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C3 glomerulopathy associated with both hypertensive retinopathy and purtscher-like retinopathy

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ABSTRACT

Purpose: This article reports the case of a 21-year-old woman with both hypertensive retinopathy and Purtscher-like retinopathy in association with C3 glomerulopathy.

Observations: The patient was referred for bilateral painless vision loss with posterior pole cotton wool spots, optic disc edema, and confluent retinal whitening suggesting a mixed picture of hypertensive retinopathy, with initial blood pressure 236/152, and Purtscher-like retinopathy. She was subsequently diagnosed with C3 glomerulopathy which likely caused her severe hypertension and which likely occurred alongside Purtscher-like retinopathy due to a shared pathogenesis of complement dysregulation. Follow up examination and imaging revealed gradual improvement in visual acuity, almost complete resolution of fundus exam abnormalities, improvement in macular nonperfusion, resolution of disc leakage and choroidal leakage, resolution of macular edema, and residual outer retinal hyperreflective foci in both eyes.

Conclusion and importance: This case represents the first report of both Purtscher-like retinopathy and hypertensive retinopathy occurring in association with C3 glomerulopathy. It supports investigation of anti-complement therapy as a potential treatment for Purtscher-like retinopathy.

1. Introduction

The complement system has long been recognized as playing a role in the pathogenesis of several nephropathies, with an association between hypocomplementemia and glomerulonephritis first reported over 100 years ago.[1] Some common glomerulonephritides, such as lupus nephritis and postinfectious glomerulonephritis, have complement deposited alongside immune complexes. In contrast, the rarer C3 glomerulopathies are characterized by the deposition of mostly C3 and are consistent with primary defects of complement regulation.[2] C3 glomerulopathies, and kidney disease in general, are important causes of secondary hypertension with resulting ocular manifestations if left untreated. Complement system overactivation is also purportedly involved in the pathogenesis of Purtscher-like retinopathy, an occlusive chorioretinopathy caused by an expanding list of underlying systemic disease. To our knowledge, C3 glomerulopathy has not been reported to be associated with Purtscher-like retinopathy. We describe here a case of a young patient with severe vision loss and clinical features consistent with both Purtscher-like retinopathy and Grade IV hypertensive retinopathy who was subsequently diagnosed with C3-related kidney disease.

2. Case report

A 21-year-old white female was referred to the retina clinic for consultation following diagnosis of bilateral central retinal vein occlusion (CRVO) at an outside institution. The patient, whose past medical history included hydronephrosis in utero, dysautonomia with spells of palpitation and tachycardia, celiac disease, and recovered COVID-19 infection, was in her usual state of health until approximately 6 weeks prior to presentation at which time she developed daily headaches. After approximately 2 weeks of these headaches, she presented to urgent care and was diagnosed with a sinus infection and given antibiotics. Her systolic blood pressure during that visit was incidentally noted to be in the 180s. Her sinus symptoms improved with antibiotics but her headaches persisted, and she also developed blurry vision, first in her right eye and subsequently in her left eye two weeks later. Given worsening

