Vocal fold hyalinosis in Urbach-Wiethe disease, a rare cause of hoarseness

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Abstract. Vocal fold hyalinosis in Urbach-Wiethe disease, a rare cause of hoarseness. Background: Lipoid proteinosis is an autosomal recessive disorder characterized by hyalin deposits in the skin and mucosa of the upper aerodigestive tract; currently, no treatment exists. Nearly all patients experience hoarseness and speech difficulties, due to hyalin deposition in the vocal folds and diminished mobility in infiltrated lips, tongue, and palate. Methods: We describe a patient with extensive hyalin plaques on the vocal folds, which resulted in near-aphonic hoarseness. Hyalin deposits in the vocal folds and skin were treated with laser resection. Results: Both the vocal folds and skin improved in appearance, with smoother surface epithelium. However, the patient’s speech remained impaired, due to extensive hyalin plaques in the mouth, tongue, and lips. The voice improved only temporarily. Conclusions: Laser resection of hyalin plaques in the vocal folds and skin is a feasible treatment for lipoid proteinosis. However, speech may remain severely limited, due to impaired tongue and lip movement.

Introduction

Hyalinosis cutis et mucosae, or lipid proteinosis, is a rare autosomal recessive disorder characterized by the deposition of hyalin in the skin, mucosa of the upper aerodigestive tract, and a variety of organs (esophagus, stomach, rectum, genitals).¹ It was first recognized as lipoproteinosis by a Viennese dermatologist (Urbach) and otorhinolaryngologist (Wiethe) in 1929;² hence it was called Urbach-Wiethe disease. In 2002, Hamada et al.³ mapped the disorder to chromosome 1q21. They identified mutations in the extracellular matrix protein 1 (ECM1) gene that caused lipid proteinosis. Histologically, the disorder is characterized by extensive dermal and submucosal intercellular deposits of hyalin material that can be stained with periodic acid-Schiff (PAS).³

The disorder is very rare; to date, approximately 300 cases have been described in the literature. There is a remarkably high incidence in South Africa, which comprises about one quarter of the world population of patients with lipid proteinosis. Presumably, this high incidence is due to a founder effect; it has been estimated that the mutation was introduced into South Africa in the mid-seventeenth century by German immigrants.³

Patients typically present with hoarseness, due to laryngeal lesions, and newborn infants may exhibit a weak voice when crying. In some cases, severe airway obstruction may necessitate tracheotomy.² The skin lesions typically present as vesicles and hemorrhagic crusts that resolve with scar formation during the first years of life. Gradually, diffuse infiltration and thickening of the skin leads to a yellow, waxy appearance, which results in the development of papules and nodules on the face and extensor aspects of the extremities. Hyalin infiltrates the lips, tongue, and palate, which causes further speech difficulties for the patient.² Intracranial, bean-shaped suprasellar-temporal calcifications may appear on radiologic examinations of the skull. These calcifications may cause epilepsy or seizures, but they have also been reported in patients free of neurologic symptoms.⁴⁻⁷ There is currently no effective treatment for lipid proteinosis. To our knowledge, no previous study has described a laser surgery treatment that could improve hoarseness caused by hyalinosis of the vocal folds. Here, we present the case of a patient with lipid proteinosis that was treated for hyalinosis of the vocal folds with carbon dioxide laser treatment, and postoperatively, the voice improved.
Due to the uncertainty of voice quality outcome with laser treatment of the vocal folds, the patient chose not to receive (laser) resection to remove the thickened mucosa of the vocal folds. Oral pain was treated with a topical anesthetic gel. Over the years, he underwent regular checkups in our outpatient clinics with laryngoscopy, which showed stable, infiltrated mucosa, as described above.

The intensity of hoarseness varied from time to time. Initially, the patient was treated with local corticosteroids and antibiotics. However, this treatment had no effect on the skin lesions. Therefore, methotrexate, acitretin, and later, oral dimethyl sulfoxide were started. All systemic treatments intensity from month to month. Due to the uncertainty of voice quality outcome with laser treatment of the vocal folds, the patient chose not to receive (laser) resection to remove the thickened mucosa of the vocal folds. Oral pain was treated with a topical anesthetic gel. Over the years, he underwent regular checkups in our outpatient clinics with laryngoscopy, which showed stable, infiltrated mucosa, as described above.

Case report

The patient was 41 years old and had a long history of lipoid proteinosis. He was first referred to our otorhinolaryngology clinic for hoarseness and oral pain. His history showed that his voice had always been hoarse and that he had progressive, warty hyperkeratosis on the extremities and face. He also experienced temporal epilepsy. He had two brothers that also showed signs of hyalinosis, but no other affected family members. A physical examination, which included flexible laryngoscopy, showed irregular white plaques on the tongue, frenulum, soft palate, uvula (Figure 1), and hypopharynx. In the larynx, the epiglottis was disfigured with irregular thickening (Figure 1), irregular vocal folds, and exophytic white papules (Figure 2). The patient reported that the hoarseness varied in intensity from month to month. Due to the uncertainty of voice quality outcome with laser treatment of the vocal folds, the patient chose not to receive (laser) resection to remove the thickened mucosa of the vocal folds. Oral pain was treated with a topical anesthetic gel. Over the years, he underwent regular checkups in our outpatient clinics with laryngoscopy, which showed stable, infiltrated, thickened mucosa, as described above. The intensity of hoarseness varied from time to time. Initially, the patient was treated with local corticosteroids and antibiotics. However, this treatment had no effect on the skin lesions. Therefore, methotrexate, acitretin, and later, oral dimethyl sulfoxide were started. All systemic treatments

Figure 1
Laryngoscopic images display features of lipoid proteinosis. Laryngoscopic images show (top) white, infiltrated plaques in the mucosa of the soft palate and uvula; (bottom) extensive hyalin deposition in the epiglottis.

