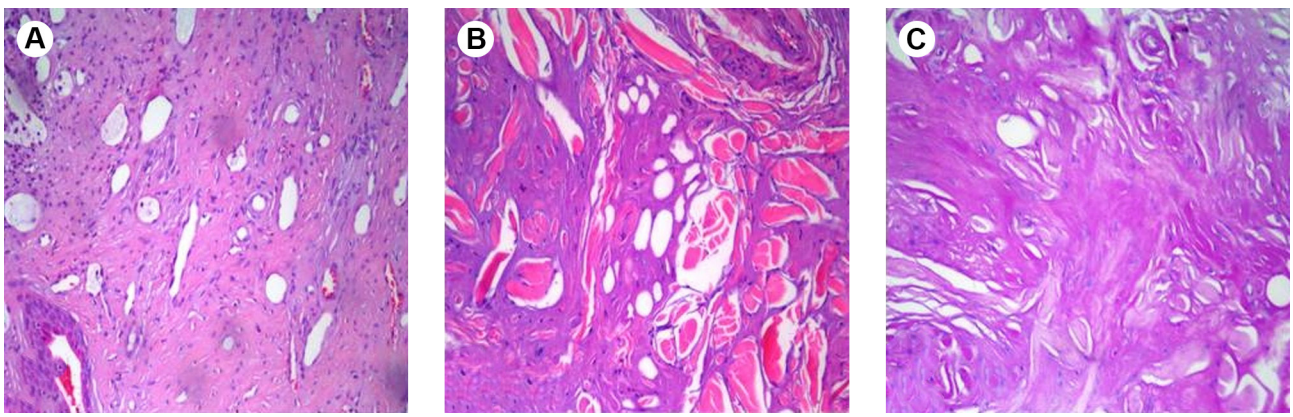

Figure 3. A: Lower lip biopsy performed in 2015 showing moderately cellular connective tissue and mucosal epithelium remnants (Hematoxylin and eosin, original 10× magnification). B: Biopsy of the anterior third of the tongue showing diffuse hyaline extracellular material permeated by thick mature collagen fibers (Hematoxylin and eosin, original magnification 10×). C: PAS highlighting perivascular deposition of hyaline material in a diffuse pattern (original magnification of 10×).

although some authors have drawn attention to a high risk of relapse of clinical manifestations some time after completion of treatment (12,19).

LP has a benign course, with lesions progressing until early adulthood, without affecting life expectancy. Early diagnosis of LP may warrant treatment that, although controversial, aims to reduce stigma and improve the quality of life for affected individuals.

Resumo

Este relato descreve o processo diagnóstico de uma doença rara em uma criança brasileira do sexo feminino. A paciente, inicialmente com 7 anos de idade, apresentava múltiplos nódulos submucosos esbranquiçados, de consistência fibrosa, no lábio inferior, mas com um laudo patológico inconclusivo. Quando completou 9 anos de idade, ela apresentou exacerbação dos achados clínicos originais, que envolveram o lábio superior, mucosa bucal, língua e frênulo lingual. Além disso, lesões dermatológicas foram observadas nos membros e no rosto da criança, assim como rouquidão. O exame histopatológico da mucosa bucal revelou tecido conjuntivo denso com focos hialinos, que foram positivos com coloração periódica com ácido-Schiff (PAS) e resistente à digestão da diástase. Os achados clínicos e histopatológicos levaram ao diagnóstico de uma doença genética rara com menos de 300 casos relatados - proteinose lipoide. A ressonância magnética revelou depósitos de cálcio em amígdala cerebral e a nasofaringolaringoscopia revelou lesões em cordas vocais. Atualmente, a paciente está estável e em acompanhamento multidisciplinar, mas nenhum tratamento foi recomendado até o momento.

