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Catastrophic retinal vascular occlusion and vision loss due to crystal deposition in end-stage kidney disease treated with peritoneal dialysis

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ABSTRACT

Purpose To report two cases of catastrophic retinal vascular occlusion and crystalline retinopathy due to presumed oxalosis and hyperphosphatemia.

Observations We describe two unrelated patients with end-stage kidney failure (ESKD) treated with peritoneal dialysis that developed rapid bilateral vision loss due to severe retinal vascular occlusion. Multi-modal retinal imaging studies demonstrated crystalline deposits. Plasma phosphorus and oxalate levels were markedly elevated compared to persons with normal kidney function. One patient harbored a heterozygous variant of unknown significance in the Alanine–Glyoxylate Aminotransferase (AGT) gene. Intense hemodialysis and diet modification reduced phosphorus and oxalate levels.

Conclusions and importance This report serves to raise awareness of hyperphosphatemia and oxalosis in dialysis patients to alert providers so that they can act to decrease the potential risk of vision loss.

Crystalline retinopathy includes a variety of conditions that result in refractile retinal deposits that can by clinically distinguished during dilated fundus examination. It is associated with different etiologies including genetic, toxic, degenerative, idiopathic and iatrogenic causes.[1] Crystals can be located in all layers of the retina or in the choroid,[2,3] may also be scattered in the macula or throughout the retinal periphery.[4] Retinal vascular occlusion due to crystalline deposition is a rare identity. We report two cases of catastrophic retinal vascular occlusion and vision loss presumed to be due to calcium phosphate and calcium oxalate deposition following ESKD and other contributing factors.

Case

A 32-year-old female with a history of type 1 diabetes since the age of

15 presented in February 2022 with progressive vision loss over several months. Blood sugar control was poor, with previous hemoglobin A1C measurements up to 17.0 %. Most recent A1C was 6.7 %. Past medical history was also remarkable for non-obstructive coronary artery disease and ESKD requiring peritoneal dialysis since 2019. The patient had transient peripheral neuropathy with manifestations resembling Guillain-Barre Syndrome in April 2022. After a five-day treatment regimen with intravenous immune globulin the neurological findings abated.

At baseline eye examination in February 2022, visual acuity of the right eye was 20/30 right eye and 20/25 left eye. Slit lamp exam showed normal anterior segment without crystals in the conjunctiva, cornea, anterior chamber, or iris. Retinal examination of each eye indicated the presence of patchy crystalline deposits in retinal vessels without evidence of retinal hemorrhage or neovascularization. Three months later, vision was decreased to 20/400 in both eyes, and diffuse whitening of the entire retinal arterial tree was noted bilaterally (white arrow heads in Fig. 1A and B). Multiple cotton wool spots were present in an arc

temporal to the optic nerve head in both eyes, with no retinal hemorrhage or neovascularization (black arrow heads in Fig. 1A and B). Wide field fluorescein angiography illustrated diffuse retinal circulation loss, with a narrow ring of preserved retinal circulation around the optic nerve head in each eye (Fig. 1C). The patient subsequently developed vitreous hemorrhage from retinal and iris neovascularization that was treated with serial intravitreal injections of bevacizumab (1.25 mg in 0.05 mL) at three-month intervals. Visual acuity has remained 20/400 in both eyes.

