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Late-onset retinal oxalosis in primary hyperoxaluria type 2

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ABSTRACT

Purpose: To report a previously undescribed case of late-onset vision loss due to retinal oxalosis in a patient with primary hyperoxaluria type 2 (PH2).

Observations: An 82-year-old female with a history of biopsy-proven oxalate nephropathy developed vision loss 8 months after end stage kidney disease. She developed progressive retinal ischemia secondary to crystal deposition. She was presumed to have retinal oxalosis, and genetic testing confirmed PH2. Her retinopathy occurred once renal clearance fellow below hepatic oxalate production. The only effective treatment is kidney transplantation, but this patient was not a candidate.

Conclusions and Importance: To date, this is the most delayed-onset and severe reported case of progressive ischemic retinopathy from PH2. Patients with systemic oxalosis should be referred for genetic testing, as there are new RNA interference treatments approved for other subtypes of primary hyperoxaluria.

1. Introduction

Primary hyperoxaluria (PH) refers to a rare group of genetic disorders with defective oxalate metabolism leading to increased oxalate production. They are inherited in an autosomal recessive manner, with an estimated prevalence of 1 in 58,000 individuals worldwide.[1] With untreated PH, recurrent nephrolithiasis and progressive nephrocalcinosis can result in end stage kidney disease (ESKD), and the progressive rise in serum oxalate levels from reduced renal clearance leads to systemic oxalate crystal deposition in various organs including the heart, bones and eyes.[1] Three subtypes (PH1-3) are categorized by genetic defects in *AGXT*, *GRHPR*, and *HOGA1* in the oxalate metabolism pathway respectively.[1] Type 1 disease (PH1) comprises 70–85 % of PH patients with ESKD by 20–30s with a cumulative renal survival 43 % by age 40.[1] There is a wide phenotypic spectrum of PH1 including an early infantile manifestation.[1] Type 2 disease (PH2) comprises about 8–10 % of PH patients, with patients developing stage 5 chronic kidney disease by approximately 45 years, with 82 % cumulative renal survival by age 40.[1,2] We report a rare case in which a patient with PH2 developed ESKD in her 9th decade of life, with subsequent rapid visual decline due to retinal ischemia from oxalate crystal deposition.

2. Case report

An 82-year-old female presented with acute-onset blurred vision in both eyes. Her past ocular history was significant for non-exudative age-related macular degeneration and normal-tension glaucoma. Her past medical history included a right nephrectomy at age 15 after a decade of recurrent nephrolithiasis and pyelonephritis. She had been referred to nephrology for rapid decline in renal function, 8 months prior to presentation with blurry vision, prompting a kidney biopsy that revealed tubular luminal and parenchymal oxalate crystals with interstitial fibrosis and tubular atrophy (Fig. 1A and B). She was started on peritoneal dialysis 2 months later.

On presentation, her visual acuity measured 20/25 in the right eye and 20/40 in the left eye. Slit lamp exam showed clear and well-centered intraocular lenses in both eyes. Fundus exam revealed macular drusenoid deposits, cotton wool spots, and intra- and extra-vascular refractile crystalline deposits (Fig. 2A and B). Optical coherence tomography (OCT) showed diffuse punctate hyperreflective foci preferentially in the inner retina and trace subfoveal fluid in both eyes (Fig. 2A',B'). Fluorescein and OCT angiography (Fig. 3B) demonstrated widespread macular capillary nonperfusion. The presumed diagnosis was retinal oxalosis given the kidney biopsy findings of oxalate nephropathy. Her

