Retinal potpourri: It isn't rare if it's in your chair!

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Disclosures

Speaker/Advisory Board/Consultant:

- Optovue (Visionix)
- iCare
- Apellis
- Iveric Bio
- LKC technologies

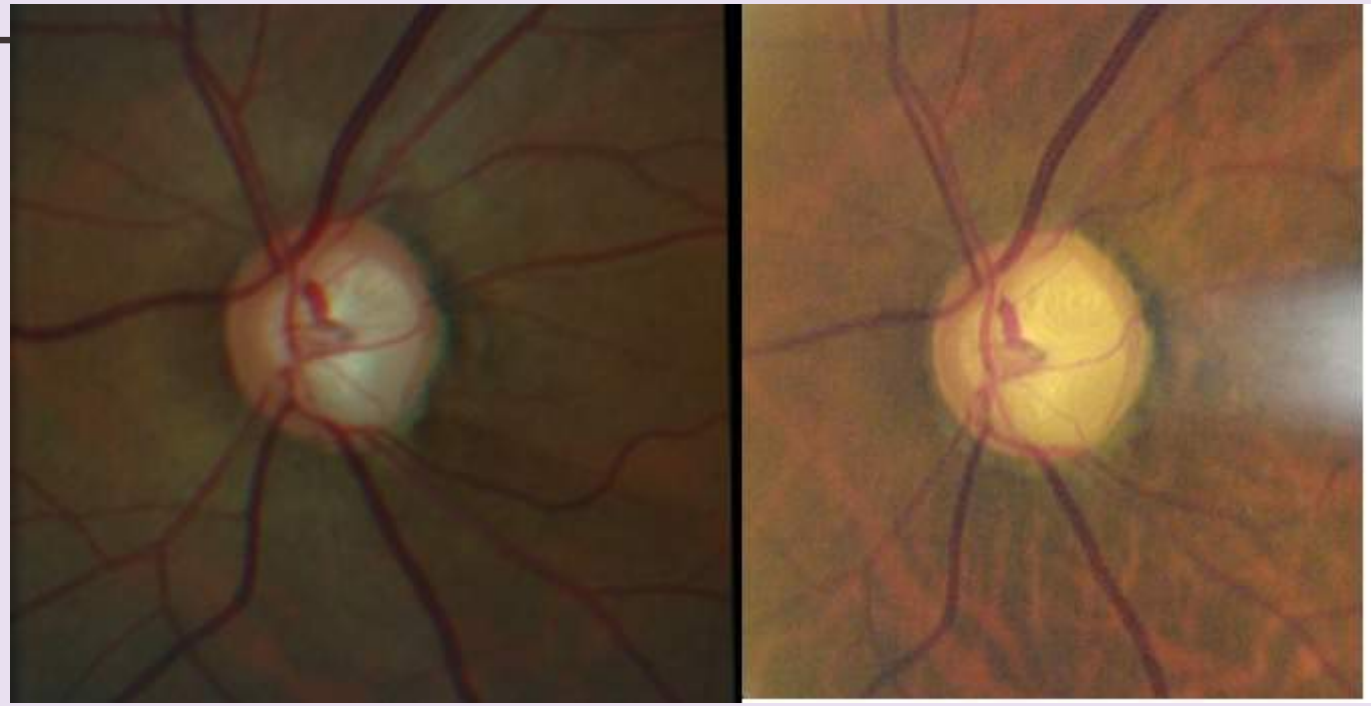
Case 1

Let's look at the case…

49-year-old African American Male

- PMH: Unremarkable
- BCVA: CF 1 FT OD, 20/20 OS
- (+)APD OD
- CF: Abnormal superior OS
- TAP: 14mmHg OD, OS
- Medications: Alphagan-P 0.1%

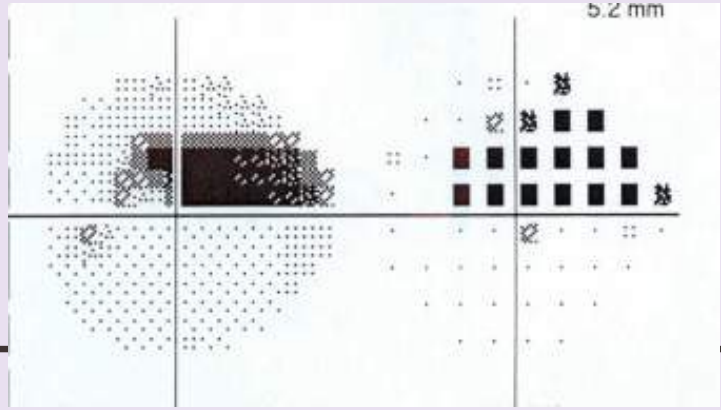
"I have been blind in my right eye since childhood…and I have glaucoma in my left eye."

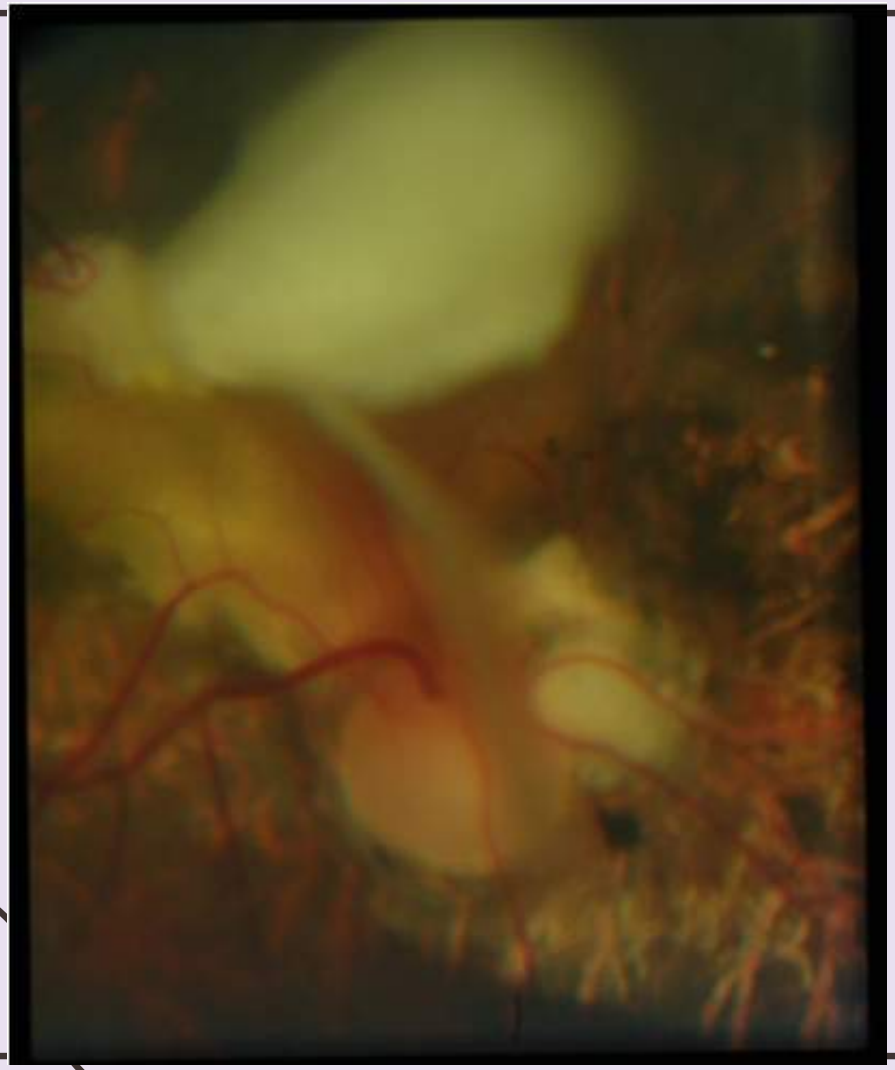


OS:
Good Eye?

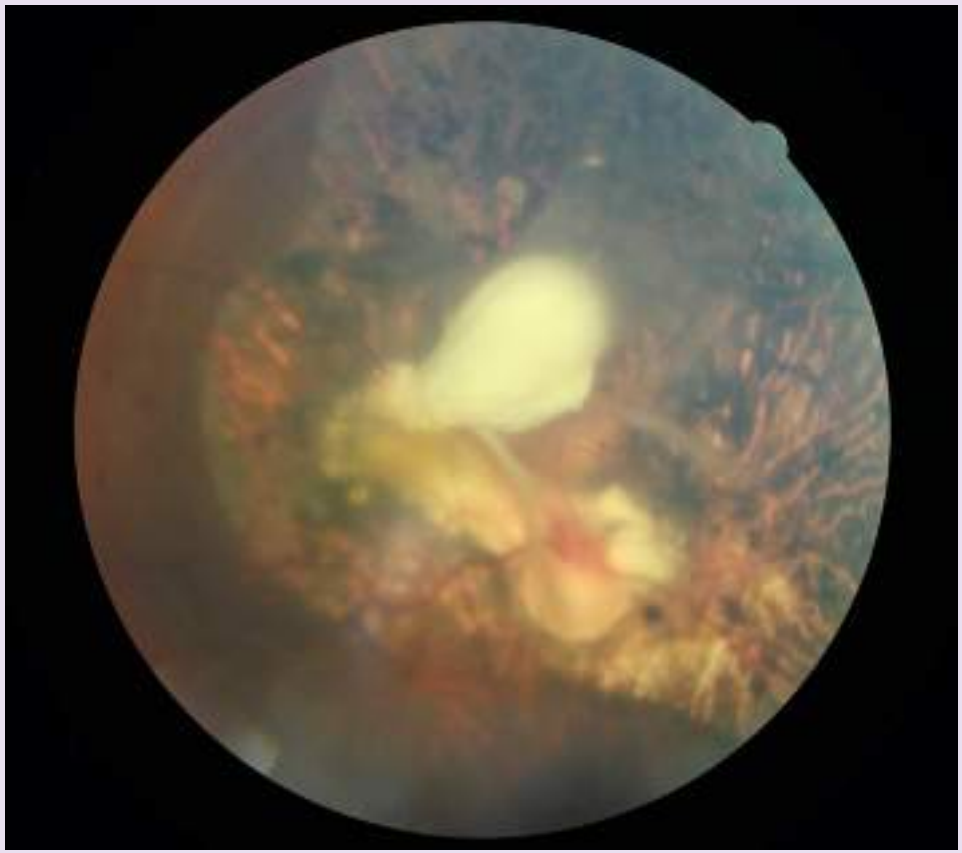
Then (2014) ...

and now



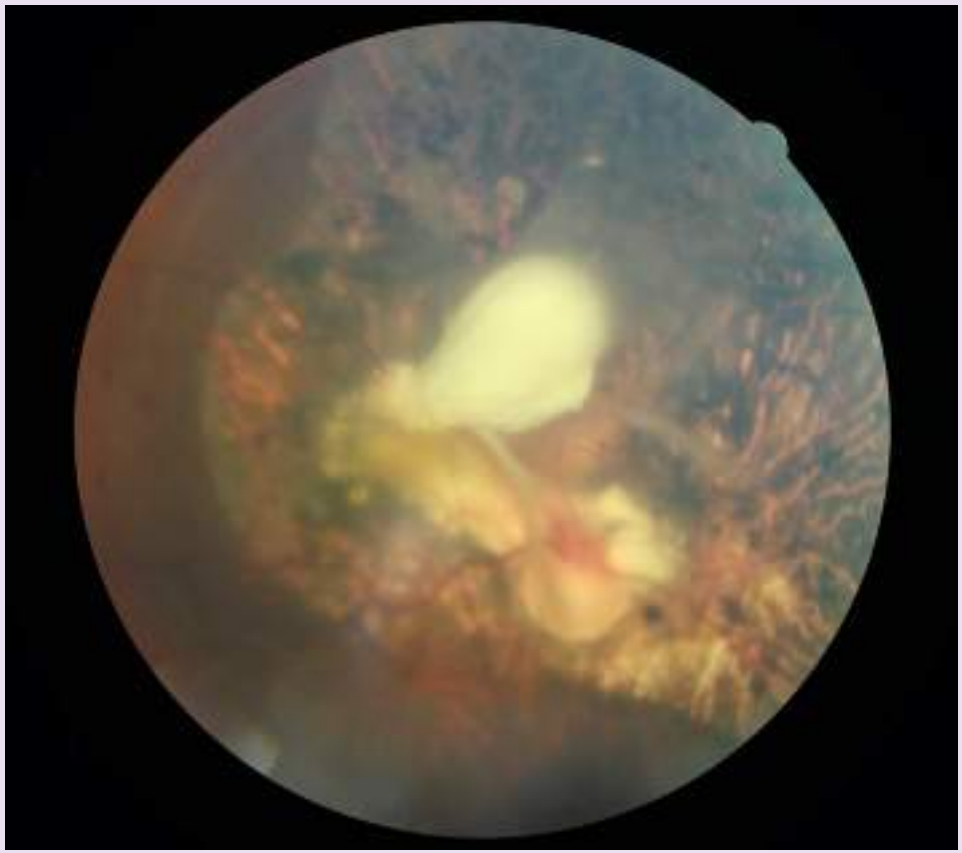


What about his right eye???



1. Retinoblastoma
2. Persistent fetal vasculature
3. Toxoplasmic retinochoroiditis
4. Toxocariasis

So...What is the clinical picture most consistent with?



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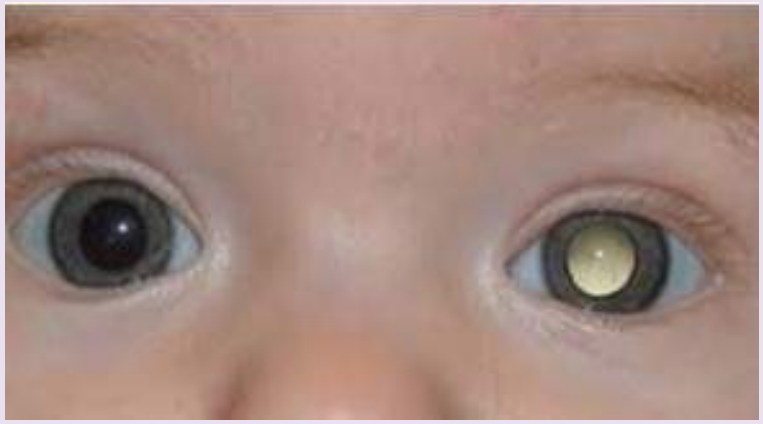
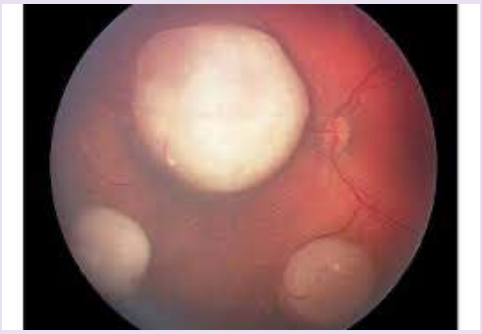
So...What is the clinical picture most consistent with?

Retinoblastoma

Why?....*Leukocoria*....

- One of the primary signs of retinoblastoma.



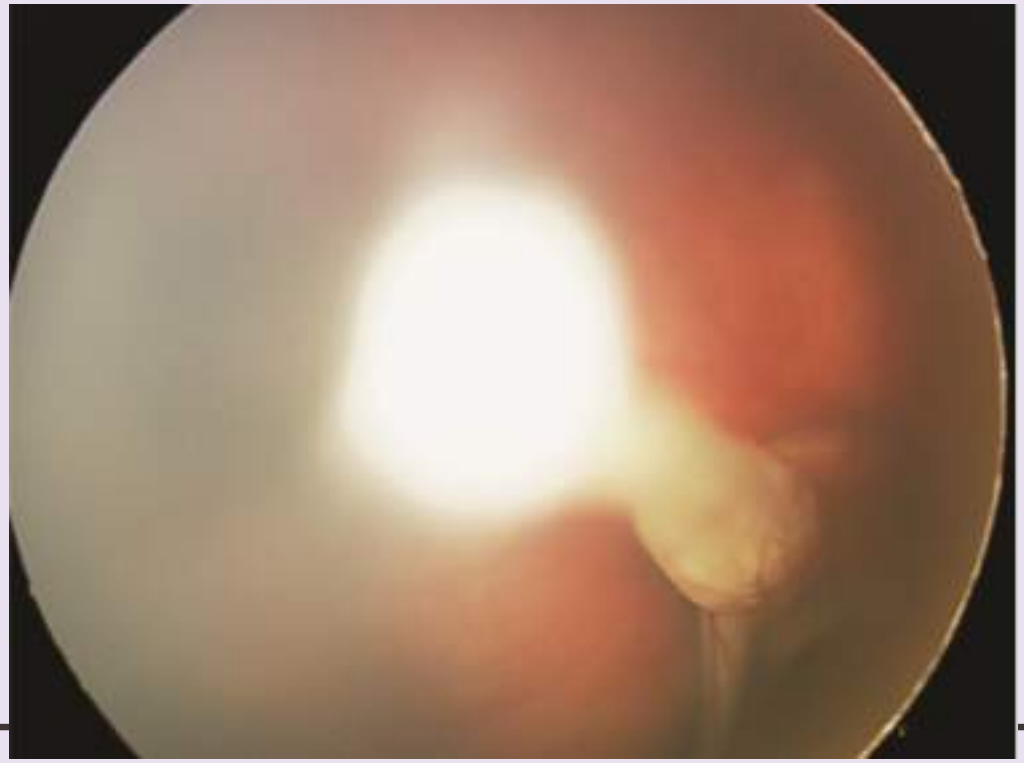


***However, a number of other conditions may also present with leukocoria, and it is critical to differentiate retinoblastoma from these so-called pseudoretinoblastomas for proper management.

https://www.willseye.org/disease_condition/retinoblastoma/

Persistent Fetal Vasculature

Persistent hyperplastic primary vitreous

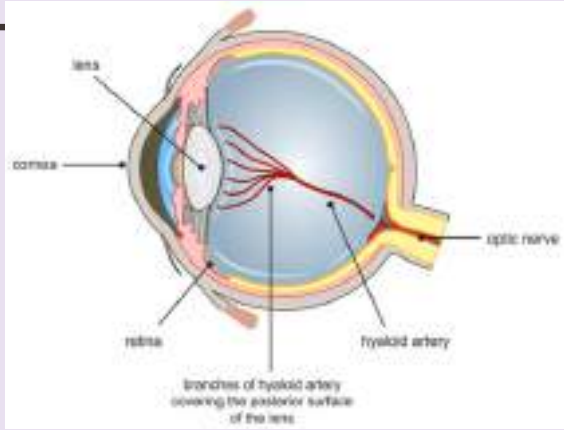


- Developmental disorder
- Second most common cause of infantile leukocoria

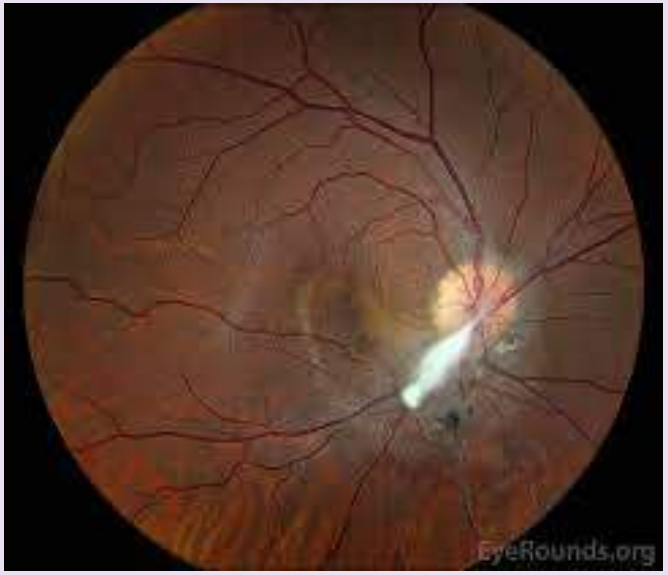
What is it???

Persistent Fetal Vasculature

Persistent hyperplastic primary vitreous



Vascular structures present during eye development fail to wither (regress)

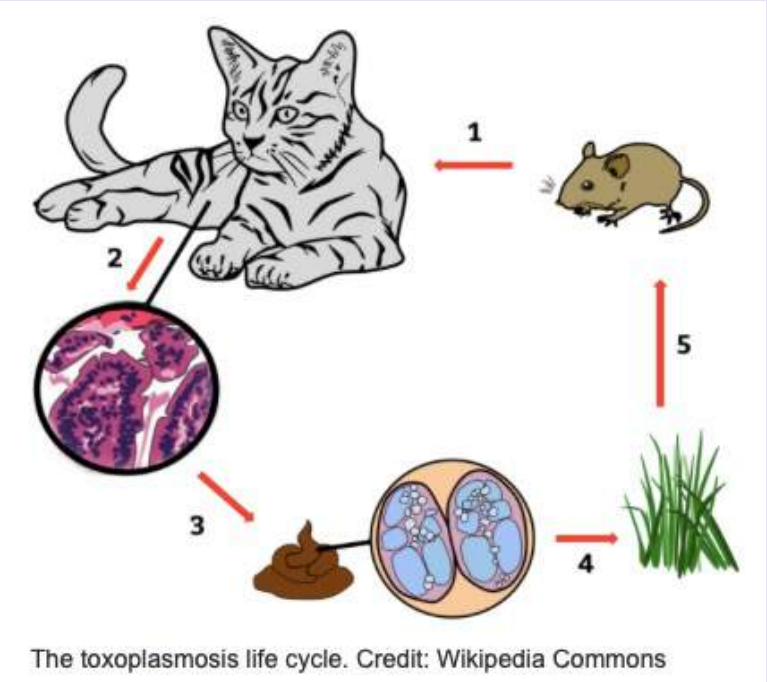


- Disease is non-progressive; but as the eye grows dangerous sequelae may ensue

Toxoplasma Retinochoroiditis

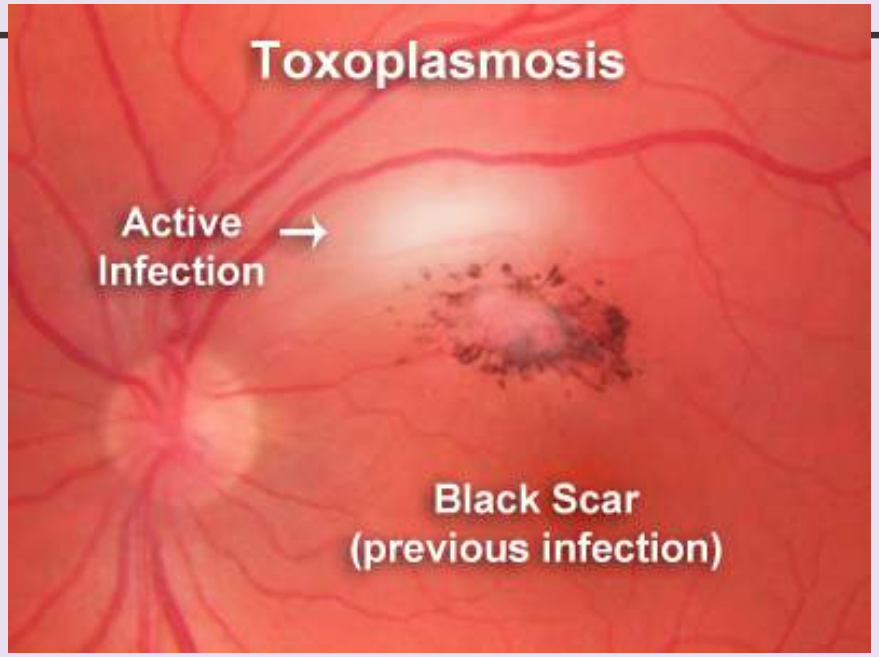
Cats serve as a host for this parasite (*Toxoplasma gondii*) and can pass the oocysts in their feces. They acquire the pathogen by eating small infected rodents.

Also contracted through eating contaminated food.



The toxoplasmosis life cycle. Credit: Wikipedia Commons

Toxoplasma: A Cat-astrophe??



Toxoplasmosis is the most common cause of posterior uveitis.

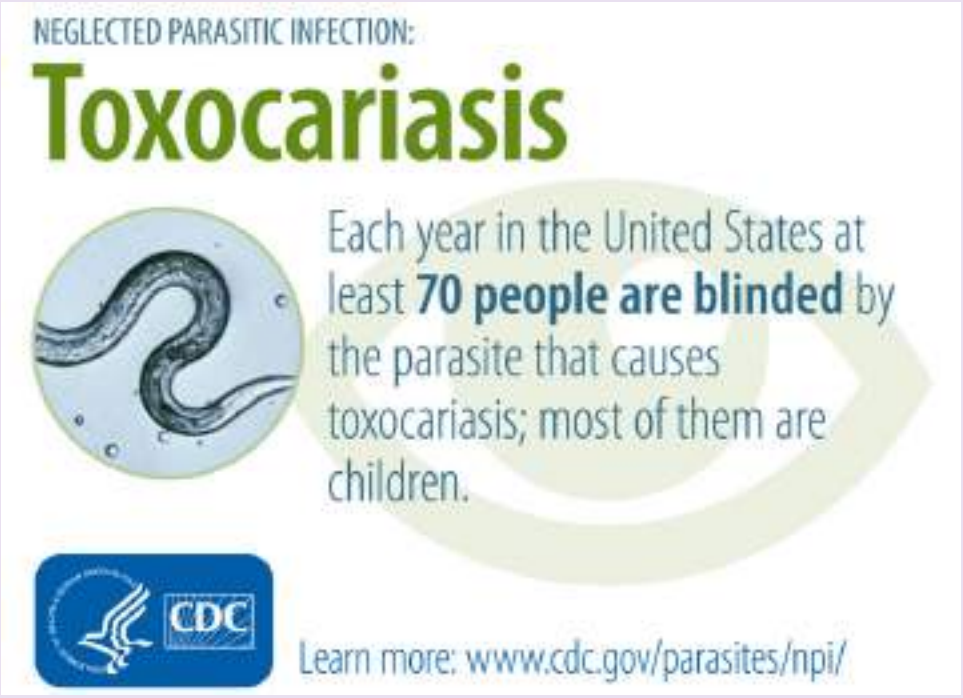
Classic findings include a white fundus lesion with overlying, intense vitreous cells that frequently is described as “headlights in a fog.”

What if you knew this...

- This patient liked to play in the sandbox as a child, and often put the dirty sand in his mouth
- The patient reported exposure to dogs and puppies as a young child
- The patient reports terrible vision in his right eye since childhood
- The patient grew up in Puerto Rico, in a socioeconomically disadvantaged area

https://amdbook.org/content/neovascular-phenotypesrap-retinal-angiomatous-proliferation

And the final DDx?



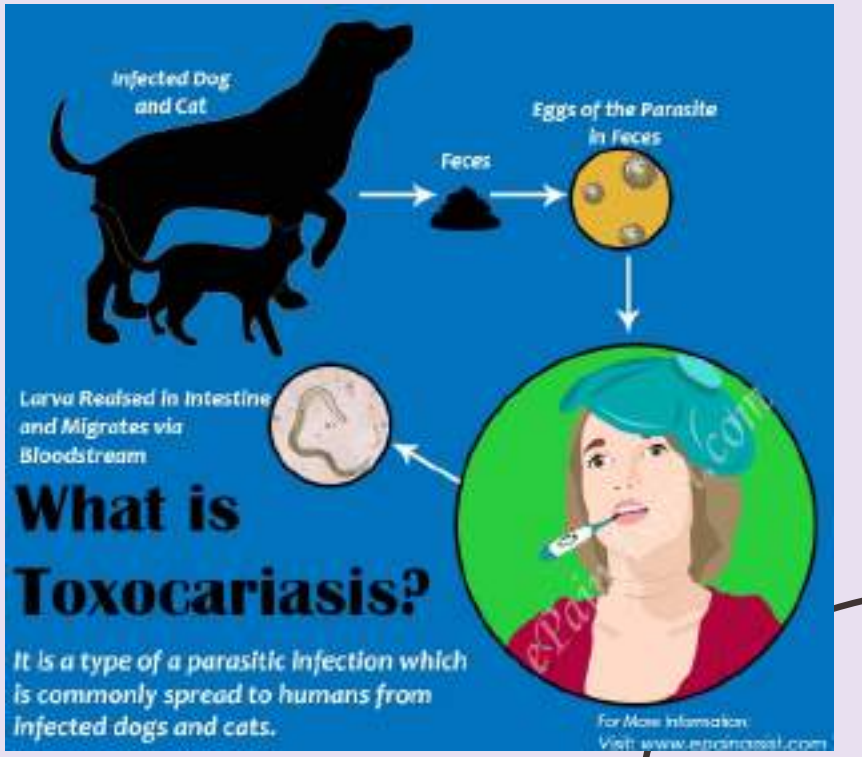
Toxocariasis is an infection transmitted from animals to humans (zoonosis)

Caused by the parasitic roundworms found in intestines of dogs (T. canis) and cats (T. catis)

How do we get it?