References

1. Sercu S, Zhang M, Oyama N, Hansen U, Ghalbzouri AE, Jun G, et al. Interaction of extracellular matrix protein 1 with extracellular matrix components: ECM1 is a basement membrane protein of the skin. J Invest Dermatol 2008;128:1397-1408.
2. Frenkel B, Vered M, Taicher S, Yarom N. Lipoid proteinosis unveiled by oral mucosal lesions: a comprehensive analysis of 137 cases. Clin Oral Investig 2017;21:2245-2251.
3. Van Hougenhouck-Tulleken W, Chan I, Hamada T, Jenkins T, McLean WH, et al. Clinical and molecular characterization of lipoid proteinosis in Namaqualand, South Africa. Br J Dermatol 2004;151:413-423.
4. Mittal HC, Yadav S, Malik S, Singh G. Lipoid Proteinosis. Int J Clin Pediatr Dent 2016;9:149-151.
5. Callizo M, Ibáñez-Flores N, Laue J, Cuadrado V, Graell X, Sancho JM. Eyelid lesions in lipoid proteinosis or Urbach-Wiethe disease: case report and review of the literature. Orbit 2011;30:242-244.
6. Deshpande P, Guledgud MV, Patil K, Hegde U, Sahni A, Huchanahalli Sheshanna S. Lipoid proteinosis: a rare encounter in dental office. Case Rep Dent 2015:670369.
7. Sargenti Neto S, Batista JD, Durighetto AF Jr. A case of oral recurrent ulcerative lesions in a patient with lipoid proteinosis (Urbach-Wiethe disease). Br J Oral Maxillofac Surg 2010;48:654-655.
8. Lee MY, Wang HJ, Han Y, et al. Lipoid proteinosis resulting from a large homozygous deletion affecting part of the ECM1 gene and adjacent long non-coding RNA. Acta Derm Venereol 2015;95:608-610.
9. Cedrim SD, RosaDJF, Machado RF, Toledo FA, Neto MPM. Lipoid proteinosis. Case Report. Rev Bras Clin Med 2010;8:77-79.
10. Rey LK, Kohlhase J, Möllenhoff K, Dekomien G, Epplen JT, Hoffjan S. A Novel ECM1 Splice Site Mutation in Lipoid Proteinosis: Case Report plus Review of the Literature. Mol Syndromol 2016;7:26-31.
11. Mirancea N, Hausser I, Metze D, Stark HJ, Boukamp P, Breitkreutz D. Junctional basement membrane anomalies of skin and mucosa in lipoid proteinosis (hyalinosis cutis et mucosae). J Dermatol Sci 2007;45:175-185.
12. Singh S, Mittal S, Bhari A, Bhari N: Lipoid proteinosis. BMJ Case Rep 2017;20:2017.
13. Fonseca EC, De Fendi LI, Andretta PS, Martin RT, Ottaiano JA. Urbach-Wiethe syndrome: a case report. Arq Bras Oftalmol 2007;70:689-692.
14. Dertlioglu SB, Çalık M, Çiçek D. Demographic, clinical, and adiologic signs and treatment responses of lipoid proteinosis patients: a 10-case series from Sanlıurfa. Int J Dermatol 2014;53:516-523.
15. Hortensius R, Terburg D, Morgan B, Stein DJ, van Honk J, de Gelder B. The dynamic consequences of amygdala damage on threat processing in Urbach-Wiethe Disease. A commentary on Pishnamazi et al. (2016). Cortex 2017;88:192-197.
16. Brajac I, Kastelan M, Gruber F, Peris Z. Hyalinosis cutis et mucosae: a 30 year follow up of a female patient. Eur J Dermatol 2004;14:310-313.
17. Feinstein JS, Buzza C, Hurlemann R, Follmer RL, Dahdaleh NS, Coryell WH, et al. Fear and panic in humans with bilateral amygdala damage. Nat Neurosci 2013; 16:270-272.
18. Zhang R, Liu Y, Xue Y, Wang Y, Wang X, Shi S, et al. Treatment of lipoid proteinosis due to the p.C220G mutation in ECM1, a major allele in Chinese patients. J Transl Med 2014;12:85.
19. Gündüz O, Sahiner N, Atasoy P, Senyücel C. Acitretin treatment for lipoid proteinosis. Case Rep Dermatol Med 2012;2012:324506.

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