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Multimodal Imaging Reveals Bilateral Idiopathic Multiple Retinal Pigment Epithelial Detachments: A Case Report

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Multimodal Imaging Reveals Bilateral Idiopathic Multiple Retinal Pigment Epithelial Detachments: A Case Report

Abstract

Background: Retinal pigment epithelial detachment (RPED) is a nonspecific finding that is common in several ocular diseases; however, cases of bilateral idiopathic multiple RPEDs are rare. Less than 50 cases have been reported to date. Bilateral multiple RPEDs are usually idiopathic and benign in nature but can infrequently be associated with various ocular and systemic diseases, including central serous chorioretinopathy (CSC). The potential role of genetic factors in this condition remains elusive. We present a case where multimodal imaging assisted in revealing the diagnosis as well as discuss the potential implications of some of the genetic findings for this patient.

Case report: A 30-year-old male presented with a chief complaint of mild, bilateral central blur of one-year duration. Health history was positive for type 2 diabetes mellitus.

Conclusion: Multimodal ophthalmic imaging is useful in ruling out various differential diagnoses in posterior segment care, as well as monitoring for progressive changes such as sensory retinal detachment and choroidal neovascularization. Bilateral idiopathic multiple RPED is a rare condition that may represent an atypical form of CSC. There is currently no preferred treatment, besides observation, as visual prognosis is typically good.

Keywords

multiple bilateral retinal pigment epithelial detachments, optical coherence tomography, idiopathic, metamorphopsia, multimodal imaging, serous detachment, retinal pigment epithelial detachments, genetic testing

Background

There are four main types of retinal pigment epithelial detachments (RPEDs): drusenoid, serous, vascularized, and hemorrhagic (which may be considered a variant of vascularized).[1-4] RPED is a separation of the retinal pigment epithelium from the underlying Bruch's membrane. Drusenoid RPEDs are primarily associated with age-related macular degeneration (AMD). These appear as yellow or white colored lobular lesions with scalloped edges that appear on optical coherence tomography (OCT) as shallow detachments of the RPE with underlying drusen.[1,3,5] Drusenoid RPEDs, though typically bilateral, can be asymmetric and are usually the smallest of the RPED types.[6] Serous RPEDs are the most common form of idiopathic bilateral multiple RPEDs.[3,5] Serous RPEDs display a similar ophthalmoscopic appearance to the drusenoid type; the main difference is that they are translucent. Compared to drusenoid RPEDs, the serous type exhibits less of a yellow appearance due to the absence of drusen or lipid deposits.[3] In addition, OCT shows a hyporeflective area under the RPE in the serous type.[1,3,5]

Vascularized RPEDs are associated with choroidal neovascularization (CNV) subtype 1, which presents with neovascularization underneath the RPE and above Bruch's membrane.[5] These RPEDs typically have irregular margins, are notwell circumscribed, and are commonly associated with surrounding lipid accumulations or sub-RPE hemorrhage.[5] Vascularized RPED lesions may exhibit anotched appearance at the border of a circular or oval lesion.[3]

Multiple bilateral RPEDs are a rare finding. Clinically, they can be identified by several spots of RPE disturbances that may appear as fluid filled, circular, and slightly raised. They occur more frequently in males than females, and typically present between 20-60 years of age.[6] RPEDs are typically unilateral and serous in nature and have been widely identified in eyes with central serous chorioretinopathy (CSC).[4,6] While an RPED may occur in CSC, the hallmark of CSC is a well-defined serous detachment of the sensory retina. Patients with CSC may be asymptomatic or complain of blurry vision, metamorphopsia, and/orscotoma depending on the location of the lesion(s).