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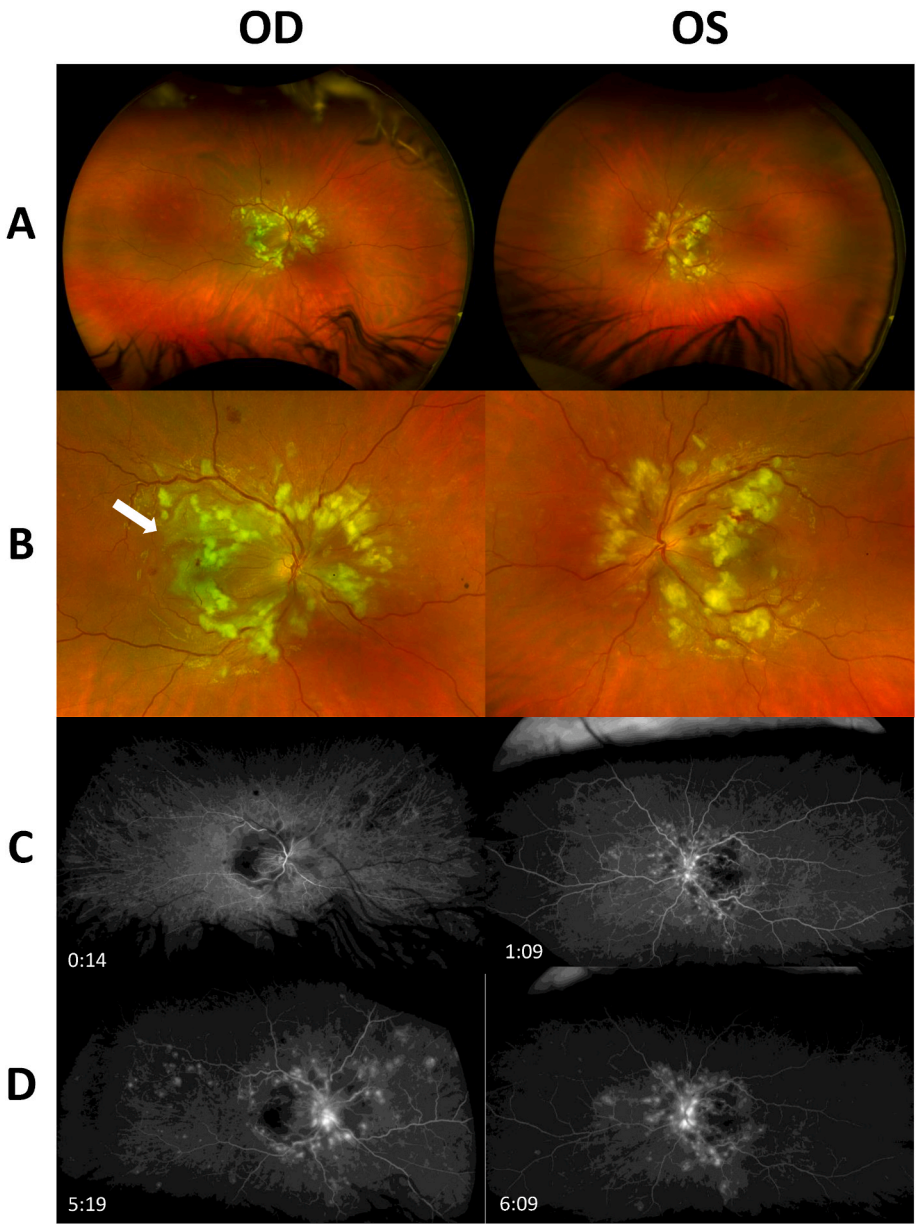

Fig. 1. Fundus photos and fluorescein angiography at initial presentation. At initial presentation, fundus photography showed optic nerve edema and multiple cotton wool spots, Purtscher flecken (white arrow example), and rare dot and blot hemorrhages in posterior pole of both eyes (B) and no lesions in the peripheral retina of both eyes (A). Early (C) and late (D) phase fluorescein angiograph showed optic disk leakage, multiple choroidal infarcts, and macular nonperfusion in both eyes.

symptoms, she presented to an outside ophthalmologist for additional evaluation and was diagnosed with bilateral CRVO with cystoid macular edema, which was believed to be secondary to oral contraceptive use. For her macular edema, she was treated with bilateral intravitreal aflibercept injections, first to the right eye and then to the left eye three days later. Because her vision did not significantly improve, she presented for a second opinion one day after injection of the left eye.

