KBB Uygulamaları 2019;7(1):51-58
doi: 10.5606/kbbu.2019.89421

Case Report / *Olgu Sunumu*

Lipoid proteinosis (Urbach-Wiethe disease): A rare entity and review of the literature

Lipoid proteinozis (Urbach-Wiethe hastalığı): Nadir bir durum ve literatürün incelenmesi

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ABSTRACT

Lipoid proteinosis (LP) is a rare disease. It may affect the skin, oral mucosa, pharynx, larynx and all visceral organs. In this article, we describe a 32-year-old female patient who applied with complaint of white swelling in mouth, limiting the movement of lip, and hoarseness. Papule-like itchy rashes particularly around the hands, elbows, and lips were observed in physical examination and bilateral blepharosis in eye examination. In videolaryngostroboscopy, thickened vocal cords and yellow papule formations covering the entire supraglottic region and oral mucosa drew attention. In punch biopsy samples taken from larynx and sublingual regions, hyperkeratosis-patterned multilayered epithelial and subepithelial amorphous hyaline material deposition was observed. In histochemical examination, positive staining with periodic acid-Schiff in basal membrane and negative staining with Congo red were obtained. We established a diagnosis of LP according to typical vocal cord involvement and histopathologic, genetic and clinical findings.

Keywords: Extracellular matrix protein 1; genetics; larynx; lipoid proteinosis; Urbach-Wiethe disease.

ÖZ

Lipoid proteinozis (LP) nadir görülen bir hastalıktır. Cilt, oral mukoza, farenks, larenks ve tüm iç organları etkileyebilir. Bu çalışmada ağız içerisinde dudak hareketini kısıtlayan beyaz renkli şişlik ve ses kısıklığı yakınması ile başvuran 32 yaşında bir kadın hasta sunuldu. Fizik muayenede özellikle el, dirsek ve dudaklar çevresinde papül benzeri döküntü ve göz muayenesinde iki taraflı blefaroz gözlendi. Videolarengostroboskopide, vokal kordlarda kalınlaşma ve tüm supraglottik bölgeyi ve oral mukozayı tutan sarı papül oluşumları dikkat çekti. Larenks ve sublingual bölgelerden alınan punch biyopsi örneklerinde, epitel ve subepitelyal yerleşimli hiperkeratoz paternli çok katmanlı amorf hiyalin materyal birikimi gözlendi. Histokimyasal incelemede, bazal membranda periyodik asit-Schiff ile pozitif ve Kongo kırmızısı ile negatif boyanma elde edildi. Tipik vokal kord tutulumu ve histopatolojik, genetik ve klinik bulgulara göre LP tanısı kondu.

Anahtar sözcükler: Ekstraselüler matriks protein 1; genetik; larenks; lipoid proteinozis; Urbach-Wiethe hastalığı.

Lipoid proteinosis (LP) has been first defined by Urbach and Wiethe in 1929 as "lipoidosis cutis et mucosae".[1] It is a rarely seen and recessively-inheriting hereditary disease.[2-4] Pathogenesis of LP is not known. Although it was named lipoidosis, it is thought that the hyaline material accumulating is a carbohydrate protein complex containing various levels of lipid.[5-9] Various studies have shown that LP might develop as a result of mutation in extracellular matrix protein 1 (ECM-1) gene in 1q21 chromosome.[9-11] Although it has been initially thought to be limited with skin and consequently oral mucosa and pharynx and larynx

Received: February 22, 2018 *Accepted:* July 20, 2018

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Citation:

Doğan M, Hıra İ, Balta B, Bayram A, Mutlu C. Lipoid proteinosis (Urbach-Wiethe disease): A rare entity and review of the literature. KBB Uygulamaları 2019;7(1):51-58.

due to characteristic involvements in those regions, it is now known that this disease can affect all visceral organs.[9-15] Larynx involvement can be determined since birth due to hoarsening and weak voice of crying that are generally the first symptoms of the disease.[16,17]

From a histological aspect, in organs involved, positive (+) staining with periodical acid-Schiff (PAS) and dermal and submucosal extracellular/perivascular deposition of amorphous material are typical.[6] Particularly, papular lesions may occur at the eyelid edges and vocal cords. Hoarseness appears due to involvement of vocal cords. Besides the involvement of skin and vocal cords, anomalies such as papules and plaques, xerostomia, dysphagia, loss of teeth, abnormal tooth development, and mental retardation are observed.[3,15-17] Its histopathologic characteristic is deposition of pastel, eosinophilic, PAS(+), and hyaline-like material in papillary dermis, dermo-epidermal composition around the dermal veins and skin adnexal, mucosa and visceral organs.[17-20]