Figure 2
Laryngoscopic images display pre- and post-laser treatment appearance of the vocal folds. Laryngoscopic images show (top) pre-laser treatment: the true vocal folds are thickened by hyalin deposition. Note the mucosa of the false vocal folds appears normal; (bottom) post-laser treatment: the surface of the true vocal folds. The most anterior part of the left vocal fold was not resected with the laser to prevent synechia of the anterior commissure.
were discontinued due to lack of improvement. Carbon dioxide (CO₂) laser treatment was performed on the patient’s hands, and this resulted in marked improvement in the cutaneous lesions (Figure 3).

When the patient was 55 years old, the hoarseness gradually increased, until the patient was nearly aphonie. At that moment, in light of the success of laser treatment on his cutaneous lesions, we decided to perform CO₂ laser surgery to remove the thickened mucosa of the vocal folds. The surface of both vocal folds was removed with the laser in a single-stage operation. We left a small portion of the anterior mucosa intact on the left vocal fold to avoid excessive scarring of the anterior commissure. This strategy aimed to reduce the chance of the anterior vocal folds developing a synechia (Figure 2).

**Results**

Histopathologic examination of the removed tissue showed deposition of eosinophilic, homogeneous material. In some areas, PAS-positive material was found in the subepithelial lamina propria, and in other areas, it occurred deeper than the lamina propria (Figure 4). Six weeks after surgery, the patient’s voice had gradually improved, and the surface of the vocal folds had significantly improved. At six months after surgery, the patient’s voice had only slightly better than before surgery; however, when laryngoscopy was performed in the outpatient clinic, the mucosa of the vocal folds appeared smooth, with only nodular irregularities on both arytenoids. Most importantly, the patient’s speech was permanently, severely impaired due to the lack of flexibility in the mucosa of his tongue, mouth, and lips.
Discussion

Currently, there is no curative treatment for lipoid proteinosis. Various oral drugs have been used to treat lipoid proteinosis, including dimethyl sulfoxide, different generations of retinoids (etretinate and its metabolite, acitretin), D-penicillamine, and corticosteroids. However, the outcomes have not been consistently successful. Only single case studies have reported successful treatments, and typically, the success has been transient, with a delay in disease progression. The patient in the present study had previously received local therapy, methotrexate, acitretin, and dimethyl sulfoxide, but no effect was observed.

Skin lesions, mostly facial, can at least temporarily be reduced with CO2 laser treatment,10 dermabrasion,11 and surgical treatment.12 However, long-term results have not been consistently reported. In our patient, lesions on the hands markedly improved with CO2 laser treatment.

Almost all patients with lipoid proteinosis experience hoarseness, due to hyalin deposits in the vocal folds. Speech is further hampered by thickening of the mucosa on the epiglottis, tongue, and frenulum. Previous studies have described the use of CO2 laser treatment for treating laryngeal hyalinosis. However, it was mostly performed to reduce airway obstruction in severe cases to provide relief from dyspnea and stridor. Kroukamp et al.13 described a patient with stridor, where laser treatment was used to remove severe hyalinosis on the vocal folds to reduce airway obstruction. That treatment reduced the stridor, but also weakened the voice. Two years post-treatment, the patient again presented with stridor. Hanke et al.14 described a patient with hyalinosis of the vocal folds that was removed with laser treatment, but they did not report the indication or the result. Savage et al.15 described a case where interarytenoid disease was successfully removed to improve the voice, but the details were lacking and no follow-up was reported. Our patient reported that his voice had improved from the pre-operative condition during the first months after laser resection; but, after six months, the hoarseness had not significantly improved from the pre-operative condition.

CO2 laser treatment has been well established for other benign lesions of the vocal folds, including polyps, papillomas, nodules, and granulomas. It was also successfully used to treat various rare pathologies, such as laryngeal paraganglioma.16 In patients with extensive laryngeal hyalinosis that resulted in obstruction, laser treatment appeared to provide appropriate management for maintaining a patent airway without tracheotomy. Our patient, however, did not experience dyspnea or stridor, but near-aphonic hoarseness. We removed severely thickened mucosa infiltrated with hyalin from both vocal folds in a single-stage laryngoscopic operation with a CO2 laser. After treatment, the patient experienced improvement, albeit limited, in the voice. Also, laryngoscopy revealed that the surface lining of the vocal folds had improved. The patient will be followed with regular checkups in our outpatient clinic.

Conclusion

This study demonstrated that, for patients with severe hoarseness close to aphony, even in the absence of symptoms of airway obstruction, laser treatment of the vocal folds is an appropriate approach. This treatment can improve the voice and quality of life in patients with lipoid proteinosis, for which no medical treatment currently exists.

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