Anuria from ESRD prevented urine analysis; hence, systemic oxalate levels were measured by plasma analysis. Plasma oxalate was elevated at 28 µmol/L (reference range <2.0) in August 2022. The phosphorus level was also elevated at 22.3 mg/dL (reference range 2.5–4.5 mg/dL). Since the oral phosphate binders were unable to lower phosphorus levels, dialysis was switched from peritoneal to high intensity hemodialysis 6 days per week. Six months later, the oxalate levels decreased to 4.9 µmol/L, and phosphorus levels decreased to 6.5 mg/dL. Targeted genetic testing was done by next-generation sequencing (NGS) by Invitae, which is a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory. Variants in three genes (*AGXT*, *GRHPR*, and *HOGA1*) associated with primary oxalosis (PO) were evaluated. It disclosed a variant of unknown significance of the *AGXT* gene (c.508G > A).
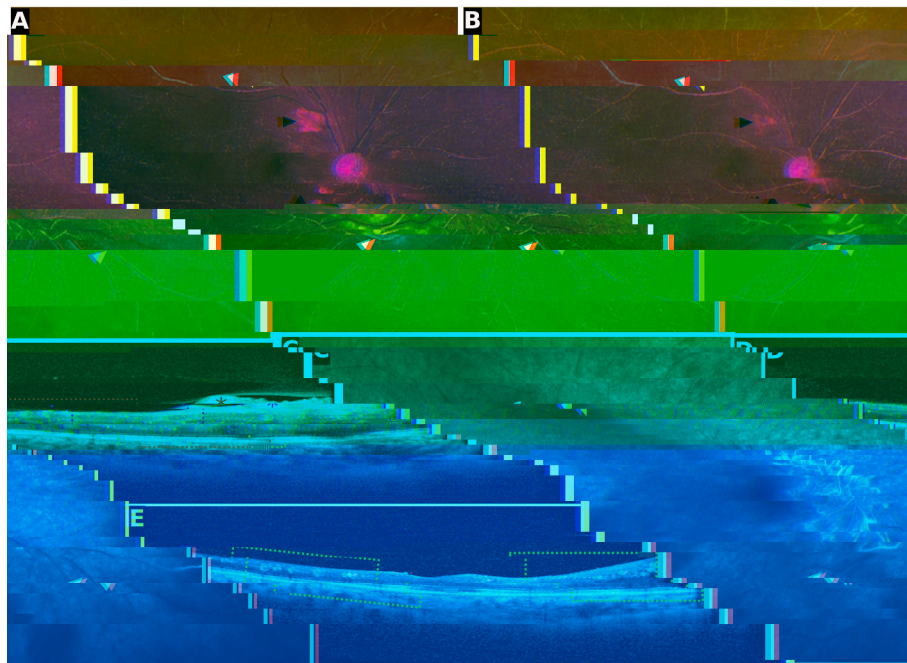
Case

A 57-year-old male with hypertension initially presented to ophthalmology in January 2019 with a 17-year history of type 2 diabetes mellitus treated with insulin for the prior 9 years. Past medical history was also remarkable for ESKD managed with peritoneal dialysis for the prior 2 years. Visual acuity was 20/25 in each eye, and he was diagnosed with proliferative diabetic retinopathy (PDR) with retinal neovascularization in both eyes. After four monthly bilateral intravitreal injections of bevacizumab for PDR, the patient was lost to follow up.

The patient returned 20 months later (September 2021) with visual acuity decreased to counting fingers in the right eye and stable vision at 20/25 in the left eye. Ophthalmic exam revealed iris neovascularization with elevated intraocular pressure (IOP) and vitreous hemorrhage of the right eye. Micro-pulse cyclophotocoagulation was performed for management of neovascular glaucoma. He subsequently developed neovascular glaucoma in the left eye with decreased vision to 20/80. In April 2022, an Ahmed glaucoma draining device was placed in the left eye, with additional treatment with micro-pulse cyclophotocoagulation in October 2022 to further lower the IOP.

A series of fundus examinations in 2021 demonstrated progressive accumulation of crystals in the lumina of retinal arteries over several months in both eyes. Ultra-wide field color photography (Fig. 2A and B) and fluorescein angiography (Fig. 2C) showed diffuse whitening of retinal arteries with crystals, accompanied by severe retinal vascular occlusion in each eye. Optical coherence photography (Fig. 2D) illustrated intraarterial hyperreflective crystals. At the most recent visit, visual acuity was no light perception in the right eye and 20/500 in the left eye.

The first plasma oxalate level was elevated at 26.9 µmol/L (reference range <2.0) and phosphorus level was also elevated at 8.1 mg/dL (reference range 2.5–4.5 mg/dL), despite the use of sevelamer and dietary guidance. The peritoneal dialysis regimen was therefore intensified to improve his overall oxalate clearance, and his phosphate binder regimen was also intensified to prevent calcium phosphate co-crystallization. Same as Case 1, targeted genetic testing was done by NGS with a CLIA certified laboratory, Invitae. There were no genetic variants identified in the three genes associated with PO. Further follow up has not been possible because the patient moved out of state.

