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Diagnostic and Therapeutic Challenges Section of Retina

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Dear Editors of Retina Journal

Please find enclosed our manuscript entitled: **"Diagnostic and Therapeutic Challenges"** that we would like to submit for consideration in the Diagnostic and Therapeutic Challenges section in Retina Journal.

After asking several experts for their opinion. This manuscript is presented for discussion of diagnosis. It was conducted to report unusual intra-retinal white-greyish lesions and multiple pigmented lesions mimicking "bear tracks" spreading throughout the superior hemi-retina, involving peripheral areas, posterior pole and macular area. The features of these lesions were described with an Optical Coherence Tomography imaging technology, Wide Field colour and Fundus Autofluorescence. We also provide some differential diagnoses for discussion.

We hope that the style and contents of our article are in agreement with the requirements of the Journal but please do not hesitate to contact us should the need arise.

Yours sincerely,

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Diagnostic and Therapeutic Challenges

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This case is submitted by Drs. Salvador Pastor-Idoate [1,2], Heinrich Heimann[3], Pearse A. Keane[4], and Konstantinos Balaskas[1]; commented by Dr. Brandon J. Lujan.

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Case Report

A 29-year-old woman was referred to our center in November 2014, after a routine examination in her local optician, to assess multiples naevi in the periphery of the fundus. These areas of pigment have not been described to the patient in the past. The patient had no ocular complaints and no previous medical history, ocular history or systemic treatments. She had no family history of visual problems, was born of non-consanguineous parents, and was otherwise well. The best corrected visual acuity was 20/20 in the right eye (RE) and 20/25 in the left eye (LE). The entire examination was normal except for the retina in the left eye.

Examination in the LE showed unusual intra-retinal white-greyish lesions and multiple pigmented lesions mimicking “bear tracks” spreading throughout the superior hemi-retina, involving peripheral areas, posterior pole and macular area. The inferior retina looked unremarkable. The fundus appearance of the RE was completely normal.

A detailed vitreoretinal examination was performed along with spectral domain (Spectralis®) optical coherence tomography (OCT) (Figure 1A and 1B) and Wide Field

color (Figure 2A, 2B, 3C) and Fundus Autofluorescence (WF-FAF) (Optos PLC, Dunfermline, Scotland) (Figure 3A and 3B). OCT scans taken at the level of the unusual white-greyish lesions and pigmented lesions in the LE showed two types of lesion patterns. Mild-reflective masses in the inner plexiform layer with slightly optical shadowing posterior to the lesion and hyper-reflective patches in the RPE-Bruch's complex layer without optical shadowing posterior to the lesion, respectively. Fundus Autofluorescence (FAF) just showed hypo-fluorescent round structures, corresponding with the hyper-reflective patches in the OCT scans. T he patient was observed without any intervention.

Three weeks later the ophthalmic examination was unchanged. The patient was observed without any change in her symptoms. No further investigations were made because of lack of evidence of an inflammatory cause.

We believe that the pigmented lesions present in the LE represent Grouped Congenital Hypertrophy of the Retinal Pigment Epithelium (Grouped CHRPE). Indeed they present with a typical configuration of larger lesions in the peripheral retina becoming smaller with increased proximity to the optic disc. The unilateral presentation in the absence of family history or gastro-intestinal symptoms would not warrant further investigation to exclude familial polyposis in this case. The associated unusual intra-retinal white-greyish lesions were rather more puzzling. Our differential diagnoses for such lesions include the following ones:

1. Multiples hamartomas of the retina[1-2]
2. Intraretinal RPE migration into the neurosensory retina[3]
3. Unilat RPE Dysgenesis[4-5]

4. Massive Reactive Gliosis[6-7]

What are these lesions in the inner plexiform layer in the OCT scans?

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Commentary

Dr. Brandon J. Lujan (San Francisco, California): Salvador and co-authors present a diagnostic challenge of an asymptomatic 30 year-old woman with intra-retinal whitish lesions. No past medical history or extra-ophthalmic exam findings are given, but the lesions have been evaluated by multimodal imaging and a differential can be formed primarily from the optical coherence tomography (OCT) studies.