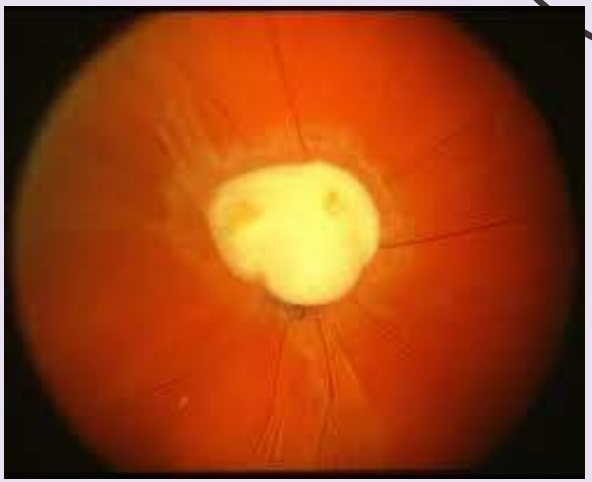
Adults and *<u>children</u>* can become infected by accidentally swallowing dirt that has been contaminated with dog or cat feces that contain infectious *Toxocara* eggs.

Although it is rare, people can also become infected from eating undercooked meat containing *Toxocara* larvae.



Ocular manifestations….

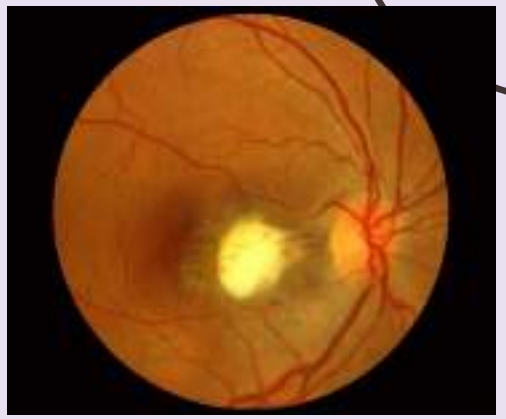
- Larva induces chronic inflammation
  - Anterior Uveitis
  - Posterior Uveitis (more common)
  - Vitritis
  - Chorioretinitis

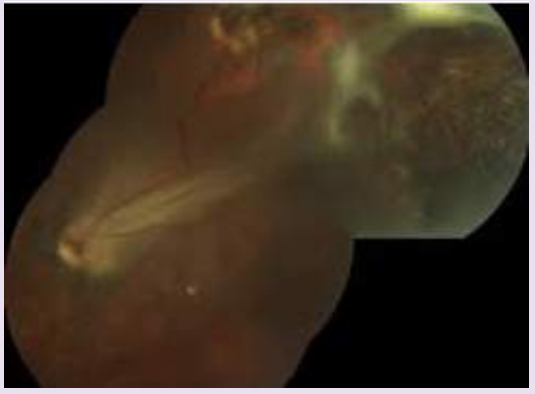


Granuloma= Larva trapped in eye from inflammation: Large, white mass lesion

How does it get into the eye?

Larvae migrate to the eye through:
(1)the central retinal artery reaching the posterior pole,
(2)the long ciliary arteries, or
(3)the vitreous reaching the pars plana

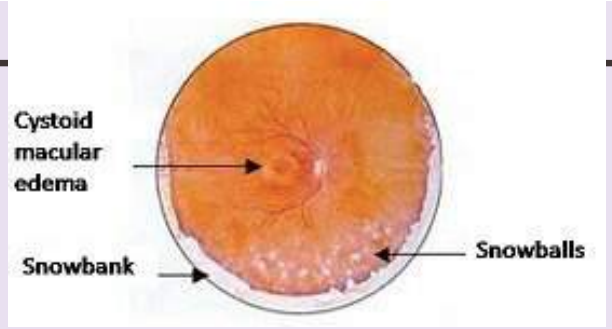


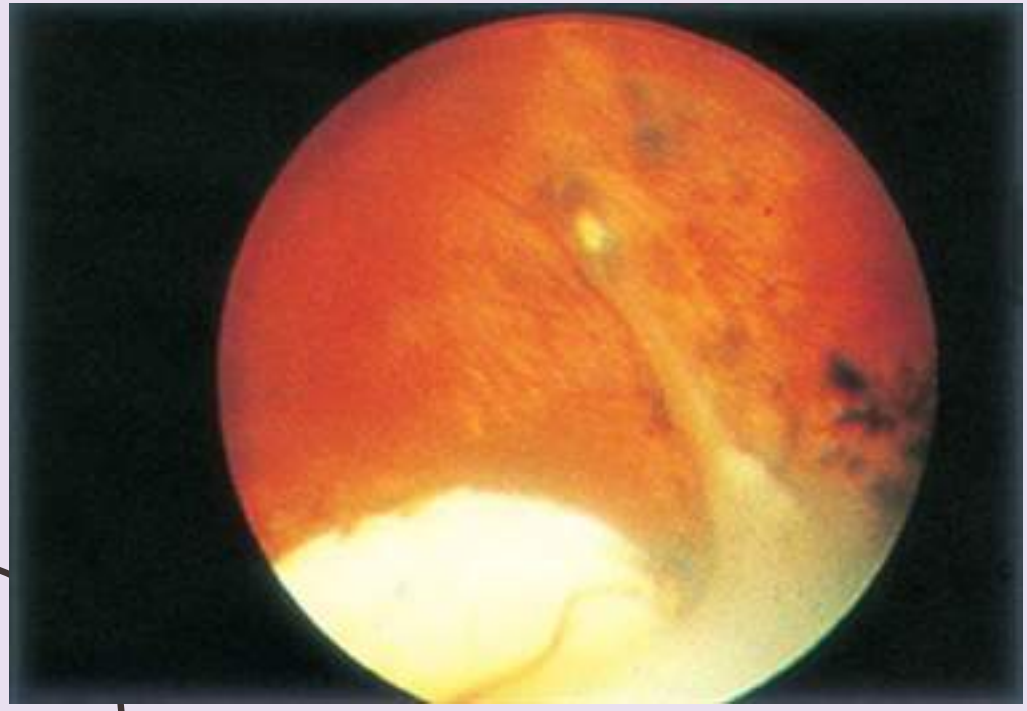


All produce inflammation and the formation of granuloma

Fibrous traction bands

https://www.retina-eidon.com/Eidon-images/Eidon-images.html

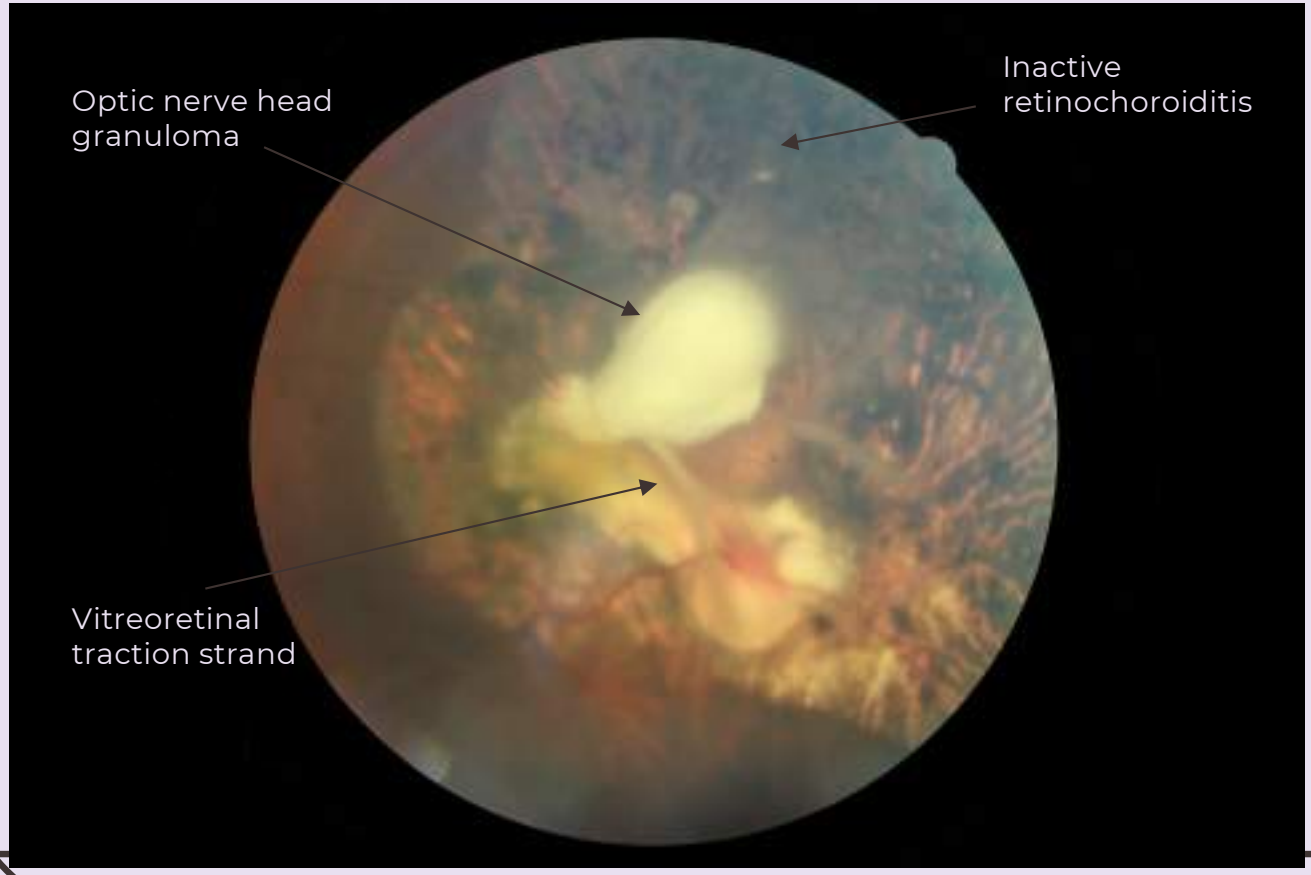




Vitreous opacification can be accompanied by immune complexes in periphery “snowballs”, “snowbanks” (Pars plana) and tractional bands leading to RD

https://www.vision-and-eye-health.com/uveitis.html

Back to our patient.....



Review: What are some ocular manifestations of ocular toxocariasis?

- A. Vitritis
- B. Tractional Retinal Detachment
- C. Retinochoroiditis
- D. Granuloma
- E. Strabismus
- F. All of the above

https://amdbook.org/content/neovascular-phenotypesrap-retinal-angiomatous-proliferation

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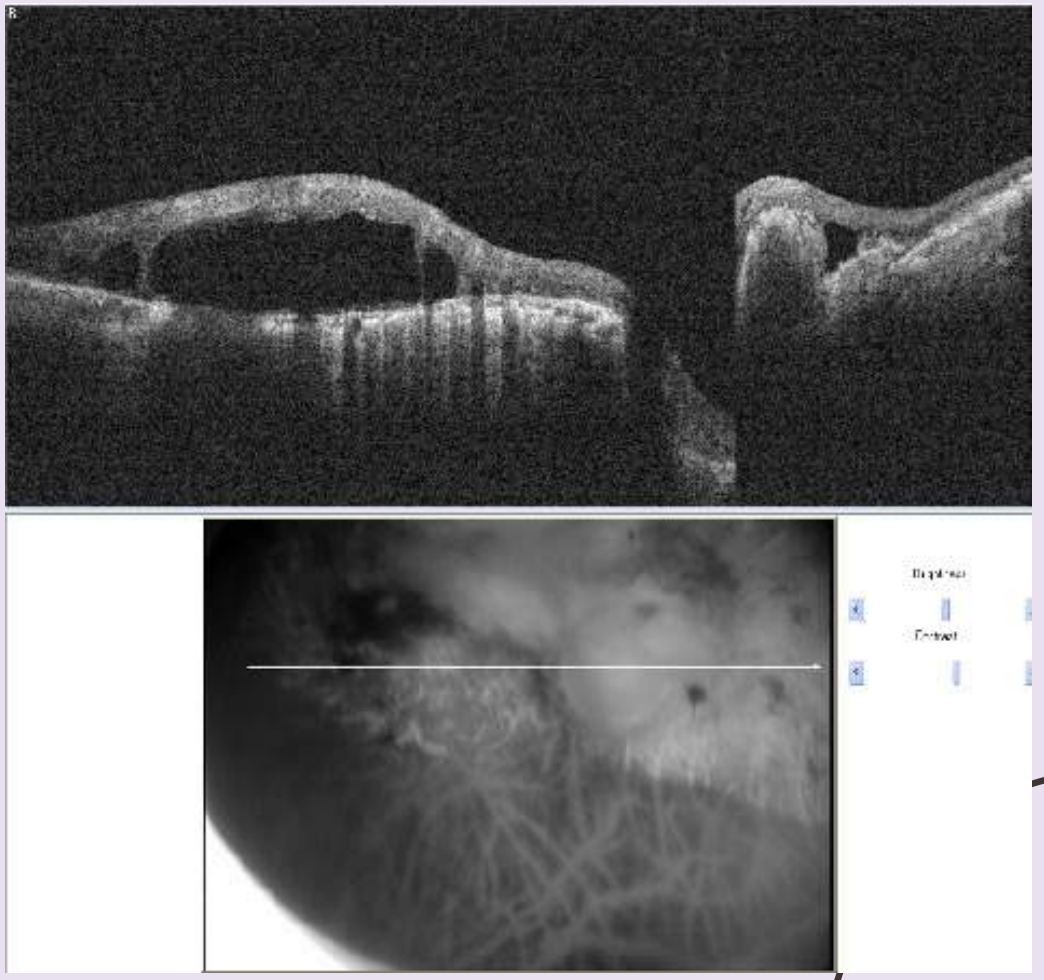
Ancillary Testing… SD-OCT!

Line scan through ONH and peripapillary tissue



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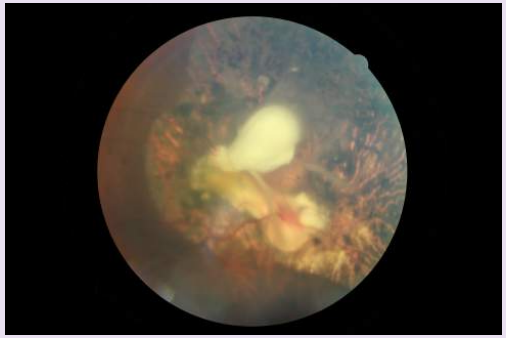
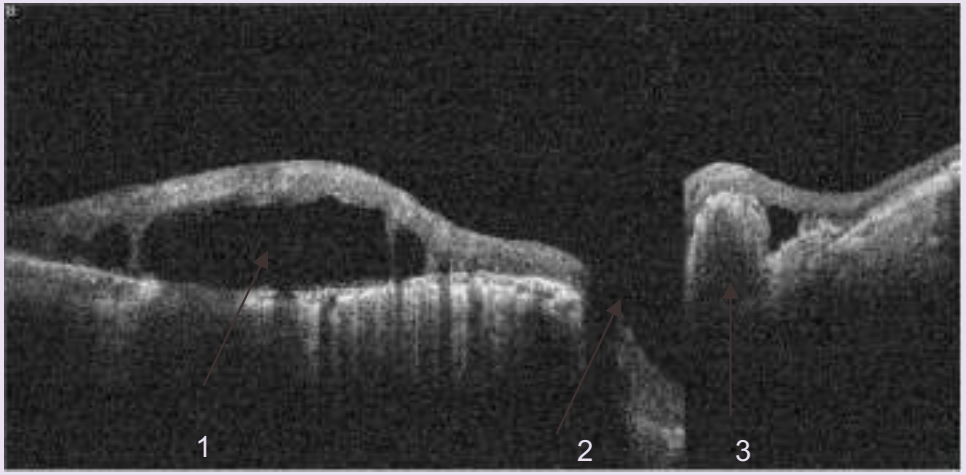
What is the OCT showing?

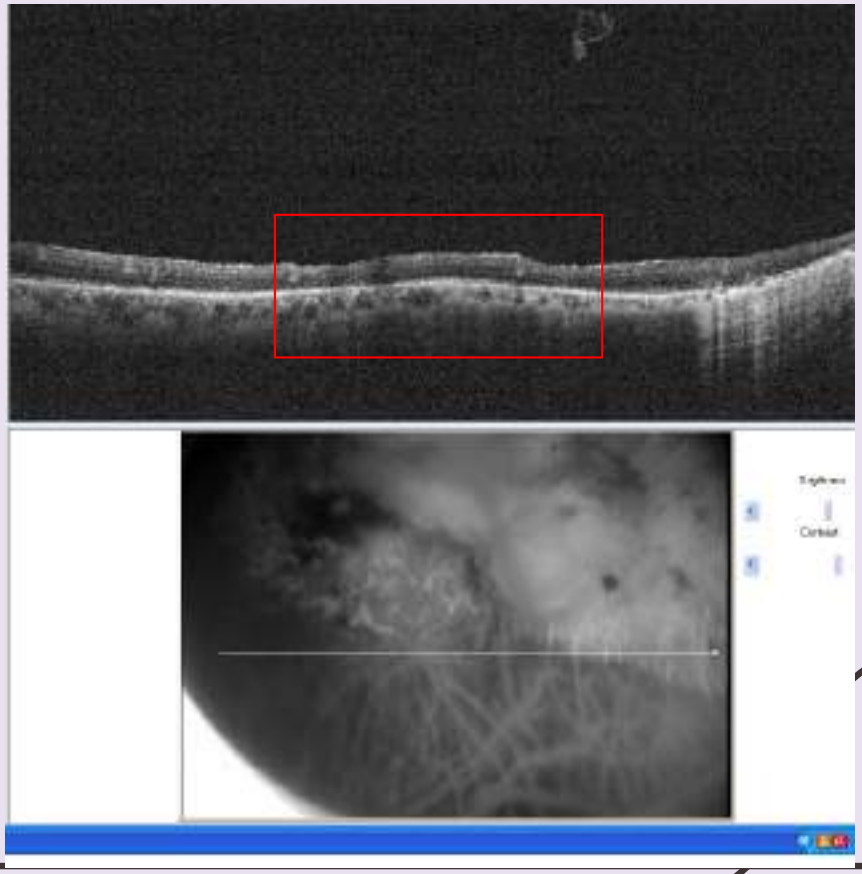


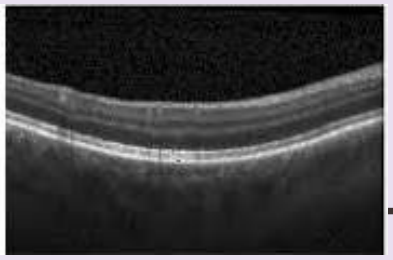


1. Neurosensory detachment
2. ONH
3. Hyper-reflective, dense lesion nasal to the optic nerve associated with granulomatous tissue on the nerve

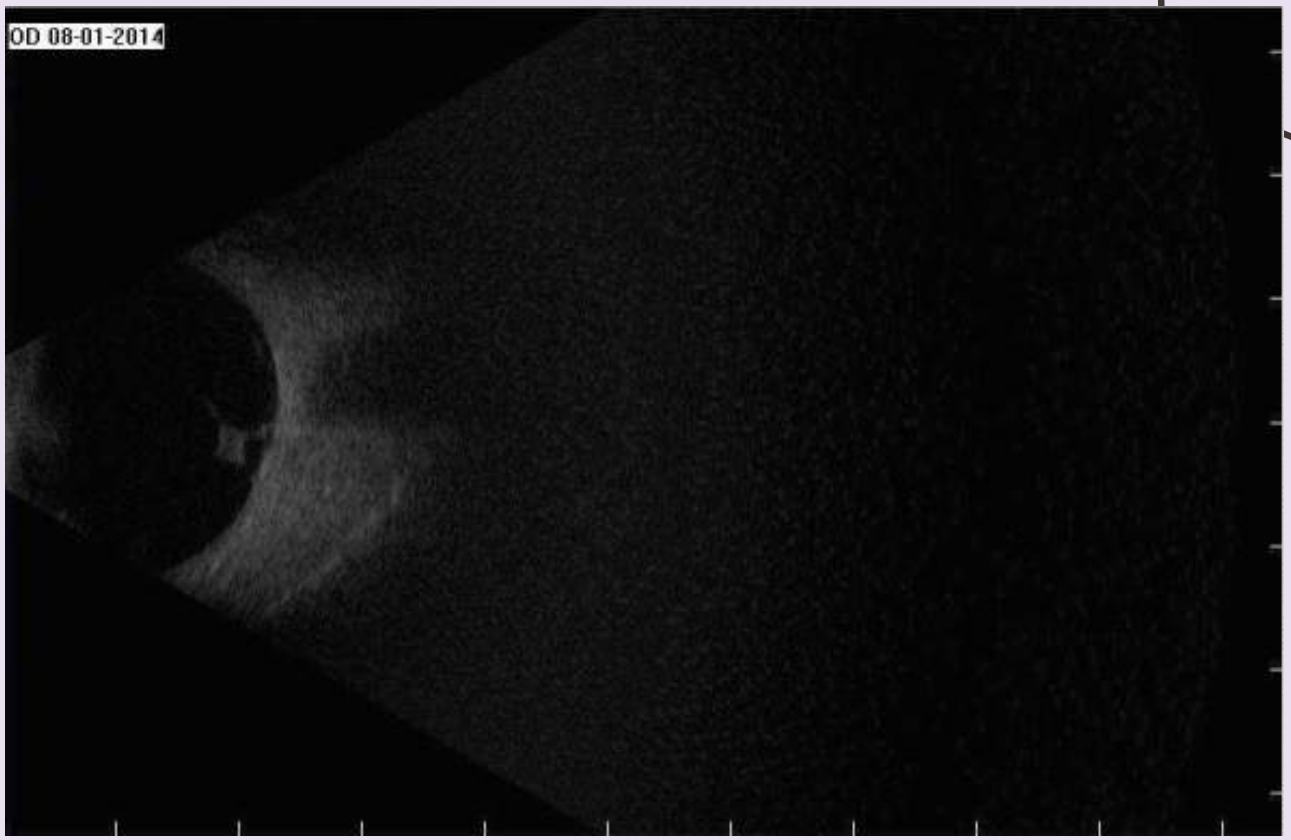
What about the retinal scan?

- Attenuation of retina, RPE and choroid
- Thinning of inner and outer retina





Ultrasound



Presentation…

Patients (usually children) will present with decreased vision, strabismus, leukocoria… mimicking many other diseases!!

So.. How do we make the diagnosis???

Laboratory testing:

- Serum IgG (ELISA): 90% specificity and sensitivity
- Intraocular fluid

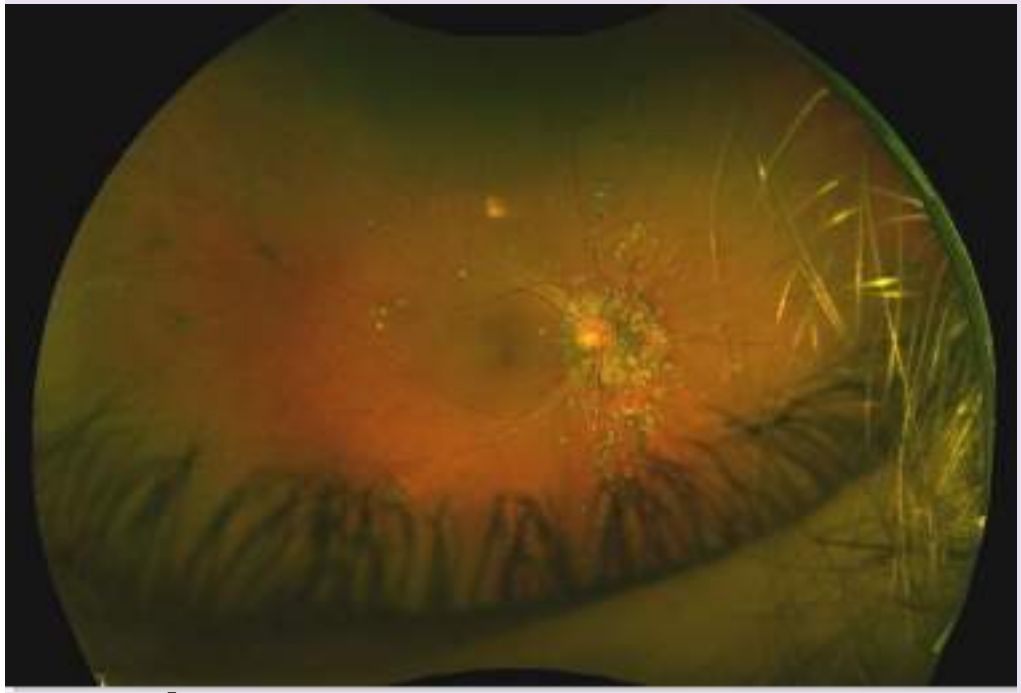
Case 2

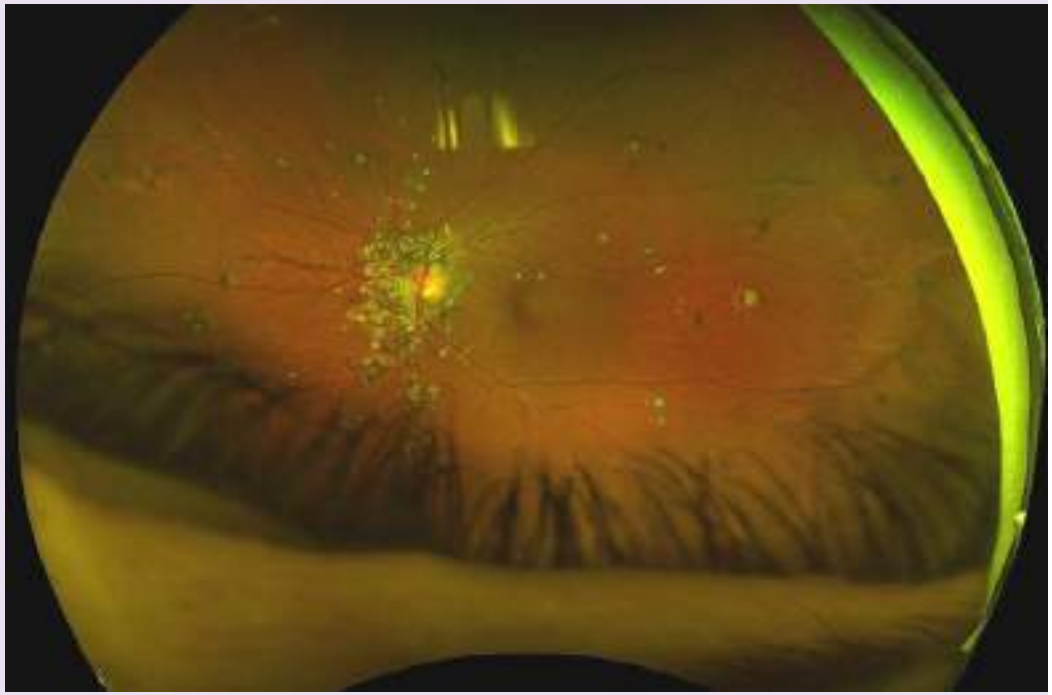
39-year-old Hispanic female

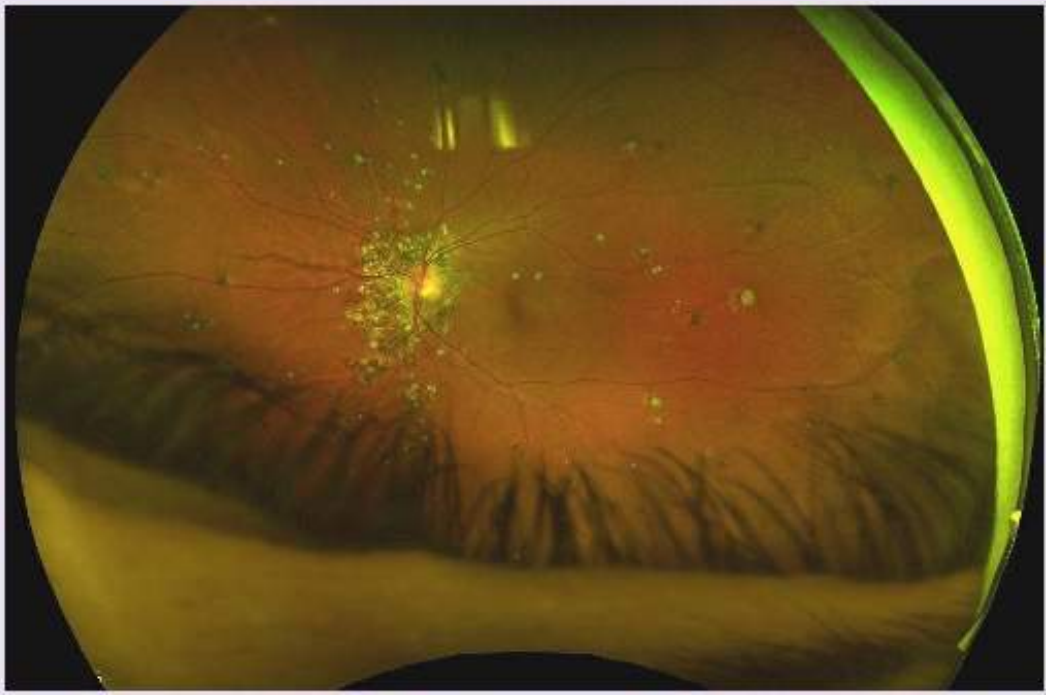
- Blurry vision OU without glasses
- BCVA 20/20 OD, 20/20 OS

Routine eye examination… I was told that I have “retinal scars” when I was 19.