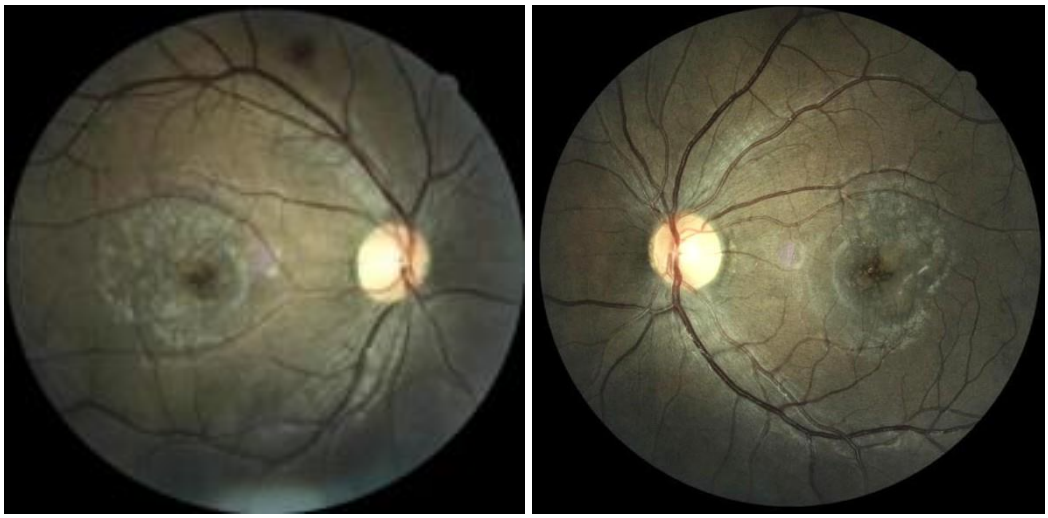
Clinical signs of CSC include subtle or obvious changes to the RPE on funduscopy, as well as the characteristic neurosensory detachment. Fundus autofluorescence (FAF), fluorescein angiography (FA), and indocyanine green angiography (ICGA) are useful imaging technologies in the assessment of CSC. Active CNV should be promptly treated, as it is the most common cause of severevision loss in patients with RPED.[2,6,7]

Case Report

A 30-year-old male of Mexican ancestry presented as a new patient to our primary care clinic with a chief complaint of mild, bilateral central blur in both eyes of one-year duration. The blur remained constant and consistent throughout the year prior to his visit without additional symptoms. His spectacle correction provided little improvement;

however, the patient's visual discomfort was minimized using tinted filters. Ocular history revealed an absence of trauma or surgery and the patient reported a "congenital macular deformation" that was diagnosed two years earlier. The patient's health history was positive for type 2 diabetes mellitus since 2011, which was managed by his primary care provider. His last blood sugar level was 180 mg/dL fasting (that morning) and his last glycosylated hemoglobin A1c was 7.0%. The only medication he was taking at the time of the visit was Novalog (insulin aspart) at an unreported dosage. His family ocular history was non-contributory, and his family systemic history was positive for type 2 diabetes. Surgery history included an appendectomy in 2016. He denied smoking, recreational drug use, and alcohol consumption.

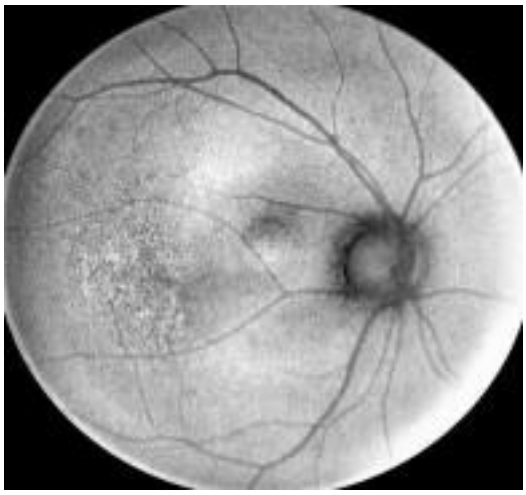
Entering visual acuities without correction were 20/25 right eye and 20/20 left eye at distance and 20/20 at near for both the right and left eyes. Refraction showed right eye prescription of -0.50 sphere and left eye -0.25- 0.50 x105 with similar visual acuities with and without correction. When encouraged, the patient could reach 20/20-2 right eye and 20/20 left eye. His entrance testing and slit lamp anterior segment findings were all unremarkable. Intraocular pressures were 18 mm Hg right eye and left eye with Goldmann tonometry. Dilated funduscopy with 1% tropicamide and 2.5% phenylephrine revealed a mottled pattern of RPE disturbances within each macula. A few microaneurysms were noticed in each eye. A single dot and blot hemorrhage was observed in the right eye and was indicative of moderate nonproliferative diabetic retinopathy (NPDR), while the left eye had mild NPDR.There was no evidence of diabetic macular edema in either eye (Figures 1 and 2). The optic nerves appeared pink and healthy with a cup to disc ratio of 0.40 and 0.35 ratio right and left eye respectively. A peripheral retinal examination revealed no hemorrhages, holes, tears, or detachments in either eye.