The highest resolution OCT image of the retinal lesions in question is found in Figure 2, which demonstrates a hyper-reflective, smooth, round intrinsic lesion that appears to be centered at the junction of the inner nuclear layer (INL) and inner plexiform layer (IPL). There is some heterogeneity within the lesion such that there is more hyper-reflectivity at its inner boundary. This lesion appears associated with the OCT signature of superficial retinal vasculature, discreet focal hyper-reflectivity with distal attenuation or “shadowing”. There is a mass effect on the inner retinal layers with inward displacement of the moderately thinned IPL, ganglion cell and nerve fiber layers. There is a similar mass effect on the outer retina with outward displacement of the INL, synaptic outer plexiform layer (OPL), Henle fiber layer (HFL), and outer nuclear layer (ONL). There is the suggestion of compression of the ONL deep to the lesion, though without being able to visualize the ONL/HFL boundary clearly this cannot be confirmed. The external limiting membrane is continuous, but bowed outward. The reflectivity of the ellipsoid zone is attenuated and the interdigitation zone (IZ) is not visible distal to the lesion. While the photoreceptor inner-segment thickness length appears essentially normal, there is a clear decrease of the photoreceptor outer-segment lengths compared to the surrounding retina, consistent with the focal loss of the IZ band. The retinal pigment epithelium and choroid appear intact and unremarkable.

There is a smaller lesion additionally identified in Figure 2 which is obscured in the figure by a white asterisk that the authors have indicated represents a retinal vessel. However, the presence of vasculature within the substance of the inner nuclear layer would be abnormal, and is likely not the case here. If this additional lesion were due to vasculature present in the INL/IPL interface, then this would be abnormally large for the superficial capillary plexus that resides there, and would be expected to demonstrate distal signal attenuation. Consequently, this smaller lesion likely represents another instance of the larger pathology found at the INL/IPL interface nasal to it.

Figure 3 shows the extent of the multiple foci of the lesions, and their consistent layers of origin and mass effect on the surrounding retina. Additionally, there are some slivers of hypo-reflectivity that appear within these hyper-reflective lesions. This figure also demonstrates the second pathologic feature of this case, congenital hypertrophy of the retinal pigment epithelium (CHRPE), which is seen as increased RPE hyper-reflectivity and distal choroidal attenuation. Some of the distinct hyper-reflective lesions have CHRPE deep to them, yet some do not. Additionally, some CHRPE exists away from the retinal lesions, making the relationship between these lesions unclear. No volumetric comparison of these features is presented to fully evaluate.

There are several diagnostic categories that should be considered based on the intraretinal OCT appearance of the hyper-reflective lesions. These can be broken down into ischemic conditions, inflammatory or infectious sequelae, neoplasm, or non-neoplastic malformations.

Vascular events include cotton wool spots (CWS) stemming from ischemia or infarction of the nerve fiber layer, and paracentral acute middle maculopathy (PAMM)

secondary to deep capillary ischemia. CWS can appear as globular hyper-reflective masses, and can be seen to have a mass effect on the surrounding retina, and can even impinge on the photoreceptor layers .[1] However, they are centered and appear to emanate from the nerve fiber layer, unlike this case where there is a relatively normal ganglion cell layer and nerve fiber layer overlying it. PAMM lesions do involve the INL predominantly and can cause hyper-reflectivity of it as well as the IPL. [2] While PAMM can cause some thickening of these retinal layers due to cell body swelling, this is generally quite limited and wouldn't cause the massive appearance of these lesions present in this case. Most importantly, CWS and PAMM have a relatively brief life cycle and would be expected to change somewhat over the 3-week time period slightly, and eventually cause local retinal layer thinning. The authors have indicated that these lesions remained unchanged, so ischemia can be excluded from consideration.

Infectious etiologies such as those due to *Toxoplasmosis gondii* in posterior outer retinal toxoplasmosis should be considered and have been associated with globular lesions affecting the inner retina representing areas of focal retinitis.[3] However, the absence of involvement of the outer retinal, chorioretinal scars, vitritis, or associated symptomatology indicates that this diagnosis can be eliminated.