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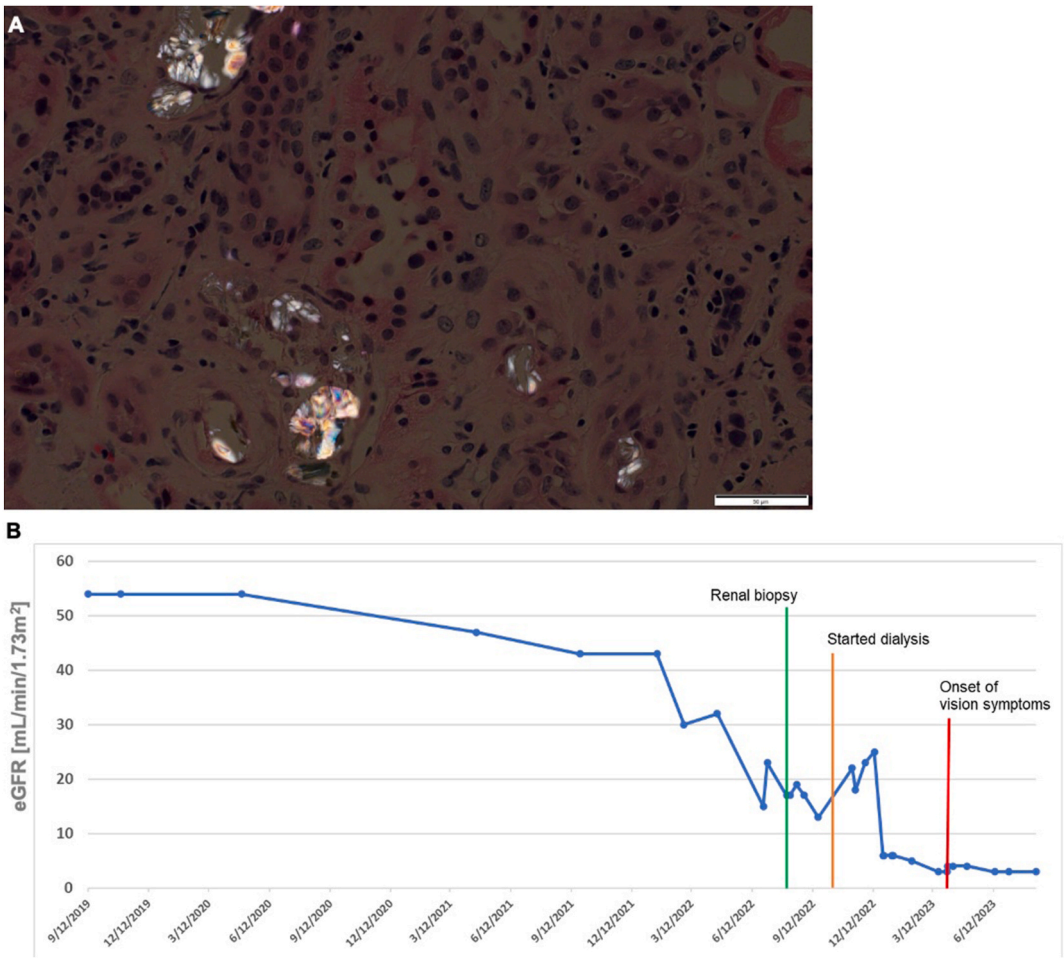

Fig. 1. Renal Biopsy and Function. A. H&E stained renal biopsy section shows mild interstitial fibrosis and tubular atrophy. Under polarized light, calcium oxalate microcrystals (bright regions) are visible in tubular lamina and in the interstitium. Scale = 50 μm. **B.** Estimated glomerular filtration rate (eGFR, CKD-EPI 2021) over time. The patient had a nephrectomy at age 15. Her remaining kidney function slowly began to decline in 2020 at age 89. There was a sharp decline in March 2022, approximately 1 year prior to onset of vision symptoms. It is believed that systemic oxalosis occurs after eGFR falls below 30–40 mL/min/1.73m2 because hepatic oxalate production exceeds renal removal. A renal biopsy confirmed oxalate nephropathy 8 months prior to vision symptoms. Patient started dialysis 6 months before vision symptoms.

plasma oxalate level was elevated to 95.5 μmol/L (reference range ≤2). She was referred for genetic testing given high clinical suspicion of PH to determine if she would be a candidate for novel RNA interefence (RNAi) therapies that are only available for PH1.[3]

She underwent Next Generation Sequencing on an Illumina Platform with a 3 gene primary hyperoxaluria panel (Invitae Corporation (CLIA certified), San Francisco, CA). She was found to have a homozygous frame shift variant, c.103delG (p.Asp35Thrfs*11), in the glycolate reductase/hydroxide-pyruvate reductase (*GRHPR*) gene. This variant leads to a premature termination event and is predicted to lead to loss of function and is classified as pathogenic by ACMG criteria (PVS1, PM3, PM2, PP5) confirming PH2 disease.[4] The c.103delG variant has an allele frequency of 0.066 % (gnomAD) in those of non-Finnish European ancestry and is the most common homozygous variant reported in patients with PH2.[5]

The retinal oxalate deposition steadily progressed with worsening vascular nonperfusion and widespread ischemia leading to neovascularization and vitreous hemorrhages in both eyes (Fig. 2C and D). She underwent avastin injections and panretinal photocoagulation in both eyes. At her most recent visit 9 months after presentation, her visual acuity had decreased to hand motions in both eyes. A trial of high-frequency hemodialysis was recommended for improved oxalate clearance, but the patient elected to continue with peritoneal dialysis.

3. Discussion

Here we presented a patient with autosomal recessive PH2 from a homozygous null variant in GRHPR, who developed progressive vision loss due to severe retinal oxalosis in the 9th decade of life. Although retinal oxalosis is a known complication of PH, there is a paucity of information on the retinal manifestations of PH2.[4] In the largest case series, only one patient had mild subretinal oxalate deposition with kidney failure by age 57.[4] This is unlike our patient who presented with probable subretinal, intraretinal, and intravascular oxalate deposition. In Fig. 3, we show extensive deep capillary nonperfusion on OCTA with extensive hyperreflective foci on en-face and structural imaging. This highlights well the crystalline deposition, seen on clinical examination.