CASE REPORT

A 32-year-old female patient applied to our polyclinic with complaint of white swelling under the tongue (Figure 1) limiting the movement of lip together with hoarseness claimed to start after tonsillectomy at third age. In physical examination, papule-like itchy rashes particularly around the lips and hyperkeratotic plaques on hands and elbows were determined (Figure 2). Moreover, bilateral blepharosis was observed in eye examination. In videolaryngostroboscopy, thickened vocal cords and edematous epiglottis and white lesions were noted, besides the attention-grabbing yellow papule formations covering the entire supraglottic region and mouth mucosa (Figure 3). In punch biopsy samples taken from larynx and sublingual regions, hyperkeratosis-patterned multilayered epithelial and subepithelial amorphous hyaline material deposition was observed. This deposition was also observed particularly around the veins. In histochemical examination, positive staining with PAS in basal membrane and negative staining with Congo red were obtained. Our case was diagnosed with LP characterized with typical vocal cord involvement and classical histopathologic and clinical findings. A written informed consent was obtained from the patient.

Genetic-Materials and Methods

Sequence acquisition

Reference gene sequence, coding sequence and amino acid (aa) sequences of ECM1 were retrieved through National Center for Biotechnology Information (NCBI) database; NCBI ID: NG_012062.1, NM_004425.3 and NP_004416.2, respectively. The coding transcript length is 1,623 nucleotides that results in ECM1 protein of aa 540 residues.

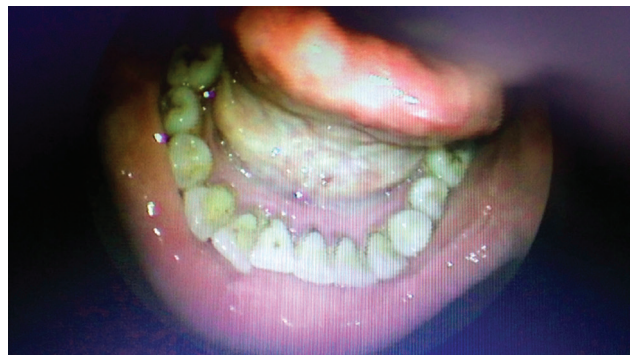

Figure 1. Sublingual deposits and inability to protrude tongue.

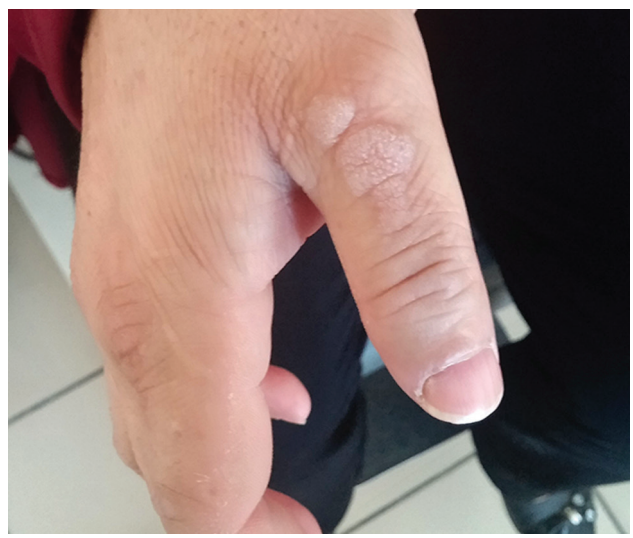

Figure 2. Hyperkeratotic plaque on dorsum of first finger.

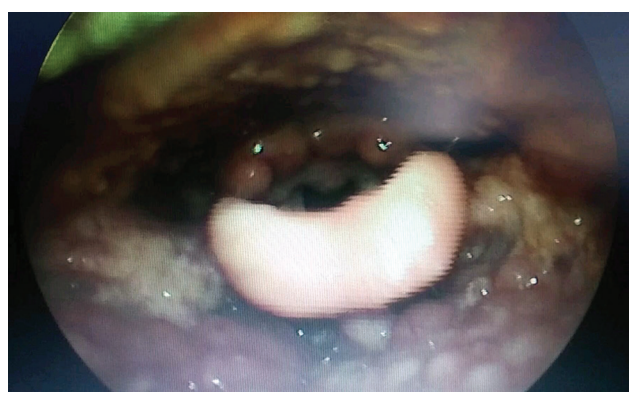

Figure 3. Supraglottic deposits.