The authors suggest several possible diagnoses including intraretinal RPE migration, unilateral RPE dysgenesis, massive retinal gliosis, and multiple hamartomas of the retina.

RPE migration into the neurosensory retina should not be considered for a variety of reasons. Initially, there is no significant distal signal attenuation from these lesions. Secondly, there is a uniformity and smoothness of these retinal lesions that

would not be expected in RPE migration, where variability of the signal and a more punctate appearance is expected. Finally, true RPE migration is rarely imaged internal to the HFL.

Unilateral RPE dysgenesis (URPED) can similarly be excluded as it is characterized by contiguous RPE changes with a circumpapillary scalloped border that would have been apparent on FAF imaging, and would demonstrates dramatic outer retinal and RPE loss on OCT. Massive retinal gliosis has been diagnosed in patients with NLP eyes undergoing enucleation specimens and this diagnosis would not apply to an asymptomatic patient with multiple lesions much smaller than a millimeter in diameter.

While the authors suggest the broad diagnostic category of multiple hamartomas of the retina, they only reference papers suggesting combined hamartoma of the retina and the retinal pigment epithelium. Because combined hamartoma can contain features of retinal and RPE involvement, the diagnosis is tempting to consider in this case where there is both retinal and underlying RPE hyperpigmentation. However, while fluorescein angiography was not presented, the OCT appearance does not suggest that there are significant vascular changes characteristic of combined hamartomas. Additionally, the multifocal nature of the retinal lesions presented in this case, the absence of overlying epiretinal membrane, or retinal disorganization make this diagnosis untenable. However, other types of multiple hamartomas must be considered, and are ultimately the most likely diagnosis in this patient.

Retinal astrocytic hamartomas are benign, vascularized glial tumors of the retina that may be acquired and congenital and have been described in by Stratus OCT.[4] In

this series of 15 cases there was a subtype of lesions that is not contiguous with the optic nerve and consisted of a smooth hyper-reflective mass that appeared to emanate from the inner retina. Further, this did not contain internal cystic spaces, nor was it associated with exudation. While the lesion of this subtype shown as the example showed signal loss deep to the lesion, it is likely that this was due to limitations of time-domain OCT without the benefits of broader bandwidth light sources, better detectors and frame-averaging. This subtype of astrocytic hamartoma is most consistent with the findings presented in this Diagnostic Challenge.

The pathology of astrocytic hamartomas has been depicted, first by McLean et al, where the appearance of origination in the INL/IPL interface[5] mirrors that of the SDOCTs in the present case. While pathology was obtained from a larger lesion than what is presented here, it is interesting to note that there were some internal vascular changes and a loss of the photoreceptor inner and outer segments apparent immediately below the lesion.

One final possibility that must be considered in this case is spontaneously regressed retinoblastomas, or retinocytomas. These are tumors of undifferentiated retinal precursor cell lines that have been reported at the junction of the INL and IPL and resemble the whitish translucent lesions found in this case.[6] However this diagnosis is extremely unlikely given that each of the nodules in this case are at essentially the same state of progression and relatively the same size. Furthermore, there is any evidence of calcification or pattern of pigment change to suggest prior neoplastic lesions.

CHRPE exists unilaterally in this patient in an unmistakable “bear tracks” pattern, and is not in itself a diagnostic challenge. Given that there is not exact spatial co-localization it is difficult to state with confidence that there is a relationship between these hamartomas and the CHRPE. If each hamartoma had underlying CHRPE and each CHRPE had overlying hamartoma it would be highly suggested that they are correlated. Given that CHRPE is such a common finding it is more likely that these are independent processes rather than there being a causal relationship, however further genetic analysis may demonstrate otherwise.

The likely diagnosis of this case is multiple astrocytic hamartomas and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Multiple astrocytic hamartomas have been previously described, almost exclusively in the context of the tuberous sclerosis complex (TSC). The presentation of this syndrome can be subclinical and may originate after funduscopic examination. The possibility of TSC should be further evaluated by dermatological and neurological examination in addition to neuroimaging and genetic analysis[7] before a definitive diagnosis can be made.

