Lipoid Proteinosis: A Rare Cause of Hoarseness

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Summary: Lipoid proteinosis is a rare cause of voice problems. Hoarseness is often the first clinical manifestation of this disorder and can present years before any other symptom. Therefore, it is very important as an otorhinolaryngologist to be familiar with the main characteristics of this disease. We present a case report and a review of current literature to provide a concise overview of this frequently missed diagnosis.

Key Words: Lipoid proteinosis–Urbach-Wiethe disease–Hoarseness–Skin lesions–Voice.

INTRODUCTION

Lipoid proteinosis, also known as Urbach-Wiethe disease or hyalinosis cutis et mucosae, is a very rare autosomal recessive disease. The disease is characterized by a deposition of hyaline material in the skin and mucous membranes of various organs, leading to typical symptoms such as a hoarse voice, a thickened sublingual frenulum, oral erosions, skin lesions, and eyelid papules.[1]

Hoarseness is often the first clinical manifestation of this disease and can present years before any other symptom. Therefore, it is very important as an otorhinolaryngologist to be familiar with the main characteristics of this disease.

Currently, no case-control studies about this subject are described in the literature. Only several hundreds of cases have been reported until now and therefore still little is known about the exact etiopathogenesis, course, prognosis, and treatment of this disease. We present a case report and a review of current literature to provide a revision of this rare and frequently missed diagnosis.

MATERIALS AND METHODS

A literature review of the PubMed, Cochrane, and EMBASE database was performed using *(Urbach-Wiethe OR (lipoid proteinosis)) AND (dysphoni* OR aphoni* OR hoarse*)* as the search term. All articles about patients with lipoid proteinosis who had voice complaints were included in this paper. Due to the lack of large case-control studies, we included case reports, editorials, if they included a case report, and case series. Books and opinions were not included. We excluded all articles in other languages than English, Dutch, French, German, or Spanish and all old articles (older than 1990) of which no online text was available. The searches retrieved a total of 306 records, of which 149 met our inclusion criteria. Only studies that provided additional information are presented in the references.

CASE REPORT

A 32-year-old woman presented at the ear, nose, and throat clinic with hoarseness since childhood. She did not have complaints of dyspnea, dysphagia, or weight loss and had no history of smoking. The only medical history she had was a peptic ulcer.

Clinical examination revealed a very dry and thick skin (Figure 1) and multiple beaded papules along the eyelid margins (Figure 2). Additionally, she had a rigid, fibrotic tongue with induration at the tongue base. There were no palpable adenopathies. Fibrolaryngoscopy demonstrated a thickening of the epiglottis and tongue base without any ulcerations (Figure 3). Furthermore, the arytenoids had an edematous appearance. The vocal folds appeared irregular (Figure 4); stroboscopic evaluation showed an absent mucosal wave and an extended glottal gap possibly because of hypertonia.

Hematological and biochemical examinations showed no abnormalities. A biopsy of the tongue was sent for anatomopathologic evaluation and a computed tomography of head and neck was performed for further investigation. The biopsy of the tongue was completely normal and except for a lipomatous involution of the left parotid gland, the computed tomography of head and neck did not show any pathologic findings.

A biopsy of the arm was taken and a deposition of pale hyaline material was found around the capillaries and between the collagen bundles in the superficial dermal layer. This material stained positive for periodic acid-Schiff (PAS) and negative for Congo red. Subsequently, the diagnosis of lipoid proteinosis was made. No genetic tests were performed.

Unfortunately, almost immediately after diagnosis, the patient, who was a refugee, disappeared. Therefore, no further treatment could be started.

LITERATURE REVIEW

Lipoid proteinosis is a very rare autosomal recessive disease. It occurs worldwide, but the previous literature has stated that it is more common in certain geographic areas such as South Africa[2] and in areas in which consanguineous marriages are still common.[3]

The disease is most likely caused by loss of function mutations in the extracellular matrix protein 1 (ECM1) gene on chromosome 1q21. ECM1 is a secreted glycoprotein, which probably plays a role in epidermal differentiation, binding of dermal collagens and proteoglycans, and regulation of angiogenesis.[4] So far, more than 50 mutations in the ECM1 gene in chromosome 1q21 have been reported. Almost half of the patients carry nonsense or missense mutations in exon 6 or 7. The exact underlying pathophysiology of lipoid proteinosis remains unknown. ECM1 has been shown to inhibit bone mineralization, to contribute to epidermal differentiation, and to stimulate angiogenesis. It is likely that ECM1 contributes to protein binding of interstitial