Routine Eye Examination??

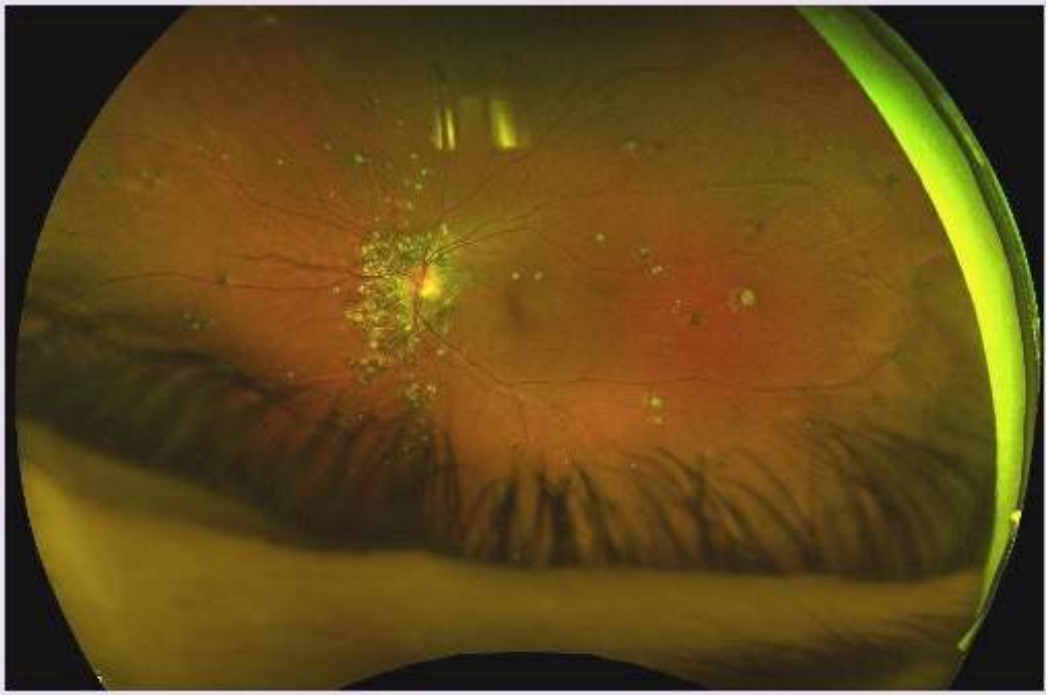






What could this be?

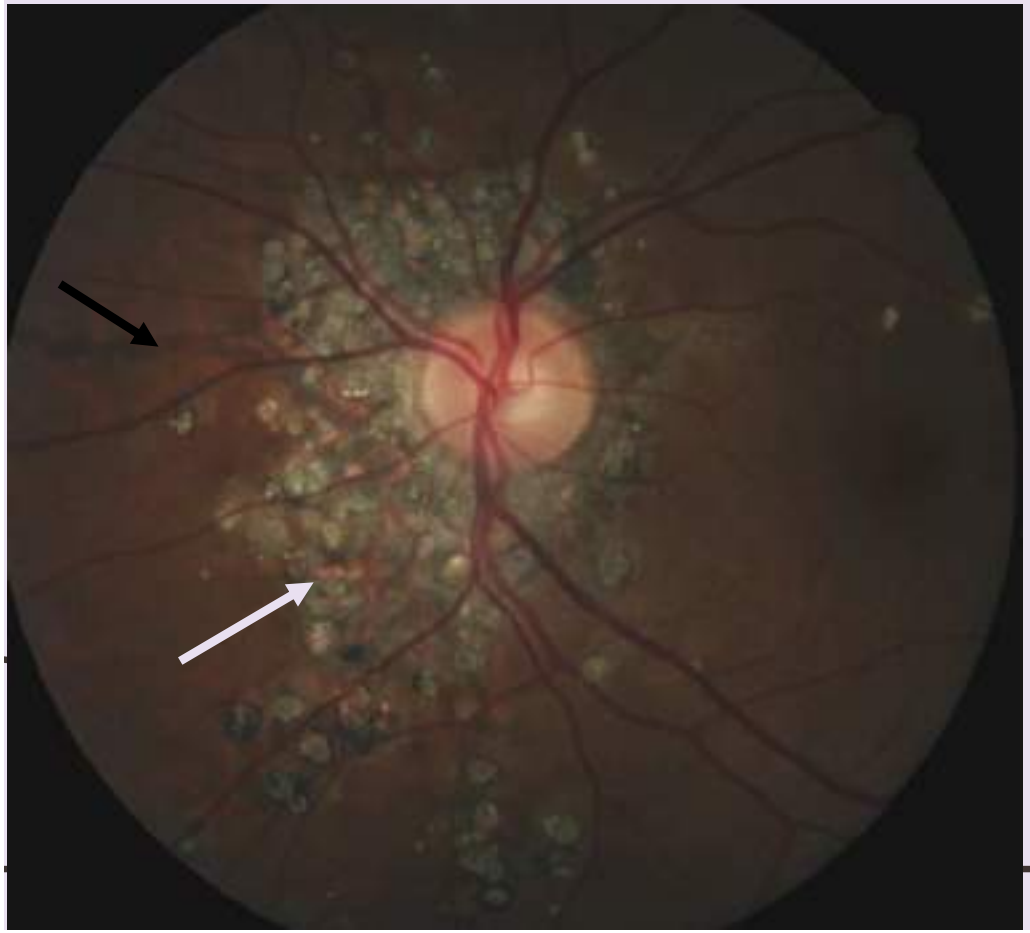
1. Multifocal choroiditis
2. Birdshot chorioretinopathy
3. Traumatic chorioretinitis
4. Serpiginous choroiditis?
5. Something else???

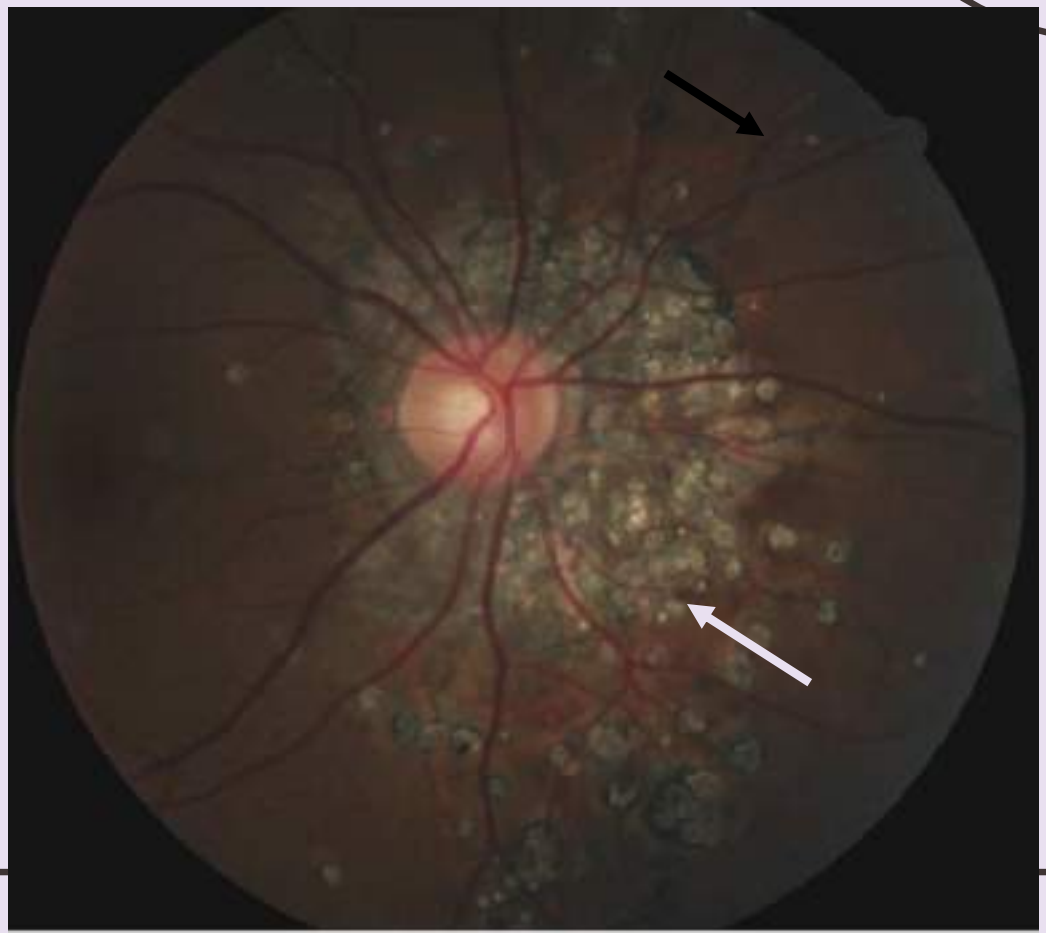



What could this be?

1. Multifocal choroiditis
2. Birdshot chorioretinopathy
3. Traumatic chorioretinitis
4. Serpiginous choroiditis?
5. **Something else???**

Not sure..... Let's look a bit closer!



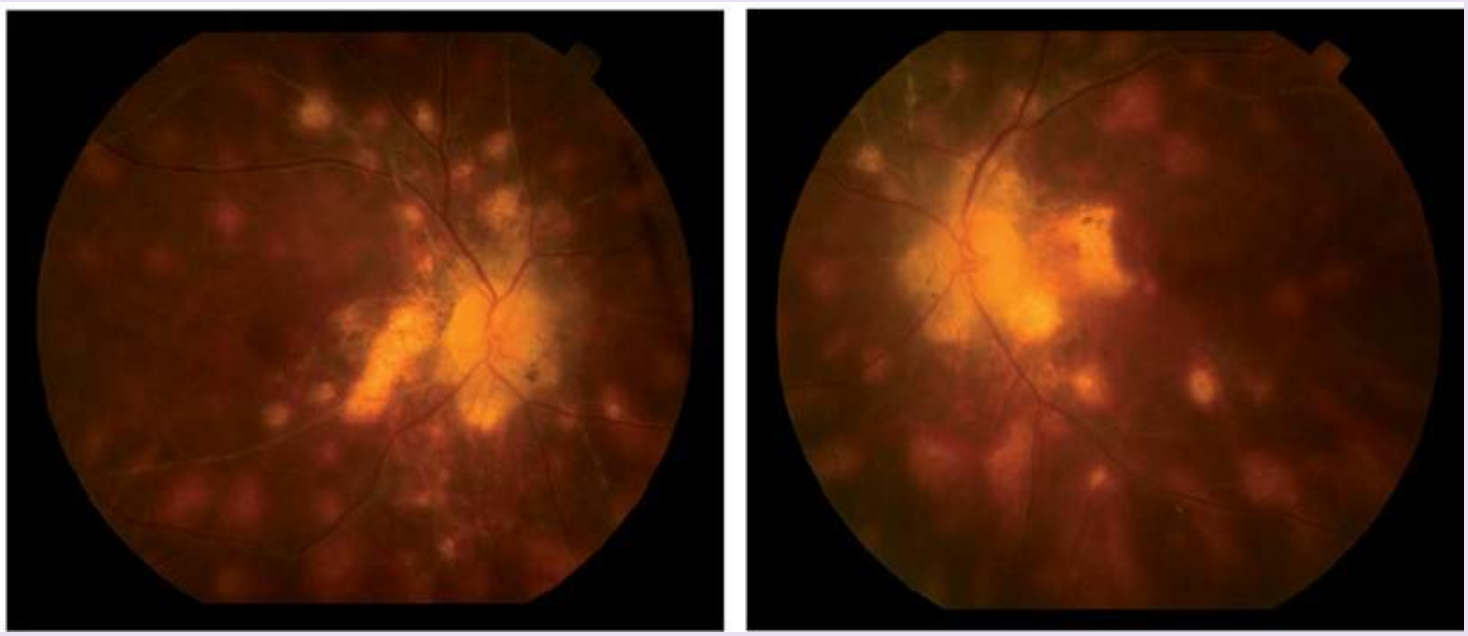


What is multifocal choroiditis?

CELLS!!! ANTERIOR OR POSTERIOR

- Spontaneous, <u>inflammatory</u> condition presenting with multiple lesions in the retina and choroid
- Episodes of inflammation that can occur unilaterally or bilaterally

Birdshot Chorioretinopathy



- Bilateral
- HLA-B29 Association

- Blurred vision, floaters, photopsia, scotoma, nyctalopia

Birdshot chorioretinopathy (BSCR) is a chronic posterior uveitis characterized by multiple cream-colored, hypo-pigmented choroidal lesions

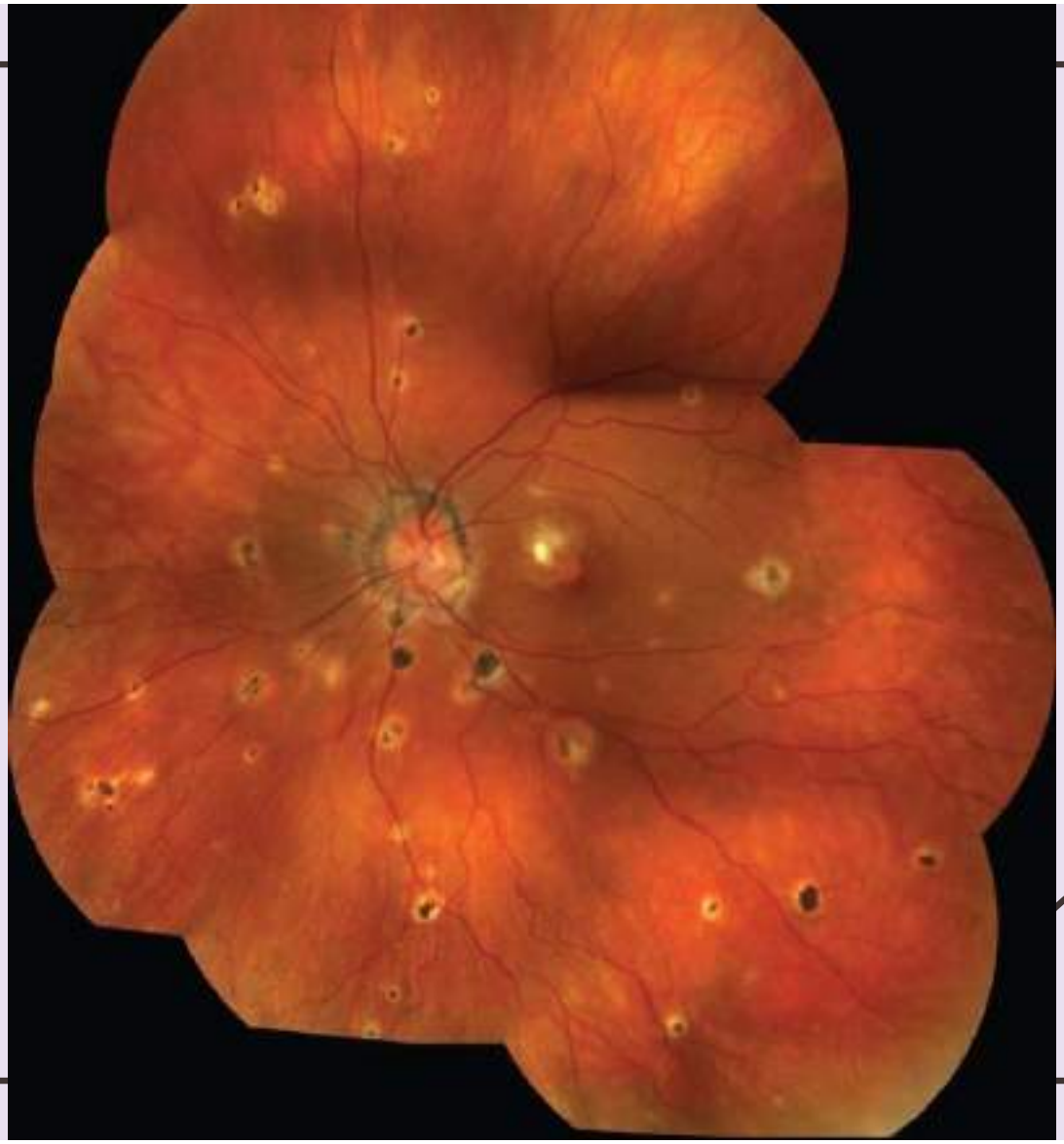
Serpiginous Choroiditis

Rare, bilateral, idiopathic inflammatory disorder that results in geographic destruction of the retinal pigment epithelium (RPE), retina, and choriocapillaris.

- Chronic
- Recurrent

- 30-60 y/o
- Asymptomatic unless macula involved
- Inflammatory etiology (HLA-B7)

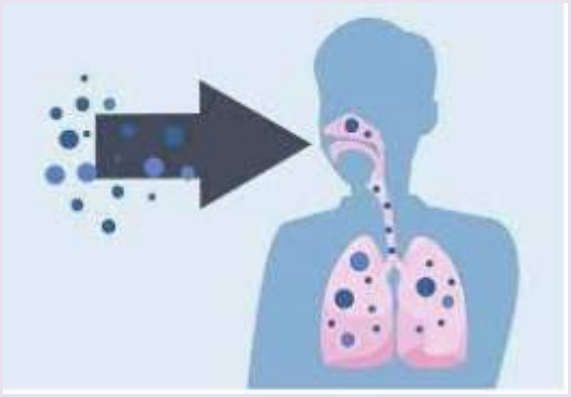
Histoplasmosis??



https://www.aao.org/bcscsnippetdetail.aspx?id=2dc7aa22-a872-40a0-abb8-592c8c06fc48

Histoplasmosis

Histoplasmosis is a disease you can get when you breathe infected airborne spores from the fungus *Histoplasma capsulatum* into your lungs.



It enters the air when people disturb soil when plowing fields, sweeping chicken coops, or digging holes. Endemic in Ohio and Mississippi River Valleys.

Ocular Histoplasmosis:
How do we make the diagnosis?

Inflammatory, multifocal chorioretinal disorder

POHS diagnosis is defined clinically by the following triad of signs:

- Peripapillary atrophy (PPA)
- Histo spots, which appear as “punched-out” lesions, along with similar macular scars
- CNV or subsequent disciform scarring

**At least two of these three criteria must be met

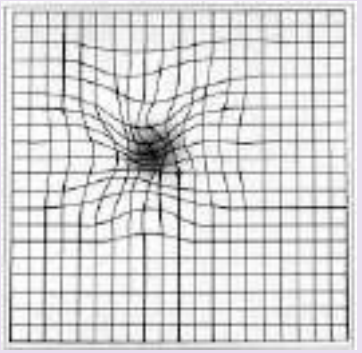
Ocular Histoplasmosis (POHS)

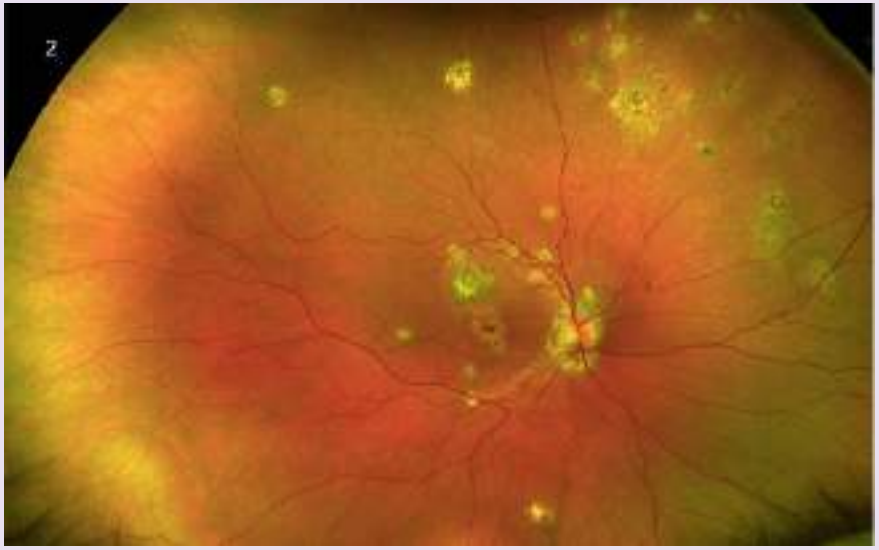
The infection can move from the lungs into the eyes, leading to vision loss.

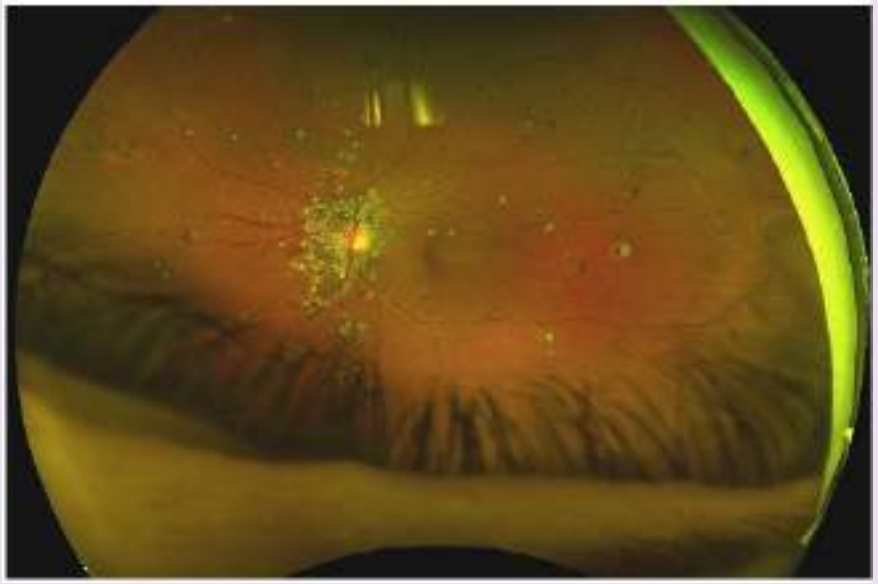
What are the symptoms of OHS?

OHS usually doesn't cause any symptoms in the early stages. But over time, you may notice:

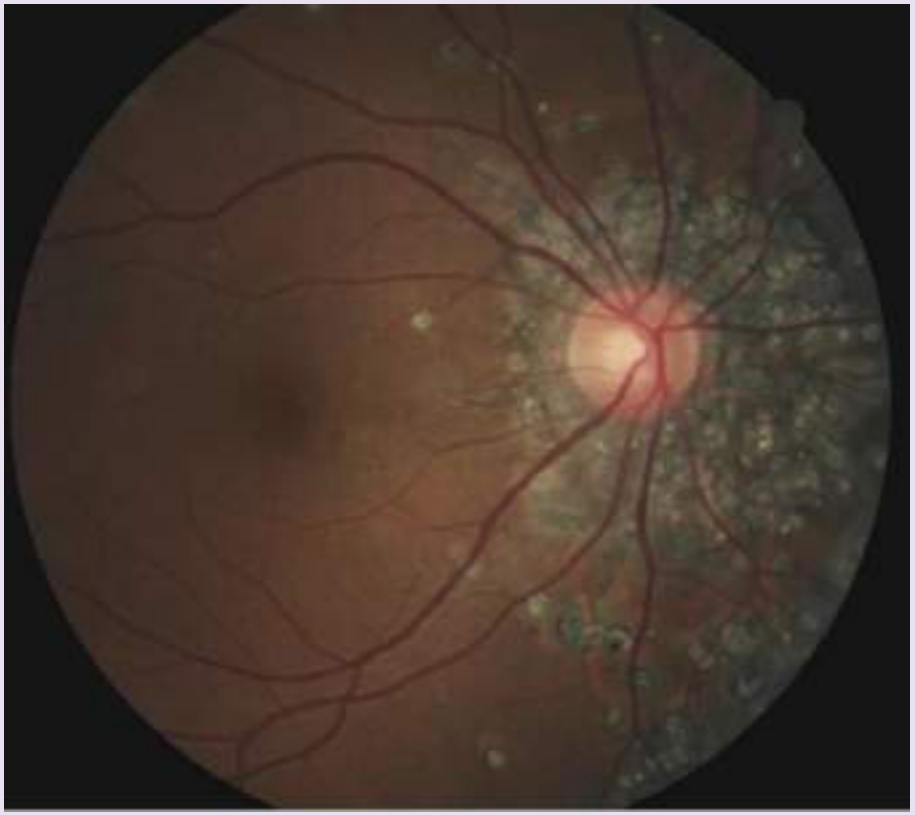
- Straight lines looking crooked or wavy
- Blind spots in your vision

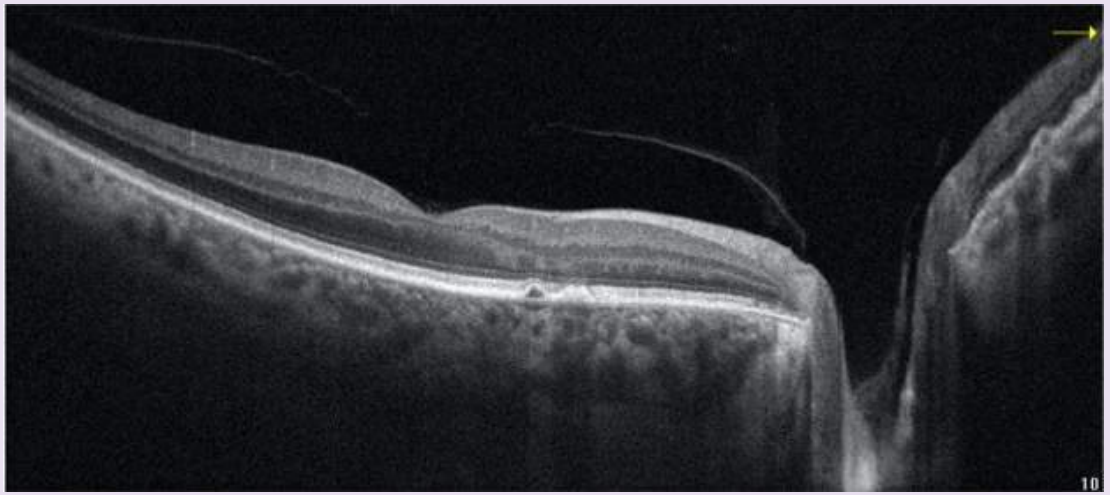


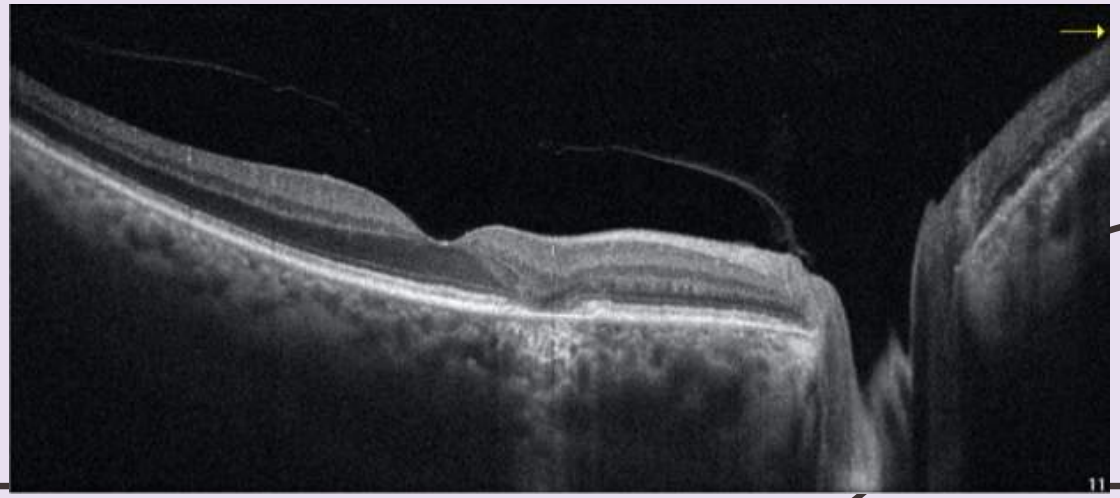




Back to our patient:







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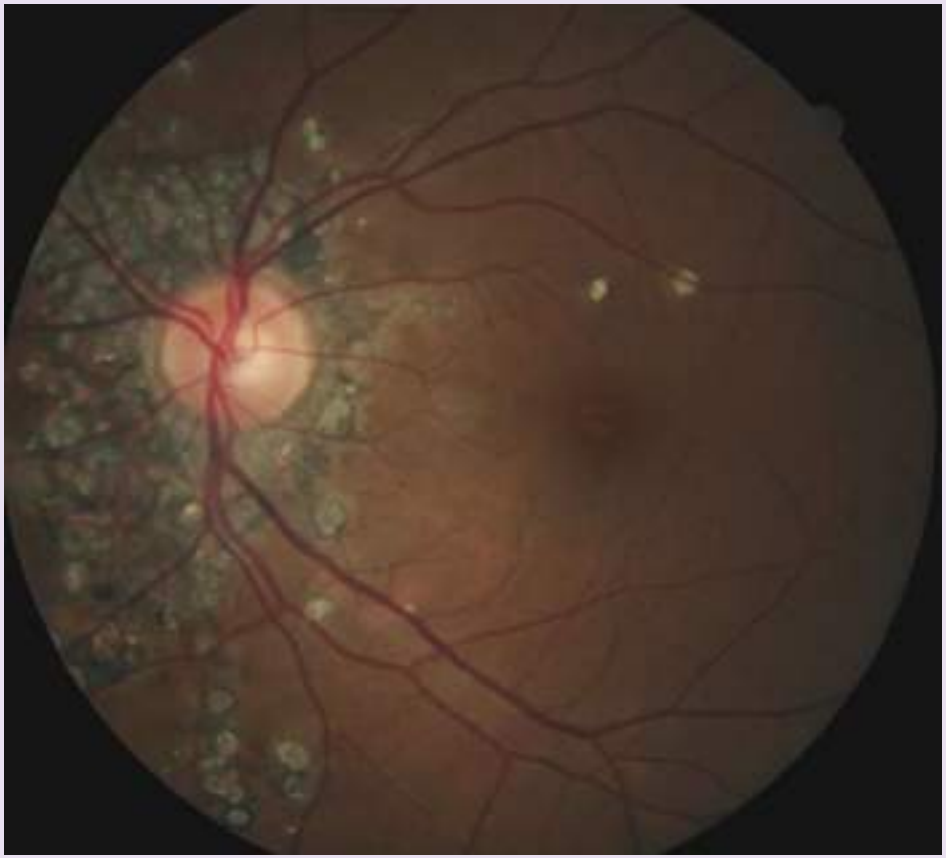
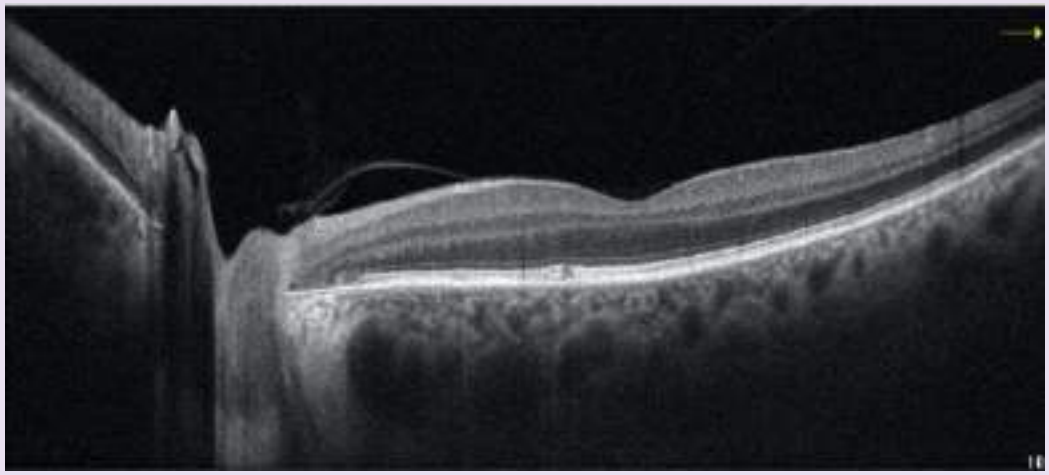
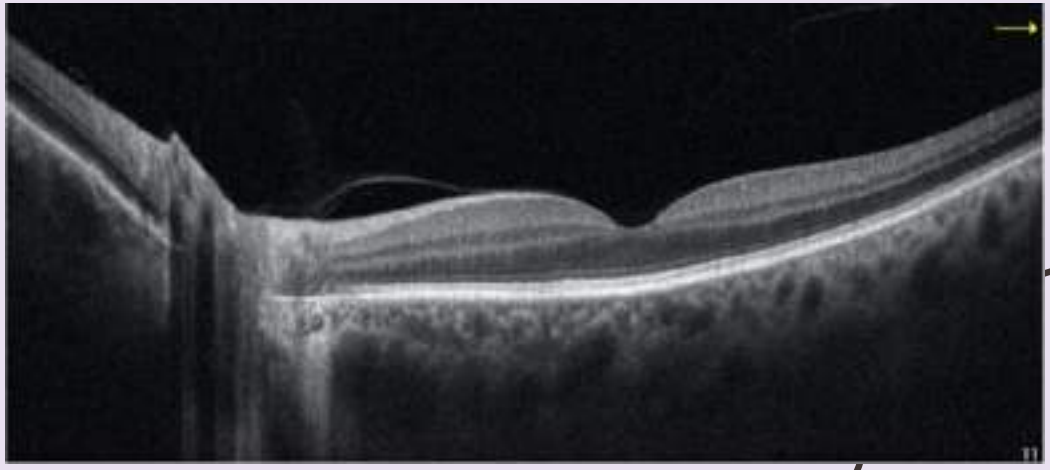
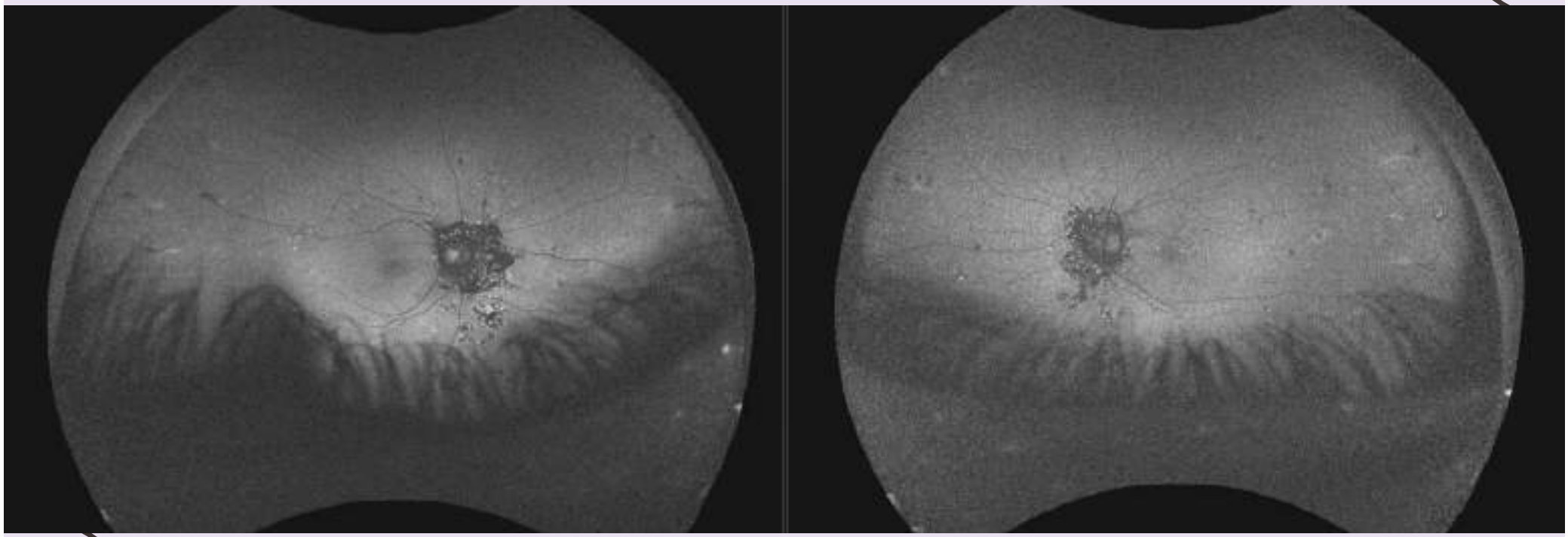






Fundus Autofluorescence

Hyper versus Hypo



Nonpigmented macular chorioretinal scars, which are distinguished by their round, hypoautofluorescent appearance

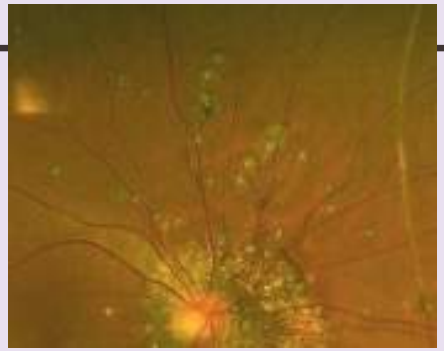
COME TO FIND.....

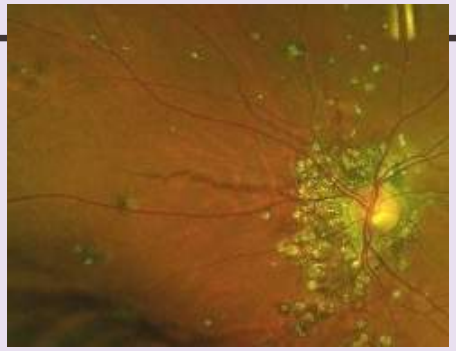
He grew up working with chickens on a farm

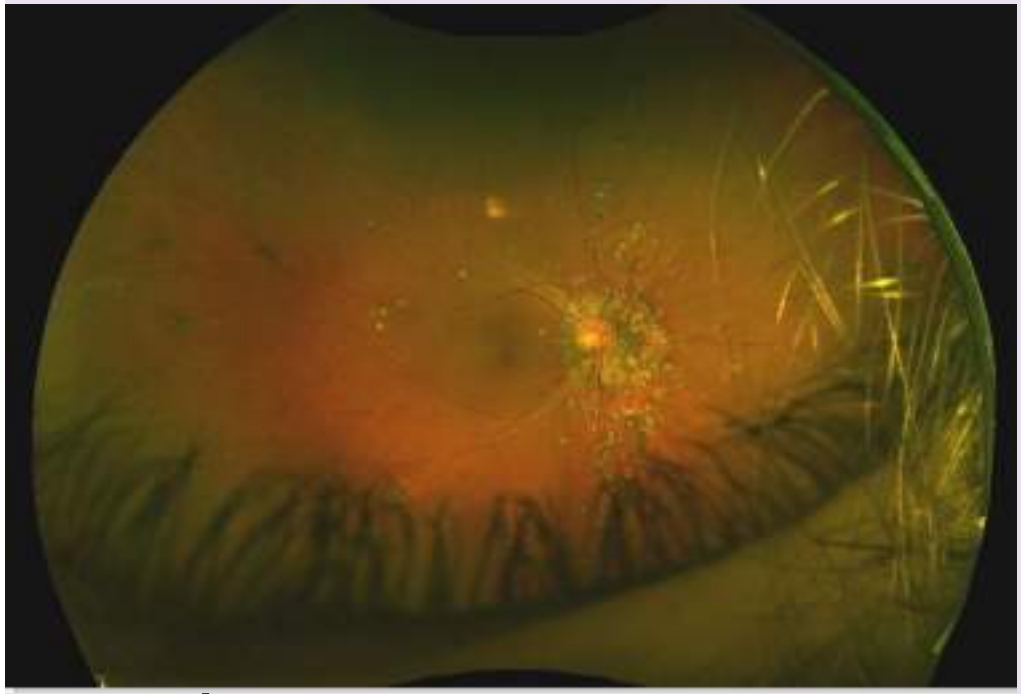
AND

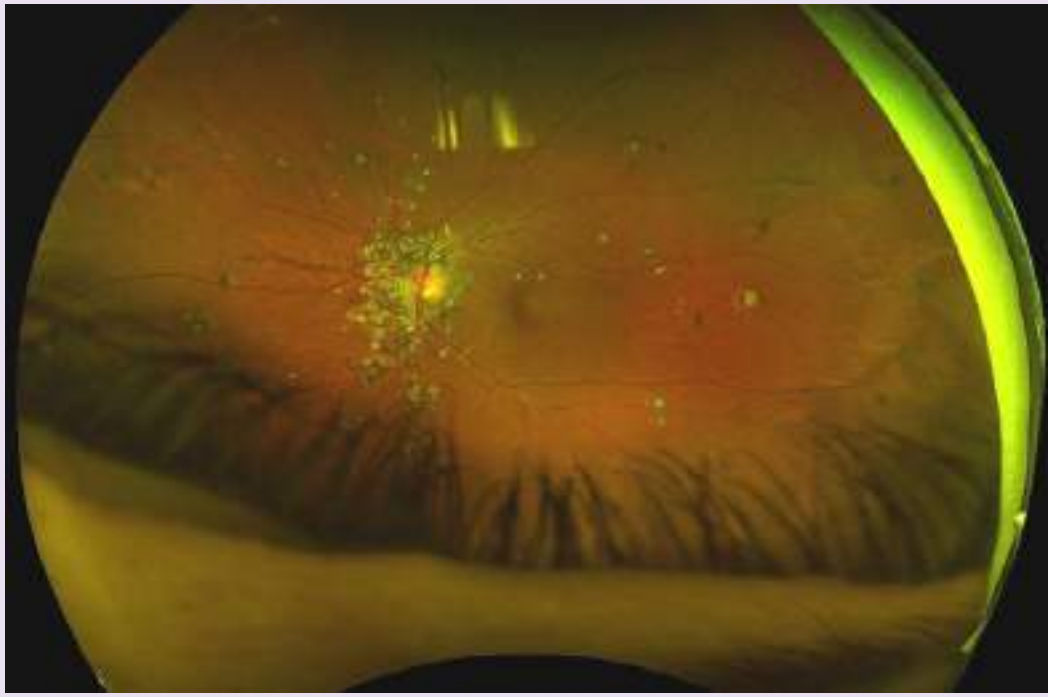
His daughter has lung disease from Histoplasmosis!!

But what else?



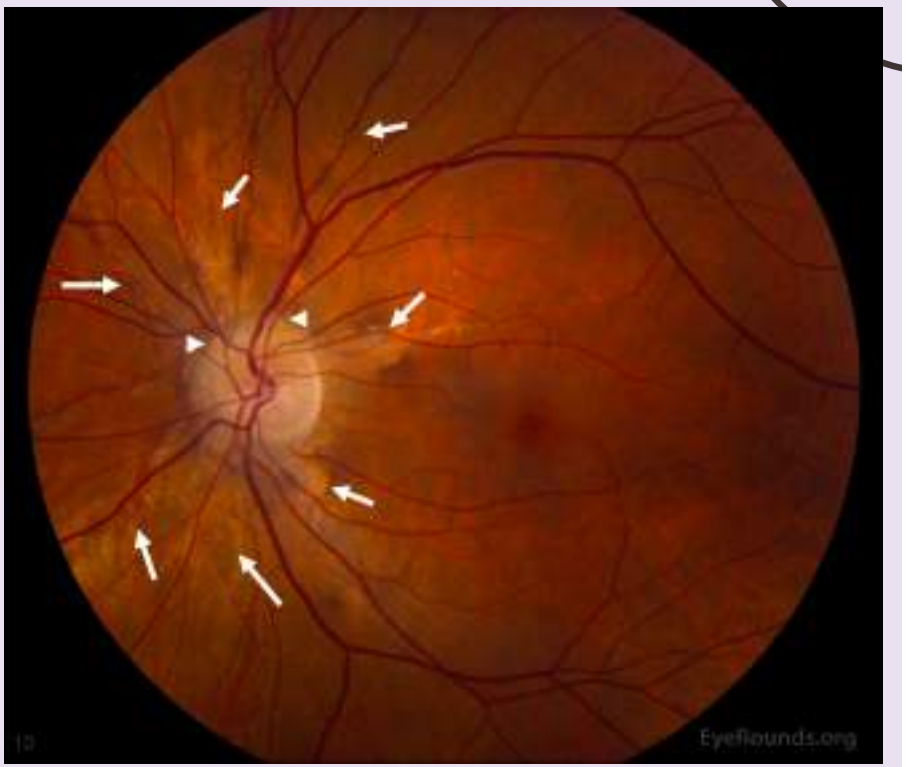




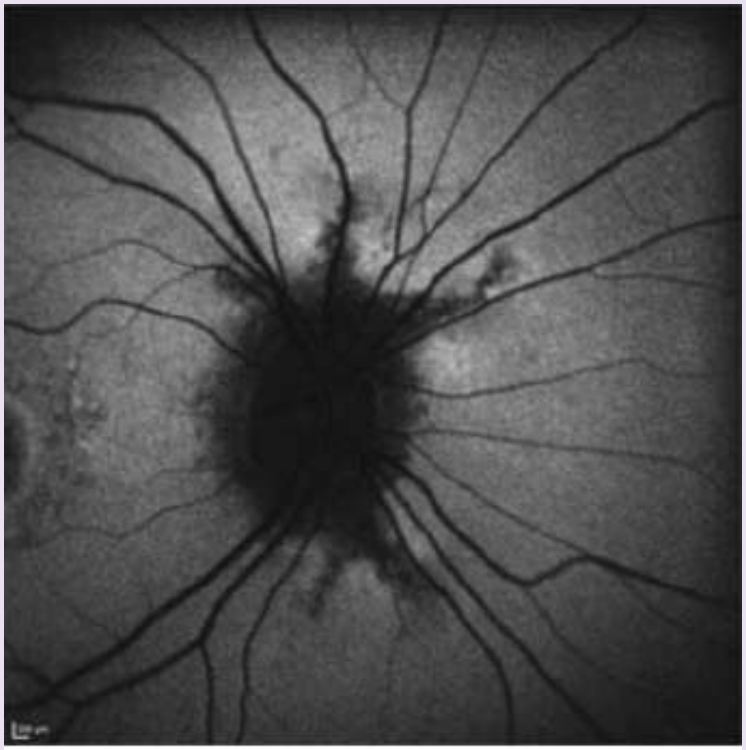


Angioid Streaks

- P — Paget's
- E — Ehler's Danlos
- P — Pseudoxanthoma Elasticum
- S — Sickle Cell
- I — Idiopathic



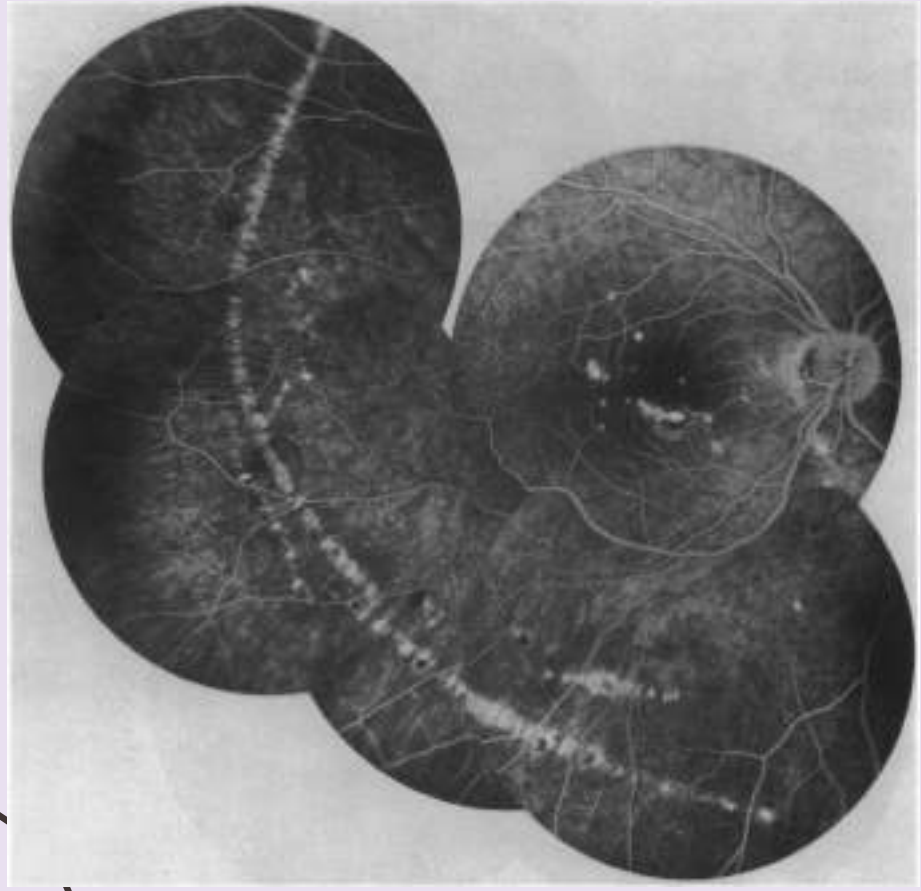
And others!!

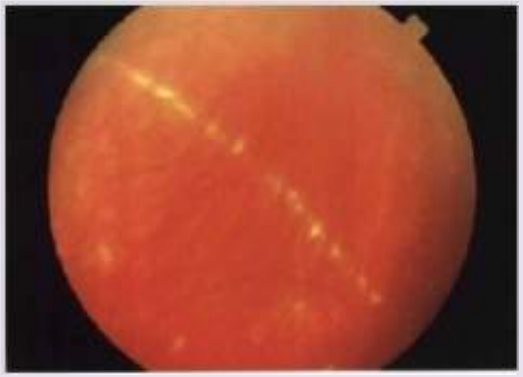


Fundus Autofluorescence: Angioid Streaks

Angioid streaks appear as irregular lines of reduced autofluorescence running outwards from the optic disc

https://www.researchgate.net/figure/Autofluorescence-imaging-showed-central-area-of-reduced-autofluorescence-at-the-fovea_fig2_221763300





Linear streaks; 5% of POHS… But, not Angioid streaks??

https://bjo.bmj.com/content/bjophthalmol/73/7/528.full.pdf

"Patients can have as many diseases as they damn well please."

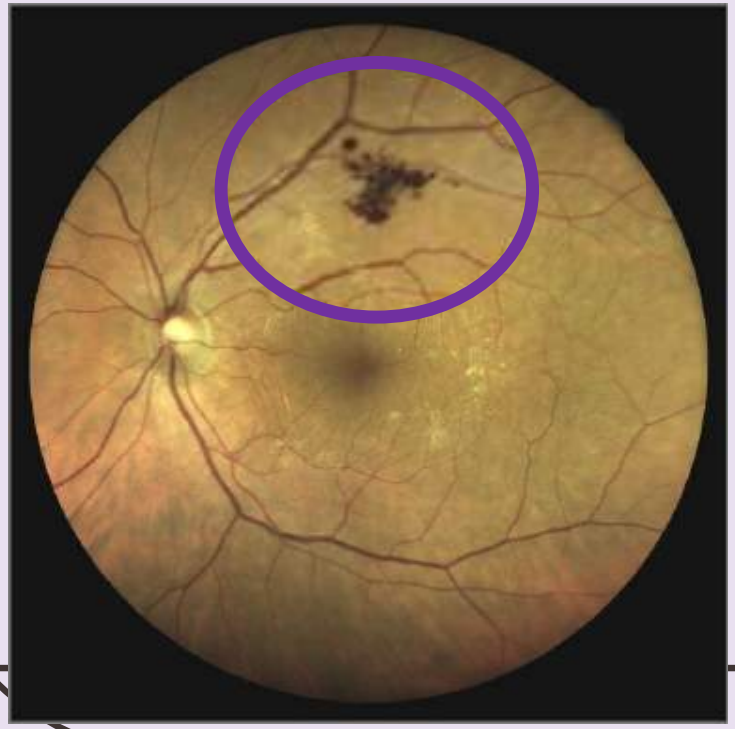
- Hickam's Dictum
  Dr. John B Hickam

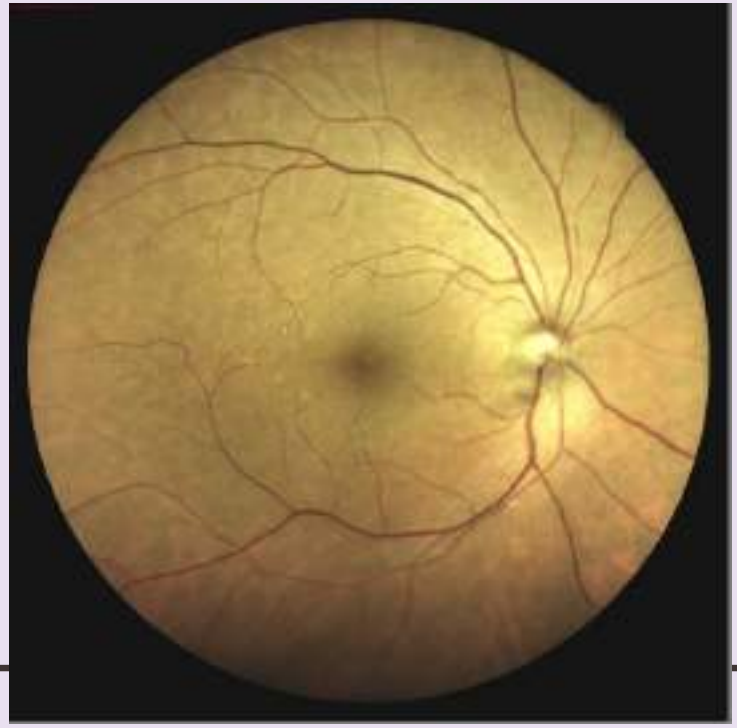
Case 3

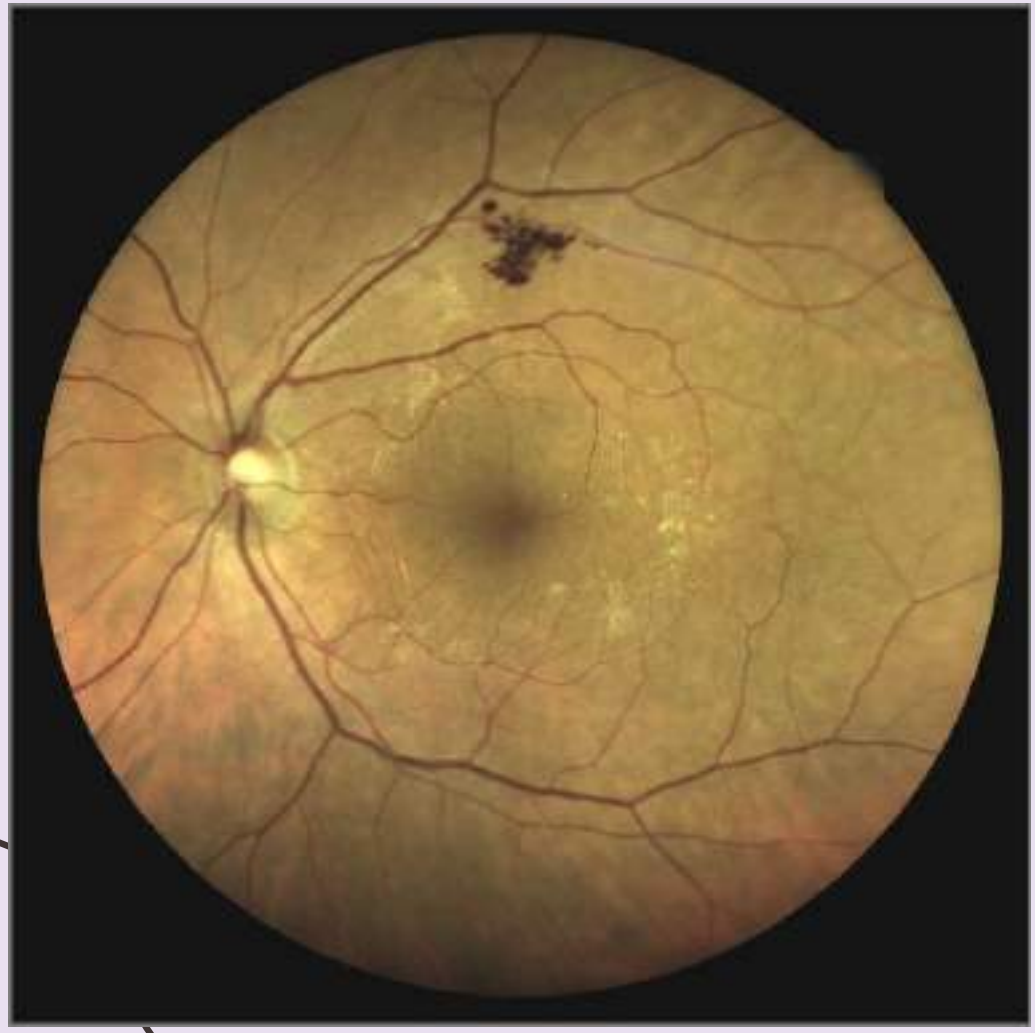
67-year-old Hispanic female

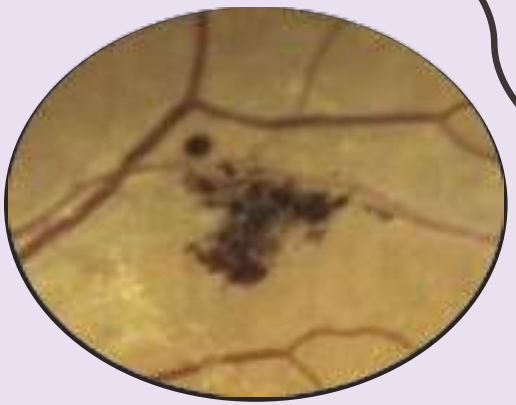
Comprehensive eye examination; blurry vision OU; S/P Lasik 15 years

- BCVA 20/20 OD; 20/25 OS





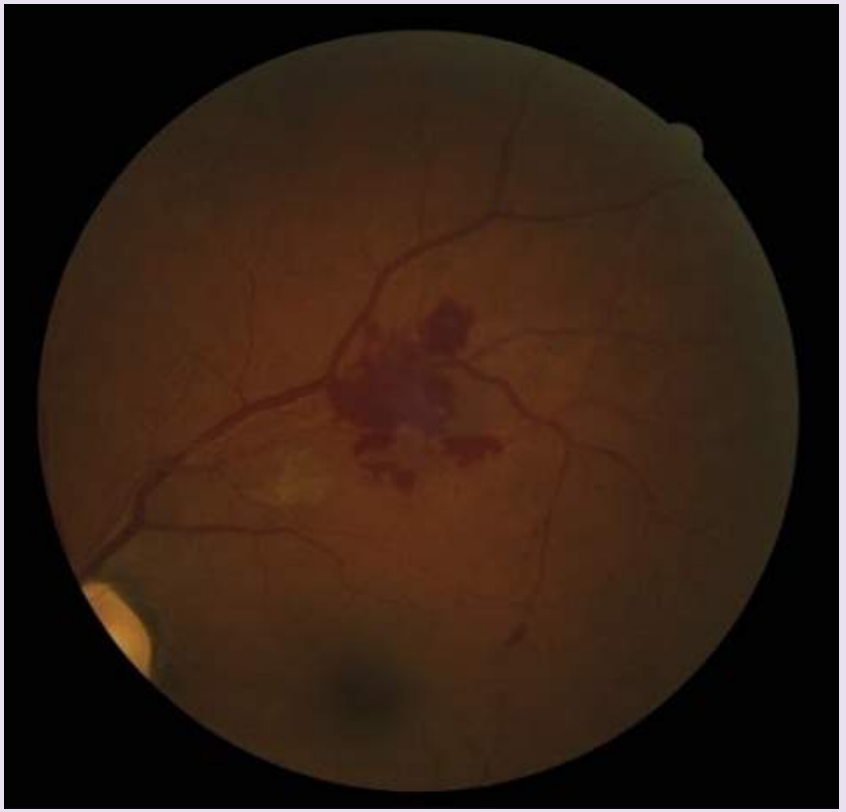




What could this be?