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Editor's Note: Drs. Pastore-Idoate, Heimann, Keane, and Balaskas have presented a 29-year-old woman with multiple peripheral pigmented lesions in her left eye. The presenters feel that the pigmented lesions represent Grouped Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE) and give a differential diagnosis for the puzzling grayish-white intraretinal lesions.

I. Multiple hamartomas of the retinal detachment
II. Intraretinal RPE migration
III. URPED
IV. Massive reactive gliosis

They ask for clarification concerning the lesion in the inner plexiform layer on their SB-OCT studies.

Dr. Brandon Lujan consults for us on this case and makes a detailed analysis of the lesion in question. Based on the OCT findings, he adds to the differential diagnosis of these lesions.

I. Ischemia

A. Cotton-wool spots

B. Paracentral Acute Middle Maculopathy

II. Inflammatory/Infectious

A. Toxoplasmosis (outer retinal)

III. Tumor

A. Retinal astrocytic hamartoma

B. Retinocytoma

He then reviews the differential diagnosis provided by the presenters. He discards the notion of RPE migration, URPED, and combined retinal-RPE hamartomas. He offers retinal astrocytic hamartoma as a diagnostic possibility. He references Shields paper, noting that there was a subgroup in that series where the lesions were not contiguous with the optic nerve and consisted of a smooth hyper-reflective mass that emanated from the inner retina. He feels that this subtype of astrocytic hamartoma is most consistent with the case presented in this challenge. He discusses and eliminates another whitish tumor reported at the junction of the INL and IPL, retinocytomas.

Dr. Brandon Lujan concludes his analysis of this case by noting the relationship between multiple astrocytic hamartomas and tuberous sclerosis. He recommends further evaluation by dermatological and neurological specialists, neuroimaging, and genetic analysis.

We thank Drs. Pastore-Indoate, Heimann, Keane, and Balaskas for their case, and Dr. Brandon Lujan for his consultation.

Figures

Figure 1. Optical coherence tomography scans at presentation.

A-I. Horizontal OCT line scan through the fovea of the RE.

A-II. Horizontal OCT line scan through the fovea of the LE showing small mild-reflective lesions at inner plexiform layer.

Figure 2.

A-I. Horizontal OCT line scan of the LE through the white greyish lesion (yellow arrow).

A-II. Magnification of the horizontal OCT line scan showing a mild-reflective mass in the inner plexiform layer with slightly optical shadowing posterior to the lesion at inner plexiform layer (yellow asterisk). White asterisk corresponds with the retinal vessel.

Figure 3.

A-I. Horizontal OCT line scan of the LE through the superior vascular arcade crossing the two types of lesions.

A-II. Color fundus photograph of the LE revealing the unusual intra-retinal white-greyish lesions and multiple pigmented lesions. The white-greyish lesions and the pigmented lesions in the color fundus picture correspond with the black and white lesions respectively in the grayscale of the OCT.

A-III. Horizontal OCT line scan showing two types of lesion patterns. Mild-reflective masses in the inner plexiform layer with slightly optical shadowing posterior to the lesion (yellow asterisks) and hyper-reflective patches in the RPE-Bruch's complex layer without optical shadowing

posterior to the lesion, respectively (purple asterisks). White asterisks correspond with the retinal vessels.

Figure 4.

A-I. Color fundus photograph of the LE showing the lesions spreading throughout the superior hemi-retina, involving peripheral areas, posterior pole and macular area.

A-II. Color fundus photograph of the RE.

A-III. Color fundus photograph of the LE showing the inferior hemi-retina, apparently normal.

Figure 5.

A-I. Fundus autofluorescence photograph of the RE.

A-II. Fundus autofluorescence photograph of the LE showing hypo-fluorescent round structures, corresponding with the hyper-reflective patches in the OCT scans.

