A different case report reported that an exudative retinal detachment owing to nephrotic syndrome associated with minimal-change disease was completely resolved after a 5-day course of oral prednisolone 50 mg once daily. Our case and the case involving oral corticosteroid use suggest that systemic corticosteroids can serve as an effective main treatment of retinal complications associated with nephropathy. The case involving oral corticosteroid use involved a shorter duration of vision loss and a seemingly healthy patient with minimal change disease. In contrast, our case involved a longer duration of vision loss and the patient was known to have end-stage renal failure. Intravenous corticosteroid use was a more appropriate match for the severity of vision loss, hypertensive crisis, and nephropathy of this patient. We suggest that a short course of intravenous corticosteroids is an appropriate and effective treatment for patients presenting with severe retinal complications, hypertensive crisis, and severe immune-mediated nephropathy. Oral corticosteroids may be more appropriate in less severe situations.

Intravenous corticosteroids are an effective treatment for retinopathy secondary to a membranous-nephropathy-associated hypertensive crisis. We suggest that ophthalmologists consider treating severe retinopathy secondary to an immune-mediated nephropathy with systemic corticosteroids and comanagement with internal medicine colleagues over treatments localized to the retina.

**Supplementary Materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2020.06.007.

**Supplementary Fig. 1**—Red-free colour fundus photography of the right eye at 4 months after the hypertensive crisis. Permanent retinal epithelium atrophy is visible months after the hypertensive crisis. The image can help ophthalmologists recognize damage resulting from a hypertensive crisis months to years after the crisis occurred.

**Supplementary Figs. 2–10**—Optical coherence tomography and colour fundus photography at initial presentation with hypertensive crisis and at 4 months after treatment.
isolated cases RP. In contrast to white dot syndromes and initially diagnosed with nonspecific retinal atrophy or pigmentary changes, many patients are waxy disc pallor, attenuated retinal vasculature with or without retinal arteriovenous anomalies, multiple evanescent white dot syndrome, retinal degenerations or retinal inflammation. They considered supportive criteria to include photopsias, scotomas, dyschromatopsia, nystagmus or photoaversion, systemic autoimmune disease, and acute or subacute vision loss. npAIR is a diagnosis of exclusion that requires extensive testing and follow-up to rule out paraneoplastic and other causes of vision loss. However, npAIR may mimic other conditions such as paraneoplastic AIR (e.g., cancer-associated retinopathy and melanoma-associated retinopathy), white-dot syndromes (e.g., acute zonal occult outer retinopathy [AZOOR] and multiple evanescent white dot syndrome), retinal degenerations (e.g., RP and cone-rod dystrophy), and infectious and noninfectious uveitides, further complicating its diagnosis.

Because fundus examination may be unremarkable or can demonstrate nonspecific signs of retinal degeneration such as waxy disc pallor, attenuated retinal vasculature with or without retinal atrophy or pigmentary changes, many patients are initially diagnosed with nonspecific retinal degenerations or isolated cases RP. In contrast to white dot syndromes and uveitides, there is usually minimal inflammation in npAIR. Although both RP and npAIR are more likely to have cystoid macular edema than AZOOR, intraretinal bone spicule migration is rare in both npAIR and AZOOR, which can help differentiate between these conditions. Finally, AZOOR is defined by unique features on multimodal imaging such as zonal degeneration of the outer retina and retinal pigment epithelium (RPE) on both fundus autofluorescence (FAF) and optical coherence tomography (OCT).

Herein we present 3 cases of asymmetric npAIR with the presence of a unilateral hyperautofluorescent ring in all cases and in 2 cases additional asymmetric FAF changes that should caution the clinician to consider this rare presentation of the disease.

Three cases of asymmetric npAIR were identified. All patients were young with noncontributory family history for retinal dystrophies and no history of consanguinity in the family. Age-appropriate cancer screening was negative, including a normal dermatological examination, carotid and vertebral artery Dopplers, and abdominal and pelvic ultrasonography in all patients. Anterior segment and intraocular pressures were within normal limits. Funduscopic examination revealed no vitritis or waxy disc pallor OU. All patients had constriction of Goldmann visual fields in affected eyes, with attenuation of full-field electroretinograms and positive ARAs. Patients 1 and 3 had positive anti-enolase antibodies, whereas patient 2 had negative anti-enolase antibodies. Patient 1 had positive anti-recoverin antibodies, whereas patients 2 and 3 had negative anti-recoverin antibodies. Patient demographics and ancillary testing are summarized in Table 1. Figures 1 and 2 summarize the FAF and OCT findings, respectively. In all cases, npAIR was entertained as a diagnosis of exclusion after other possible causes were ruled out. In all cases, patients were followed for over 12 months with no suggestion of another possible pathology with either slow progression or stabilization of their condition. All 3 patients met the established essential diagnostic criteria for npAIR. Although patients 1 and 3 demonstrated areas of normal, hyper-, and hypo-autofluorescence they did not demonstrate a lesion with a true trizonal pattern, and over 3 years of follow-up these cases did not progress to develop atrophy consistent with a diagnosis of AZOOR. In these cases, OCT through the border of the lesion did not demonstrate a trizonal pattern of involvement consistent with a diagnosis of AZOOR. All 3 patients deferred treatment owing to disease stabilization or concerns of side effects.