1. Retinal hemorrhages
2. Capillary Hemangioma
3. Retinal cavernous hemangioma

Retinal Hemorrhages



Since age 19 ??

https://www.allaboutvision.com/conditions/retinal-hemorrhage/

Retinal Tumors: Breaking it all down....

Neural (Nerve) Tumors

- Retinoblastoma

Nerve cells in the retina develop genetic mutations which cause the cells to continue growing and multiplying resulting in a tumor.

Vascular Tumors

- Hemangioma
  - Retinal Capillary hemangioma
  - Retinal Cavernous hemangioma

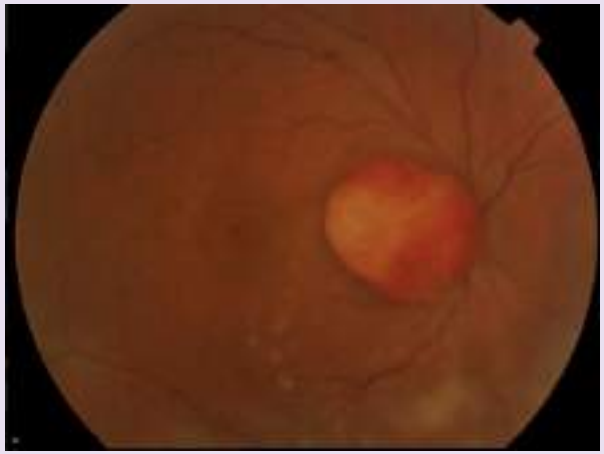
Glial Tumors

- Astrocytic Hamartoma
- Astrocytoma

Benign retinal tumors composed of glial cells

Retinal Capillary hemangioma (Retinal hemangioblastoma)

Hemangioma:
Benign vascular tumor derived from blood vessel; ONH or retinal



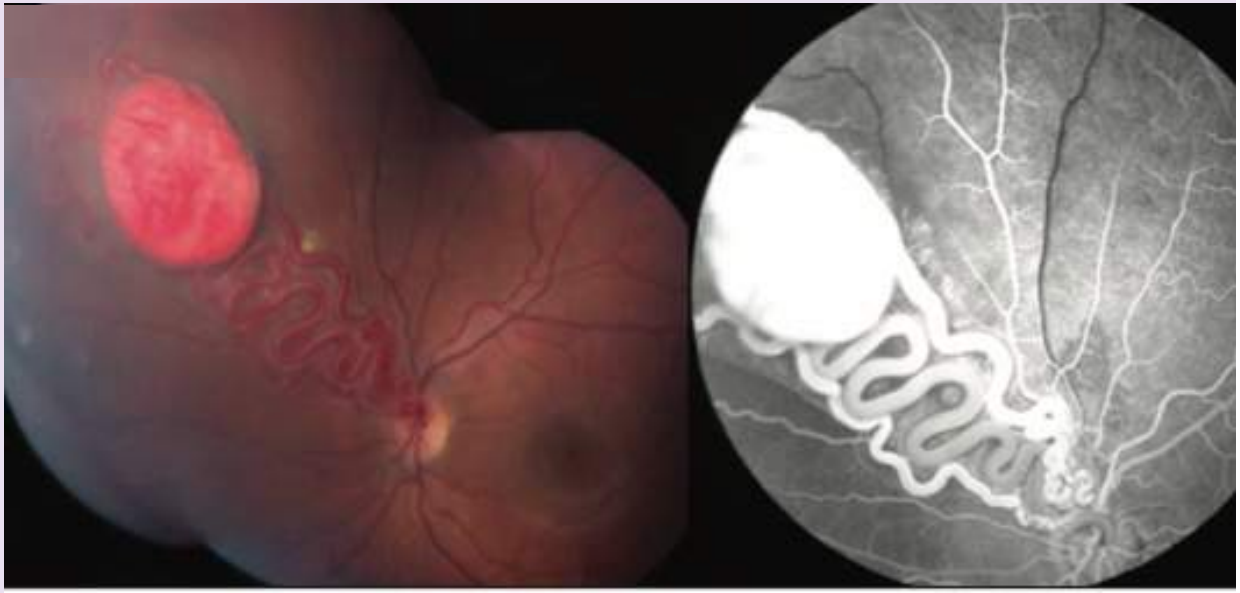
https://www.sciencedirect.com/science/article/abs/pii/S2173579411000326

Retinal Capillary hemangioma

- No sex predilection
- Average age at diagnosis= 25

- Reddish, orange mass

Dilated retinal vessels feeding and draining the tumor



https://assets.bmctoday.net/retinatoday/pdfs/0715RT_Mini_Shields.pdf

Von-Hippel Lindau: (Most common systemic association)

- Bilateral, multiple or solitary retinal hemangiomas

Characterized by the growth of various benign or malignant tumors of the retina and the brain, along with cysts of several visceral organs such as the kidneys, pancreas, and adrenal glands and reproductive organs

https://www.medicalopedia.org/649/von-hippel-lindau-syndrome/

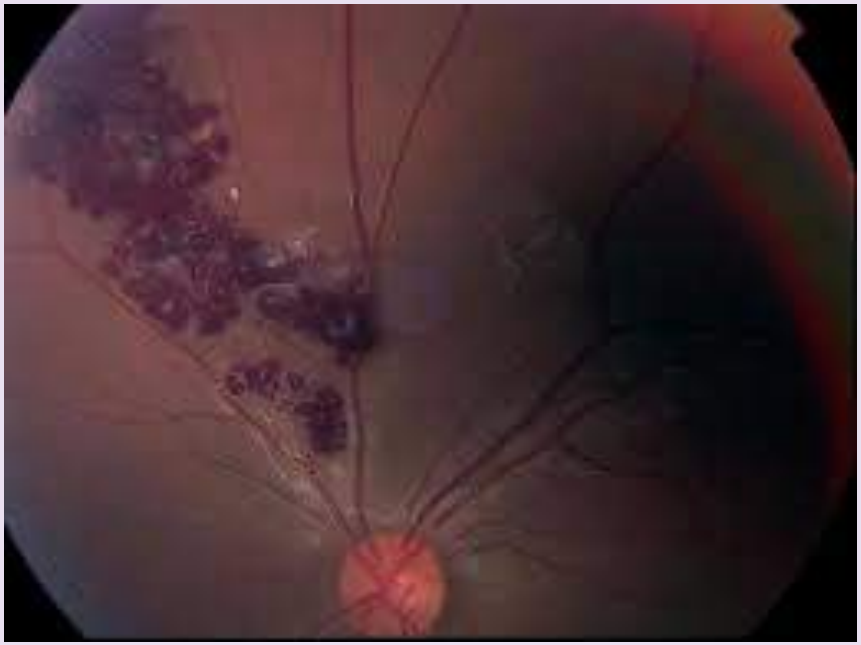
Retinal Cavernous Hemangioma

Cavernous hemangioma of the retina (CHR) is a rare retinal vascular hamartoma

"Benign growth made up of cells that don't belong there"

"Cluster of grapes"

- Cluster of dark intraretinal venous aneurysms
- No feeding artery
- Typically located along retinal vein

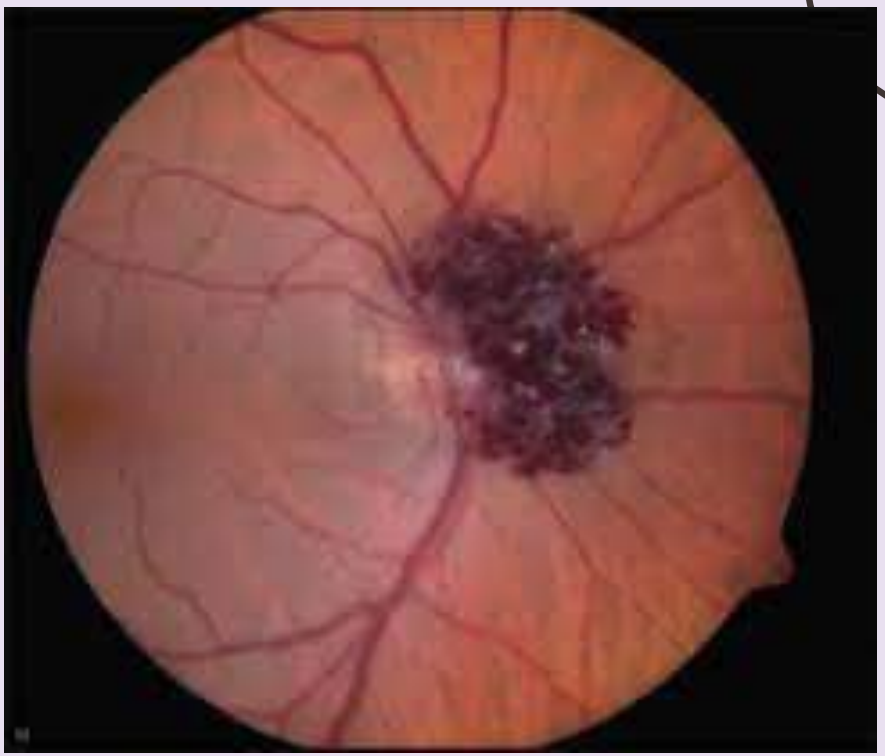


https://imagebank.asrs.org/file/10385/cavernous-hemangioma-of-the-retina

.....And more!

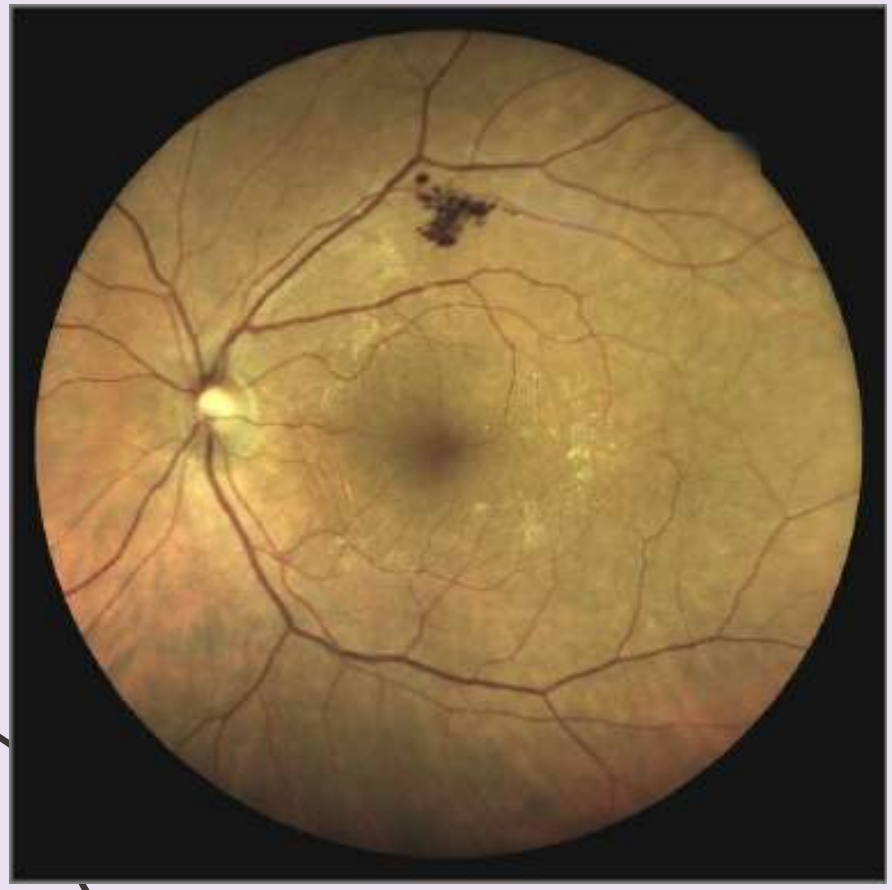
- >90% in Whites
- Primarily females
- Unilateral unifocal lesion

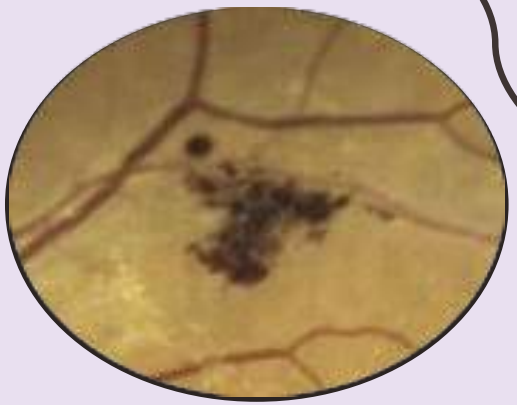
Can be associated with similar skin and central nervous system lesions (14% intracranial involvement)



https://entokey.com/cavernous-hemangioma/

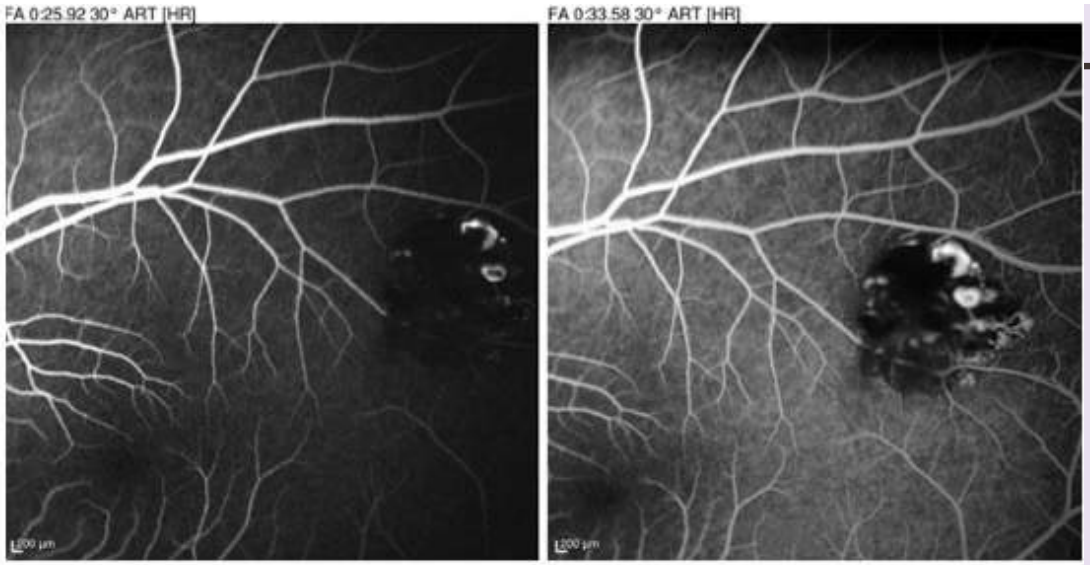
Back to our patient:



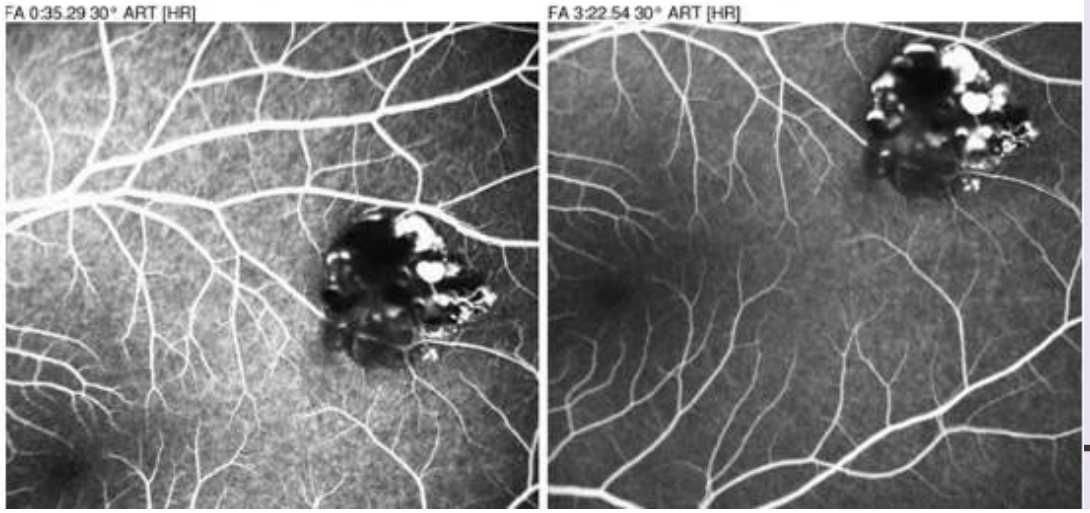


What could this be?

1. Retinal hemorrhages
2. Capillary Hemangioma
3. **Retinal cavernous hemangioma**



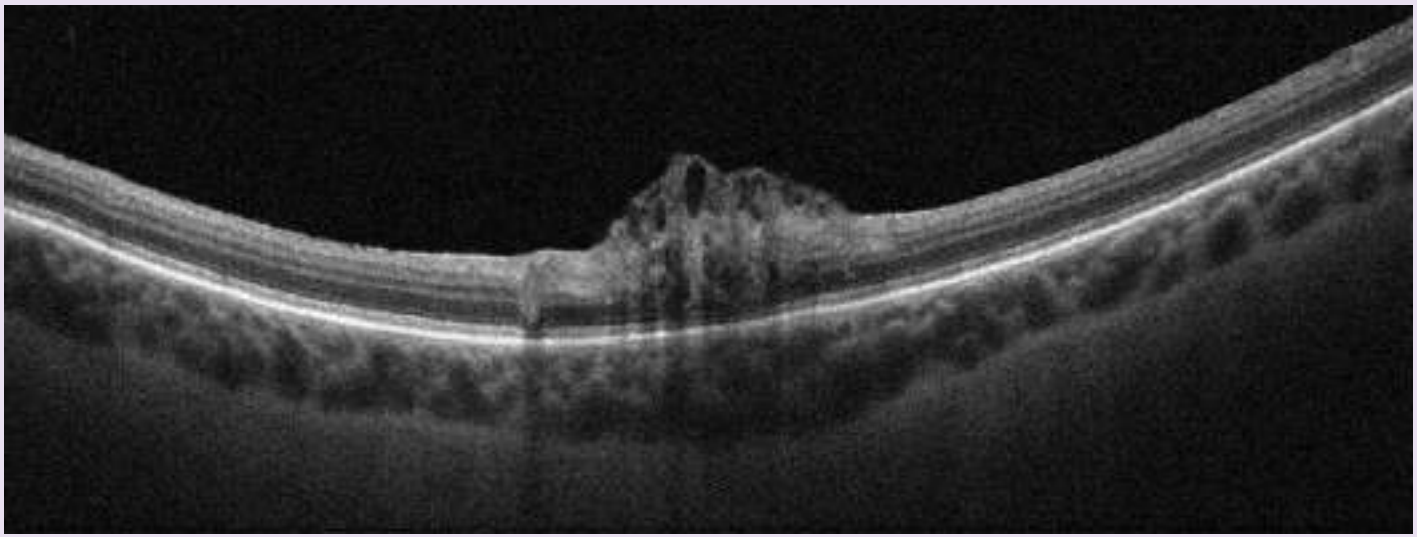
Hypofluorescence in early phase



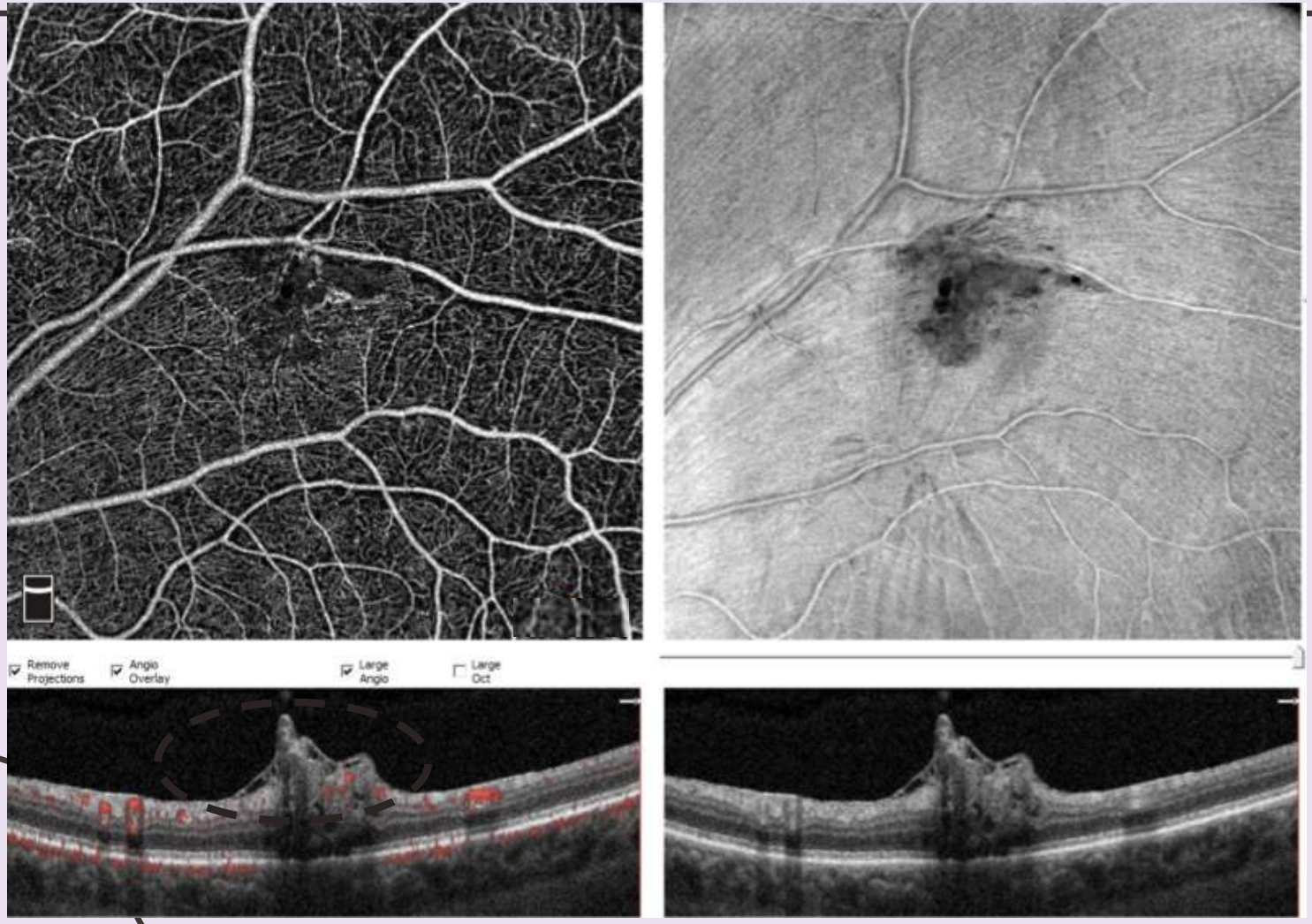
Fluorescein Angiography

Pooling of dye in upper half of saccule in late phase giving an appearance of "**fluorescein cap**". No leakage!

https://assets.bmctoday.net/retinatoday/pdfs/0715RT_Mini_Shields.pdf

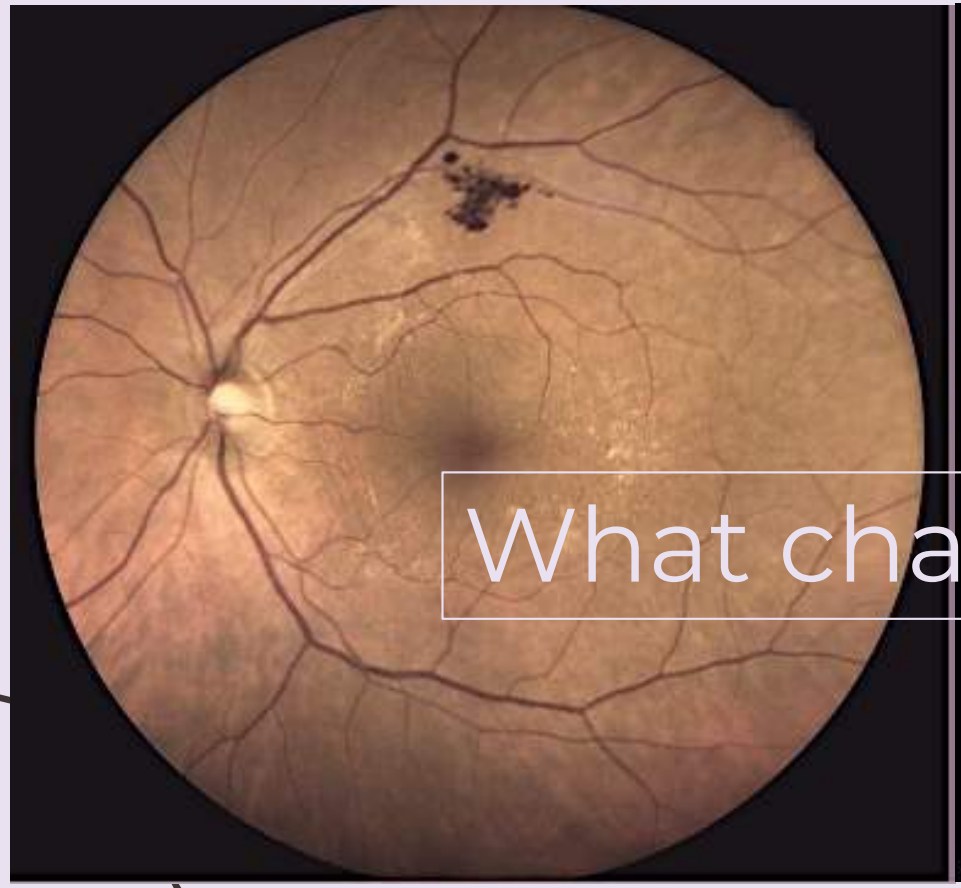


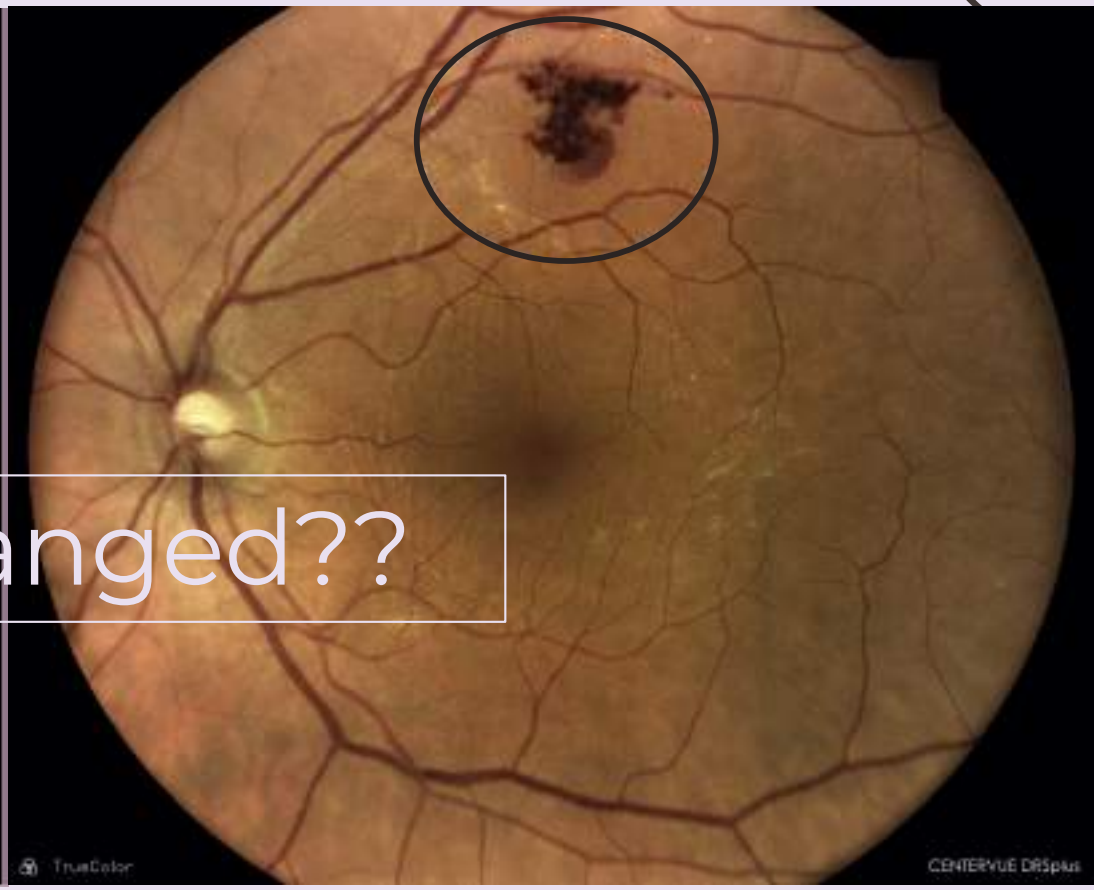
OCT shows ‘grape bunch’ multilobulated cavernous spaces located under the internal limiting membrane.