Figure 1

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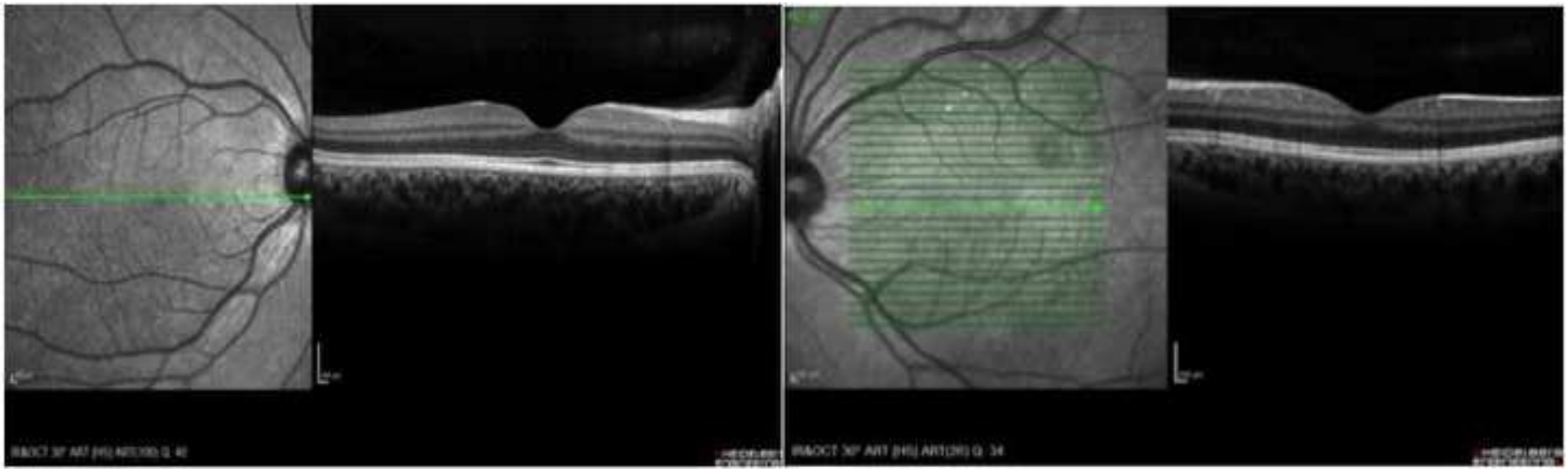

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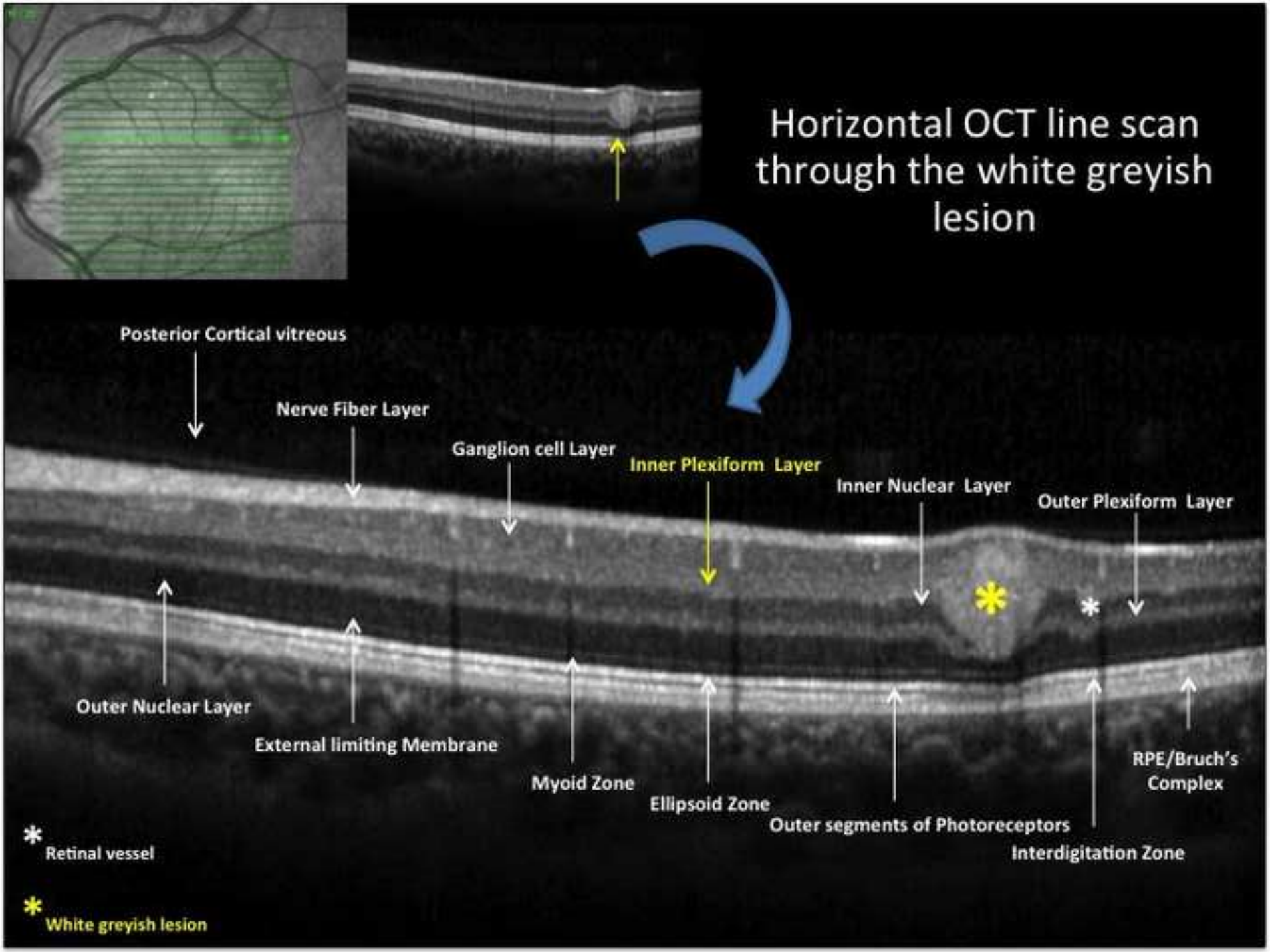