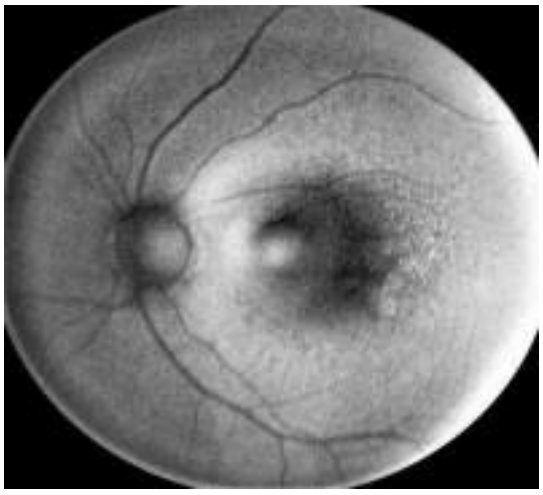


Figures 1 and 2: Honeycomb pattern of multiple RPEDs can be appreciated within the maculae. A blot retinal hemorrhage can be seen superiorly in the right eye.

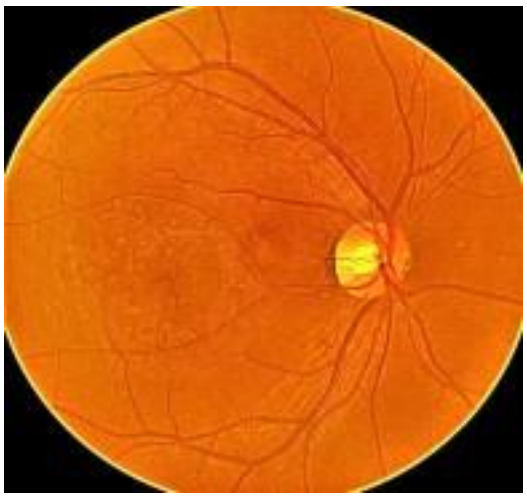
Further investigation with Amsler Grid testing revealed mild central metamorphopsia in each eye. Multicolor/spectral imaging, FAF, and OCT confirmed multiple serous RPEDs of various sizes in both eyes spanning 2-to-2.5-disc diameters in and around the

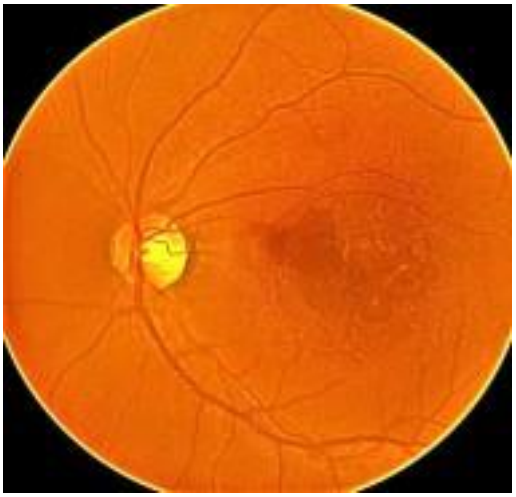
fovea (Figures 3-8) of each eye.



