

# A Novel Case of Proliferative Diabetic Retinopathy in a Patient with Cone Rod Dystrophy

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## Abstract

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Diabetic retinopathy and retinal dystrophies rarely present concurrently due to the protective effect of retinal dystrophies against diabetic retinopathy, and there is sparse documentation on the co-existence of diabetic retinopathy and retinal dystrophies. This report describes a rare case of proliferative diabetic retinopathy (PDR) in a patient with cone rod dystrophy (CRD). This co-existence is not only unique in its presentation, it also highlights the important role of ancillary testing including fundus autofluorescence, fluorescein angiography, optical coherence tomography, and full field electroretinography. Genetic testing can also aid in the diagnosis. The pathophysiology of the concurrent development of these conditions is discussed. This case underlines the need for further investigation into the pathophysiology of diabetic retinopathy, particularly in patients with retinal dystrophies.

## KEY WORDS

Diabetic retinopathy, genetic testing, cone rod dystrophy, retinitis pigmentosa, inherited retinal dystrophies

## INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide with an estimated global prevalence of 22.27% among people with diabetes mellitus (DM).<sup>1</sup> Cone rod dystrophies (CRD) are inherited retinal dystrophies with an estimated prevalence of 1 in 40,000,<sup>2</sup> which makes them much more rare than DR. Previous studies have shown that retinal dystrophies such as retinitis pigmentosa (RP) may reduce the risk of the development of DR.<sup>3-5</sup> Additionally, proliferative diabetic retinopathy (PDR) is uncommon in patients with RP.<sup>6</sup> Due to the similarities in the pathophysiology, clinical findings and genetics of CRD and RP,<sup>2,7</sup> the presence of CRD would be expected to be protective against the development of DR, and the coexistence of PDR and CRD should be rare. This case report describes a unique presentation of PDR in a patient with CRD, and the ancillary and genetic testing that aided in the diagnosis. The pathophysiological considerations relating to the rarity of the co-existence of these two conditions are investigated.

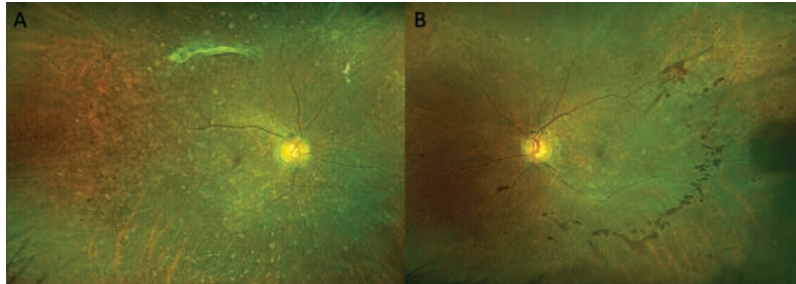
## CASE REPORT

A 56-year-old Asian male presented for a diabetic eye exam. He had no visual complaints and his ocular history was unremarkable. His medical history was significant for uncontrolled non-insulin dependent type 2 DM for more than 20 years. He had previously been admitted for diabetic ketoacidosis, and his most recent HbA1C was 9.9%. He was also hypertensive with a recent blood pressure of 130/74 mmHg, and he had been diagnosed with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome two years prior. His last CD4 count was 197 cells/uL and his viral load was undetectable. His medical history was also significant for prostate hyperplasia, depression, and previous treatment for syphilis. His medications included amlodipine, aspirin, atorvastatin, escitalopram, dapagliflozin (Farxiga<sup>®</sup>), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya<sup>®</sup>), alogliptin/metformin (Kazano<sup>™</sup>), lisinopril, and alfuzosin (Uroxatral<sup>®</sup>).

Ocular examination revealed a best corrected visual acuity of 20/25+1 (6/7.5+1) in the right eye and 20/40-3 (6/12-3) in the left eye. Confrontation visual fields, extraocular muscle motilities, pupils and monocular color vi-