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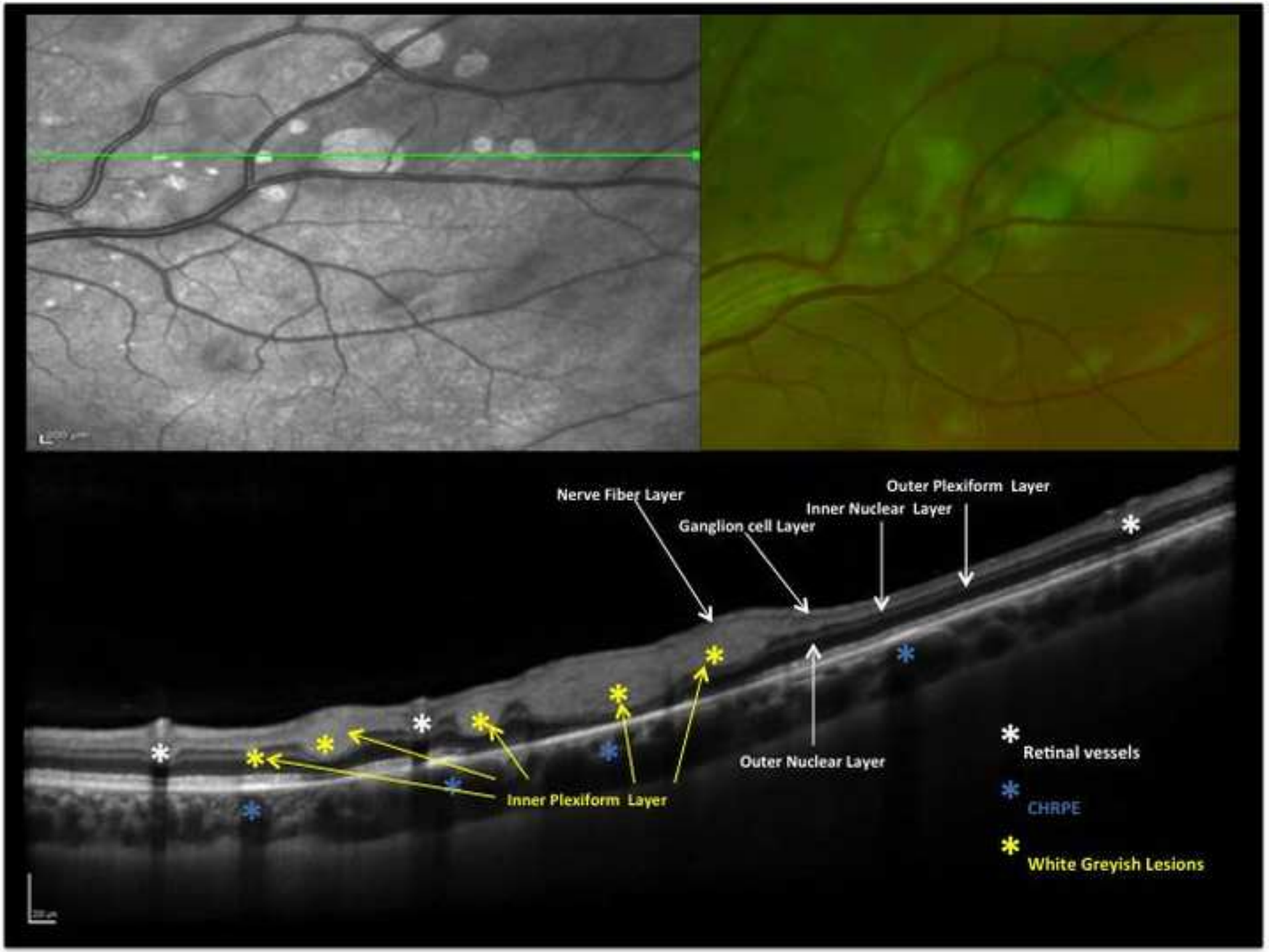