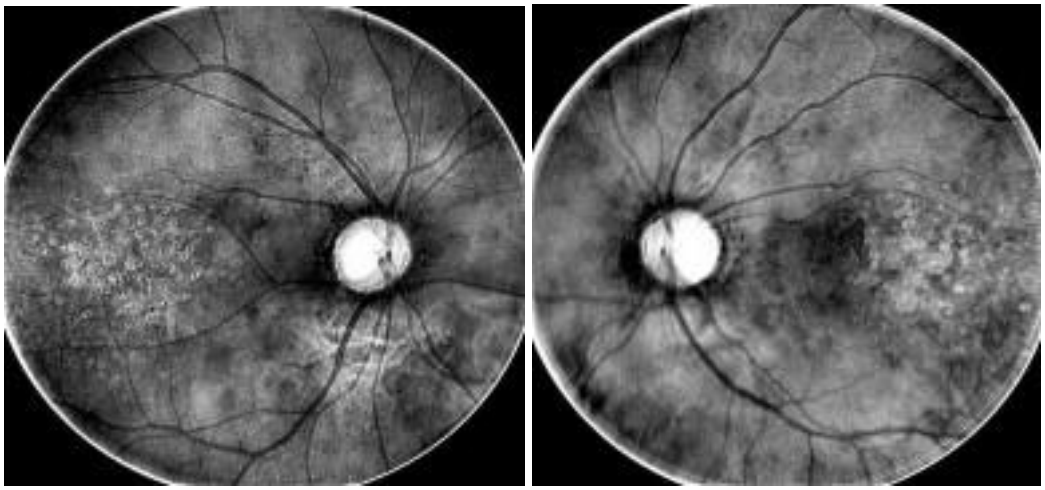


Figures 3 and 4: Fundus autofluorescence (FAF) amber highlights the granular appearance of the RPE with areas of both hyper- and hypo-autofluorescence within each macula. Note the OS (Figure 4) macula appears to have more extensive hypo autofluorescence due to RPE atrophy. This appearance may be partially due to image artifacts from the instrument.



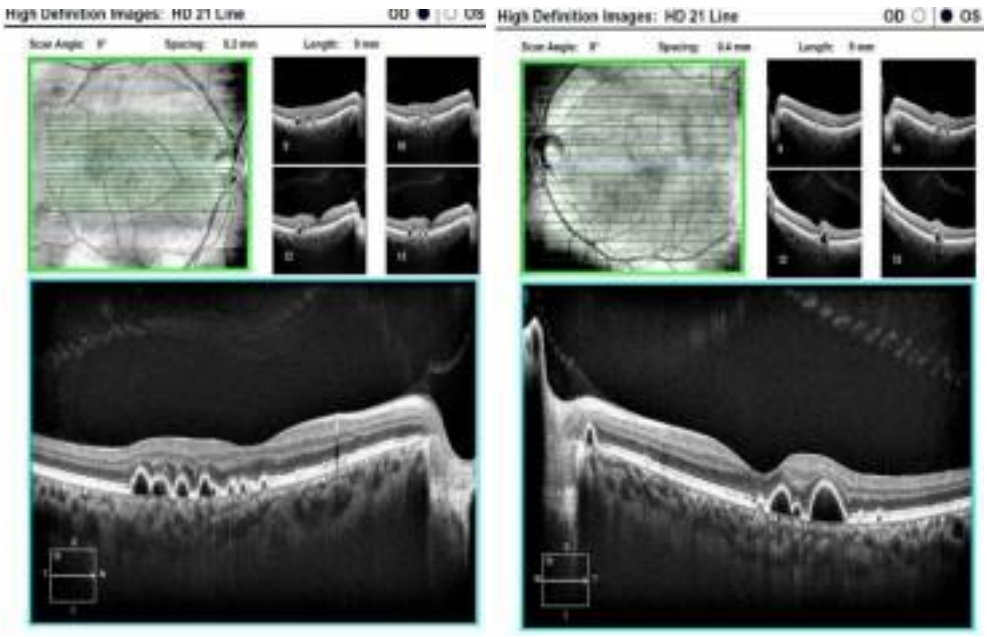


Figures 5 and 6: Multispectral imaging (MSI) red/green composite showing another contrast view of the multiple areas of circular RPEDs in each macula. Also note the pattern of hypo- and hyper-pigmentation in each macula, indicating degradation of the RPE. This can impact visual function.



Figures 7 and 8: MSI infrared imaging reveals numerous RPEDs (i.e., pattern of "translucent bubbles") in each macula as well as RPE atrophy (dark area) in the central macula of the OS (Figure 8).

OCT angiography (OCT-A) confirmed the absence of CNV in each eye on the cross-sectional images (B-scans) as well as the *en*-face coronal (C-scan) images (Figures 9-14).



Figures 9 and 10: OCT HD 21-line raster scans reveal multiple serous RPEDs in both eyes. Note that some RPEDs in the OS (Figure 10) appear to be of larger size. There was no contamination of the ellipsoid zone band in either macula; this is consistent with the patient's good visual function.