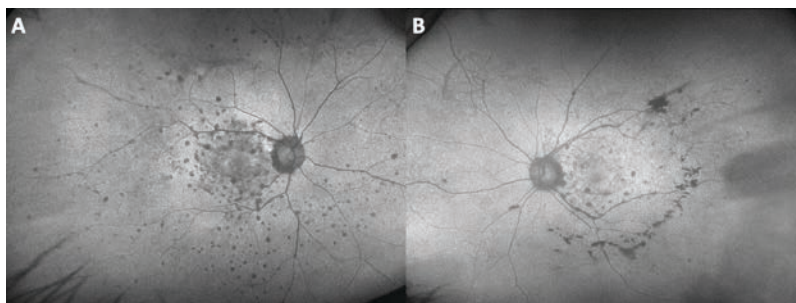
sion testing were normal in both eyes. Intraocular pressures were normotensive in both eyes, and anterior segment examination revealed mild cataracts in both eyes. Dilated fundus examination in both eyes was remarkable for neovascularization of optic discs (NVD), diffuse dot blot hemorrhages in all quadrants, arterial attenuation with crossing changes, and subtle white-yellow subretinal lesions throughout the posterior pole and extending into the mid-periphery (Fig. 1). The right eye also showed a band of fibrotic tissue along the superior arcade causing localized retinal traction, and the left eye had scattered pre-retinal hemorrhages.

**Figure 1:** Fundus photos showed PDR with NVD in the right eye (A) and left eye (B) and pre-retinal hemorrhage of the left eye. Scattered white-yellow subretinal lesions are visible throughout the posterior pole with extension into the mid-periphery of the right eye more than the left eye.



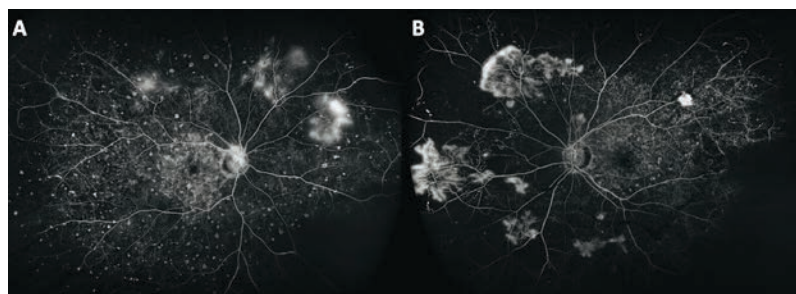
Fundus autofluorescence (FAF) was performed and revealed hypo-autofluorescence of the white-yellow subretinal lesions seen in the clinical exam (Fig. 2). These areas of hypo-autofluorescence correlated to areas of atrophy of the retinal pigment epithelium (RPE) and outer retinal layers, with the right eye more involved than the left eye.

**Figure 2:** Fundus autofluorescence of the right eye (A) and left eye (B) revealed hypo-autofluorescence of the lesions noted on the fundus photos. These areas of hypo-autofluorescence correlated to areas of RPE and outer retinal atrophy. No hyper-autofluorescence was noted in either eye.



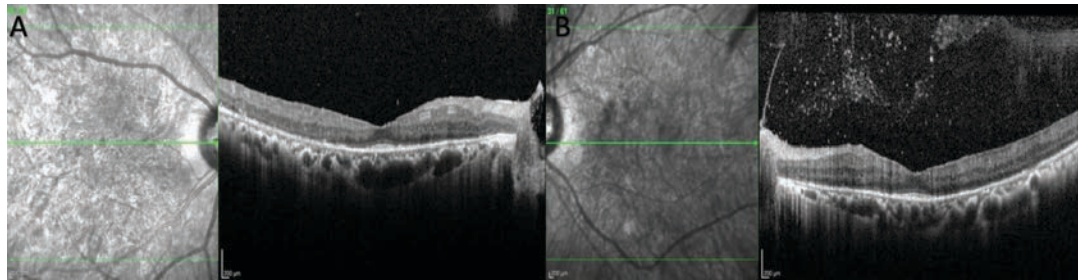
Fluorescein angiography (FA) was performed to evaluate the severity of the DR (Fig. 3). FA revealed bilateral NVD and NVE with extensive capillary dropout and poor perfusion. The white-yellow subretinal lesions noted on funduscopy were visualized as hyper-fluorescent window defects on FA secondary to RPE and outer retinal atrophy.

**Figure 3:** Fluorescein angiography of the right eye (A) and left eye (B) demonstrated PDR of both eyes with NVD, large areas of capillary dropout and poor perfusion. Window defects were visualized in the areas of the white-yellow subretinal lesions indicating areas of RPE and outer retinal atrophy.



Optical coherence tomography (OCT) of the macula (Fig. 4) revealed foveal-sparing outer retinal atrophy with loss of the parafoveal ellipsoid zone bilaterally, implicating involvement of the parafoveal photoreceptors. Automated perimetry field testing was unreliable but demonstrated central defects in both eyes.

