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CLINICAL PATHOLOGIC REVIEWS

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Ophthalmic Manifestations and Histopathology of Infantile Nephropathic Cystinosis: Report of a Case and Review of the Literature

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Abstract. Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine, in many organs and tissues. Infantile nephropathic cystinosis is the most severe phenotype. Corneal crystal accumulation and pigmentary retinopathy were originally the most commonly described ophthalmic manifestations, but successful kidney transplantation significantly changed the natural history of the disease. As cystinosis patients now live longer, long-term complications in extrarenal tissues, including the eye, have become apparent. A case of an adult patient with infantile nephropathic cystinosis is reported. He presented with many long-term ocular complications of cystinosis. After 4 years of follow-up, the patient died from sepsis. Pathology of the phthisical eyes demonstrated numerous electron-transparent polygonal spaces, bounded by single membrane, in corneal cells, retinal pigment epithelial cells, and even choroidal endothelial cells. The ophthalmic manifestations and pathology of infantile nephropathic cystinosis are discussed and reviewed in light of the current report and other cases in the literature. (**Surv Ophthalmol 52**:97–105, 2007.

Key words. cystine • cystinosis • eye • histopathology • infantile nephropathic cystinosis • lysosome

Cystinosis was initially described by Aberhalden in 1903.[2] Cystinosis is a rare autosomal recessive metabolic disorder characterized by the intracellular accumulation of cystine, the disulfide of the amino acid cysteine.[29,43,44] The responsible gene, *CTNS*, encodes cystinosin, a 367 amino acid integral membrane protein that transports cystine out of the lysosome.[37,61,89] As a result of deficient or absent cystinosin, cystine accumulates within lysosomes and forms crystals in many tissues, including the kidneys, bone marrow, pancreas, muscle, brain, and eye.

Based on age of onset and severity of symptoms, several cystinosis phenotypes have been described.[44] They are nephropathic and non-nephropathic. Nephropathic cystinosis further divides to infantile (classic) and intermediate (juvenile-onset or adolescent). Non-nephropathic cystinosis was formerly called benign or adult type cystinosis[19] but

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is now termed *ocular cystinosis*. Infantile nephropathic cystinosis, the most common and severe phenotype, presents with growth retardation and renal tubular Fanconi syndrome between 6 and 12 months of age and, if untreated, leads to renal failure by approximately 10 years of age.[44,83] Intermediate (late-onset nephropathic) cystinosis manifests the same symptoms but with a later age of onset.[44,47,83] Ocular cystinosis presents only with corneal crystal deposition but no associated systemic manifestations.[19,44,83] Different *CTNS* mutations produce the three different phenotypes, that vary based upon the amounts of residual cystinosin activity.[5,6] Here we report a clinicopathological case of infantile nephropathic cystinosis in an adult patient and review the literature regarding the disorder's early ophthalmic manifestations and late-onset ocular complications.

Case Report

This infantile nephropathic cystinosis patient was initially seen at the National Eye Institute (NEI) at 31 years of age for initiation of topical cysteamine therapy. He was enrolled in a protocol approved by the NEI Institutional Review Board and gave written informed consent. He complained of longstanding photophobia and foreign body sensation in his corneas. Past ophthalmic history included a keratoplasty in his right eye and bilateral ischemic diabetic retinopathy. On ocular examination best corrected visual acuity was 20/400 in the right eye and 20/320 in the left eye. Slit-lamp examination revealed early band keratopathy in both eyes. Whereas the donor cornea in the right eye was crystal-free, the host corneal bed and the left cornea exhibited abundant corneal crystals. Both irides were thickened and packed with crystals and posterior synechiae could be visualized in the right eye. Funduscopic examination of the right eye revealed intraretinal crystals with macular and peripheral pigmentary changes (Fig. 1A). A limited view of the left fundus prevented clear delineation of macular changes in the left eye, but indocyanine green videoangiography revealed a submacular choroidal neovascular membrane with feeder vessel; intraretinal crystals were also detected, as we previously reported (Fig. 1B).[90] Humphrey visual fields and electroretinography confirmed the presence of retinopathy. The patient failed to comply with the hourly regimen of topical cysteamine treatment. His ophthalmic complications progressed and included recurrent spontaneous hyphema and hemorrhages in the vitreous and retrobulbar space of the right eye secondary to anticoagulation therapy. When seen at the NIH Clinical Center in follow-up at the age of 33, the right eye had become phthisical. Both eyes had developed severe band keratopathy that prevented any further evaluation (Fig. 2).

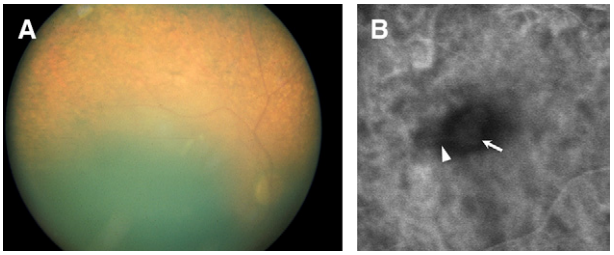

Fig. 1. Fundus photograph of the right eye (*A*) and ICG-V image of the left fundus (*B*). Typical retinal pigmentary changes are obvious in the retinal periphery of the right eye (*A*). A subfoveal choroidal neovascular membrane (arrow) with contiguous feeding vessel (arrowhead) are evident in the left eye (*B*). Please note the poor quality of the fundus photograph, due to the cornea opacification and the inadequate dilation achieved secondary to the posterior synechiae.

The patient died from sepsis at the age of 35. Autopsy findings included necrotizing peritonitis involving the small bowel and colon, fibrinous pericarditis and pleuritis, ascites, systemic and pulmonary edema, and hemorrhagic urocystitis. There were hepatic and splenic infarctions, cardiomegaly, and atherosclerosis, along with findings typical of cystinosis, such as short stature, retarded sexual development, atrophic kidneys, and a small thyroid gland. Particular attention was paid to the eyes that were donated for pathology.

Pathological Findings

ROUTINE HISTOLOGY

Macroscopic examination revealed a calcified and phthisical right eye (Fig. 3B), measuring 17 (AP) × 20 (H) × 17.5(V) mm, whereas the left eye measured 20 × 23 × 22.5 mm. A central ulceration surrounded by a small amount of hemorrhage was also noted in the right cornea (Fig. 3A). Both eyes were decalcified for processing.

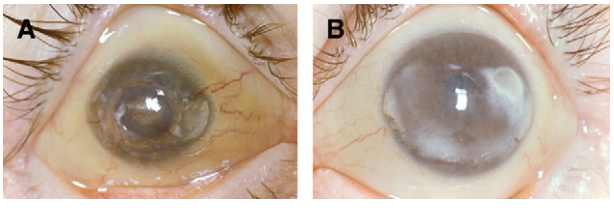

Fig. 2. Slit lamp photograph of right eye (*A*) and left eye (*B*). Calcification is present in both corneas. Severe cornea neovascularization is seen in the right cornea.