On presentation, her best-corrected visual acuity (BCVA) was 20/600 in her right eye and 20/150 in her left eye. Intraocular pressure was 15 mmHg in the right eye and 13 mmHg in the left eye. Anterior segment examination was normal and did not show any neovascularization of the angle or iris in either eye. Fundus exam demonstrated optic nerve head edema, extensive cotton wool spots throughout the posterior pole, confluent macular retinal whitening, rare dot-blot hemorrhages, and multiple peripheral hypopigmented choroidal spots in both eyes (Fig. 1 A, B). Optical coherence tomography (OCT) showed patchy inner retinal opacification and substantial intraretinal and subretinal fluid of both eyes (Fig. 5 A). Fluorescein angiography (FA) showed macular nonperfusion, multiple areas of early blockage, and multifocal late choroidal leakage without vascular leakage in both eyes (Fig. 1C, D). Severe hypertensive retinopathy and concurrent occlusive vasculitis was suspected and therefore the patient was referred urgently to the emergency department.

In the emergency department, her initial blood pressure was 236/152. Large vessel occlusion was excluded by CT angiography of the brain, neck, and abdomen. Her comprehensive metabolic panel was significant for a creatinine of 3.5, and her urinalysis was notable for blood and protein. The patient was admitted to the intensive care unit for hypertensive emergency and management of acute renal failure. Over the next few days, the patient noted mild subjective visual improvement with improved blood pressure control. An MRI brain taken on her first inpatient day and MRI cervical spine and thoracic spine taken on her second inpatient day showed a longitudinally extensive hyperintense lesion on T2/FLAIR, suggestive of atypical posterior reversible encephalopathy syndrome (PRES), but the differential also included Longitudinal Transverse Myelitis due to neuromyelitis optica (NMO), MOG antibody disease, or acute disseminated encephalomyelitis (ADEM), so a lumbar puncture (LP) with CNS demyelination panel on