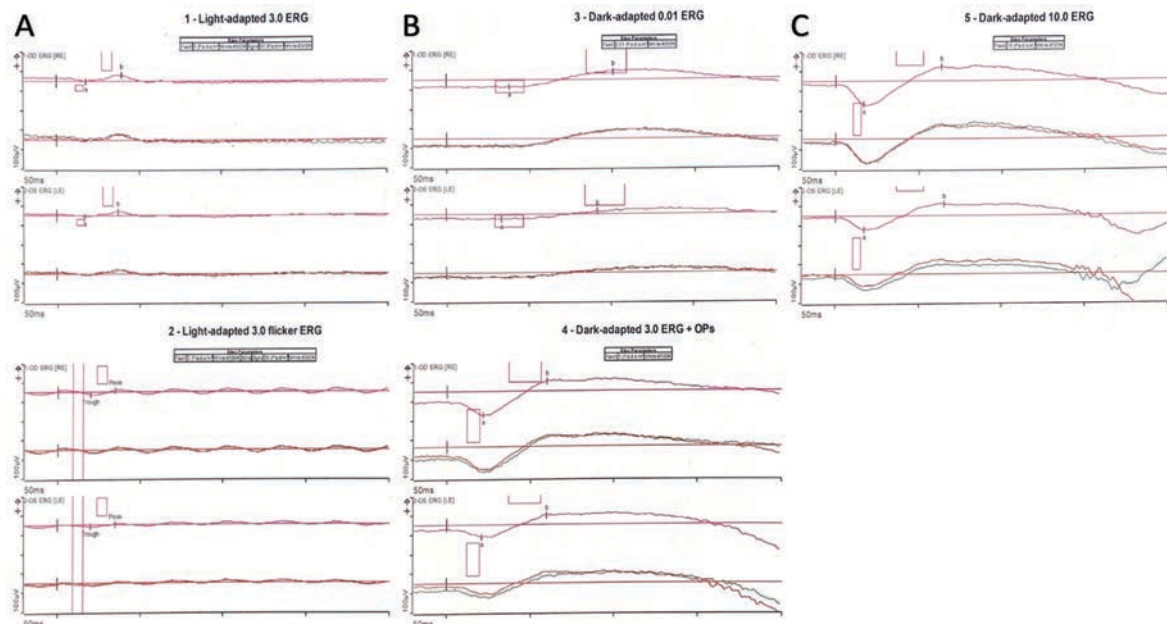
**Figure 4:** OCT macula of the right eye (A) and left eye (B) revealed foveal-sparing outer retinal atrophy with loss of the parafoveal ellipsoid zone in both eyes. The left eye also showed some low-grade vitreous hemorrhage.



Based on the clinical presentation of bilateral white-yellow subretinal lesions on fundoscopy and FAF, FA and OCT findings of diffuse outer retinal atrophy, a retinal dystrophy was suspected. While the patient initially denied any visual complaints, upon further probing, he did acknowledge some difficulty while driving at night for the previous 3-4 years. Differential diagnoses included CRD, RP, Stargardt disease, cone dystrophy, congenital stationary night blindness, Leber congenital amaurosis, and hydroxychloroquine toxic retinopathy. Hydroxychloroquine toxic retinopathy was ruled out based on the patient's medication history. To differentiate among the inherited retinal dystrophies, full field electroretinography (ERG) and genetic testing were recommended.

Full field ERG testing (Fig. 5) demonstrated reduced cone amplitude and latency, normal rod amplitude and latency, and reduced rod-cone amplitudes and latencies. Genetic testing with the Invitae Inherited Retinal Disorders Panel<sup>®</sup> (Invitae Corporation) revealed that the patient had a heterozygous mutation of the tubulin tyrosine ligase-like 5 (TTLL5) gene, which is known to be associated with CRD.<sup>8</sup>

**Figure 5:** Full-field ERG of both eyes. Under light-adapted conditions, the cone photoreceptors demonstrated reduced cone amplitude and latency (A). Under dark-adapted conditions, rod photoreceptors demonstrated a normal rod amplitude and latency, but a reduced rod-cone amplitude and latency (B-C).