Patient 1 was a 33-year-old woman who presented with symptoms of several years duration of decreased vision in the right eye greater than the left. Her medical history included latent pulmonary tuberculosis treated years before her presentation with subsequent normal eye examinations and chest x-rays. She was on medications. Best-corrected visual acuity (BCVA) was 20/30 and 20/40 in the right and left eye, respectively. No retinal artery attenuation was seen OU; however, atrophic RPE changes with RPE mottling were seen and greater in OD than OS. FAF demonstrated a hyperautofluorescent ring in the macular area OD more than OS and other asymmetric FAF changes. Patient 1 noted slow progression over time but deferred treatment owing to concerns about systemic side effects and those related to childbirth.

Patient 2 was a 30-year-old woman who presented with progressive unilateral visual field constriction in her right eye over several years. She was otherwise healthy and on no medications. BCVA was 20/25 and 20/20 in the right and left eyes, respectively. The funduscopic examination OD revealed mild retinal artery attenuation and RPE mottling without bony spicules was seen. Funduscopic examination OS was within normal limits. FAF showed a hyperautofluorescent ring in the macular area OD with mottled patches of hypoautofluorescence in the posterior pole. FAF OS was within normal limits. Patient 2 noted stabilization of her disease after 12 months.
Patient 3 was a 37-year-old man who was referred for retinopathy found on routine optometry examination. He was asymptomatic and otherwise healthy and on no medications. BCVA was 20/16 and 20/20 in the right and left eyes, respectively. Funduscopic examination OU revealed no retinal vessel attenuation. In the right eye, mild RPE atrophy without pigmented deposits was seen, and in the left pigmented deposits around the superior arcade were seen. FAF OD demonstrated patches of hyperautofluorescence through the posterior pole without a hyperautofluorescent ring, whereas in the left eye it showed an hyperautofluorescent ring in the macular area with mottled patches of hypoautofluorescence on the superior arcade. Spectral Domain- Optical Coherence Tomography (SD-OCT) imaging was within normal limits OD. Patient 3 remained asymptomatic from his disease and his examination remained stable over the next 12 months.

All of our patients met the suggested American Uveitis Society (AUS) essential criteria for the diagnosis with

Fig. 1—Fundus autofluorescence of patients in case series. Patient 1 demonstrated hyperautofluorescent rings present in the macular area (A) OD more than (B) OS. Patient 2 demonstrated hyperautofluorescent ring in the macular area (C) OD with mottled patches of hypoautofluorescence in the posterior pole and was within normal limits (D) OS. Patient 3 demonstrated patches of hyperautofluorescence through the posterior pole without a hyperautofluorescent ring (E) OD; however (F) OS demonstrated an hyperautofluorescent ring.
negative age-appropriate cancer screening, positive serum ARAs, ERG abnormalities, and the absence of fundus lesions or inflammation to suggest another cause.

Although symmetry is not part of the diagnostic criteria, it is part of the typical presentation of this condition and to date no series has demonstrated this asymmetry. We believe that it is important for clinicians who assess retinal diseases to be aware of this unique presentation of the condition. Clinicians require a high level of suspicion when assessing patients with an asymmetric or unilateral appearing retinal degeneration and should consider a work-up including an ERG, FAF, Goldmann visual fields, ARAs, and age-appropriate malignancy screen in applicable cases.

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References


Treatments for inherited retinal degenerations are coming to Canada: brief update on a new standard of care for inherited retinal degenerations

The last 25 years brought a spectacular amount of knowledge on the genetic basis of inherited retinal disorders and a paradigm shift on how they can be managed. We entered the era of gene therapy for inherited retinal degenerations (IRDs).

October 15, 2020, was a historic day for all Canadians, as the first gene therapy treatment (Luxturna) was approved by Health Canada for an autosomal recessive IRD due to RPE65 variants. Further announcements about payment schedules and delivery platforms will follow, once defined. This announcement is in some important ways similar to the announcements of penicillin for infections (1927) and insulin for diabetes (1921). Previously, there were no treatments for infections, nor diabetes. Just like previously there was nothing for blindness due to IRDs. What we thought was not possible is becoming possible. What does this mean for our IRD patients and their caregivers? What does this mean for our practice of ophthalmology and the future of gene therapy? Here are some short answers.

The first IRDs described were retinitis pigmentosa (RP) by Donders in 1857, followed by the discovery of Leber congenital amaurosis (LCA) by Leber in 1869. For almost 150 years, ophthalmology residents were taught and patients and families were told that there is nothing to do for these devastating diseases. For ~4 million IRD patients around the world, that was a grave message. We now know that this is incorrect. There are over 270 genes underlying retinal disorders. If you want to make a difference, the first step is to identify the genetic cause of the condition and its inheritance and provide related counseling (https://www.fightingblindness.ca/resources/genetic-testing-for-inherited-retinal-diseases/).

Most of the newer therapies for IRDs require gene identification, and these are gene specific. RPE65-related IRD is a model for this.

RPE65 was discovered and cloned in 1993 by the late Dr. Christian Hamel, a Montpellier native, while he was working with Michael Redmond at NIH. Though Dr. Hamel passed away last year, he did witness the incredible revolution stemming from their discovery going from the bench to the bedside, a wonderful example of translational research but also personalized medicine.

RPE65 mutations cause severe early onset IRDs like RP and LCA. Canine and mouse studies in the late 1990s and early 2000s showed that replacing RPE65 was safe and effective in improving the retinal function and mobility of the animals that received gene therapy. The treatment consists of a subretinal injection of the normal-sequence RPE65 transgene packaged into inactivated viral particles (adeno-associated virus, AAV-2). The virus then delivers the RPE65 gene construct to the retinal pigment epithelium (RPE) cells, and the RPE65 protein is made, leading to...