The etiology of intravascular versus subretinal deposition is unknown, and likely multifactorial. As such, the retinal manifestations of systemic oxalosis are varied in the literature. For instance, in infantile PH1 there is subretinal oxalate deposition with resultant pigmentary changes and macular subretinal fibrosis.[6] It is postulated that the immature choroidal-Bruch's-RPE complex is particularly susceptible to oxalate crystallization.[6] In noninfantile PH1, they found only mild or no subretinal oxalate deposition, with some patients having high plasma levels of oxalate at the time of examination.[6] Although the PH1 and PH2 case series,[4,6] showed mild retinal changes, this is likely because most of the patients were younger, did not have ESRD, and had normal plasma

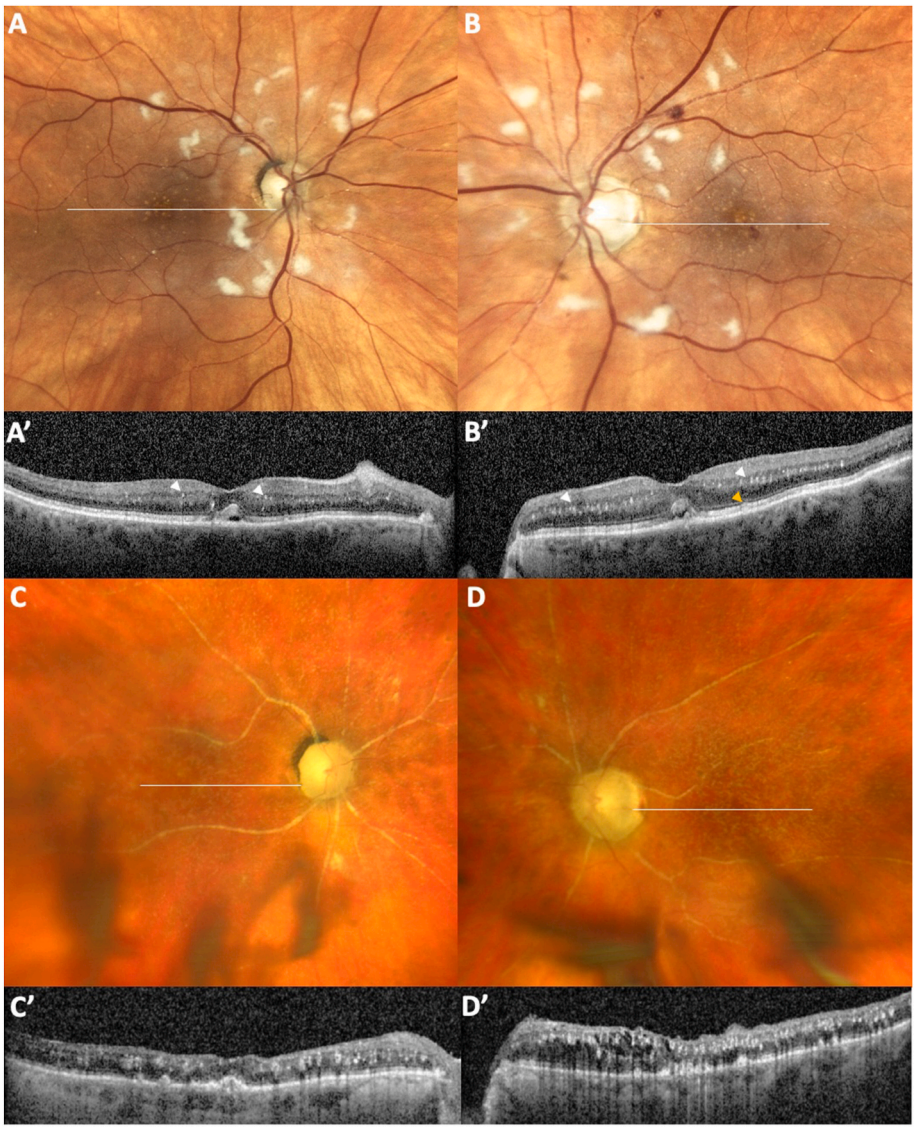

Fig. 2. Retinal Imaging at Presentation and 9 months. A-B. Fundus photographs at presentation show macular pigment mottling, cotton wool spots, and intravascular and retinal fine crystal deposition in both eyes. **A′-B'.** Optical coherence tomography (OCT) at presentation reveals diffuse hyperreflective foci (white arrows) and few sub-retinal pigment epithelium (RPE) deposits (yellow arrow). **C-D**. Fundus photographs 9 months after presentation reveal a dramatic increase in crystalline deposits intraarteriolarly and intraretinally. **C′-D'**. OCT at 9 months shows increased intraretinal hyperreflective foci. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

oxalate levels. In addition, there is limited information on the length of time with untreated disease. We postulate that the severe deposition is due to persistent, untreated disease.