## DISCUSSION

Clinical examination and retinal ancillary testing confirmed the diagnosis of PDR in both eyes. Fundus examination was ambiguous for any specific type of retinal dystrophy, and the OCT findings suggested RP. It is difficult to diagnose specific retinal dystrophies solely based on clinical presentation, and genetic testing is playing an increasingly important role in clinical practice to aid in the diagnosis of these conditions. Genetic testing in combination with ERG testing with the presence of a pathogenic heterozygous mutation of the *TLL5* gene led to the diagnosis of CRD. In humans, studies have shown that the *TLL5* gene encodes for a protein that is expressed at the base of the connecting cilium of rods and cones with staining of this protein more prominent in cones than in rods.<sup>9</sup> Consequently, *TLL5* gene mutations are predominantly found in retinal dystrophies with cone involvement and may present as cone dystrophy or CRD with an onset in later adulthood.<sup>10</sup>

CRD is an inherited retinal dystrophy that presents with central retinal degeneration and progressive photoreceptor loss.<sup>2</sup> The age of onset for CRD usually ranges from the teens to early adulthood, but cases with onset in later adulthood have been reported.<sup>11,12</sup> OCT of CRD shows diffuse outer retinal atrophy at the macula resulting in severely reduced central vision, with mid-peripheral involvement noted in later stages.<sup>12</sup> OCT of the macula in this case demonstrated foveal sparing, which is atypical in CRD but has been described previously in a variety of heterogenic retinal dystrophies.<sup>13</sup> While the mechanism of foveal sparing in these dystrophies has not been elucidated, it is not disease-specific and may present in patients with a milder genetic variant or heterozygous mutations that commonly correlate with a later age of onset and a less severe phenotype.<sup>13</sup> The foveal sparing also explained why the patient's VA was better than expected for CRD. It was also atypical to have asymmetry between the two eyes in patients with CRD. Lambertus et al. found that asymmetry in Stargardt disease, a retinal dystrophy, was more likely in patients with a later onset of disease and in those carrying a milder genetic mutation.<sup>14</sup> The asymmetry noted in our case of CRD is likely related to the later onset of his disease and the heterozygous genetic mutation. The patient's diabetic retinopathy was also mildly asymmetric and slightly more severe in the left eye than the right eye. Diabetic retinopathy changes occurring before, or concurrently with, the dystrophy may have resulted in the asymmetry. Due to the limited documentation on diabetic retinopathy in patients with retinal dystrophy, there is minimal information available on asymmetric retinal dystrophy in a patient with diabetic retinopathy. In this case, the time of onset of each condition is unknown so no definite conclusion can be drawn regarding the asymmetric presentation.

Generally, DR and retinal dystrophies are both common conditions that rarely co-exist. DR is known to be negatively correlated with retinal dystrophies like RP.<sup>3</sup> In a survey of 55 patients with both RP and DM (both insulin- and non-insulin-dependent), Arden found a total absence of DR.<sup>4</sup> Even though the sample size was small, all patients in the study had had DM for a long time (mean duration of 19 and 14.5 years for insulin-dependent and non-insulin-dependent DM, respectively). Similarly, in a nationwide Taiwanese population-based cohort study, Chen et al found that RP was associated with a reduced risk of developing PDR; however, this finding was statistically insignificant due to the small sample size.<sup>5</sup> Many studies on this subject have small sample sizes due to the limited number of cases of concurrent RP and DR. To our knowledge, there are only rare case reports of PDR in RP.<sup>6</sup>

Several theories have been proposed to explain the protective effect of inherited retinal dystrophies such as RP against DR. Retina hypoxia is thought to be the major underlying mechanism of the development of DR, and the presence of outer retinal atrophy seen in inherited retinal dystrophies reduces the retinal metabolic demand and would reduce the risk of the development of DR.<sup>4</sup> This is similar to the benefits of performing pan retinal photocoagulation (PRP) to treat severe non-proliferative DR and PDR. Another theory suggests that the loss of photoreceptors in RP and other retinal dystrophies reduces free radical production from glycolysis due to decreased metabolic demand. This reduces the risk of the development of DR since free radicals play an important role in the development of DR.<sup>4</sup> In summary, the loss of photoreceptors in RP leads to a decrease in retinal metabolic demand, a decrease in the degree of retinal hypoxia and a decrease in the production of free radicals. This results in protection against the development of diabetic retinopathy in patients with retinal dystrophies.