Figure 11: OCT-Angiography of right eye: Noninvasive technique used to appreciate retinal and choroidal vasculature. Above, angioplex *en*-face structural view reveals projection artifacts and no abnormal vasculature at the avascular (outer retina/RPE) level. Below, structural *en*-face view at the same level clearly shows areas of serous RPE detachments. The left eye showed similar findings.

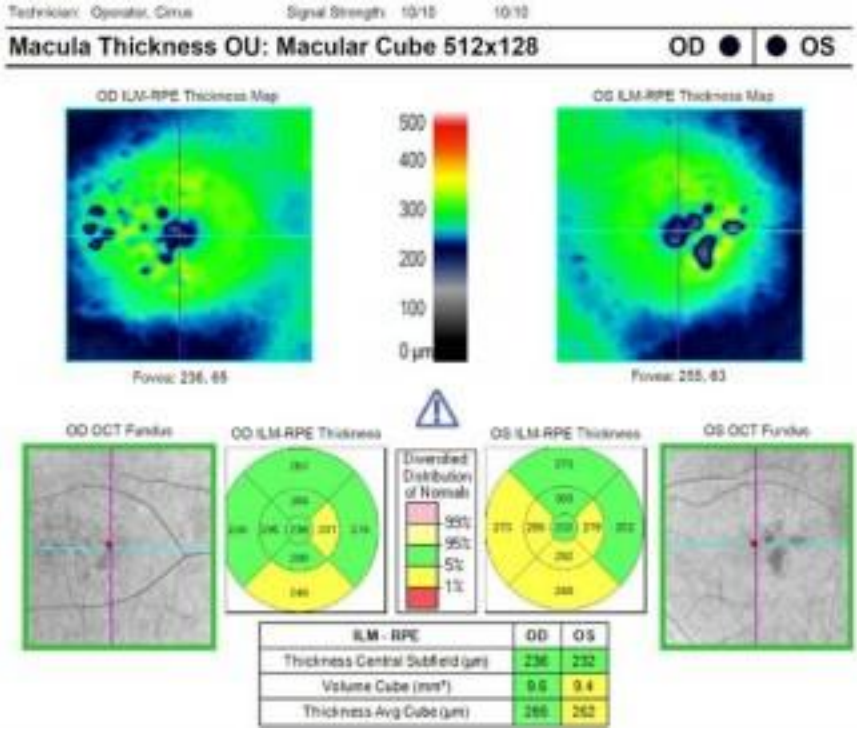
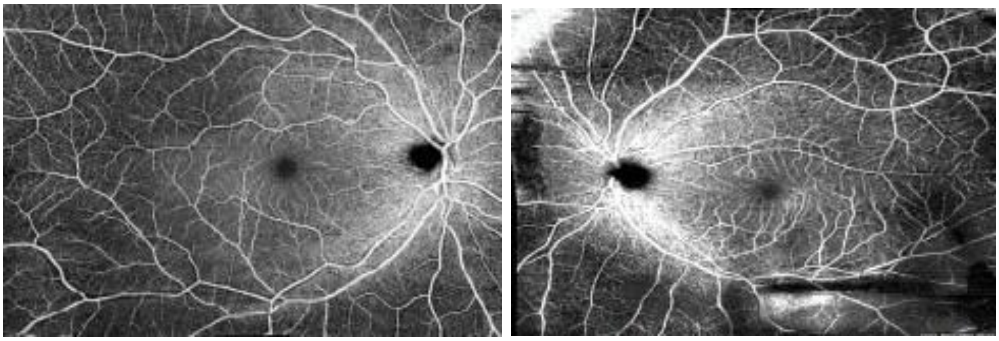


Figure 12: OCT macular cube scan retinal thickness maps (top) show patterns of serous RPEDs in each eye. Note "yellow zones" on ILM-RPE thickness maps in each eye, with more extensive areas of thin retina in the OS. Sub-RPE fluid exerts upward (anterior) force and RPE elevation, thus resulting in these findings. Note also that central subfield thickness in each eye remains within the statistical norm, again correlating with good visual function.



Figures 13 and 14: Montage OCT-A of the retinal and choroidal vasculature revealed no retinal neovascularization, no CNV, and no major areas of retinal nonperfusion. Dark areas in the image of the OS represent motion and blink artifacts.

Due to the exaggerated appearance with minimal and mild subjective symptoms, we explored whether there were any sublevel visual issues that were not apparent subjectively. Dark adaptometry and VEP were performed with unremarkable results.