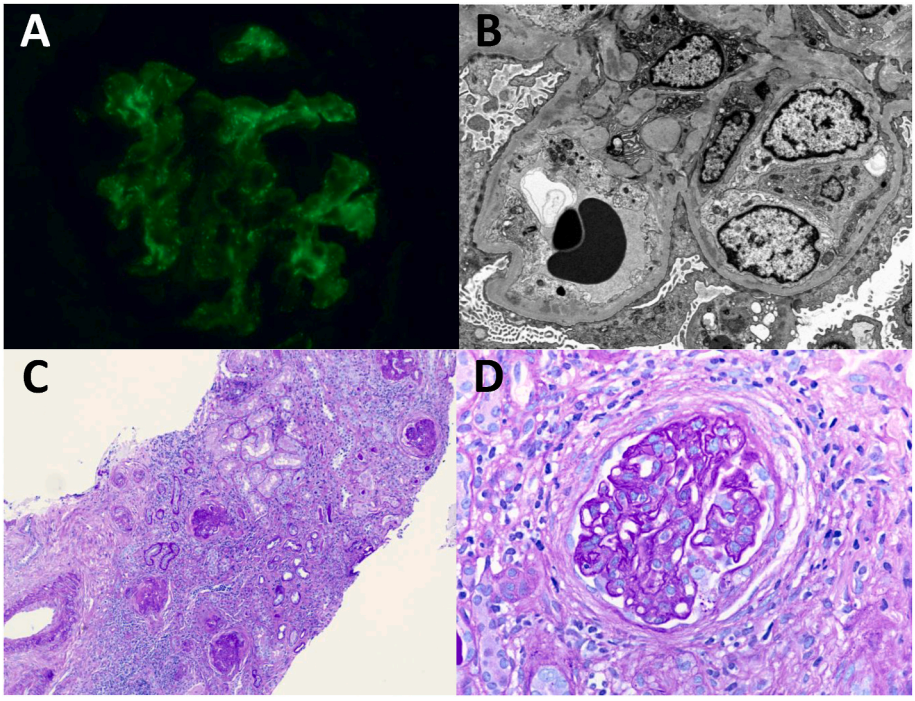

Fig. 2. Renal biopsy. C3 immunofluorescence with granular mesangial and capillary wall staining is present (A, 40x). Electron microscopy (B, 2500x) reveals mesangial and paramesangial electron dense deposits, scattered subendothelial deposits, focal endocapillary hypercellularity, and extensive podocyte foot process effacement with patchy microvillous transformation. A representative PAS-stained section (C, 200x) demonstrates several globally sclerosed or near globally sclerosed glomeruli, severe tubular atrophy and interstitial fibrosis, moderate interstitial infiltrates of predominately mononuclear cells in areas of atrophy, and focal mild intimal sclerosis of the interlobular arteries. Overall, the features are approaching an end-stage kidney. A representative PAS-stained glomerulus (D, 400x) shows a partially sclerosed capillary tuft and a fibrocellular crescent with disrupted Bowman's capsule. A few open capillary loops show mildly thickened basement membranes with occasional double contours and no significant proliferation.

CSF was ordered. The LP was bland with normal opening pressure and the panel was negative. After the patient's blood pressure was better controlled, a renal biopsy was obtained, and pathology demonstrated features of chronic glomerulonephritis, fibrocellular crescents in a few glomeruli, and isolated C3 staining on immunofluorescence consistent with C3 glomerulonephritis (Fig. 2).

A C3 nephritic factor and complement gene panel showed elevated Factor H autoantibody, undetectable C3 nephritic factor, normal C3, and two heterozygous mutations of unknown significance. For the severity of her condition, the patient was referred for renal transplant. She was discharged from the hospital after six days of admission. Repeat brain and cervical MRI revealed almost complete resolution of her neurological imaging abnormalities 12 days after the initial study and complete resolution at three month follow up. At her follow-up ophthalmology clinic appointment one week after discharge, her BCVA remained 20/600 in her right eye but improved to 20/70 in her left eye. BCVA continued to improve at subsequent visits with an eventual BCVA of 20/100 in the right eye and 20/25 in the left eye at 16 week follow up. Follow up imaging revealed almost complete resolution of fundus exam abnormalities (Fig. 3), improved macular nonperfusion and resolved disc leakage and choroidal leakage in both eyes on fluorescein angiography (Fig. 4), and resolution of macular edema with residual outer retinal hyperreflective foci in both eyes (Fig. 5).

3. Discussion

This patient met all five criteria of which Miguel et al. proposed at least three are required to diagnose Purtscher's retinopathy[3]: Purtscher flecken; low-to-moderate number of hemorrhages; cotton wool spots (typically restricted to posterior pole as here); probable or plausible explanatory etiology (here patient's renal disease and complement dysfunction); and compatible complementary investigation (here nonperfusion on FA and retinal edema on OCT). At the same time, the patient's severe hypertension, optic disc edema, and choroidal infarctions suggest Grade IV hypertensive retinopathy. The appearance of clinical features of both Purtscher-like retinopathy and hypertensive retinopathy in this patient likely represents the presence of both diseases concurrently, rather than expanding the clinical phenotype of either disease alone. While optic disc edema and macular edema have sometimes been reported to occur with Purtscher's, possibly in association with worse visual prognosis,[3] Purtscher's retinopathy may not fully explain the presence of choroidal infarctions nor the initial extent of optic disc edema. Conversely, it would also be unusual for hypertensive retinopathy alone to produce this severity of optic disc edema without significant flame hemorrhages. Instead, both retinopathies likely emerged in close association with the patient's newly diagnosed C3 glomerulopathy. Her hypertensive retinopathy likely emerged secondary to the severe hypertension induced by her renal disease. Meanwhile, given the likely role of complement activation in the pathogenesis of both Purtscher-like retinopathy and C3 glomerulopathy, the patient likely has an underlying disorder of complement dysregulation that caused both these disease entities.

An association between renal disease and Purtscher-like retinopathy has long been reported.[4–8] More recently, the first two reports of Purtscher's retinopathy in association with hypertensive crisis have emerged, one with hypertension secondary to IgA nephropathy,[9] and the other with hypertension secondary to scleroderma renal crisis.[10] In only the second of these cases was fundoscopic evidence of hypertensive retinopathy present.[10] The present case is the first report of Purtscher-like retinopathy and hypertensive retinopathy in association with C3 glomerulopathy.