Results of mutation analysis

For mutation analysis, all 10 exons including exon-intron boundaries of ECM1 were screened by Sanger sequencing. Using standard polymerase chain reaction (PCR) protocol, 250 ng of genomic deoxyribonucleic acid (DNA) in 50 µL final reaction volume was amplified. The amplification conditions were 95˚C for five minutes, followed by 35 cycles at 95˚C for 45 seconds, primer-specific annealing temperature for 45 seconds, 72˚C for 45 seconds and a final extension at 72˚C for 10 minutes. Of the PCR products, 10 µL were analyzed on 2.5% agarose gel and remaining PCR products were purified using QIAquick PCR Purification Kit (Qiagen GmbH, Hilden, Germany) and sequenced directly using BigDye® Terminator v3.1 cycle sequencing kit on an ABI 3130 genetic analyzer (Applied Biosystems, Foster City, CA, USA). Potential disease-associated mutation was confirmed by bidirectional sequencing and by assessing 50 healthy control samples. Sequences were compared with the NCBI reference sequences. Different bioinformatics tools were used to study the effect of mutation on the coding sequence of the ECM1 gene and its protein product.

Direct DNA sequencing of PCR products from exon 6, exon 8 and intron-exon boundaries of exon 9 revealed different homozygous variations in the ECM1 gene. A homozygous C>T missense genetic variation was identified at nucleotide position c.389C>T that resulted in substitution of threonine with methionine; p.T130>M (Figure 4a). This genetic variation has previously been reported as polymorphism in general population (rs3737240). A second homozygous G>A missense mutation identified at nucleotide position c.1243G>A led to the conversion of glycine into serine; p.G415S (Figure 4b). This genetic variation has also been documented as common polymorphism (rs13294).

A third genetic variation, a canonical splice site mutation, was identified in intron 8 at genomic position g. 150,485,199 where homozygous A>G change resulted in splice site variation (c.1305-2A>G) (Figure 4c). Though the Exome Aggregation Consortium (ExAC)[21] reported the genetic change as polymorphism (rs779368723) with an overall population frequency of 0.3 for this variant (ALL: G=0.0016%-AFR: 0%-AMR: 0%-EAS: 0%-SAS: 0%-NFE: 0.0030%-FIN: 0%-OTH: 0%). However, there is no data available for homozygous G allele frequency in any database (ExAC, Ensemble). In the studied subjects, no other sequence variants were observed in exonic and intronic DNA fragments of the ECM1 gene analyzed. All patients were found to be homozygous for this mutation; whereas this sequence variation was not observed in 50 healthy control subjects.

(A) Represents homozygous ACG>ATG variation at position c.389C>T; p.T130>M. (B) Represents GGT>AGT homozygous variation at position c.1243G>A; p.G415S. (C) Demonstrates homozygous 3' splice site variation at position c.1305-2A>G.

Evaluation of splice site mutation

Mutation analysis using Alamut software (www.interactive-biosoftware.com)[22] revealed that the altered nucleotide (c.1305-2A>G) is highly conserved (Figure 5). The variant is also not documented in Exome Variant Server (http://evs.gs.washington.edu/EVS/) that shows the unique nature of this variation. Since the homozygous variation c.1305-2A>G is a 3' splice site variation of intron 8, which may result in abolishing the acceptor splice site, skipping of exon 9 is very likely as predicted by Alamut. Skipping of exon 9 may result in a frame shift after aa 434 and protein truncation after aa 436 (Figure 6). The use of alternative splice site is the next possible mechanism to produce different transcripts. As predicted by Alamut and Alternative Splice Sites prediction programs,[23] another possible acceptor splice