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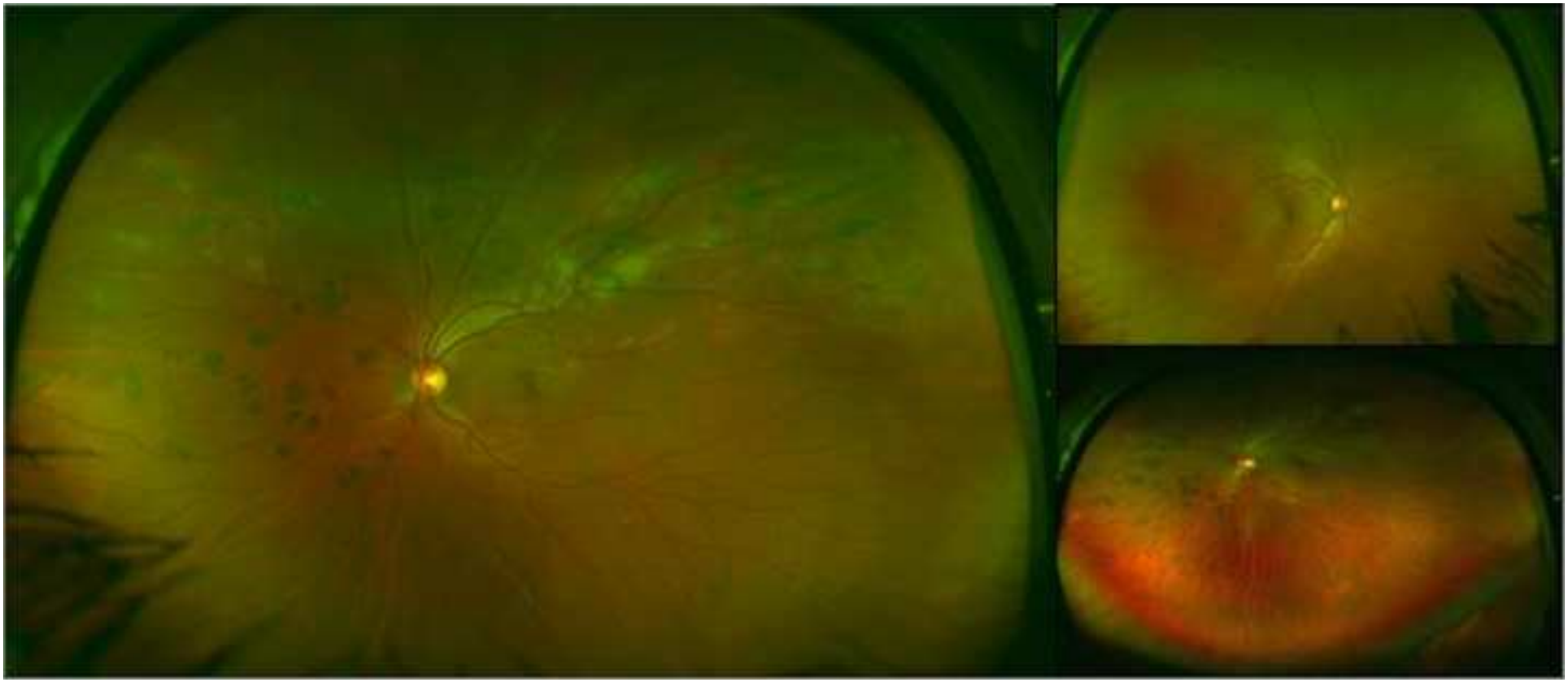