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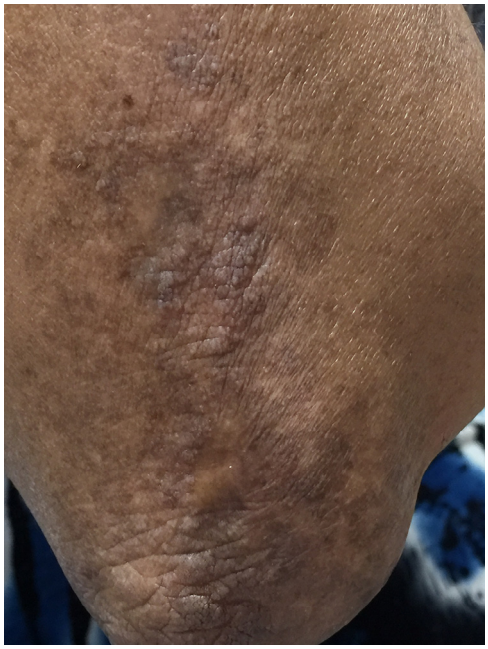

FIGURE 1. Skin. Hyperkeratosis on the elbows.

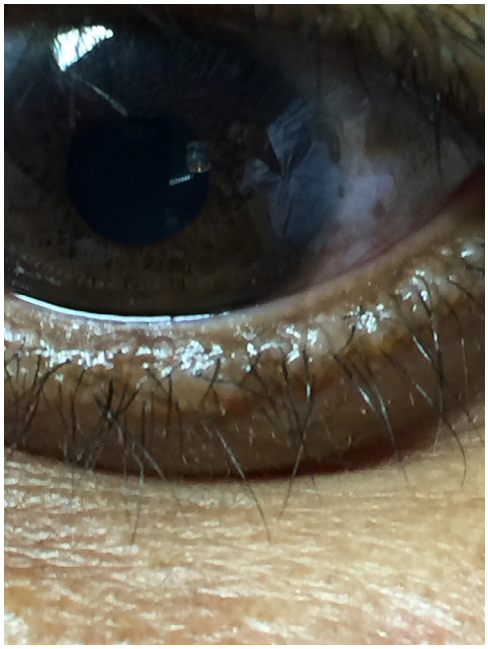

FIGURE 2. Moniliform blepharosis. Multiple beaded papules along the eyelid margins and inner canthus, which can be seen as a pathognomonic sign for the disease.

collagens, basement membrane collagens, and glycosaminoglycans as lack of the protein results in massive reduplication of basement membrane and clinically in scarring and skin infiltration.[3,5]

Hoarseness is often the first clinical manifestation of lipoid proteinosis. The hoarseness is often already present at infancy; newborn infants may exhibit a weak voice when crying. Subsequently, the voice worsens with age due to the progressive

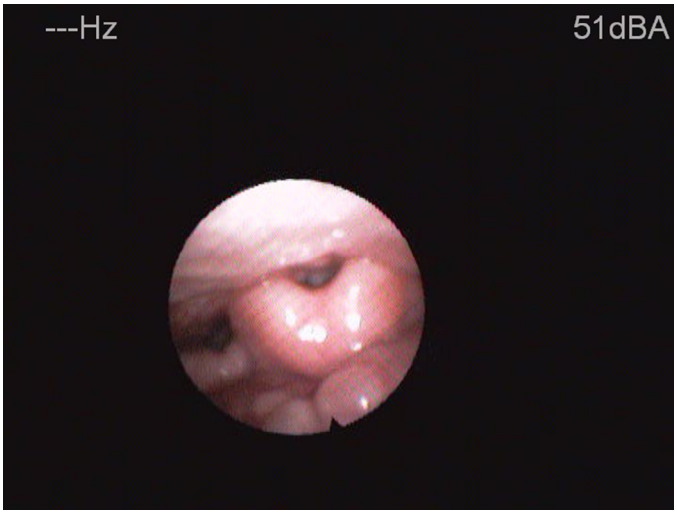

FIGURE 3. Epiglottis and tongue base. Image of fibrolaryngoscopy. Thick and fibrotic epiglottis and tongue base.

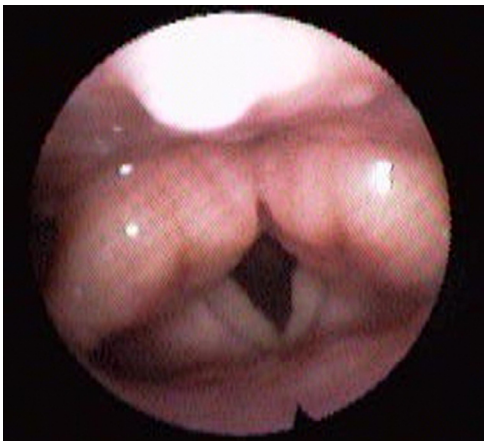

FIGURE 4. Arytenoids and vocal cords. Image of fibrolaryngoscopy. Edematous thickening of the arytenoids. Irregular vocal cords.

inelasticity of the vocal cords. In some cases, severe airway problems can occur, necessitating tracheotomy.

Fibrolaryngoscopy often shows irregular vocal cords and a thickening of the epiglottis and arytenoids. Stroboscopic examination reveals a reduced or absent vocal wave and incomplete vocal closure.