OCTA flow overlay demonstrated low-stagnant blood circulation inside retinal cavernous hemangioma

Our patient.....One year later???



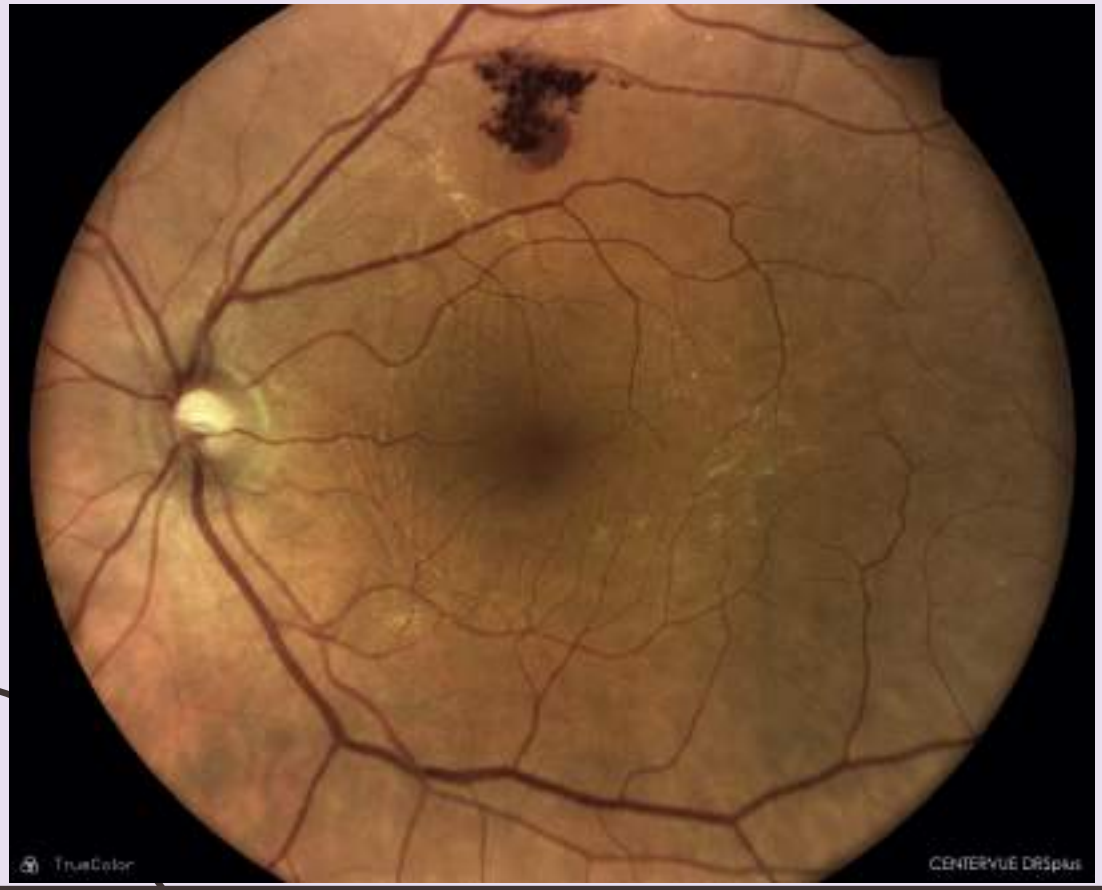


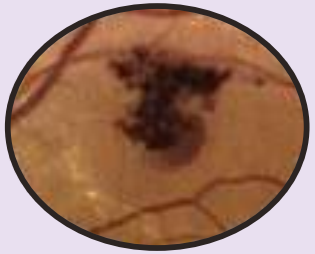
What changed??

2021

2022

Subretinal bleed....???





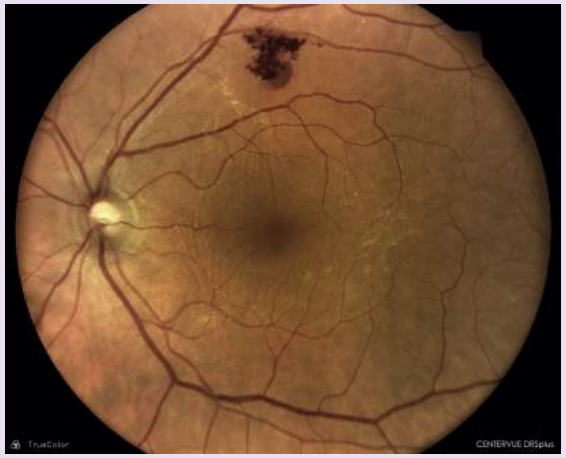
Complications of retinal cavernous hemangioma:

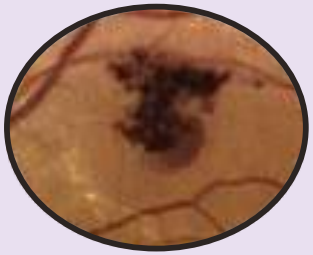
- Macular location
- Epiretinal membrane
- Vitreous hemorrhage

"....Retinal cavernous hemangiomas have rarely been reported to bleed..."

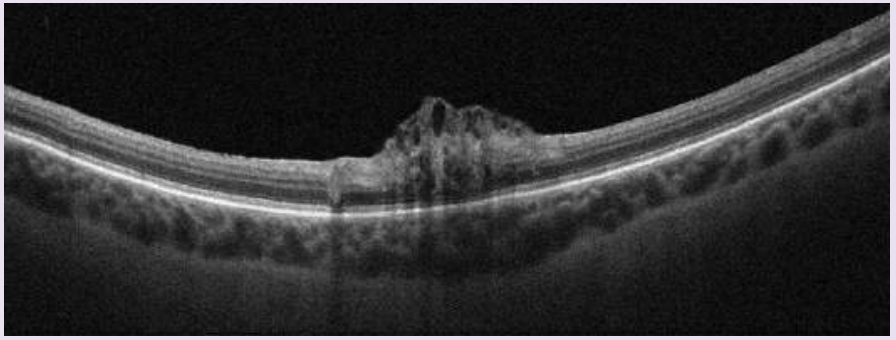
1. Colvard DM, Robertson DM, Traytmann JC. Cavernous hemangioma of the retina. Arch Ophthalmol 1978;96:2042-4
2. Gass JD, Braunste in R. Sessile and exophytic capillary angiomas of the juxtapapillary retina and optic nerve head. Arch Ophthalmol. 1980;98: 1790-1797.
3. Siegel AM. Familial cavernous angioma: an unknown, known disease. Acta Neurol Scand 1998;98:369-371

Subretinal bleed....Why?

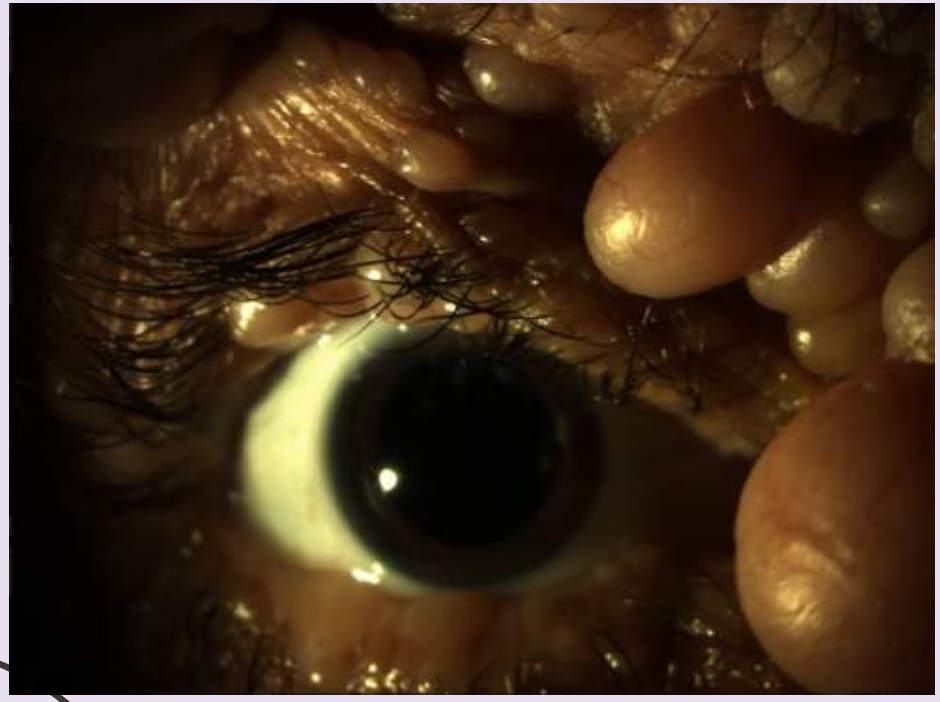




The dilated vascular sacs are in the inner retinal layers



Sequelae of a rupture??




KEEP
CALM
AND
STAY
TUNED

Case 4

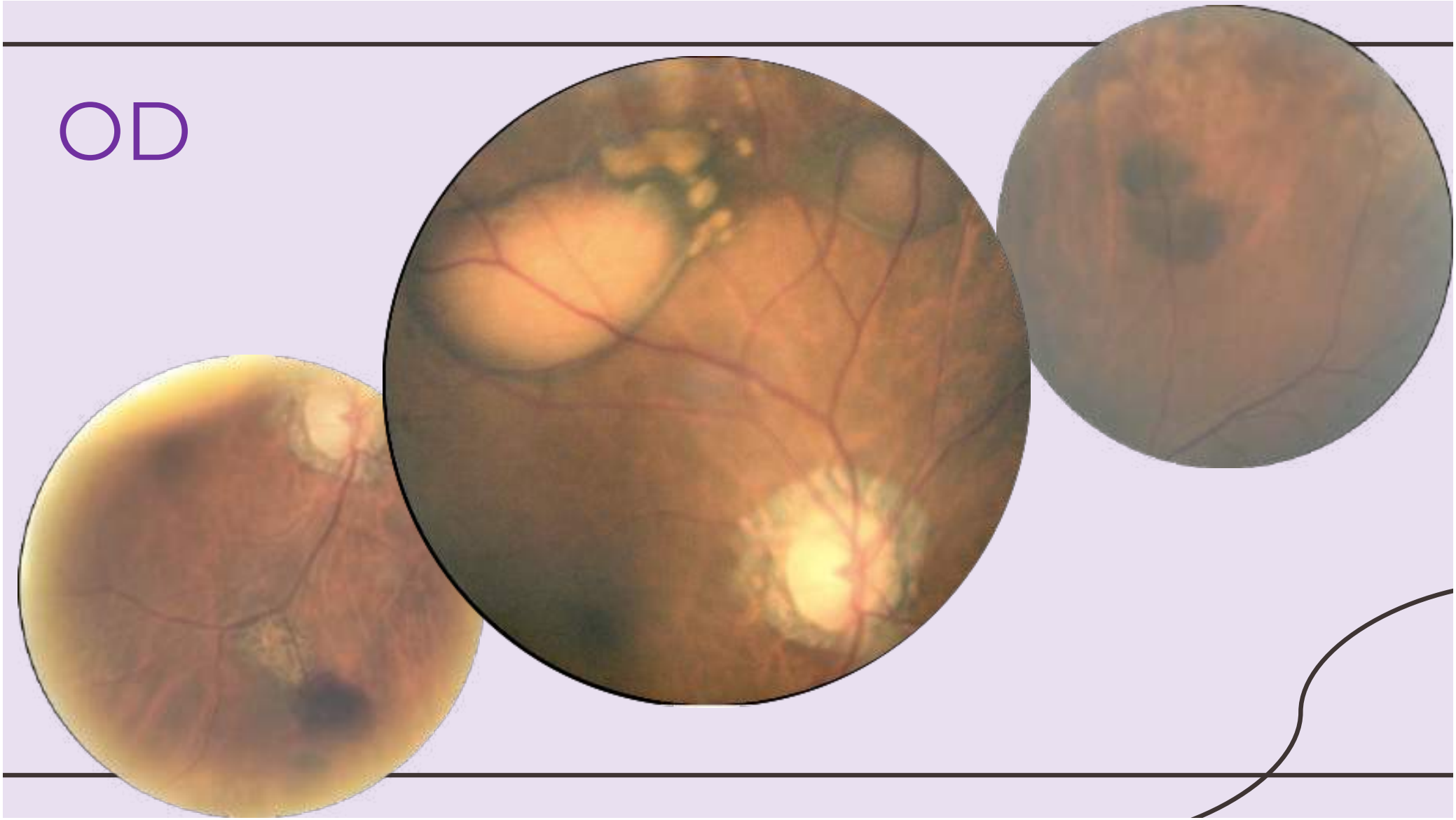
72-year-old Black Male

Presents with decreased vision bilaterally D and N

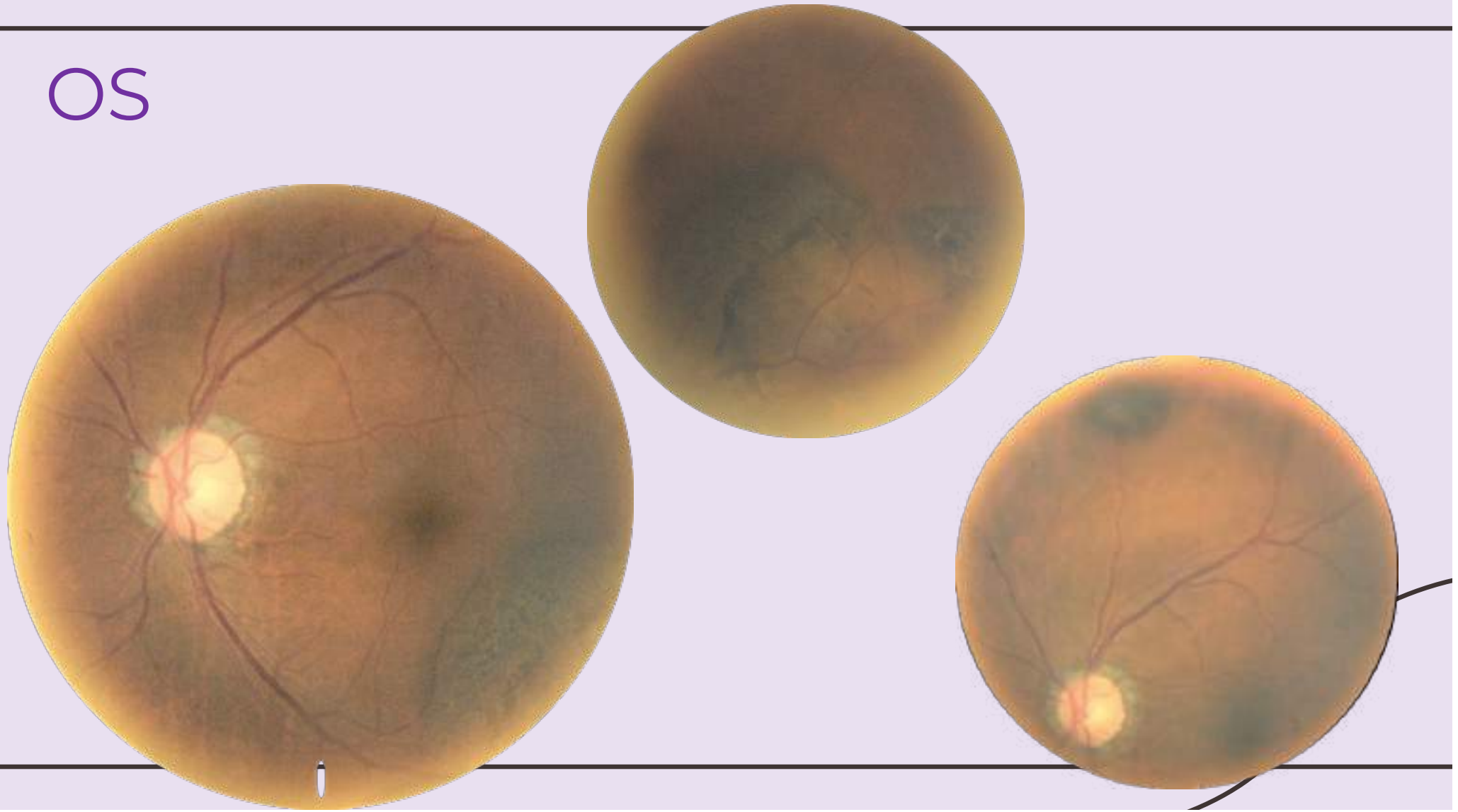
BCVA: 20/25+ OD, 20/25+ OS

PMH:
(+) HIV; CD4 Count 336: Viral load 46
(+)Hypercholesterolemia
(+)Hypertension
(+)DM 2; poor BS control

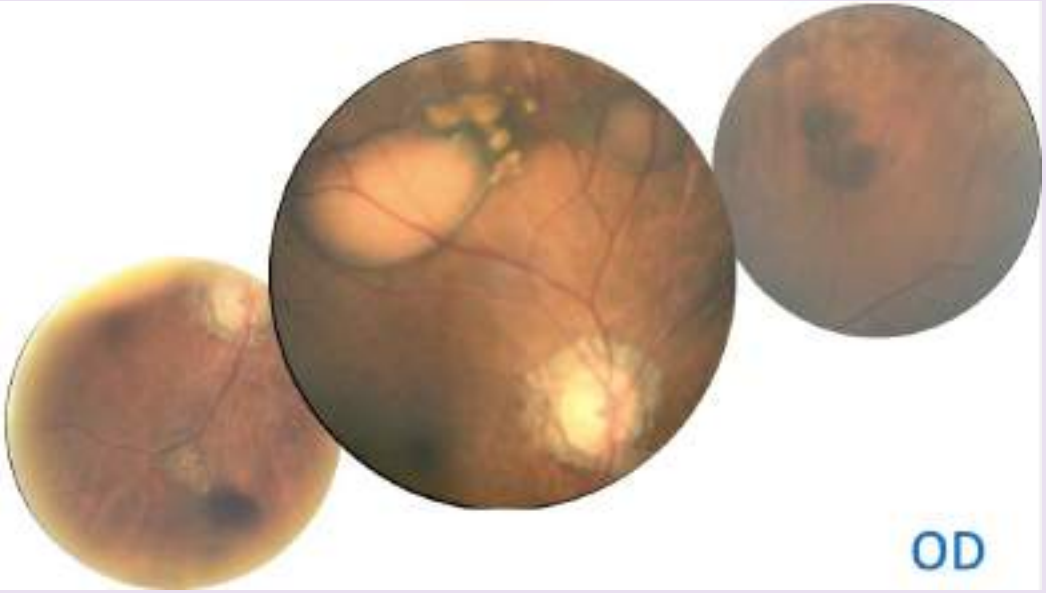
OD

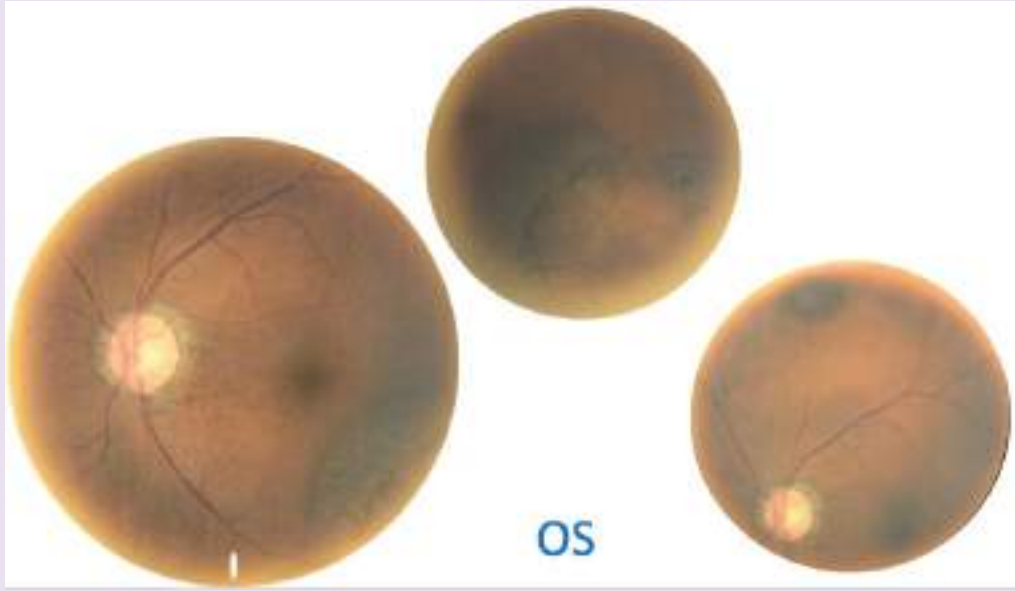


OS



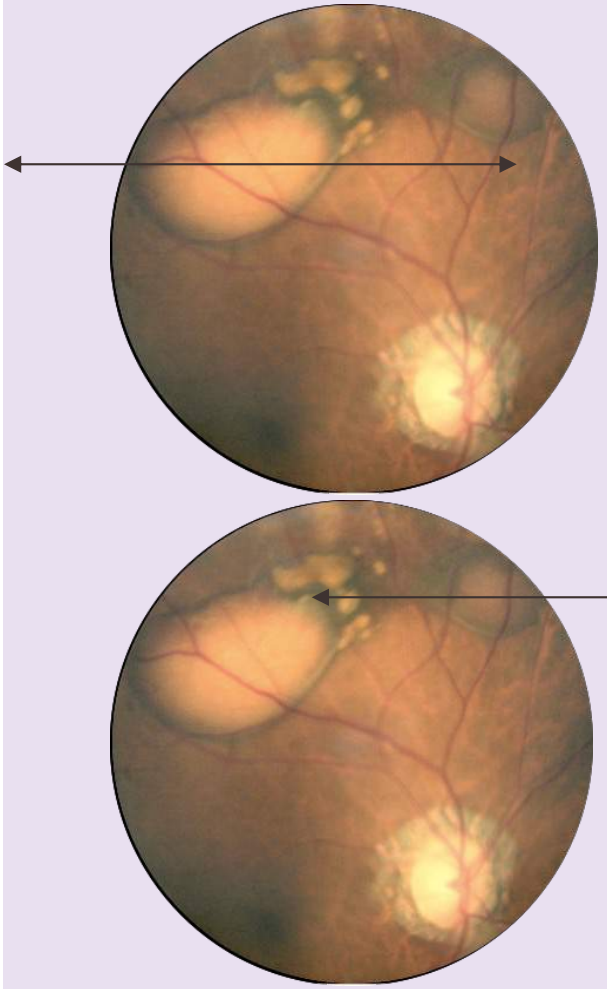
What could this be????

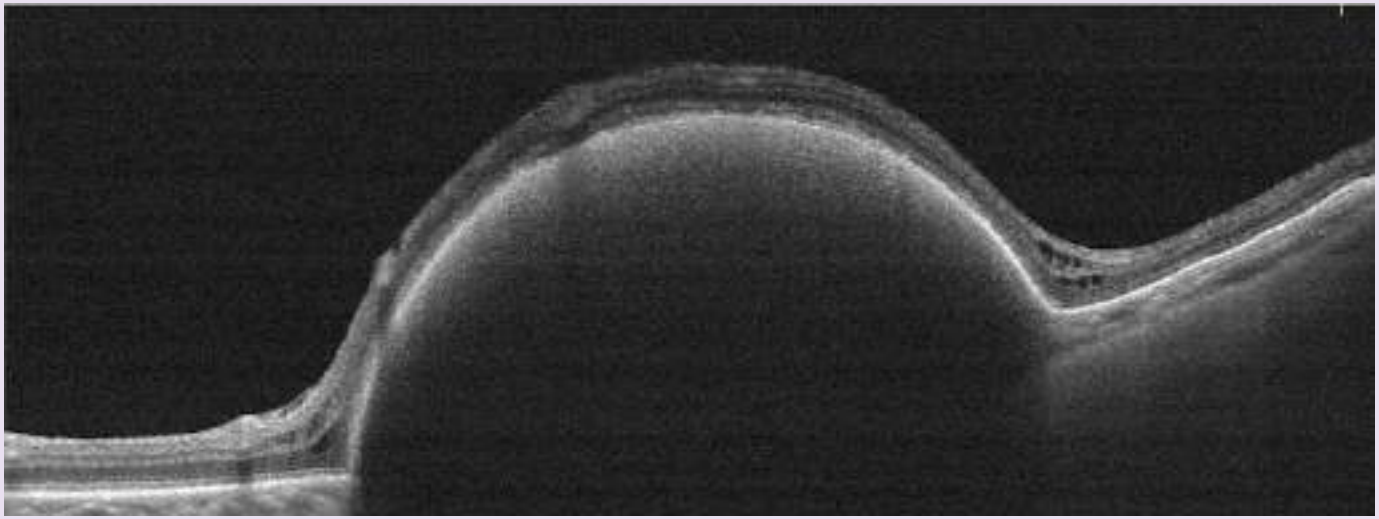


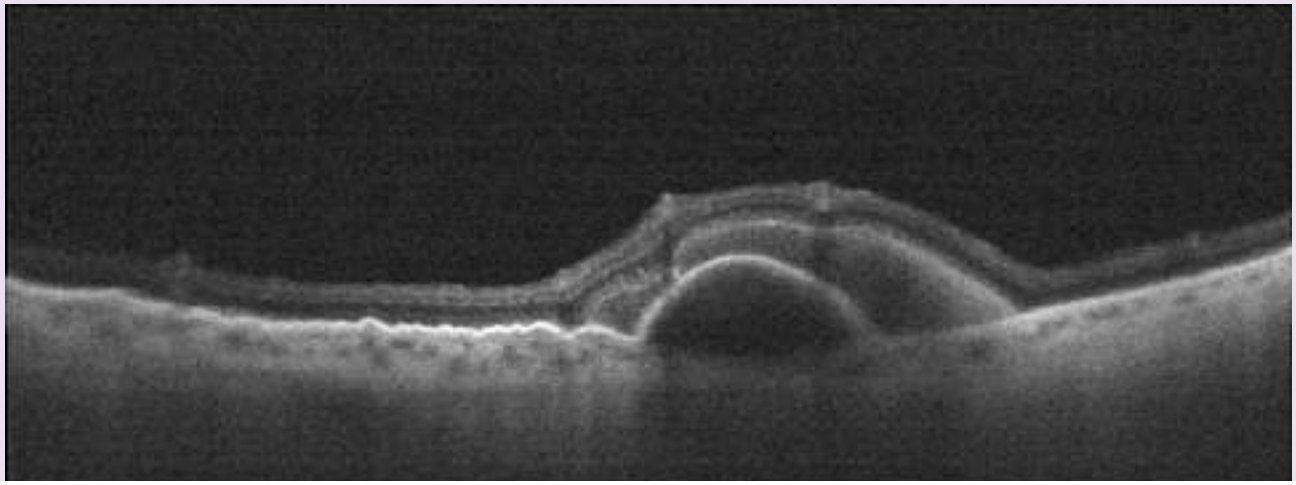


1. Choroidal melanoma?
2. Age Related Macular Degeneration?
3. Chorioretinitis?
4. Pathological myopia with neovascularization?
5. Something else?