C3 glomerulopathy is a histopathological disorder, defined by isolated (or at least dominant) C3 deposition within the glomerulus, as determined by immunofluorescence.[2] Electron microscopy is used to distinguish between the four major subtypes of C3 glomerulopathy: dense deposit disease, C3 glomerulonephritis, CFHR5 nephropathy, and familial C3 glomerulopathy.[11] These four subtypes all involve dysregulation of the alternative complement pathway in the fluid phase. Approximately 25% of cases of C3 glomerulopathy involve inherited variants in complement-related genes, the most commonly involved

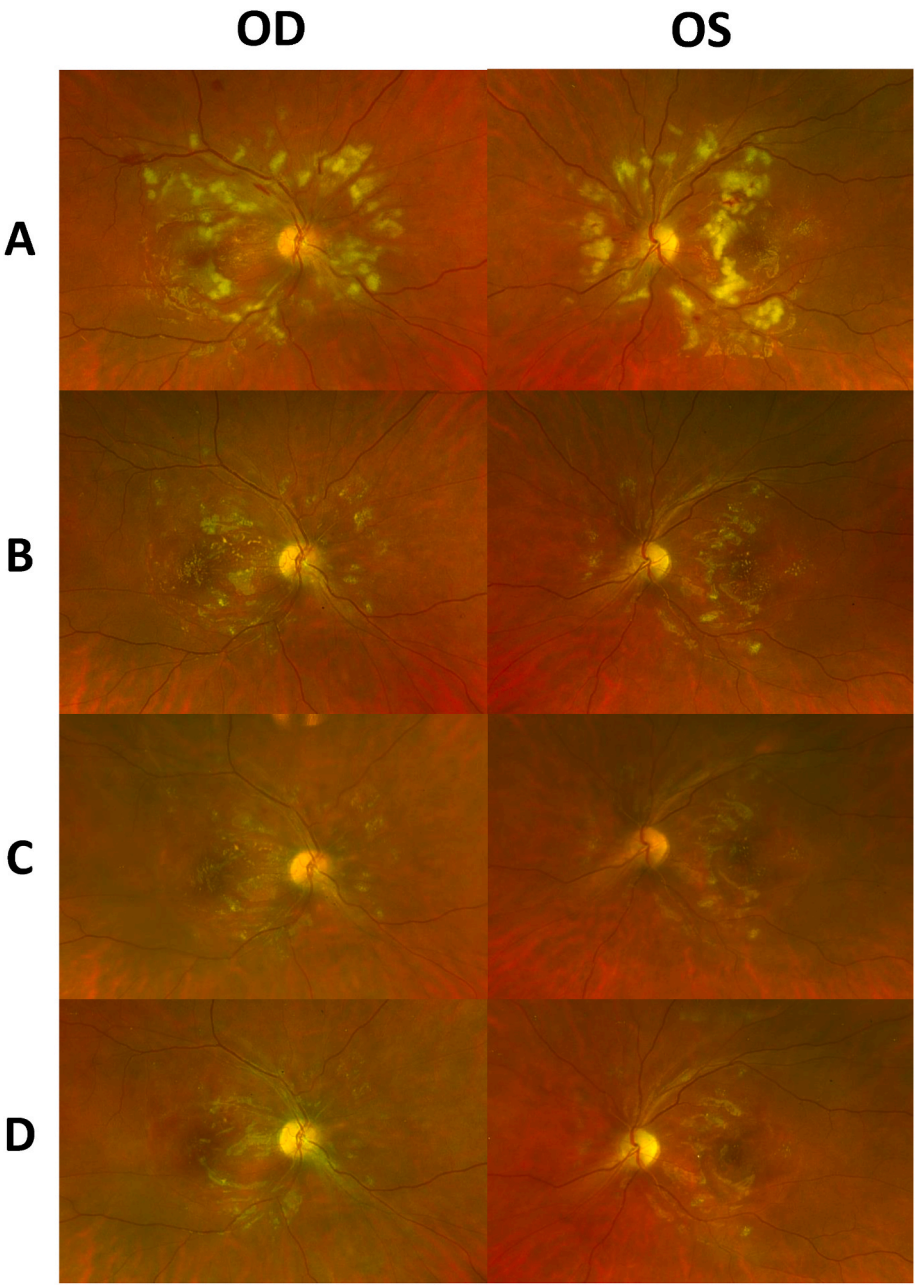

Fig. 3. Follow up fundus photography. Fundus photography at follow up of 2 weeks (A), 8 weeks (B), 10 weeks (C), and 16 weeks (D), showed progressive improvement with almost complete resolution of optic disc edema, hemorrhages, cotton wool spots, and Purtscher flecken.