Other otorhinolaryngologic symptoms include white-yellow mucosal plaques or papules, dental impressions on the tongue, and thickening of the tongue and sublingual frenulum, which often causes difficulties protruding the tongue.[1] Additionally, recurrent swelling of salivary glands occurs due to stenosis of the duct.[6]

Patients with lipoid proteinosis very often present with moniliform blepharosis, the presence of multiple beaded papules along the eyelid margins and inner canthus, which can be seen as a pathognomonic sign for the disease.[1]

Concerning dermatologic manifestations, most patients present with vesicles and hemorrhagic crusts which develop into acneiform scarring, predominantly on the face and trunk.

Hyperkeratosis and verrucous lesions may appear on the extensor surfaces, predominantly on the elbows. Other possible symptoms are alopecia and nail dystrophy.[6]

Furthermore, patients can suffer from seizures, memory deficits, social and behavioral changes, mental retardation, and aggressiveness due to calcifications in the amygdala and temporal lobes.[7–10]

Concerning diagnosis, the presence of bean or comma-shaped intracranial calcifications in the temporal lobes in the amygdala is the most common radiological hallmark, but this occurs only at a late stage of the disease. The diagnosis of lipoid proteinosis can be made by a histopathologic finding of a deposition of PAS-positive hyaline material in the submucosa or dermis. In the earliest stages of the disease, lamellar material accumulates along blood vessels, nerves, sweat glands, and hair follicles. In well-developed lesions, amorphous structureless hyaline material is deposited within the upper and mid dermis between collagen bundles and around blood vessels. In advanced stages, the hyaline material surrounds and replaces eccrine glands and other adnexal structures. The overlying epidermis may be hyperplastic and hyperkeratotic.

The material stains positively for PAS and negatively with amyloid stains such as Congo red.[1]

Additionally, genetic testing for ECM1 can confirm the disease. The life expectancy of patients with lipoid proteinosis is normal, except for rare cases with critical laryngeal deposits, compromising the airway.

Currently, there is no evidence-based treatment available for this disease because the rarity of the disorder causes a lack of large studies. The potential for causing multiple scars on the skin, however, advocates for starting the treatment as soon as possible.

Oral application of acitretin, etretinate, dimethyl sulfoxide, corticosteroids, and methotrexate has been discussed in recent literature.

Acitretin

In total, 21 patients treated with acitretin, a vitamin A derivate, were described in the literature. Of those 21 patients, 13 patients (62%) showed improvement of the skin lesions and 8 patients (38%) did not improve. Concerning voice, in three patients nothing was mentioned about the effect of acitretin on hoarseness. Of the remaining 18 patients, 13 patients (72%) had an ameliorated voice and 5 patients (28%) did not.[11–18]

Etretinate

Etretinate was described in only one patient and did not demonstrate beneficial effects.[19]

Dimethyl sulfoxide

Five patients were treated with dimethyl sulfoxide. Only in one patient (20%) minor overall improvement was described.[20] In the other four patients (80%), dimethyl sulfoxide had no effect.[17,21]

Corticosteroids

Corticosteroids were used in four patients. In one patient, there was no improvement (25%),[17] in two patients, there was a beneficial effect on oral lesions, hoarseness, and skin lesions (50%),[22,23] and in the remaining patient, a positive effect concerning the voice was noted, but this immediately worsened again after the treatment was stopped (25%).[24]

Methotrexate

Methotrexate was used in only one patient, but did not show any improvements.[17]

Surgery

Another documented treatment option for the voice problems is surgery with or without laser, excising the epithelium and superficial lamina propria. In total, 20 patients who had surgery were found in the literature. Of those 20 patients, 5 were treated with CO_2 laser and 15 were treated with cold instruments. Fourteen patients (70%) had a better voice; but unfortunately, in most cases, nothing is known about the duration of the improvement.[1,25–29] In two patients (10%) (one laser and one cold instruments), the voice was better for several months, but recurrence was documented.[17,30] One patient (5%) had no improvement,[31] and one study described improved of stridor, but not of hoarseness after laser excision.[31] Three patients (15%), of which one was treated with CO_2 laser, had a worse voice due to formation of granulation and scar tissue.[32]

No complications, information about duration of hospitalization, or need for tracheotomy were reported. Some authors suggest that together with surgery there should always be an intensive voice therapy to eliminate compensatory behaviors patients had to use before surgery.[29]

Lastly, not for improving voice, but for improving airway, a tracheostomy may be necessary. Airway problems in lipoid proteinosis are rare; the incidence of the need for tracheostomy in this disease remains unknown.

CONCLUSION

A case report and review of current literature was described to refresh the knowledge of these disorders' symptoms, diagnosis, and treatment options. Large case-control studies are necessary to further investigate pathogenesis and treatment options, but are difficult due to the low incidence of the disease.

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