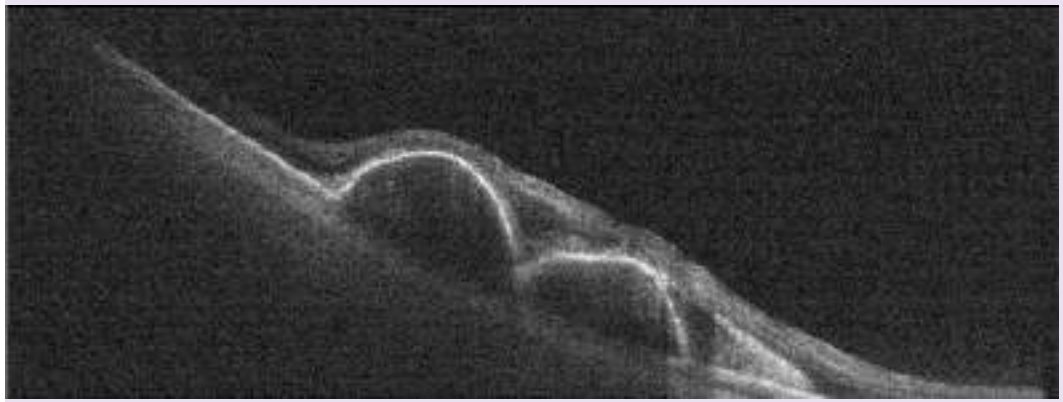
Let's look at the OCTs!

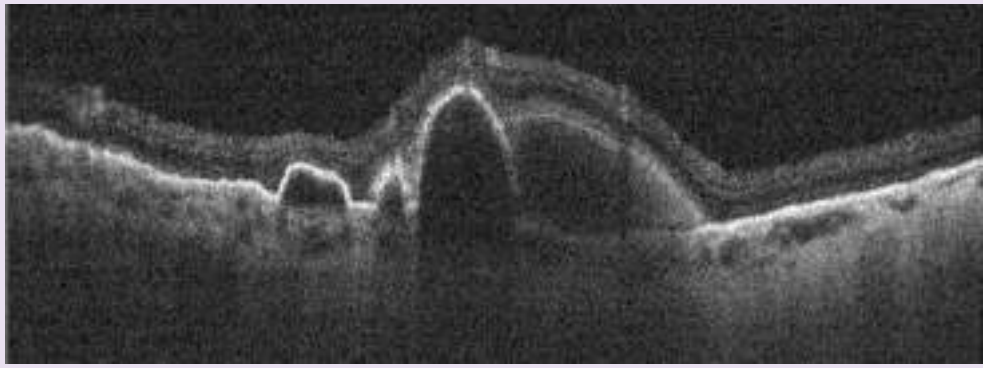


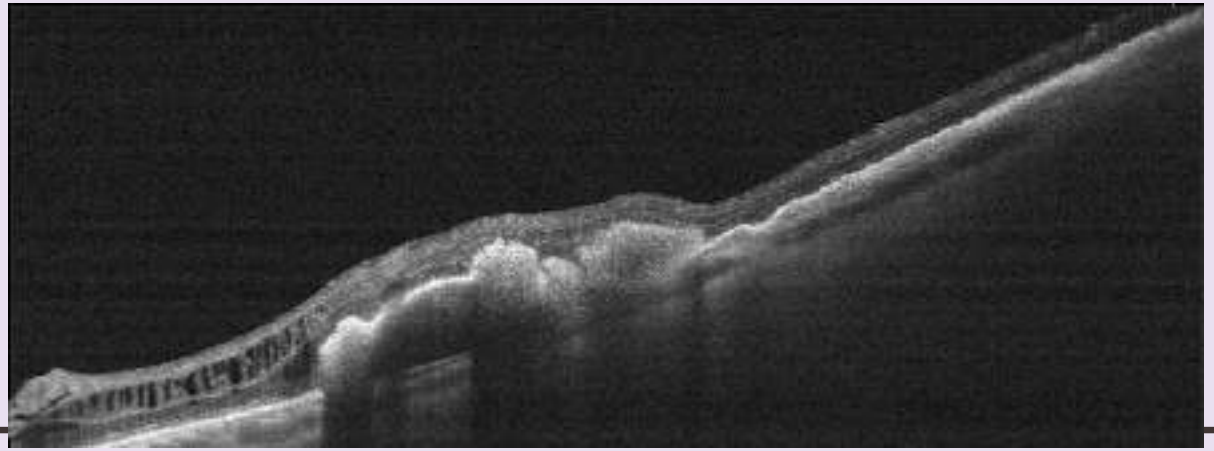




And more cuts....





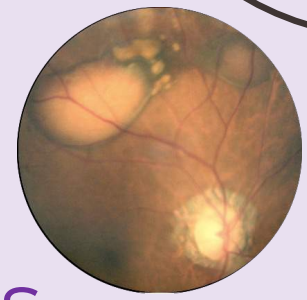


Polypoidal Choroidal Vasculopathy

- *Clinical Subtype with features of Neovascular AMD*

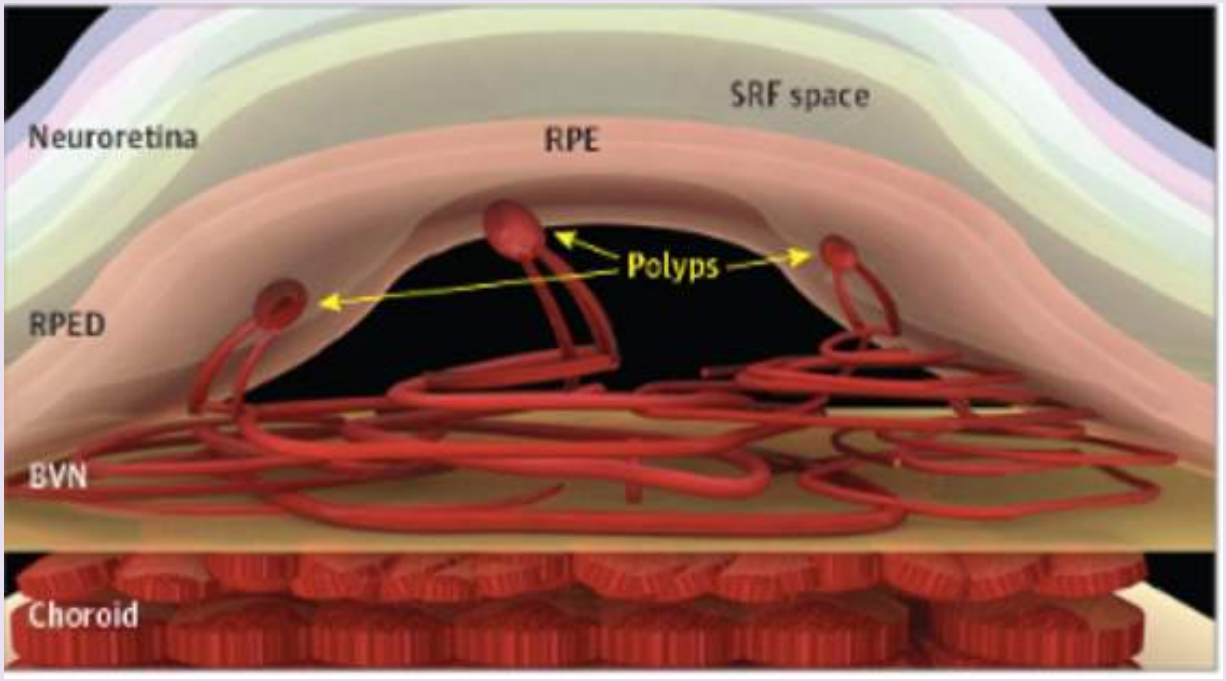
> *"Peculiar Hemorrhagic detachment of the RPE and choroid"*

Polypoidal Choroidal Vasculopathy



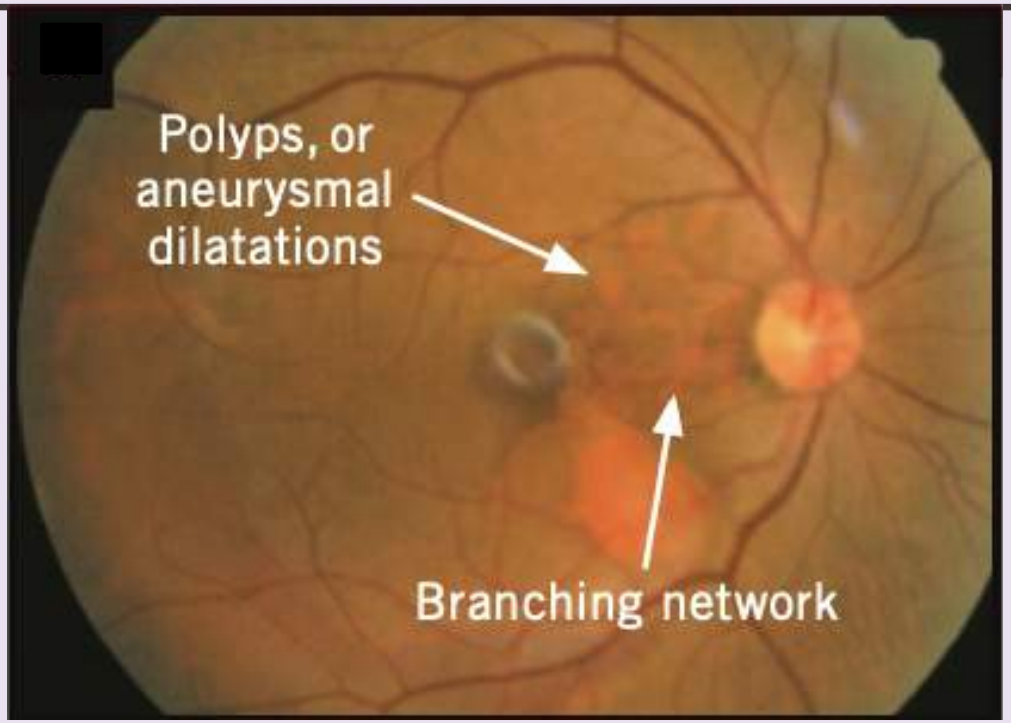
- Suspected in patient with:
  - sub-retinal orange polyp-like lesions
    - Can be macular or peripapillary
    - Rarely in arcades as well
  - Especially African or Asian descent (F>M)

Pathophysiology

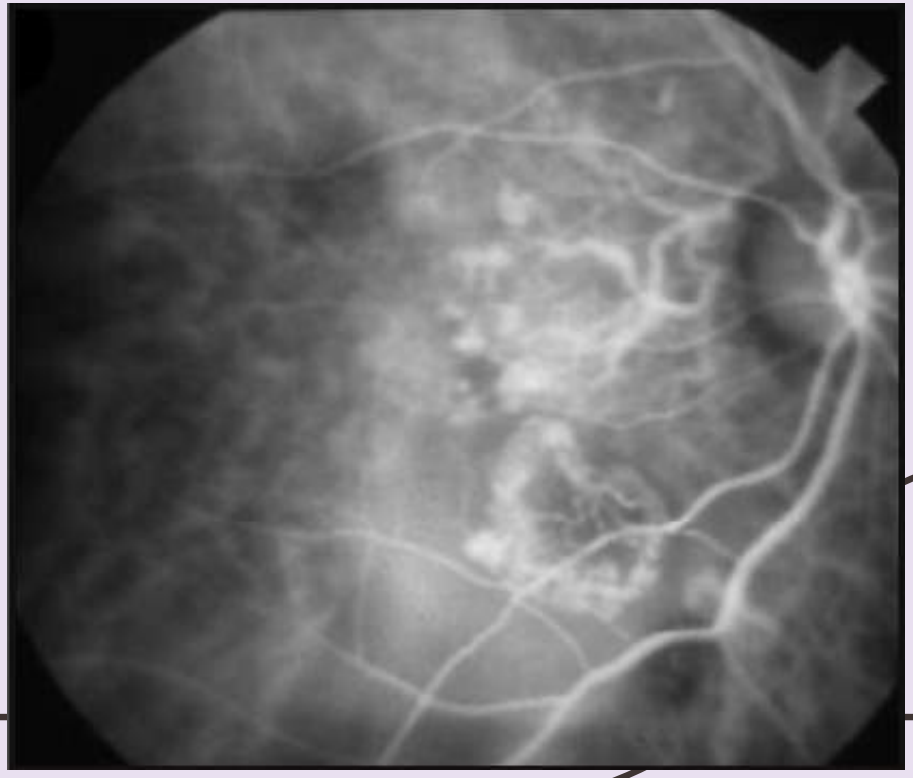


- Branching vascular network (BVN): originates in the choroid
- BVN may develop terminal, polyp-like aneurysmal dilatations

https://jamanetwork.com/journals/jamaophthalmology/article-abstract/2657209



What does this look like clinically?

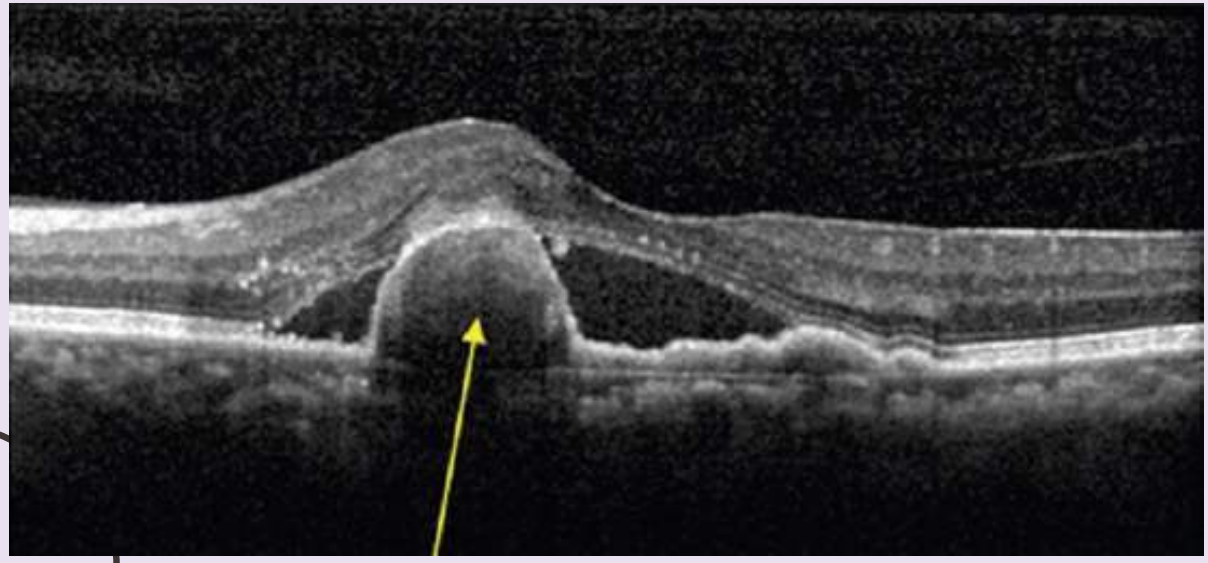


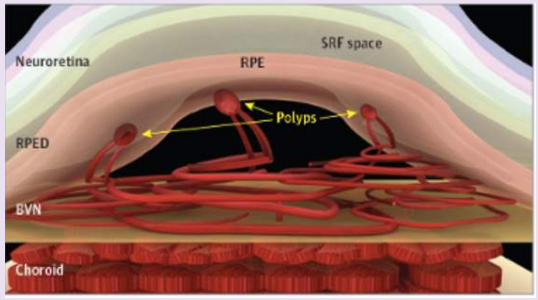
https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.slideshare.net%2FSujayChauhan1%2Fpolypoidal-choroidal-vasculopathy-60614855&psig=AOvVaw142iD7lKKS9uZ-CM_-flNa&ust=1616800593858000&source=images&cd=vfe&ved=0CIQBEK-JA2oXChMI4ILQ5snM7wIVAAAAAB0AAAAAEAI

Serosanguinous RPE detachments

Serous Fluid

Blood

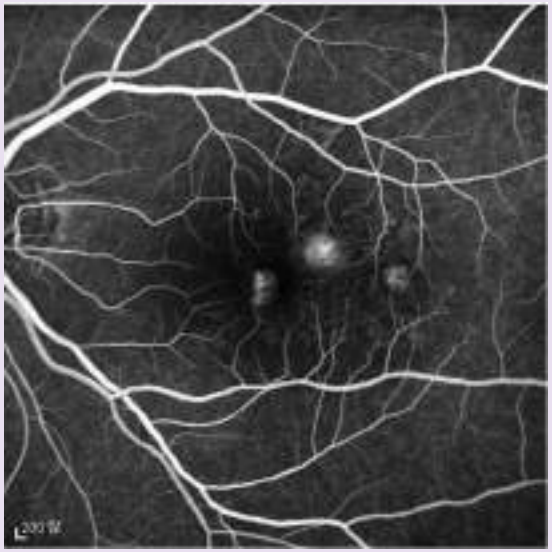


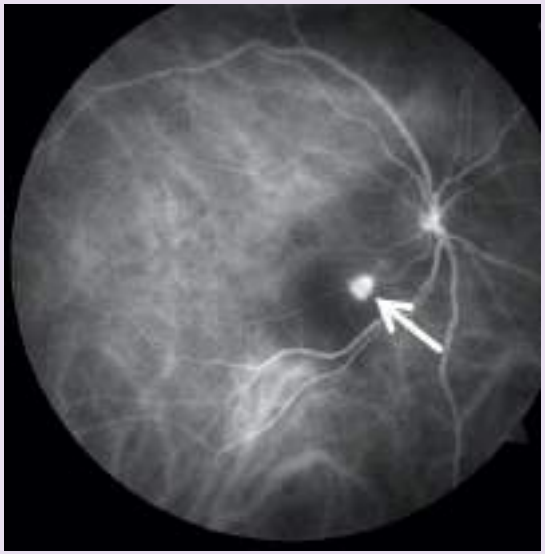


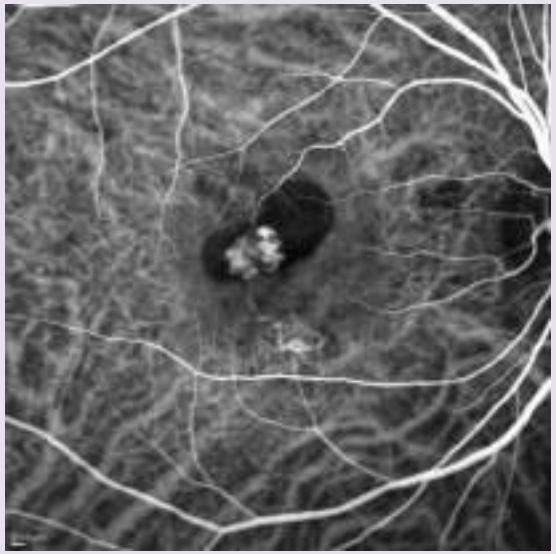
http://www.ijo.in/viewimage.asp?img=IndianJOphthalmol_2018_66_7_896_234954_f2.jpg

PCV and ICG

- Essential for detecting the choroidal network of polyps
  - Differentiation from AMD



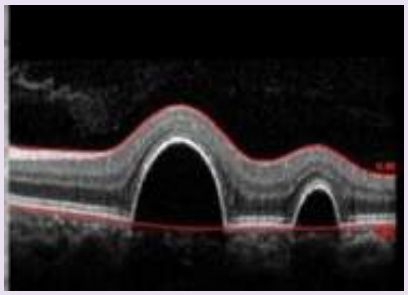


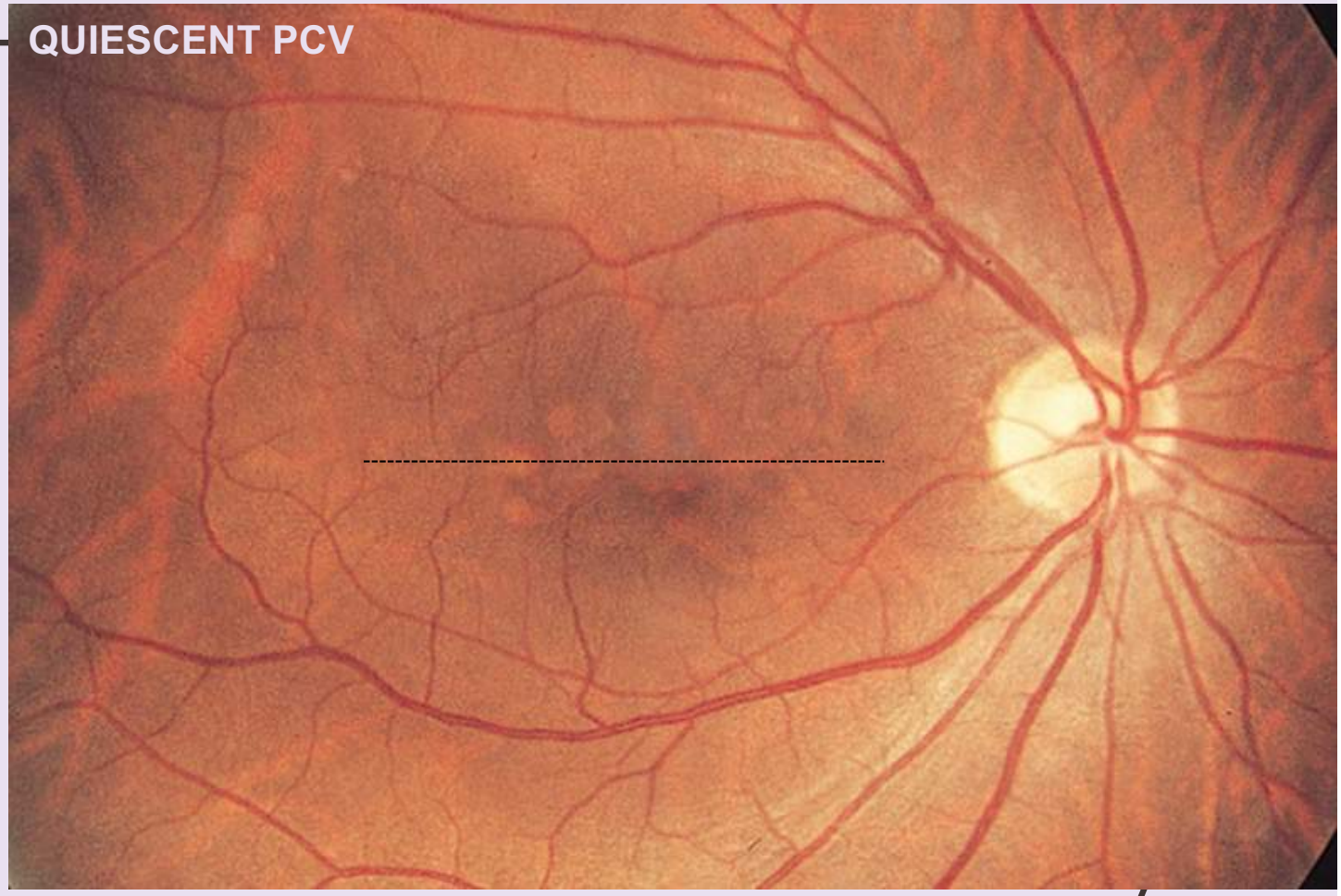


https://www.aao.org/topic-detail/polypoidal-choroidal-vasculopathy-pcv--asia-pacifi

Pigment Epithelial Detachment

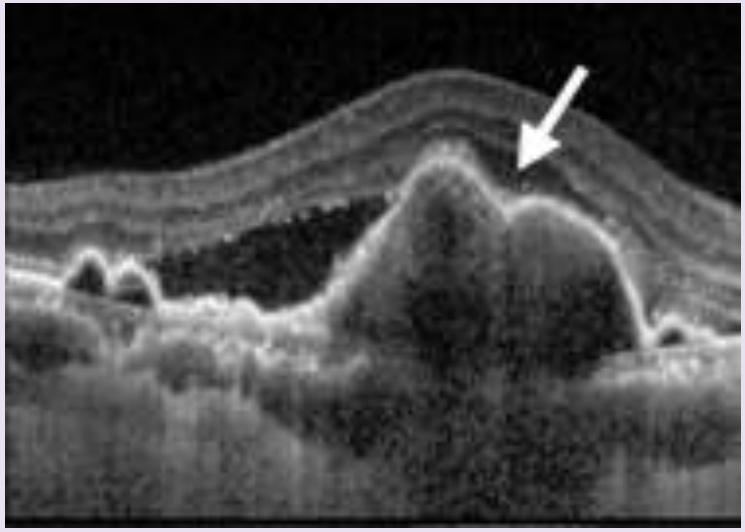
NO....hemorrhage
NO....exudate



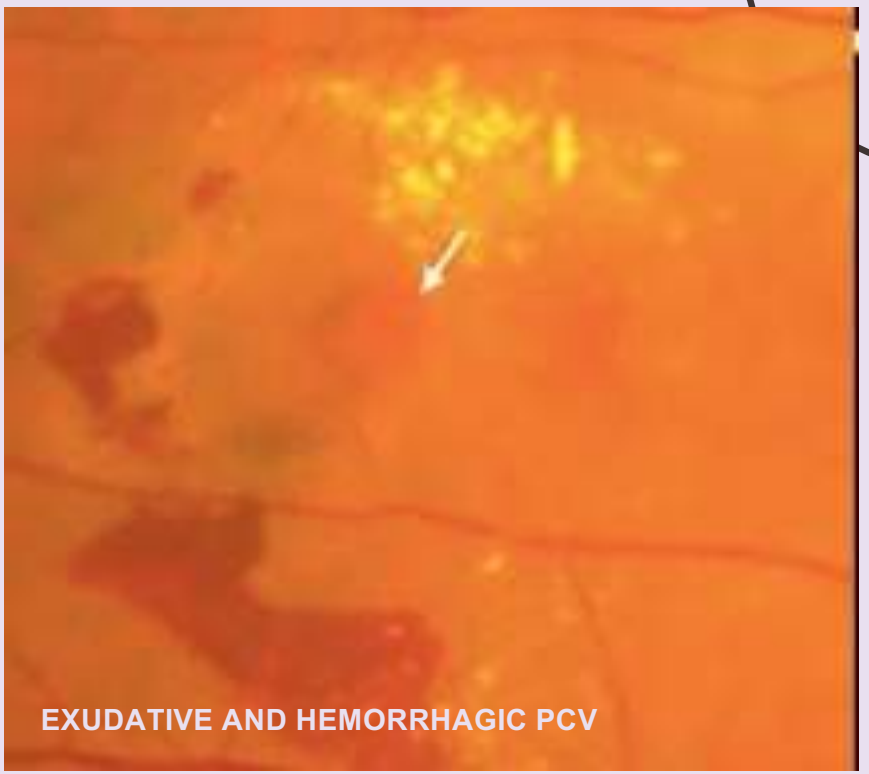


Polyps; sharp dome-like elevations

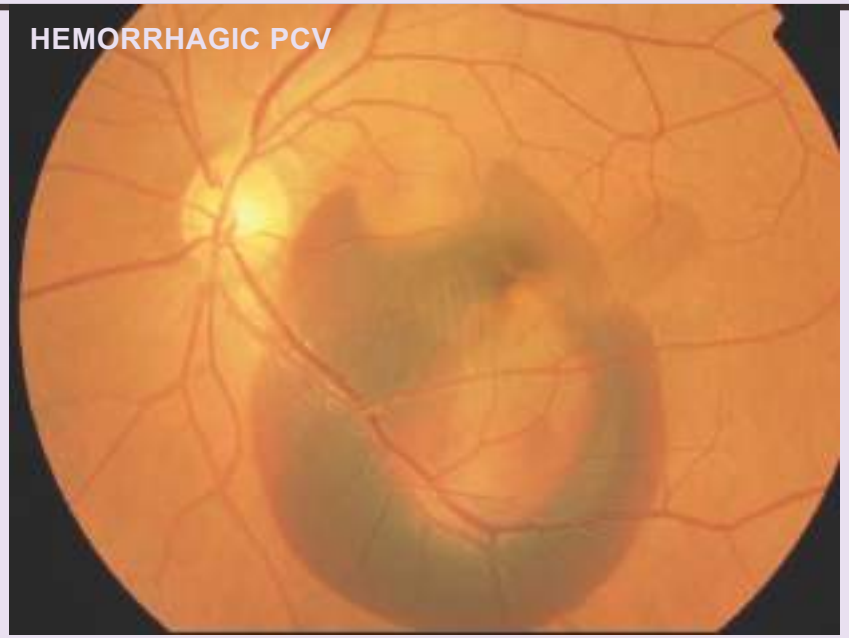
https://jamanetwork.com/journals/jamaophthalmology/fullarticle/412248