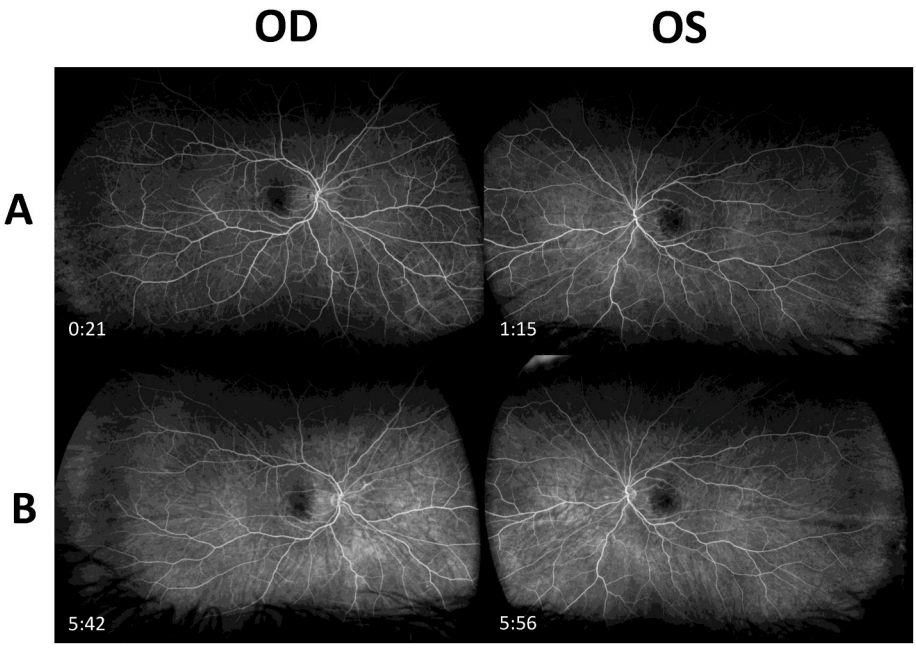

Fig. 4. Follow up fluorescein angiography. At 8 week follow up, early (A) and late (B) phase showed overall improvement with improved macular nonperfusion in both eyes and resolved disc leakage and choroidal leakage in both eyes.

being the convertase genes C3 and CFB, the complement regulatory genes CFH and CF1, and the complement activation enhancing gene, CFHR5.[2] In many other cases, the pathogenesis of C3 glomerulopathy is driven by acquired autoantibodies against various complement proteins and complexes. For example, in the present case, our patient had autoantibodies to Factor H. Overall, the most frequently implicated acquired drivers of C3 glomerulopathy are C3 nephritic factors (50–80% of patients) and C5 nephritic factors (50% of patients).[2] However, the four subtypes of C3 glomerulopathy vary in the most common associated alternative pathway abnormalities.[11]