The bilateral presentation of idiopathic multiple serous RPEDs in our patient was unusual. This condition has seldom been reported in ophthalmic literature. To investigate a possible genetic component, the patient was referred to the low vision rehabilitation service. There, he underwent testing using the Blueprint Genetics Retinal Dystrophy Plus Panel and a saliva sample. This genetic panel included 266 genes with a known role in inherited retinal dystrophy. The genetic testing was sponsored via My Retina Tracker® genetic study program.The results of the test were "negative for explaining the patient's phenotype."

Nevertheless, the following four genetic variants were identified: a missense variant in *RIMS1* gene [c.5023C>G, p.(Arg1675Gly)], a second missense variant in *ABCA4* [c.872C>T, p.(Pro291Leu)], a frameshift variant in *C5ORF42* [c.2422_2423del, p.(Leu808Valfs*7)], and the deletion of one of the two copies ofthe *NPHP1* gene. The patient was counseled about the findings by a geneticist and all his questions were answered.

The genetic variants identified in *ABCA4*, *C5ORF42* and *NPHP1* were unlikely to explain this patient's phenotype because they introduce tolerated changes in the encoded protein (i.e., *ABCA4* variant), or cause recessive forms of retinal disease (i.e., *C5ORF42* and *NPHP1* variants). The missense variant identified in *RIMS1* (also known as *CORD7*), a member of the *RAS* gene superfamily that regulates exocytosis of synaptic vesicles, has not previously been reported in the literature but is predicted to be damaging according to *in silico* analyses. Of note, a different pathogenic variant in *RIMS1* has been identified in patients with an autosomal dominant form of late onset cone-rod dystrophy (OMIM #603649). Although the variant did not seem to explain the RPEDs observed in our patient, this genetic finding is worth noting in the event that the patient begins to show symptoms or signs of a cone-rod dystrophy later in life. Since the genetic results did not explain the current symptoms or clinical findings in our patient, these variants were classified as variants of uncertain significance (VUS).

Differential Diagnoses

Several differential diagnoses were considered, including:
Ocular diseases

Central serous chorioretinopathy (CSC)	Polypoidal choroidal vasculopathy (PCV)	Central areolar choroidal dystrophy (CACD)
Hypertensive choroidopathy	Acute retinal pigment epitheliitis (Krill disease)	Pachychoroidopathy

Infectious Systemics Diseases

tuberculosis	Lyme disease
Syphylis	Herpes virus

Inflammatory or Autoimmune Systemic Diseases

Sarcoidosis	Vasculitis
Kogt- Koyanagi Harada Disease	

Other Systemic Diseases

Systemic hypercortisolism	Renal disorders
Malignant hypertension	Acute leukemia

The patient reported that he had his blood pressure taken at every diabetescheckup and had no recollection of being diagnosed with hypertension, thereforehypertensive choroidopathy was ruled out. Due to the mild severity and constant nature, Krill's disease was ruled out. PCV was tentatively ruled out due to thelack of vascularization in the RPEDs, lack of obvious vascular "polyps" onOCT-A (although FA/ICGA testing would further confirm these findings), andethnicity, as PCV tends to occur more in middle-aged African American or Asianpatients.[3] CACD is characterized by a large, demarcated area of atrophy or loss ofthe RPE, choriocapillaris, and photoreceptors. Although multispectral photographyshows similar hypo-reflective areas in early stages, genetic testing shows clinicalspecificity of 99.99% with correlation to variations in genes *GUCY2D* and*PRPH2*. The patient did not express pathogenic variants in either of these twogenes.

Two of the more common causes of RPEDs are AMD and CSC.[2,4] AMD was ruled out in this case due to the patient's age, visual function, and lack of drusen. A variant of CSC was among our differential diagnoses because although RPEDs are known to follow resolving, resolved, or chronic CSC, they have also been found to precede the disease.[4] CSC is an idiopathic disorder characterized by serous sensory retinal detachment; a feature that was absent in our patient over multiple visits. CSC is most often confined to the macula and is associated with the leakage of fluid through the RPE into the subretinal space.[4,6] Of all established CSC cases, around 10.5% have isolated RPEDs and around 4-8% areassociated with CNV, though, the data vary throughout the literature.[2,5] The

most consistent risk factors for CSC are glucocorticoid use, elevated levels of endogenous corticosteroids, and pregnancy. Another risk factor traditionally associated with CSC is psychological stress and "type A personality." A study of CSC and personality types supports this association.[8]

