

Importance of adherence to topical cysteamine in infantile ocular cystinosis: An illustrative case

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Cystinosis is an autosomal recessive lysosomal storage disorder caused by a *CTNS* gene mutation on chromosome 17p13 encoding for cystinosin, a carrier protein that transports cystine out of the lysosomes.^[1] The disease is characterized by lysosomal cystine deposits within several organs, mainly the kidneys and the eyes. Cystinosis is the primary genetic cause of renal Fanconi syndrome, which develops during the first year of life and leads to end-stage renal failure by the age of 10.^[2]

A late-onset non-nephropathic form of the disease, named ocular cystinosis, is characterized by a predominant eye involvement with a slow or even absent renal compromise. Nonetheless, ocular manifestations are important in the nephropathic and non-nephropathic forms of cystinosis and include photophobia, blepharospasm, foreign body sensation, and superficial keratopathy.^[3] These findings appear progressively during the first decade of life and are related to the accumulation of cystine crystals in the cornea and conjunctiva.

With the advent of novel therapeutics and an increased rate of renal transplantation, non-renal manifestations of cystinosis are being observed with higher frequency.^[4] In this regard, oral cysteamine, which forms a mixed compound with cystine allowing it to be transported out the lysosomes, has proven to reduce cystine accumulation and delay renal complications of cystinosis.^[5] However, its effects on ocular manifestations are minimal, once the corneal involvement has been established.^[6] Topical cysteamine formulations are also available, but have

several limitations, including that cysteamine drops need to be frozen to prevent their oxidation and must be administered every waking hour to achieve treatment effectiveness.^[7]

Here, we describe a case of ocular cystinosis that illustrates the importance of adherence to topical cysteamine for preventing symptomatic ocular manifestations.

A 14-year-old boy attended our outpatient clinic complaining of photophobia and bilateral foreign body sensation, which started 5 months before. He was diagnosed with cystinosis at the age of 2 years, for which he received treatment with cysteamine bitartrate 150 mg capsules (Cystagon, Orphan Europe S. A. R. L.) every 6 h ever since. Also, he underwent a right kidney transplant 4 years ago. Previously, he was asymptomatic and with minimal photophobia while using a topical treatment based on cold cysteamine drops (Cystaran 0.44%, Sigma-Tau Pharmaceuticals) in each eye every 6 h. However, he reported that his current ocular symptoms appeared and increased progressively in severity since the suspension of the treatment due to an interruption of the institutional supply by the manufacturer laboratory.

Other aspects of his medical history were not relevant. On admission, physical examination did not reveal any neurological, cardiological, thoracic, or abdominal abnormality. Visual acuity was 20/30 (0.67) in the right eye and 20/25 (0.80) in the left eye. Slit-lamp evaluation of the anterior segment showed the presence of needle-shaped reflective corneal opacities [Fig. 1]. The fundus examination was unremarkable, whereas the optical coherence tomography (OCT) scan of the anterior segment and macula showed hyperreflective punctiform opacities in all corneal and inner retinal layers, respectively [Fig. 2].

The patient continued to be under treatment only with oral cysteamine for 3 months, while waiting for the availability of topical therapy. Notably, his ocular manifestations remitted once cysteamine drops were reinitiated. Additional follow-up examinations showed similar findings with stable ocular involvement and no further complications or side effects of topical treatment. The legal guardian of the patient provided written consent for publication of the case.

Discussion

Ocular manifestations are common in nephropathic and non-nephropathic forms of cystinosis and result from the accumulation of cystine crystals in the cornea, conjunctiva, iris, ciliary body, and retina.^[3,4] Initially, ocular involvement is asymptomatic; however, progressive cystine deposition in the cornea causes significant photophobia and blepharospasm. Cystine crystals are found in the periphery and superficial layers of the cornea, showing a centripetal progression until all layers are involved. On biomicroscopy, cystine crystals look like