Although the pathophysiology of Purtscher-like retinopathy remains incompletely understood, it is generally accepted to involve microembolization into the retinal vascular system. The pathognomonic Purtscher flecken, for example, are likely caused by emboli to the precapillary arterioles, and the cotton wool spots reflect retinal nerve fiber layer ischemia.[12] The offending emboli are often composed of fat, platelets, or leukocyte aggregates. Complement activation also appears to be important to the pathogenesis of Purtscher's and Purtscher-like retinopathy, with complement activation observed in many of the associated etiologies, including severe trauma, fat embolism syndrome, connective tissue disorders, amniotic fluid embolism, and renal failure. Thus, complement activation has been proposed to cause vascular occlusion in Purstcher-like retinopathy either directly through activation of leukocyte or platelet aggregates or indirectly through inducing endothelial damage and activation of the clotting cascade.[13]

The relationship between Purtscher-like retinopathy, renal disease, and complement activation includes multiple potential mechanisms with differing directions of causality. On the one hand, similar to the present case, Purtscher-like retinopathy has been described as occurring in other cases of renal disease with a clear immunologic pathogenesis, including cases of chronic renal allograft rejection,[4] acute renal allograft rejection,[6] familial glomerulonephritis,[4] and renal scleroderma crisis.[7] In these cases, complement dysregulation may represent a common cause of both Purscher-like retinopathy and the renal disease. On the other hand, Pinto et al.[14] recently described a case of Purtscher-like retinopathy occurring in a patient with stable chronic kidney disease (CKD) and highlighted evidence that CKD itself can lead to complement activation[15] and is associated with altered serum complement levels.[16] In some reported cases, it has been hypothesized that chronic renal disease may have weakened the immune system, either directly or through immunosuppressive or steroid therapy, which could have predisposed the patient to a systemic infection which induced complement activation.[4,5,8,17] Finally, renal failure can necessitate hemodialysis which can in turn activate serum complement at the hemodialysis membranes.[4,18,19]

The putative importance of complement activation in the pathogenesis of Purtscher-like retinopathy, and a possibly shared pathogenesis with C3 glomerulopathy as seen in this case, suggests that therapy targeting the complement pathway may be an avenue for treatment of Purtscher-like retinopathy. Currently, there are no established therapies for Purtscher-like retinopathy; early case reports suggested benefit from steroids,[20,21] while a systematic review found steroids to be no more effective than observation.[3] Recently, eculizumab, a C5 inhibitor, has shown some efficacy in the treatment of C3 glomerulopathy[22] and there are several other new anti-complement therapies for the treatment of glomerulopathy under development.[23] Future studies will need to be completed to elucidate whether anti-complement therapy may prove useful in the treatment of Purtscher-like retinopathy.

In conclusion, we report a novel case of severe bilateral vision loss in a young patient secondary to combined hypertensive retinopathy and Purtscher-like retinopathy, in the setting of undiagnosed C3 glomerulopathy. At 16 week follow up the patient had incomplete visual recovery in both eyes, with less visual recovery in the right eye, that correlated with persistent outer retinal changes. We stress the importance of checking blood pressure in the clinic if these entities are suspected, as they may uncover an underlying hypertensive emergency. Complement dysregulation in these newly described renal diseases may become increasingly more important in the understanding of Purtscher-like retinopathy.