While multiple bilateral serous RPEDs without subretinal fluid are not typical of CSC, these findings could potentially be viewed as a precursor to the disease.[7] Several genetic variants, such as the SNP rs2070951 and the GA haplotype in the mineralocorticoid receptor *NR3C2,* have been found to be associated with chronic CSC. None of these variants were included on our genetic panel as currently there are no direct links between this gene and inherited retinal disease.[9]

Due to the benign nature, chronological history of the condition, and imaging results, a diagnosis of presumed idiopathic bilateral multiple serous RPEDs was established. The central fovea of each eye remained intact, which explains the good visual acuity and only mild metamorphopsia, even in the presence of adjacent RPE disturbances. The patient was educated on his diagnosis and genetic testing findings and was scheduled to return in 4 months for continued monitoring.He was given an Amsler grid for daily self-testing. In addition to a fundus examination, OCT, and OCTA, we will consider performing fluorescein angiography/indocyanine green angiography (FA/ICGA) to fully rule out CNV, if warranted.

Discussion

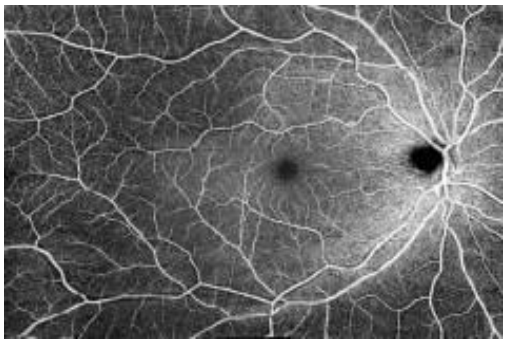
Here we present a case of bilateral idiopathic multiple retinal pigment epithelial detachments (RPEDs) in a 30-year-old Hispanic male with a chief complaint of bilateral mild blurred vision, but good visual acuity. This patient had a history of diabetes and early signs of retinopathy. With this report, we aim to provide a framework to aid in the diagnosis of idiopathic forms of RPEDs using imaging and molecular approaches for exclusion of differentials.

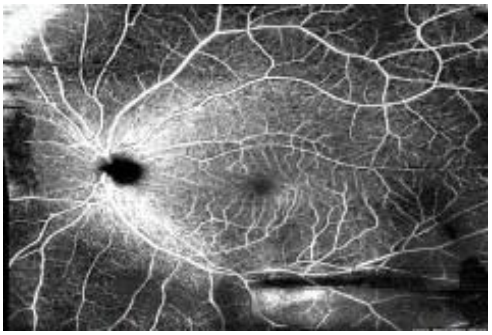
The prognosis for idiopathic bilateral multiple RPEDs is relatively good. Most cases have resulted in self-resolution with small reminiscent areas of RPE atrophy.[2-4,6] There are no current treatments suggested for idiopathic multiple RPEDs. The standard of care currently is observation due to the mostly asymptomatic nature and stability of the condition.[2,6,7] If CNV is present and active, treatment can include laser photocoagulation, photodynamic therapy (PDT), and/or intravitreal anti vascular endothelial growth factor (VEGF) agents.[2-4,6-13]

We performed multimodal fundus imaging, including color photography, FAF, multicolor imaging and OCT/OCTA. These technologies provided noninvasive evidence of the extent, size, and number of lesions. The RPEDS that we identified were several, bilateral, of various sizes, surrounding the fovea, and lacking CNV. Multimodal imaging showed the multiple RPEDs as a honeycomb pattern as well as revealing a retinal hemorrhage (Figures1 and 2). Multispectral imaging allowed different visualizations of

the RPEDs ranging from granular to "bubble-like" appearances (Figures 3-8). OCT scans showed multiple varied sized areas of sub-RPE serous fluid without hyper-reflective or hazy material underlying the retina (Figures 9 and 10).