Bilateral retinal vascular occlusion is uncommon and usually occurs

Wide angle fundus photos revealed progressive loss of vascular perfusion and the accumulation of retinal intra-arterial crystals (white arrow heads in Fig. 1A, B, 2A and 2B), and nerve fiber layer infarcts in both cases (black arrow heads in Fig. 1A, B, 2A and 2B). Mid-phase fluorescein angiography displayed areas of nonperfusion from vascular blockage with the crystalline deposition (Figs. 1C and 2C), as well as leakage from neovascularization (Fig. 2C). SD-OCT images demonstrated hyperreflective oxalate crystals confined in the vasculature of inner retinal layers (red frame in Fig. 1D, E, 2D, 2E), cystoid macular edema and swelling of nerve fiber layer at early phases (red asterisk in Figs. 1D and 2D) and thinning of inner retinal layers at later visits (Figs. 1E and 2E). Black and blue lines (Figs. 1B and 2B) indicate the locations which correspond with cross-sectional OCT image D and E respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
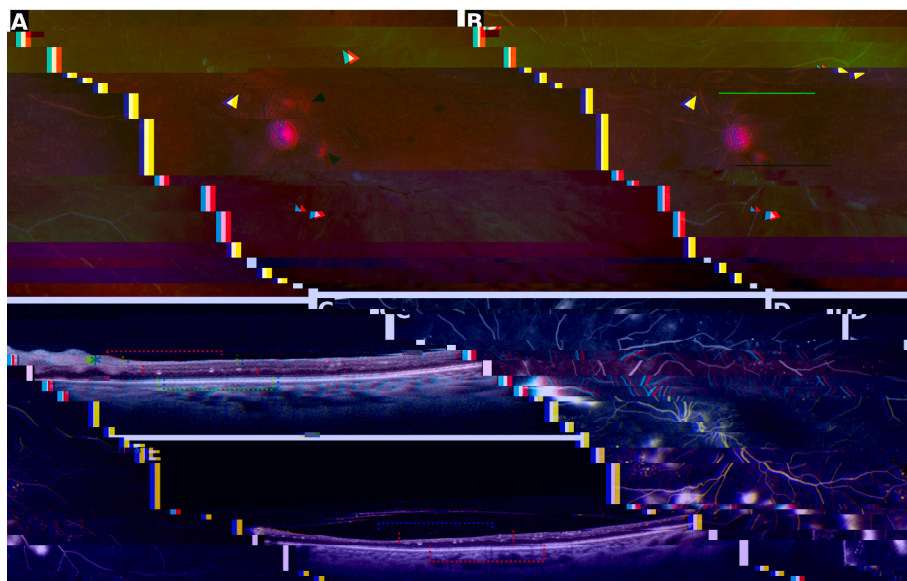
Fundus photos reviewed profound loss of vascular perfusion and the accumulation of retinal intra-arterial crystals (white arrow heads in Fig. 2A and B) over time, and cotton wool spots (black arrow heads in Fig. 2A). Fluorescein angiography displayed leakage from neovascularization and areas of peripheral nonperfusion (Fig. 2C). SD-OCT images demonstrated hyperreflective oxalate crystals confined in the vasculature of inner retinal layers (red frame in Fig. 2D and E) and swelling of nerve fiber layer (red asterisk in Fig. 2D) and thinning of inner retinal layers (Fig. 2E). Black and blue lines (Fig. 2B) indicate the locations which correspond with cross-sectional OCT image D and E respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in the presence of systemic diseases. The profound loss of retinal perfusion and progressive crystalline deposits in our cases were associated with and possibly caused by hyperphosphatemia and oxalosis. Hyperphosphatemia is commonly associated with chronic kidney disease (CKD) due to inability of the kidneys to excrete phosphate load.[5] Study showed phosphorus level greater than 5.5 mg/dL is associated with a further increased risk of cardiovascular and other mortalities.[6] The phosphorus level in case 1 was 22.3 mg/dL which is exceedingly elevated. The mechanisms of cardiovascular events and mortality due to hyperphosphatemia include arterial calcification and stiffness.[7,8] However, recent studies showed higher phosphate exposure also contribute to the microvascular dysfunction.[9,10] In vitro study showed phosphate can inhibits nitric oxide production by reducing nitric oxide synthase expression in venous endothelial cells.[9] In a population-based study, it showed high serum phosphate level, even within normal ranges, could be independently related with diminished microvascular function.[11]