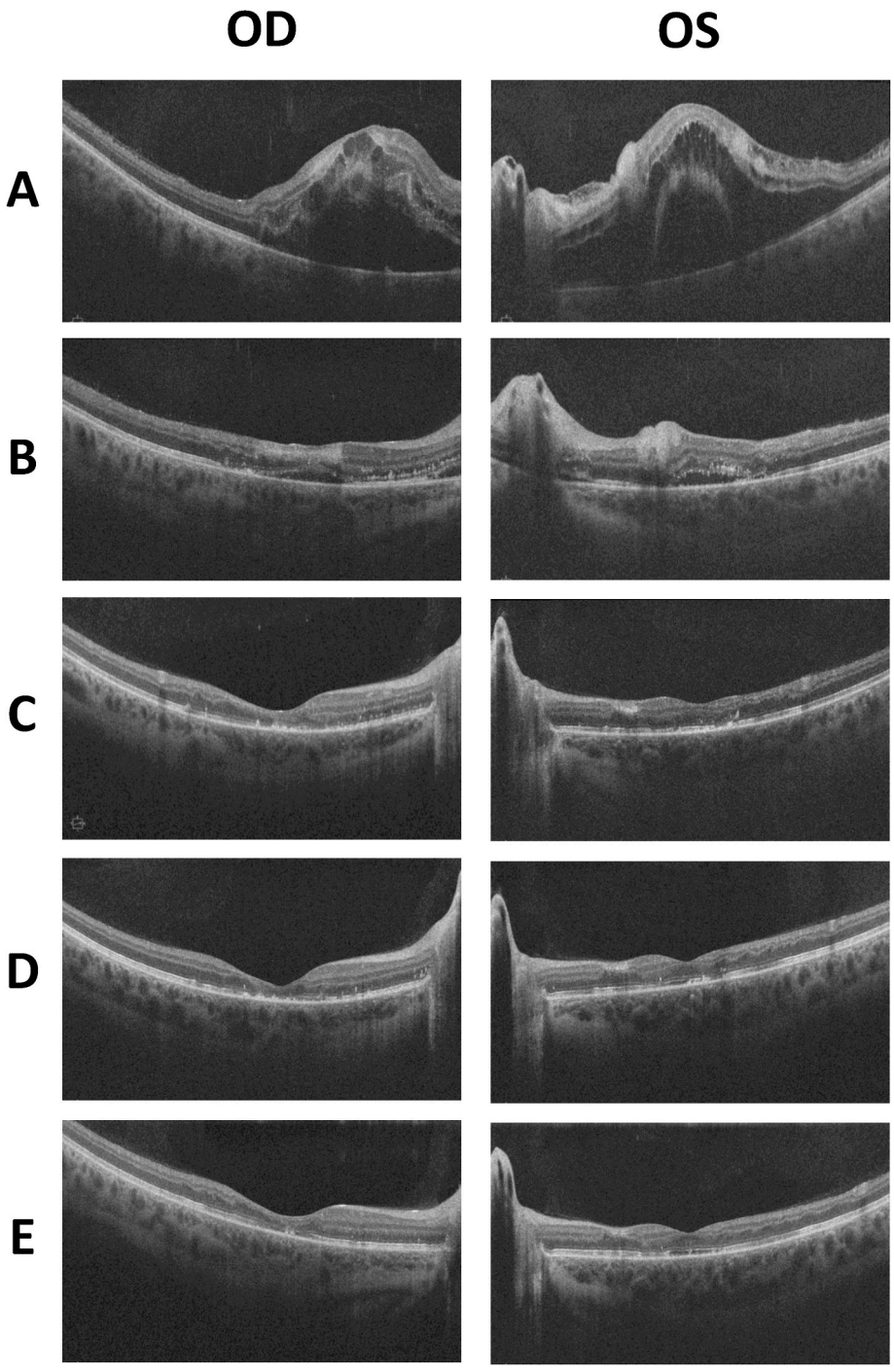

Fig. 5. Optical Coherence Tomography (OCT) macula. At initial presentation (A), OCT showed cystoid macular edema, with substantial intraretinal and subretinal fluid, and patchy inner retinal opacification in both eyes. Two week follow up (B) showed significantly improved cystoid macular edema, continued inner retinal opacification, and outer retinal hyperreflective foci in both eyes. By 8 week follow up (C), cystoid macular edema had resolved, with normalization of the foveal contour, but outer retinal abnormalities persisted and were particularly severe in the right eye. No further significant changes were seen at 10 (D) or 16 (E) week follow up.

Patient consent

Verbal consent to publish the case report was obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

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

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Declaration of competing interest

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