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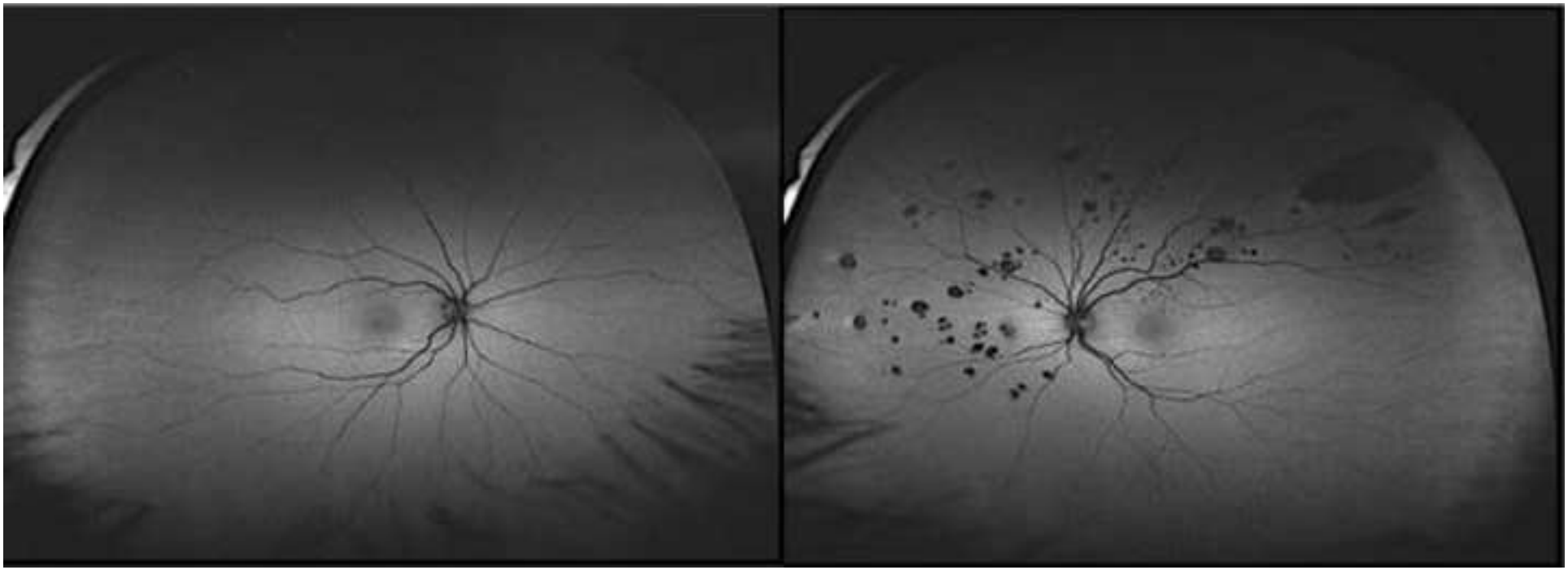

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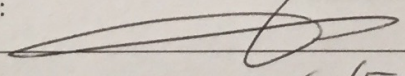
Signature: 

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