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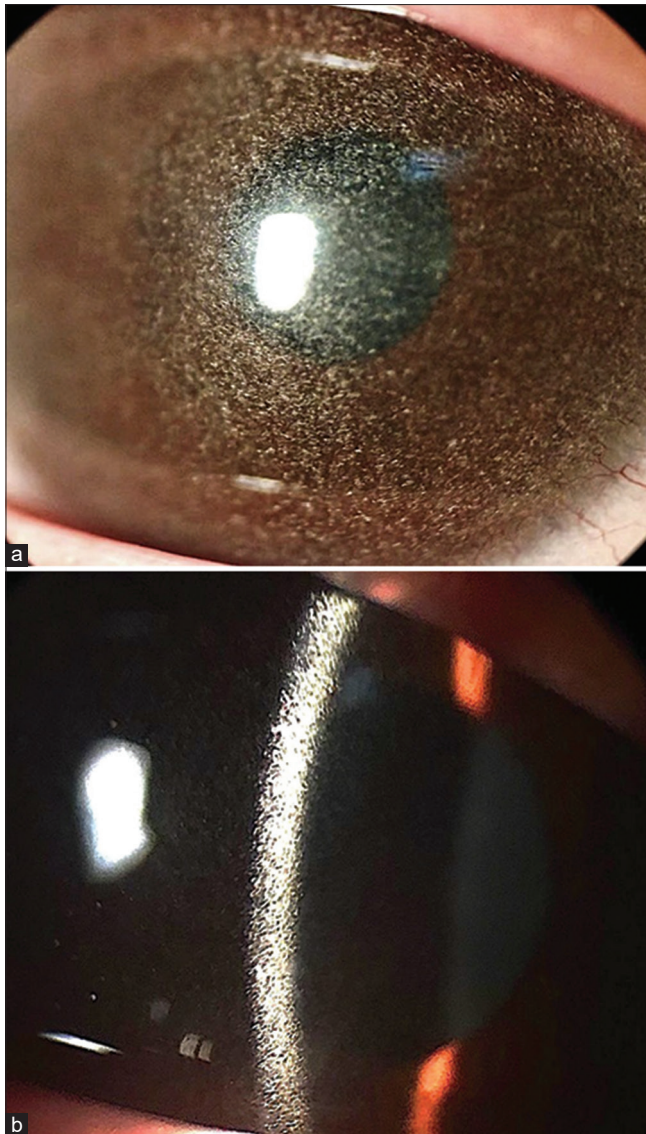


Figure 1: Corneal slit-lamp examination of an infant with nephropathic cystinosis. The examination of the anterior eye segment under diffuse illumination showed the classical golden dust appearance of the cornea (a). Meanwhile, the slit-lamp examination revealed cystine deposits that appeared as needle-shaped reflective opacities (b), with CCCS of 3.0 CCCS = corneal cystine crystal score

diffuse, needle-shaped reflective corneal opacities, having little impact on visual acuity.^[8] Superficial punctate keratopathy, foreign body sensation, and pain may develop later due to an inflammatory reaction in the epithelium and Bowman's layer of the cornea. Fundus depigmentation and mottling is the most frequent finding in the posterior segment.^[3,4]

Anterior segment OCT (AS-OCT) and *in vivo* confocal microscopy (IVCM) are often used to follow-up corneal cystine deposits. AS-OCT allows crystal depth measurement and gives an objective marker of the severity of crystal deposits; however, it cannot accurately quantify the amount of deposits. IVCM provides high-resolution images at a specific depth within the cornea, giving more precise information about the depth of crystal deposition in the cornea, being the only way to



Figure 2: OCT scan images in an infant with nephropathic cystinosis. (a) Anterior segment OCT scan showing diffuse hyperreflective punctiform opacities involving the total depth of corneal stroma. (b, c) Representative macular OCT scan of the patient's right eye showing similar opacities in the inner retinal layers, which project shadows that obscure visualization of structures underneath OCT = optical coherence tomography

analyze deposits at a cellular level, and is the most useful for quantitative assessment of treatment response.^[5]

The prognosis of cystinosis has drastically improved since the introduction of oral cysteamine, which delays renal failure progression.^[6] Although this formulation reduces retinal cystine crystal deposits, it is not effective for managing corneal involvement due to the avascular properties of this tissue. In contrast, topical administration of cysteamine drops controls corneal crystals, thus reducing the risk of complications such as erosions, scarring, and neovascularization.^[7,8] Additionally, cysteamine drops positively impact patients' quality of life, as it is associated with a decrease in photophobia and a symptomatic improvement.

Despite their benefits, topical cysteamine formulations have certain limitations, including the compound's hydrophilic characteristics that result in poor penetration through the lipophilic corneal epithelium, making it difficult to access the stroma, where the most significant number of deposits are found. Another hurdle is that cysteamine

oxidizes rapidly at room temperature. Hence, drops must be frozen, maintained cool, and used within 7 days of opening to keep their efficacy. This fact represents a great problem of treatment storage for health institutions. Finally, due to the short duration of cysteamine on the ocular surface, topical formulations must be administered up to 12 times per day.^[8,9]

These limitations demand a high patient adherence to treatment to achieve symptomatic improvement and prevent complications. The case described here exemplifies this issue well, as our patient showed a rapid relapse of ocular symptoms shortly after discontinuing cysteamine drops. Notably, during the period without treatment, the patient did not show a progression of the ocular damage, probably due to the protective effect of the oral formulation on posterior eye structures such as the retina, which has an abundant vasculature that facilitates drug penetration.

In 2017, a gel formulation (Cystadrops 0.38%, Orphan Europe S. A. R. L.) was approved by the European Medicines Agency (EMA). This formulation allows longer contact with ocular surface, hence reducing the frequency of application to one drop four times daily, which can improve patient compliance to treatment.^[5,10,11]

Our case illustrates the importance of adherence to topical treatment for maintaining ocular symptoms under control in patients with nephropathic cystinosis.

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Conflicts of interest

There are no conflicts of interest.

Author contributions

Design of the study: MB-S, MIV-B, YV-L. Patient × s evaluation and management: MB-S, YV-L. Clinical data retrieval: MB-S, MIV-B, YV-L. Drafted the manuscript: MB-S. All the authors

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