A small number of areas of serous fluid found underneath the RPE along with larger areas of serous fluid within the sensory retina are common in CSC; however, our imaging showed numerous RPEDs with no fluid under or within the sensory retina. Acutely-symptomatic CSC will typically resolve spontaneously over 1-6 months, whereas chronic CSC can be ongoing and recur. In cases of chronic CSC, progressive visual dysfunction has been shown secondary to constant RPE manipulation. The lack of fluid within the retina, as well as the stable nature of the RPEDs and lack of risk factors, did not support a diagnosis of CSC in our patient. OCT-angiography demonstrated the absence of new blood vessels (Figures 11 and 12). Currently, fluorescein angiography is still considered the gold standard for identifying CNV for all causes and types.[3,5,14] However, OCT-A is a noninvasive way to detect different types of CNV and thus motivated us to use this approach in our patient as an alternative to FA (figures 13 and 14).[14]





Figures 13 and 14: Montage OCT-A of the retinal and choroidal vasculature revealed no retinal neovascularization, no CNV, and no major areas of retinal nonperfusion. Dark areas in the image of the OS represent motion and blink artifacts.

While there are only a few reports of patients with bilateral idiopathic multiple RPEDs, a prognosis of good functional vision is expected. Ancillary testing using an Amsler Grid in this patient revealed bilateral metamorphopsia, and funduscopy revealed diabetic retinopathy (OD, OS). These two findings resultedin not only the patient having difficulty deciphering details but having issues with glare as well. Minimizing this visual noise using wavelength specific colored lens filters was suggested to the patient to enhance his vision and minimize his symptoms.[15,16] We also explained to the patient that the etiology of his condition and whether or not there is a genetic component linked to it remains elusive. Currently, about 70% of the retinal dystrophies are diagnosed at the molecular level.[17] The results of his inherited retinal dystrophy panel came back "negative," but this could be expected. We need to keep in mind that the interpretation of genetic findings was based on previous knowledge, which is lacking in regard to idiopathic bilateral multiple RPEDs. Nevertheless, we identified a new genetic variant in *RIMS1*, which is linked to an autosomal dominant form of cone-rod dystrophy

(CORD).[18] This incidental finding will become clinically relevant if the patient develops symptoms and signs of CORD later in life. A possibility of progression and manifestation of a CORD will be supported by the appearance of the lesions and their location, together with his genetic findings.

In addition to the ancillary testing that we described in this report, it is important to monitor this patient's functional vision through color vision and contrast sensitivity testing, as these are characteristic presentations in CORD. Central threshold perimetry and electrodiagnostic testing may be implemented as well. And, because late onset of CORD usually occurs before the fourth decade of life, frequent follow up is warranted.[18,19] On future visits the patient should be asked about symptoms of difficulty seeing in bright light. This would indicate a deterioration and loss of cone function.[19] From a funduscopic perspective, we would search for a "bulls-eye" dystrophic pattern followed by atrophy seen in CORD. The literature also shows that bilateral presentations of RPE changes, which are somewhat symmetrical in appearance and become atrophic over time, can also be seen.[18] Our patient's presentation could be consistent with this alternate appearance. If he does begin to exhibit these symptoms, he would, unfortunately, fall into the progressive subtype of cone dystrophies. This usually manifests later in life, along with rod photoreceptor dysfunction, and thus will adversely affect his night vision as well. Congenital and early-onset forms tend not to exhibit this feature.[19,20]

Considering the stable appearance of the patient while under our care, an observation every 4-6 months is crucial. Our multimodal diagnostic approach led us to further investigate the condition in our patient and to become better equipped to manage potential complications that may arise in the future. Genetic testing provided additional information to monitor not only disease progression, but also the potential risk for our patient's offspring should they begin to exhibit symptoms consistent with CORD. Genetic counseling was provided to properly educate our patient on the potential implications of the genetic findings with respect to inheritance patterns of the identified variants. There is a 50% probability for transmitting them to his future children. Having this foreknowledgewill help the future generations in his family obtain appropriate eye care, genetic testing, and vision rehabilitation services earlier, if needed.

Conclusion

Bilateral idiopathic multiple retinal pigment epithelial detachment is a rare condition that may degrade central visual function. Multimodal imaging and genetic analysis were valuable in providing comprehensive in-depth and overall care of this patient. To the best of our knowledge, this is the first report on a patient with multiple RPEDs undergoing a genetic panel to investigate a possible molecular basis for his condition. Although the genetic findings did not seem to explain the RPEDs, the incidental finding of the *RIMS1* variant had potential value on its own.

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