In contrast to RP, CRD is much more rare with a prevalence approximately 10 times less than that of RP, and CRD is usually more severe than RP due to the earlier involvement of central vision.<sup>2</sup> Furthermore, while RP is also known as rod cone dystrophy where rods are affected first, in CRD, cones are affected before rods. Despite these differences in the disease sequence, RP and CRD share a similar course of progressive photoreceptor degeneration; clinically, late-stage RP and CRD do not differ significantly from each other.<sup>2</sup> It has also been proposed that gene mutations that typically cause RP can also lead to CRD.<sup>2</sup> Sun et al. demonstrated a possible connection between *TLL5* and the functional variant of the retinitis pigmentosa GTPase regulator (RPGR). They suggested that *TLL5* is most likely

responsible for the glutamylation of RPGR and RPGR mutation is a major cause of RP.<sup>7</sup> This suggests that these two genes may share a common disease pathway.

Based on both the genetic and physiological similarities between RP and CRD, the loss of photoreceptors and outer retinal atrophy in CRD should reduce the retinal metabolic demand, which would then reduce the level of retinal hypoxia. Therefore, similar to RP, CRD should have a protective effect against the development and progression of DR. To our knowledge, there are no documented case reports on the co-existence of DR and CRD.

It is important to note that the patient did have HIV, which may confound the clinical picture as HIV and DM can both cause retinal vascular changes. Studies have shown that HIV infection can aggravate retinal microvasculopathy in patients with DM,<sup>15</sup> and initiation of highly active anti-retroviral therapy (HAART) can slow the progression of DR.<sup>16</sup> In this case, the patient had had DM for more than 20 years and was diagnosed with HIV approximately 2 years prior to presentation. HAART had been initiated more than one year prior to his presentation to our eye clinic. HIV infection could have played a role in aggravating the patient's diabetic retinopathy and reducing the protective effect of CRD against the development of PDR. Since the patient was not examined before and after his HIV diagnosis and initiation of treatment, the potential role of HIV on the development of DR cannot be determined. However, based on previous data, since the patient had started HAART therapy more than one year prior to presentation, it would have been expected to aid in stabilizing and slowing the progression of his DR, since HAART therapy has been reported to stabilize the progression of retinopathy as early as 3 months after the initiation of therapy.<sup>17</sup>

This case report described a patient with a history of uncontrolled diabetes who was diagnosed with CRD. Despite the proposed protective effect of CRD against DR, the patient still developed PDR in both eyes. This was likely due to the patient's history of chronic uncontrolled DM, HIV infection, and a later onset of CRD. Further investigation into the pathophysiology of the development of DR, particularly in patients with retinal dystrophies, may help identify specific risk factors in this patient population.

Management of PDR in this case involved monthly intravitreal injections of anti-VEGF in both eyes. Treatment of the peripheral retina with PRP was considered but was deferred due to the presence of retinal atrophy in the posterior pole and mid-periphery. Ablating the peripheral retina was relatively contraindicated due to the compromised status of the central retina. There is ongoing research into gene therapies that may have potential in treating patients with CRDs,<sup>18</sup> however, there are currently no treatments available to halt the progression of CRDs or to restore vision loss due to CRDs. For patients with profound vision loss due to CRDs, low vision and social work services should be provided.

## CONCLUSION

Retinal hypoxia has been known to induce the development and progression of diabetic retinopathy. Similar to the mechanism described with outer retinal atrophy in RP, outer retinal atrophy in CRD in a similar manner should reduce the metabolic demand and therefore protect against the development and progression of DR. To our knowledge, this is the first documented case of PDR developing in a patient with CRD. Not only is it unique in its presentation, it also highlights the need for further investigation into the pathophysiology of diabetic retinopathy, particularly in patients with retinal dystrophies. ●

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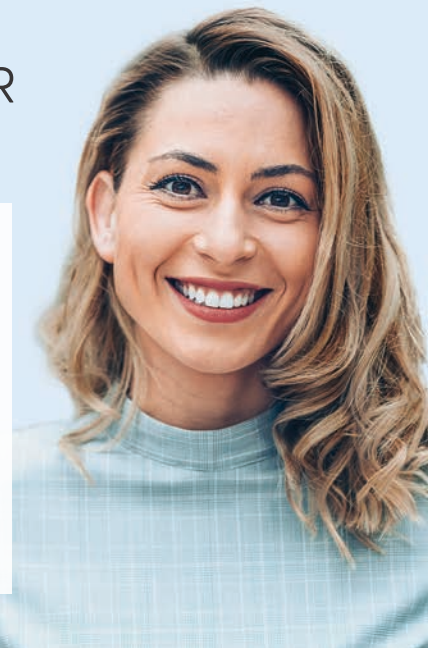
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