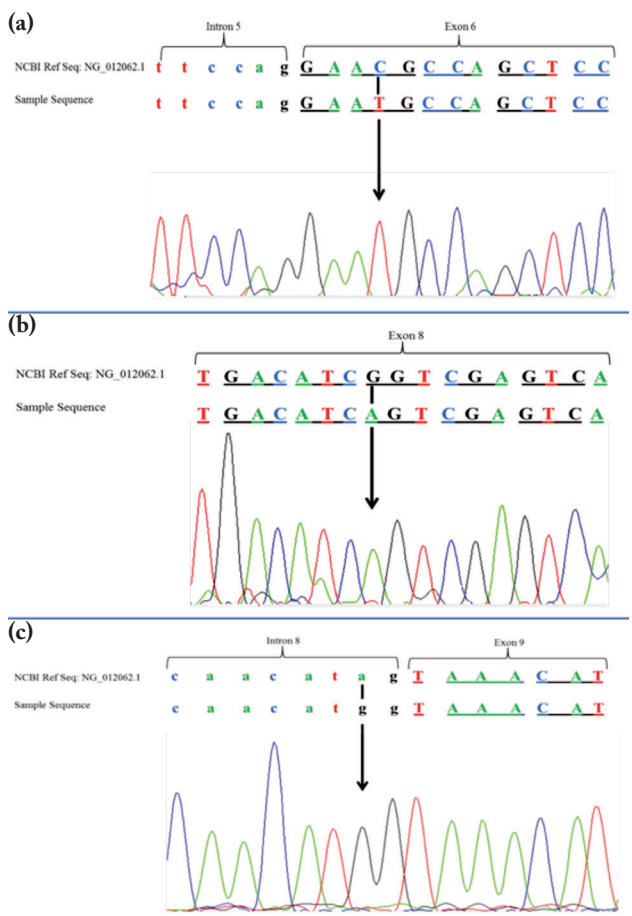

Figure 4. Electropherograms of identified genetic variations in extracellular matrix protein 1 gene.

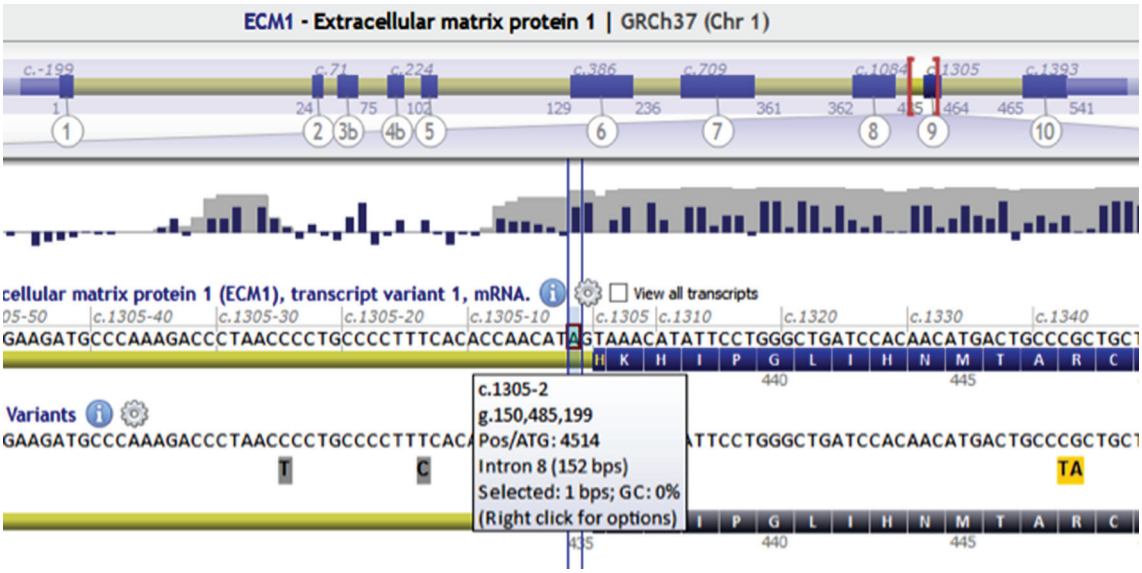

Figure 5. Showing high conservation (shown by blue bars or grey highlights) and genomic position of mutation c.1305-2A>G.

site is located in exon 9 at position c.1367 with very high consensus value of 86.9 (calculated by the Human Splicing Finder, range 1-100). However, alternative splicing will also lead to the frame shift after aa 434 and consequently protein truncation after aa 449 (Figure 7).

In both cases of either complete skipping of exon 9 or using of alternative splice site mechanism, there is a shift in aa frame and premature truncation of ECM1 protein that might be the possible explanation for genetic cause of LP in these patients (Figure 8).

