EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY

Date of Meeting: Basel, 11.-14.6.2025

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Case Numbers: O2020.255, O2024.204 und O2024.205

Material submitted: 3 digital links.

Title of Case Presentation:

CORNEAL EPITHELIUM WITH INTRACYTOPLASMIC, FINELY VACUOLATED INCLUSIONS.

CLINICAL HISTORY:

A 36-year-old female experienced problems with her right eye when she first tried to wear contact lenses and visited an ophthalmologist. He found epithelial changes and performed a therapeutic corneal abrasion in 2020. Subsequently, she presented to our clinic for a follow-up in February 2024 with a subjective, painless decrease in vision. Clinically, a diffuse epithelial feathery pattern was noted in the right eye, while the left eye was unremarkable. The visual acuity was 20/20 in both eyes, and the intraocular pressure was normal. Fundoscopy was unremarkable in both eyes. She again underwent a diagnostic and therapeutic corneal abrasion. Delicate epithelial changes in the left eye were also noted for the first time during the postoperative follow-up of the right eye. Genetic analysis performed after the histology revealed a heterozygous loss-of-function variant in the MCOLN1 gene.

OCULAR PATHOLOGY:

Light Microscopy:

The epithelium cells contained numerous vacuoles within their cytoplasme especially in the outer layers. These cells stained positively with PAS and negative with Sudan black.No dysplastic cells were presented.

Ultrastructural Microscopy:

The altered epithelial cells showednumerous vacuoles in their cytoplasm. These vacuoles contained a mixture of partly flocculent and partly lamellar material, mostely surrounded by membrane structures measuringfrom 200 to 400 nm in size.

DIAGNOSIS:

Lisch epithelial corneal dystrophy with genetically proven (confirmed)heterozygous loss-of-function variant in exon 9 of MCOLN1 gene.

DISCUSSION:

The patient presented clinically with a diffuse feathery pattern of the corneal epithelium, which is characteristic of Lisch corneal dystrophy following an unsuccessful attempt to wear contact lenses.

The lesion mostly originates from the corneoscleral limbus, with the affected epithelial cells forming a swirling pattern as they migrate toward the corneal center. Lisch corneal dystrophy may affect one or both eyes. Messmann corneal dystrophy is a differential diagnosis, as it usually presents with more centrally located epithelial cysts and fewer peripheral lesions. An epithelial dystrophy without histological confirmation cannot be entirely excluded.

Therapeutic abrasion and histological examination revealed vacuolization of the epithelial cells, which stained positive with PAS and negative with Sudan Black, consistent with previous descriptions[1].

Ultrastructural analysisshowed numerous vacuoles containing distinct, electron-dense, tangle-like material, sometimes including membranous components. Interestingly, a similar ultrastructural pattern has been described in the conjunctiva and cornea of a patient with mucolipidosis type IV (ML IV). This rare lysosomal storage disorder is associated with a mutation in the MCOLN1 gene located on chromosome 19p13, which is also implicated in Lisch corneal dystrophy,as in our patient [1, 2].

The MCOLN1 gene encodes mucolipin-1, a protein located in the membranes of lysosomes and endosomes, cellular compartments involved in digestion and recycling process. Mucolipin-1 plays a key role in lipid and protein trafficking between lysosomes and endosomes, functioning as a channel for cations to cross organelle membranes of these organelles [3].

In 2024, a multicenter study, Patterson et al. identified nine rare heterozygous MCOLN1 variants in patients withthe clinical phenotype of Lisch corneal dystrophy. These variants were found in 23 of 27 affected individuals from 13 families, with four of the nine variants also associated with ML IV. ML IV is an autosomal recessive, systemic disorder characterized by neurodegeneration and corneal opacity, usually manifesting in childhood. However,six parents of three ML IV patients carrying confirmed pathogenic MCOLN1 variants showed no clinical signs of Lisch corneal dystrophy, suggesting that MCOLN1 haploinsufficiency may be linked to reduced penetrance and variable expressivity [2]. Patterson et al. concluded that heterozygous MCOLN1 variants could be associated with incomplete penetrance of Lisch epithelial corneal dystrophy, estimating a penetrance of 0.2% for loss-of-function MCOLN1 variants based on the gnomAD database population sample. They proposed that the penetrance supports the hypothesis that Lisch epithelial corneal dystrophy opacities represent localized areas of cells with ML IV, potentially arising due to a somatic ‘second hit’ on the second MCOLN1 gene copy in these cells. This would explainunilateral and sporadic cases of the disease.

The literature also references an X-linked dominant defect at the Xp22.3 locus on the short arm of the X chromosome in Lisch epithelial corneal dystrophy. This defect was identified through linkage analysis, which distinguishes it from Meesmann epithelial corneal dystrophy in family LECD1. In the study by Patterson et al., family LECD1 also carried a pathogenic MCOLN1 variant, whereas family LECD2 had only the MCOLN1 variant without the Xp22.3 defect [2, 4].

The indication for treatment is primarily based on the clinical presentation, particularly the degree of visual impairment.There is no consensus on a standardized therapeutic approach. Debridement or abrasion is frequently performed mechanically or using alcohol, and sometimes combined with

mitomycin C. One case report showed efficacy withtopical 1% 5-fluorouracil. [5]. Refractive laser surgery, such as photorefractive keratectomy with or without mitomycin C, has also been reported [6]. Other approaches include combining keratectomy combined with local limbal cauterization to eliminate the affected limbal stem cells [7], or ablating (excision) followed by limbal stem cell transplantation [8], aiming to reduce recurrence or achieve a cure. Lisch et al. described two patients in whom epithelial changes regressed after the use of contact lenses [9].

In conclusion, MCOLN1 haploinsufficiency appears to be the major cause of Lisch endothelial corneal dystrophy. Clinical therapy isnot standardized and is oriented according to clinical findings.

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