Oxalate is derived from dietary sources, can also be synthesized by erythrocytes and liver, and is excreted in the urine.[12] Dietary oxalate may contribute 50–80 % of the oxalate excreted in the urine.[13] Endogenous sources of oxalate include ascorbic acid, protein, and precursors of oxalate, L-glycerate glycollate and glyoxylate. SO can develop in patients with renal failure especially if there is a primary or intestinal cause of hyperoxaluria leading to excess serum oxalate levels. Normal oxalate levels in ESKD are almost never observed, with mean levels around 45 μmol/L, considerably higher than the 28 and 26.9 levels observed in these two cases.[14] This disparity suggests that higher oxalate levels may exist without crystalline deposits, or that the higher levels are also accompanied by crystalline deposits that are missed because the eyes are not examined. If higher oxalate levels are typically not accompanied by crystalline deposits, there may be other factors that induced crystal deposits in the presented cases, such as elevated phosphate. In case 1 genetic testing was positive for a heterozygous variant of the *AGT* gene, which may have reduced the capacity to metabolize oxalate and further elevated the oxalate levels due to ESKD. Genetic variant was not a contributing factor in case 2. Extrarenal complications, such as central nervous system involvement, cardiomyopathy and Guillain-Barre-like syndrome, have been reported in patients with oxalosis.[15–18] The

patient in the first case description suffered from cardiomyopathy and Guillain-Barre syndrome. Oxalosis can cause multi-organ failure and premature death in the most severe cases.

To summarize, both cases with diabetes, ESKD, and peritoneal dialysis presented with progressive occlusive retinal vasculopathy associated with profound vision loss due to intraarterial crystal deposition. The course of both cases was rapidly progressive, which is not consistent with typical diabetic retinopathy. Another differential diagnosis of progressive crystalline retinopathy is calciphylaxis, which is usually presented with painful necrotic skin ulcers.[19] Neither of our cases demonstrated any skin lesions. The elevated phosphorus and oxalate levels in both cases were associated with crystalline deposition in the retina and were possibly causative. Few publications describe vision loss and retinal vascular occlusion due to hyperphosphatemia and oxalosis from ESKD, and the recognition of these associated disorders is not widely appreciated. The course can be augmented by other risk factors like high-oxalate diet or intake of large dose of vitamin C.[20,21] Although both of our cases denied any exposure to large dose of vitamin C, both patients were on oxalate-rich diet. A major purpose of this publication is to increase the awareness in physicians caring for diabetes and ESKD of hyperphosphatemia and oxalosis in ESKD, and the catastrophic ocular complication it can cause. We demonstrate stabilization of retinal perfusion following the lowering of serum phosphorus and oxalate levels with an aggressive regimen of hemodialysis and dietary modification. This implies that aggressive treatment during the early stage of vasculopathy may avert the severity of occlusive retinal vasculopathy, with the preservation of vision.

It is important that eye care providers recognize hyperphosphatemia and oxalosis-induced retinal vasculopathy at a stage in the disease when vision can be salvaged, and it is important that nephrologists be aware of the conditions that result from hyperphosphatemia and oxalosis in ESKD, so that these providers can minimize the conditions that lead to severe ocular damage. Periodic phosphate and oxalate levels and eye exams with imaging of the ocular fundus in ESKD patients may detect

the vasculopathy at an early stage when treatment can be more effective. Management of susceptible patients with low-phosphate and oxalate diet and with high-intensity hemodialysis should be considered early in the process.

Consent to publish the case reports was not obtained. This report does not contain any personal information that could lead to the identif cation of the patient.

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All authors attest that they meet the current ICMJE criteria for Authorship.

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The authors have no conf ict of interest.

None.

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