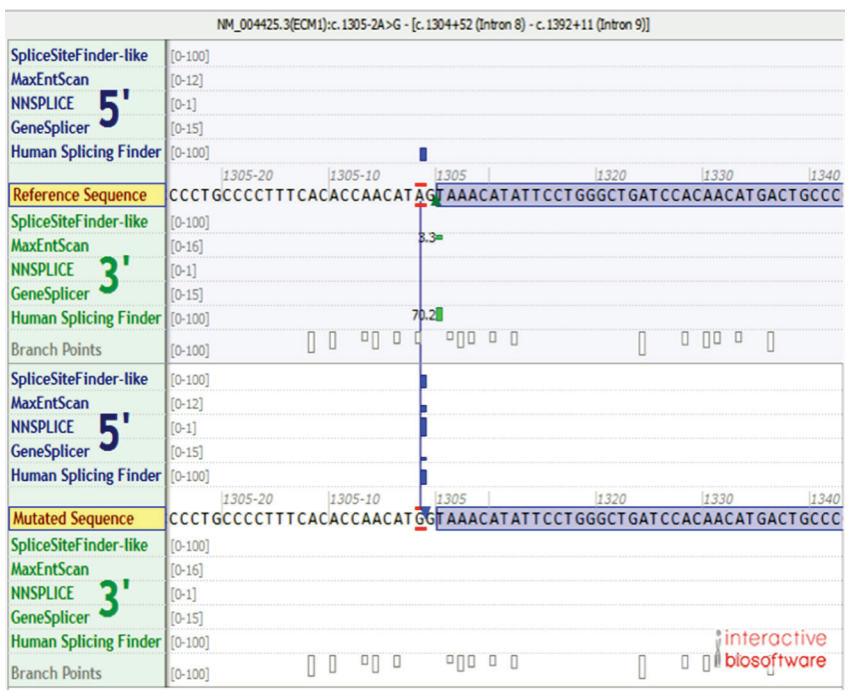

Figure 6. Splice site is abolished by c.1305-2A>G mutation. No score for mutated acceptor splice site was predicted by splice site finder programs.

Figure 7. Next possible splice site at c.1367 having very high prediction score of 86.9 (shown by arrow) that may result in a truncated protein of 449 amino acids.

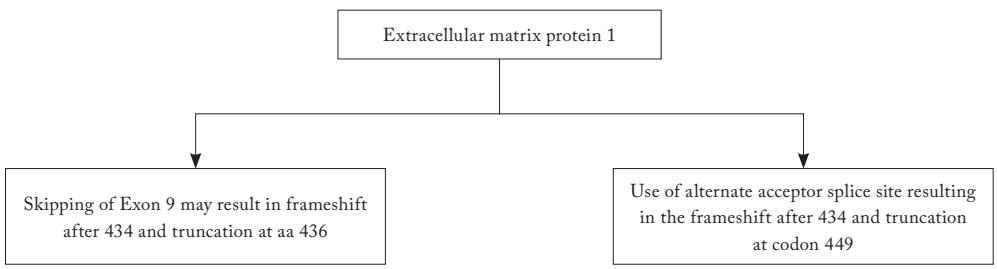

Figure 8. Schematic presentation of two possible protein products of extracellular matrix protein 1 gene carrying c.1305-2A>G splice site mutation in intron 8.

DISCUSSION

Lipoid proteinosis is a rarely seen and autosomal recessively-inheriting hereditary disease.[9] Since this disorder is observed rarely, not more than 300 patients have been diagnosed with Urbach-Wiethe disease.[24,25] The highest incidence of hyalinosis cutis et mucosae has been determined in South Africa.[26]

The typical facial appearance is characterized with waxy papules, which are also called monoliform blepharosis, on the face, besides the eyelids.[27] Hyperkeratotic plaque may develop on the frequent trauma regions such as elbows. Ankyloglossia, which is characterized with the inability to protrude the tongue, develops due to collagen deposition that leads to a thicker frenulum.[9,28] Clinical symptoms appearing mainly as hoarseness due to the involvement of vocal cords and beaded papules observed alongside the eyelids generally emerge in early childhood.[3,6,16] The classical and most easily recognizable sign is the beaded papules on the eyelid margins (moniliform blepharosis) observed approximately in two-third of the cases which are said to be pathognomonic.[29] These papules are also named "string of beads" or "eyelid beading".[30,31] Few other ocular symptoms related with the hyaline deposition have been found in conjunctiva, cornea, trabeculum and retina. Subsequently corneal opacities or secondary glaucoma due to infiltration in the trabeculum may also develop. Furthermore, the hyaline material deposition in small bowel may cause intestinal bleeding. Although

many autopsy studies have found that LP can be defined as a generalized disorder with microscopic hyaline deposition in practically every organ, the symptoms related to other visceral organs have not been clarified yet.[32,33]