There are additional case reports that have shown intravascular and retinal oxalate deposition.[7–11] For example, Munir et al. (2004) reported a case of a late-onset PH1 with similar extensive fine crystalline deposits intraarteriolarly and intraretinally.[7] In addition, Wells et al. (1989) described the histopathology of a case with inner retinal oxalate deposition in a patient with ESKD, pyridoxine deficiency, and ascorbic acid supplementation.[8]

There are some limitations to our case. We cannot say for sure the deposits are oxalate, as we do not have histopathology to correlate. Also, due to age some of her subretinal deposits could be drusen from age-related macular degeneration.

Unfortunately, once there is ESKD, neither standard hemodialysis nor peritoneal dialysis can clear the endogenous oxalate production, leading to further oxalate accumulation. Systemic oxalosis occurs once GFR falls below 30–40ml/min/1.73m^2, and renal clearance falls below hepatic oxalate production.[12] However, intensive hemodialysis with longer, more frequent sessions may be beneficial.[12] The only current effective therapy for PH2 is kidney transplantation, with or without liver transplantation, for which our patient was not a candidate. In contrast, new RNAi treatments such as lumasiran and nedosiran are approved for PH1 as they have been shown to effectively reduce hepatic oxalate production.[12] Therefore, if there is suspicion for PH, genetically testing maybe helpful to provide guidance on treatment options.

4. Conclusion

This case reinforces the need for ophthalmologists and nephrologists to screen for ocular crystal deposition in patients with crystalline nephropathy. Patients with systemic oxalosis should be promptly referred for genetic testing to determine if they have PH1, which is amenable to newly approved pharmacologic therapies. Our patient's uniquely late age at presentation suggests there is utility to genetic testing at any age for discussion of treatment options.

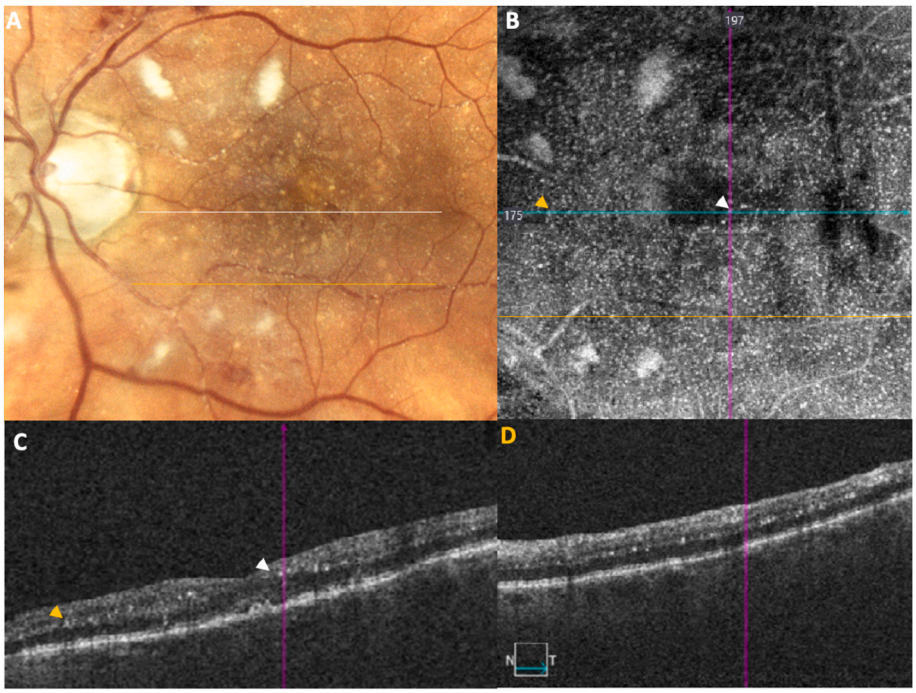

Fig. 3. Multimodal Imaging of Hyperreflective Foci at 1 month. A. Magnified photo of the macula shows intra-arteriolar, intraretinal, and subretinal deposits. **B.** OCT angiography en-face deep capillary plexus slab demonstrates remarkable deep capillary plexus flow voids with diffuse hyperreflective foci. **C-D.** Structural line scans show locations of these hyperreflective foci in the retina (white and yellow arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

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CRediT authorship contribution statement

Rupak Bhuyan: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tyler Maggio:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Christie Thomas:** Writing – review & editing, Data curation. **Meenakshi Sambharia:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Karen Gehrs:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Timothy Boyce:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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