Hoarseness has been identified as the first symptom of LP. Moreover, it was also the first finding in our case. Our patient also had tongue fissures. Skin lesions are generally seen as nodules on the face and lips (at earlier stages), and they then become hyperkeratotic.[33,34] In some patients, symptoms may be observed since birth. Since voice hoarseness occurs in neonatal period, it is one of the three entities that should be considered. The other entities to consider are congenital dysphagia and congenital hyperthyroiditis. Besides its classical appearance, skin involvement may be in different morphologies such as acne, varicella and impetigo.[6] Besides the skin and voice cord involvements, other anomalies reported in these patients are respiratory tract obstruction, infiltration in mouth mucosa in papule and plaque forms, xerostomia, dysphagia, hyposmia, teeth loss or abnormal teeth development, decreased tongue movements secondary to the thickening, epilepsy and mental retardation thought to be secondary to temporal lobe calcification.[8-11] The complications that have been reported in these patients are dental hypoplasia, gum hypertrophy, dryness of mouth, recurrent parotid and submandibular gland infections, and predisposition to respiratory distress during an episode of upper respiratory infection, due to thickened tongue and larynx.[35,36]

Neurological complications include basal ganglia calcification, usually bilaterally symmetric, which can cause seizures, subtle cognitive abnormalities and rarely spontaneous intracerebral hemorrhage.[37-40]

The classical histopathologic characteristics are pastel, eosinophilic, PAS(+) and hyaline-like material deposition in papillary dermis, dermo-epidermal composition, dermal veins around eccrine sweat glands, and in mucosa and visceral organs.[5,41] Although erythropoietic protoporphyria, popular mucinosis, lepra, amyloidosis and cutaneous xanthomonas are other entities that should be considered for diagnosis of this deposition observed in skin, voice hoarseness accompanying characteristic skin changes is accepted to be pathognomonic for LP. Among the histopathological findings, laryngeal amyloidosis is the one coming to the mind. Amyloid is observed as the subepithelial deposition or nodular mass consisting of extracellular, amorphous, and eosinophilic material. The most reliable finding is the staining with Congo red to applegreen or other colors under polarized light. Laryngeal amyloidosis is generally seen in fifth and sixth decades. Limited number of pediatric cases has been reported in the literature. Its incidence is three times higher among males than females.[6,7] Hoarseness is the most frequently observed finding.[1,8] Its etiology or pathogenesis is not known yet. No relationship has been found between laryngeal amyloidosis and smoking, alcohol use, or recurrent infection.[8,11] Pathogenetic loss of function mutations have been determined in the ECM1 gene. ECM1 is a glycoprotein having three varieties: ECM1a, ECM1b and ECM1c. EMC1 is expressed in the dermis, basal keratinocytes, endothelial cells and developing bones linked to keratinocyte differentiation, basement membrane regulation, collagen composition and growth-factor binding. The neurologic characteristics do not have any specific genotype-phenotype correlation. The mutated ECM1 gene causes the deposition of hyaline material within the dermis and around blood vessels and adnexal epithelia.[9,42] The prognosis of patients with LP is good despite the nature of disease advancing until adulthood. However, there is no effective treatment today. On the other hand, in a case study, successful clinical and histological improvement has been obtained with a continuous treatment with D-penicillamine, which is a chelating agent.[20] In another study, it has been reported that improvement has been obtained after the administration of dimethyl sulfoxide at a dose of 60 mg/kg/day.[43] Only in a few studies, oral etretinate has shown promising results.[42] Toosi and Ehsani[44] have reported that acitretin helps in improving laryngeal lesions and voice when compared to other drugs. Although both oral dimethyl sulfoxide and oral etretinate have shown promising outcomes, recent case studies have not reported any effective results.[45] Excision of the lesions using micro-laryngoscopy instruments has been shown to improve the airway and quality of voice.[30] In this case, in order to increase the voice level, we implemented laser micro-laryngoscopy and consecutive stripping to the vocal cords. Partial improvement was obtained in the voice of our patient. Respiratory tract obstruction is rare and it rarely requires tracheostomy. Dermoabrasion and chemical peeling may be performed in some cases.[20,46,47] Despite the different treatment options reported for LP, no long-time improvement or total cure has been reported.[30] In conclusion, our case ranked within the 300 cases in the literature with its classical skin involvement, blepharosis in eyes and extensive supraglottic depositions. The rare condition of our case should be kept in mind for clinical and histopathologic findings.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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