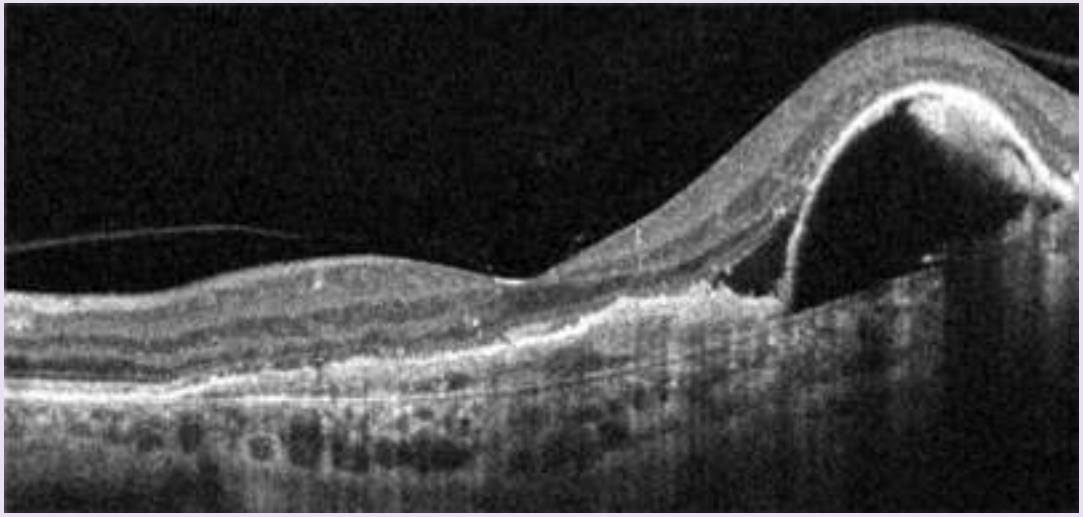


Serosanguinous Pigment Epithelial Detachments
(note turbid appearance)



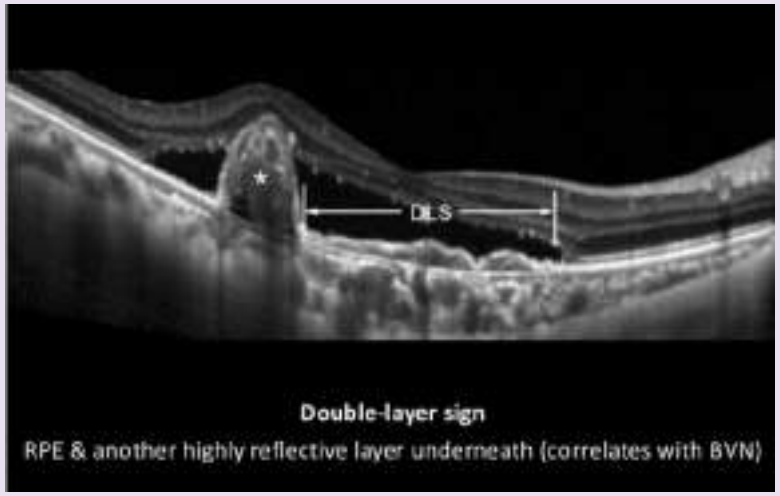
https://www.aaojournal.org/action/showPdf?pii=S0161-6420%2820%2930784-3





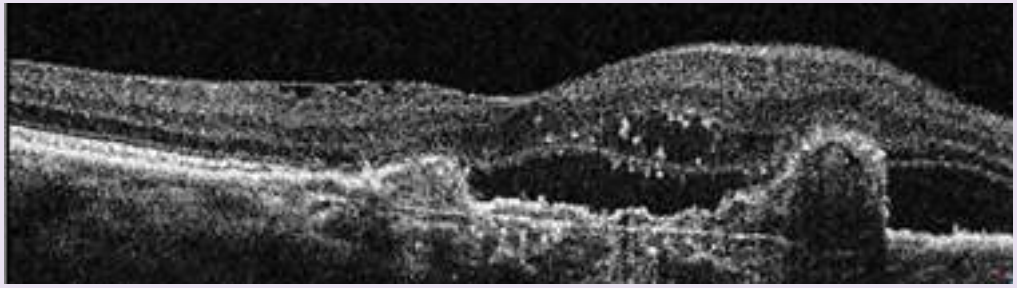
Double layer sign

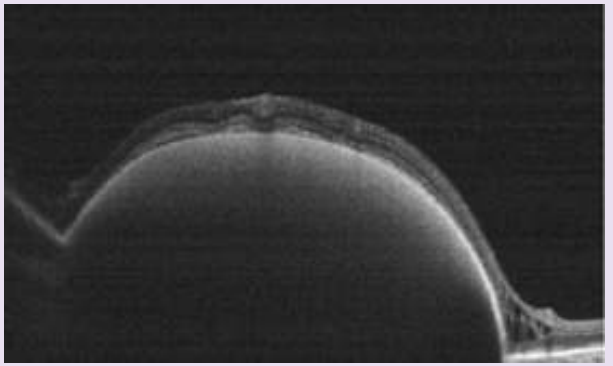
https://www.researchgate.net/figure/A-Polypoid-choroidal-vasculopathy-associated-with-subretinal-hemorrhage-in-a_fig9_285673110



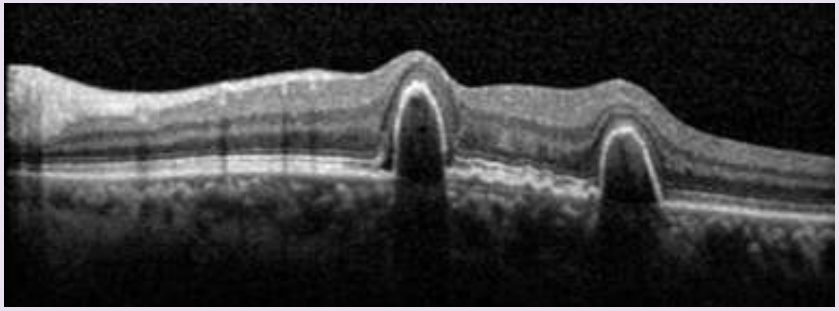
SO… how do we make the diagnosis??

Double Layer Sign





Large PEDS

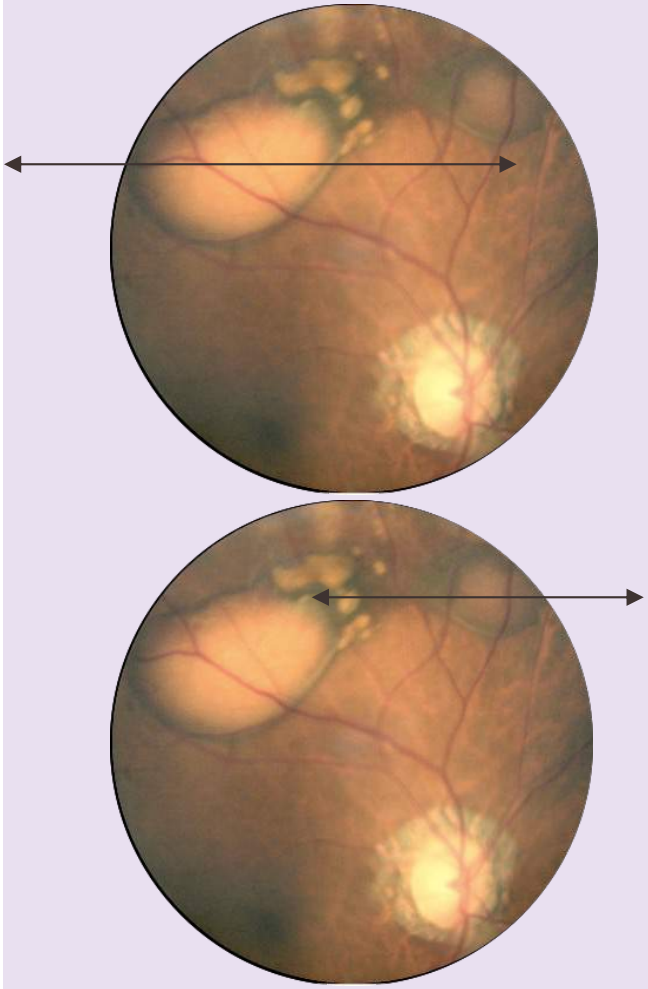


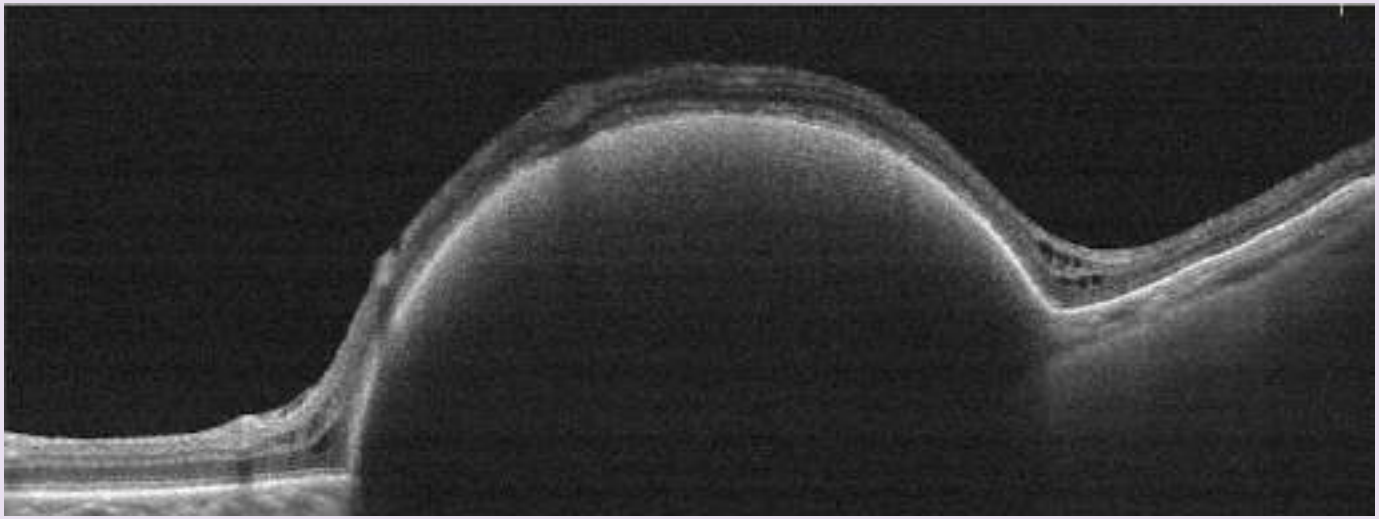
Sharp PEDs

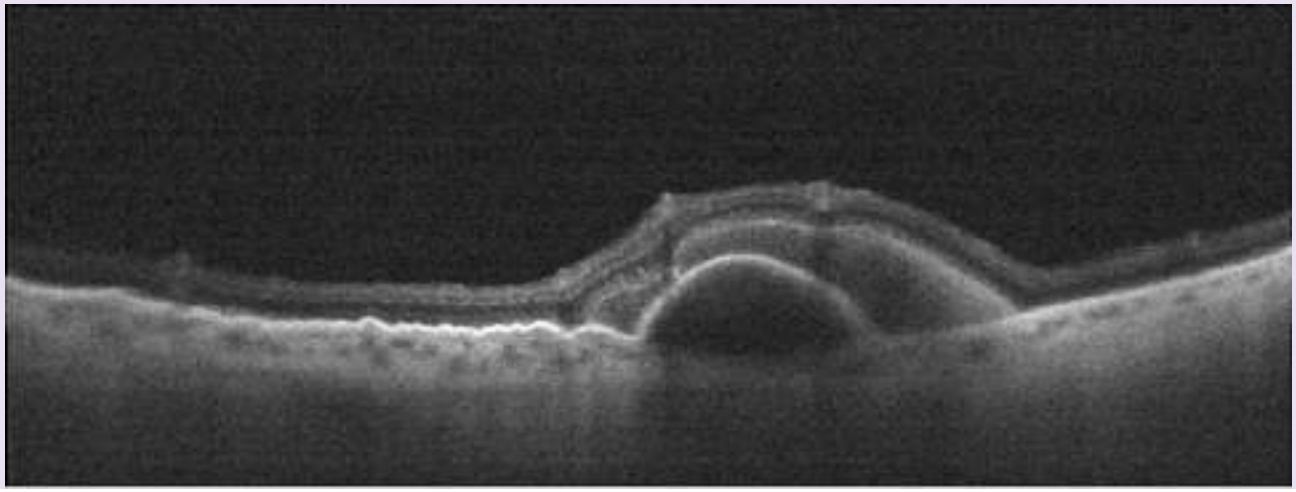
https://www.retinalphysician.com/issues/2015/april-2015/how-rap-and-pcv-can-affect-the-management-of-amd

Back to our patient:

Serosanguinous PEDs

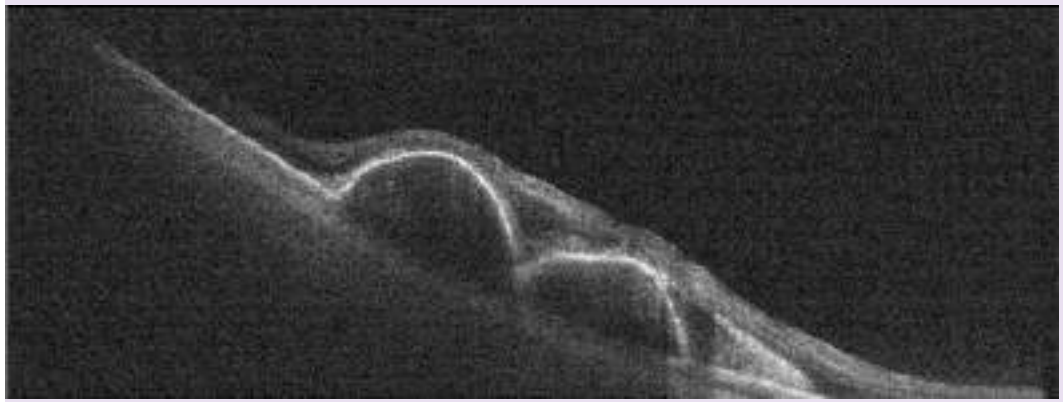


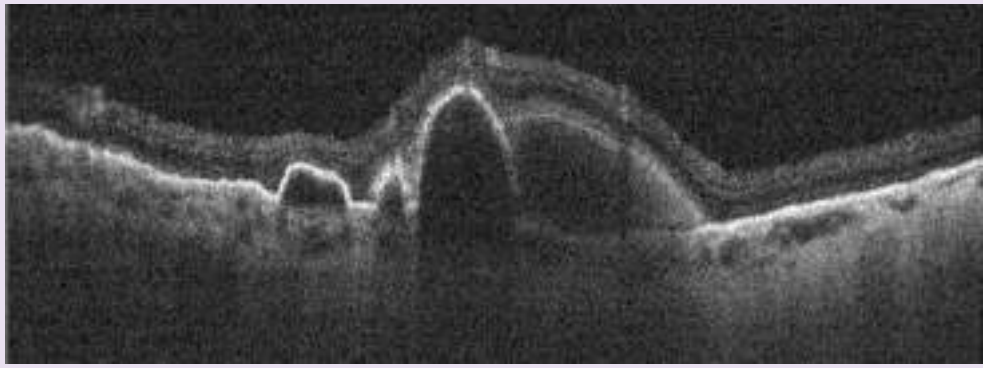


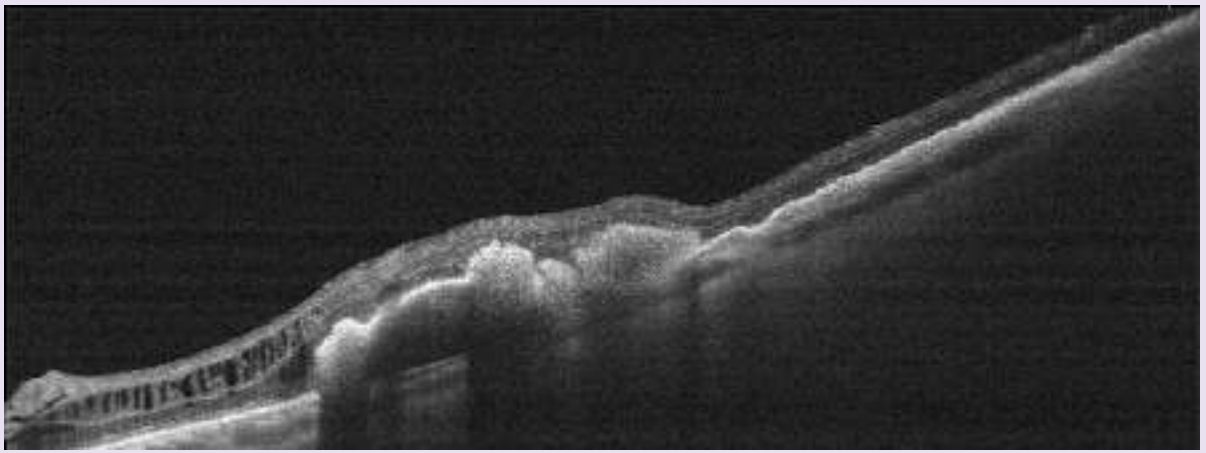


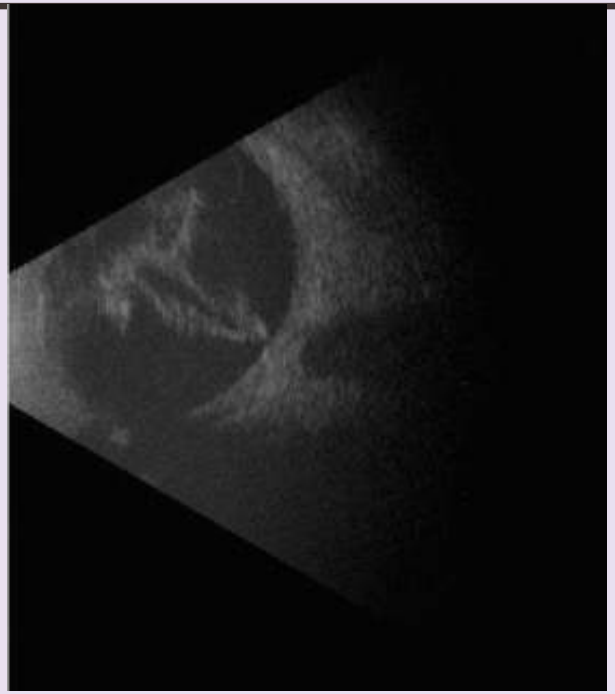
And more cuts....

Double layer sign; ?CNV

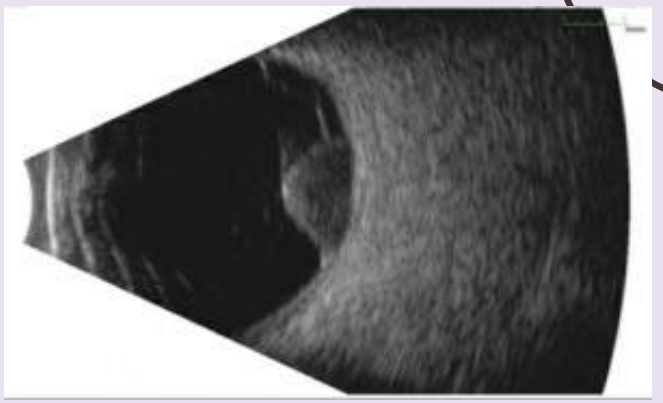


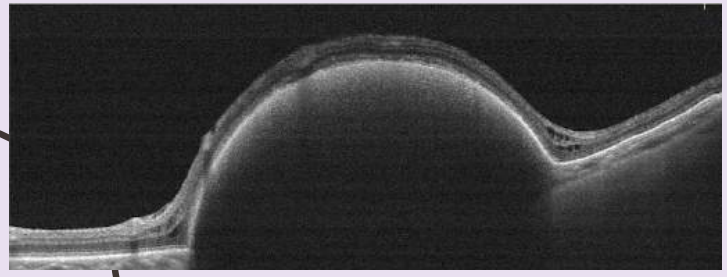


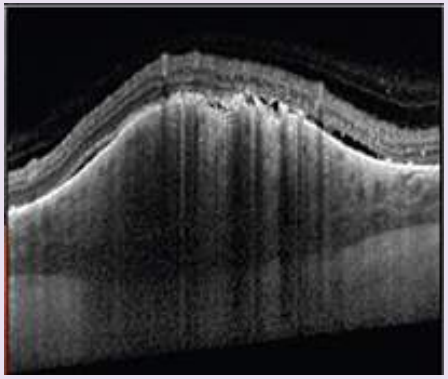




Ultrasound:
Differentiation from choroidal tumor







https://www.reviewofophthalmology.com/article/imaging-advances-for-choroidal-melanomaa

The clinical presentation of PCV is often like that of CSR or exudative AMD. The diagnosis of PCV can be challenging without ICG imaging. ICG should be considered in patients who have visible orange-red subretinal nodule(s), spontaneous massive subretinal hemorrhage, notched or hemorrhagic PED, or the lack of response to anti-VEGF therapy.

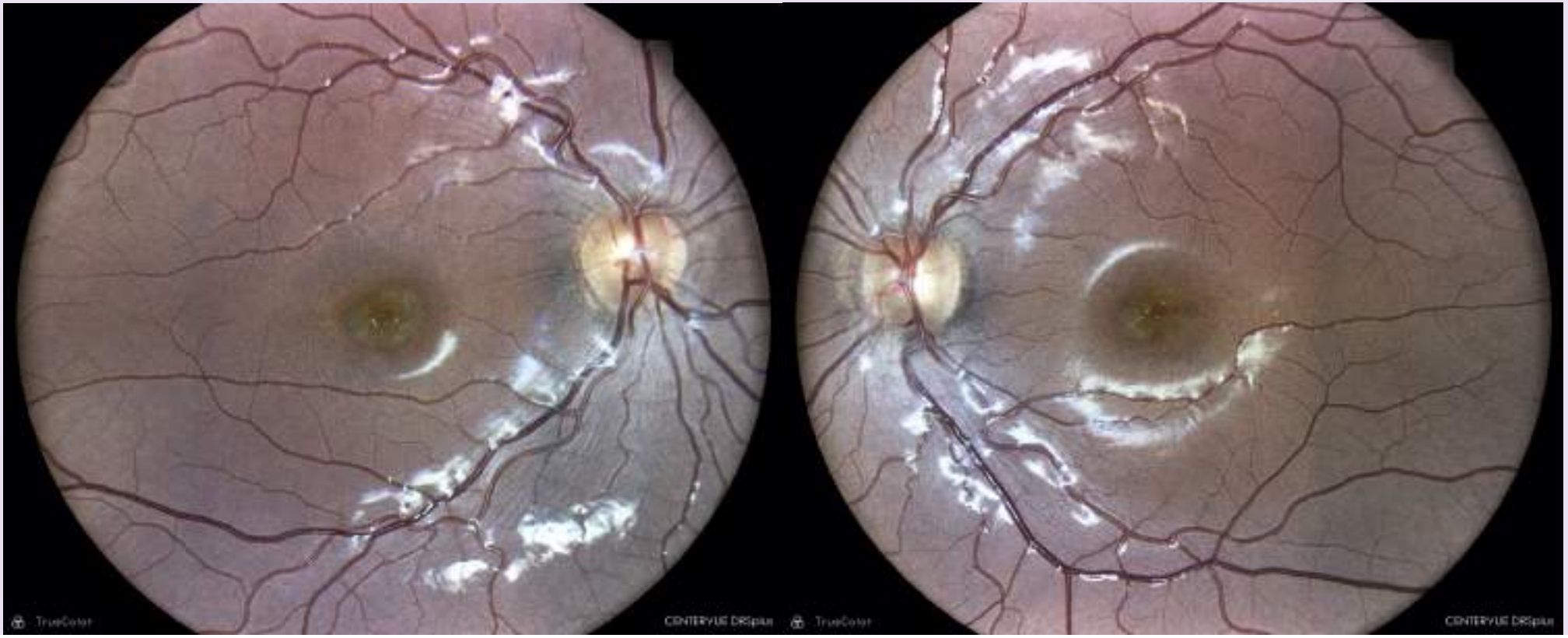
Case 5

13-year-old Black Female

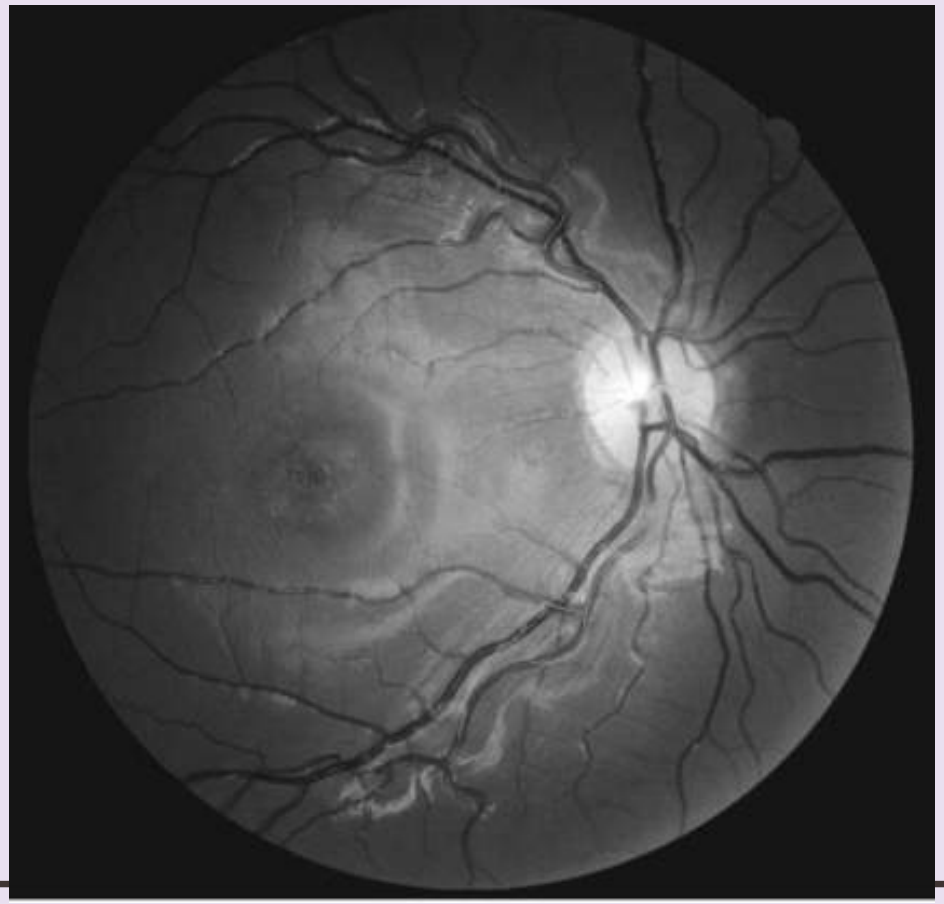
First eye exam ever!! Never had any visual problems
Mom reports that she is just NOT seeing right!

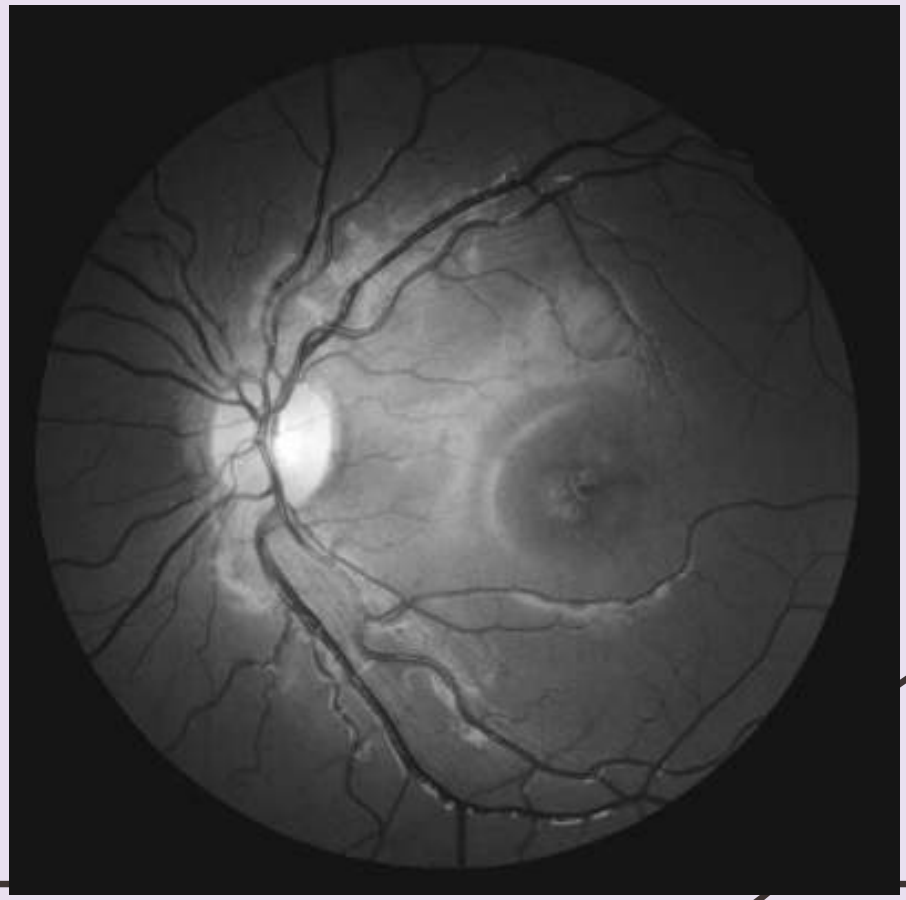
BCVA: 20/30 OD, 20/30 OS
Failed Color Vision OD and OS

"I can't see the blackboard at school and my grades are sinking!!!"

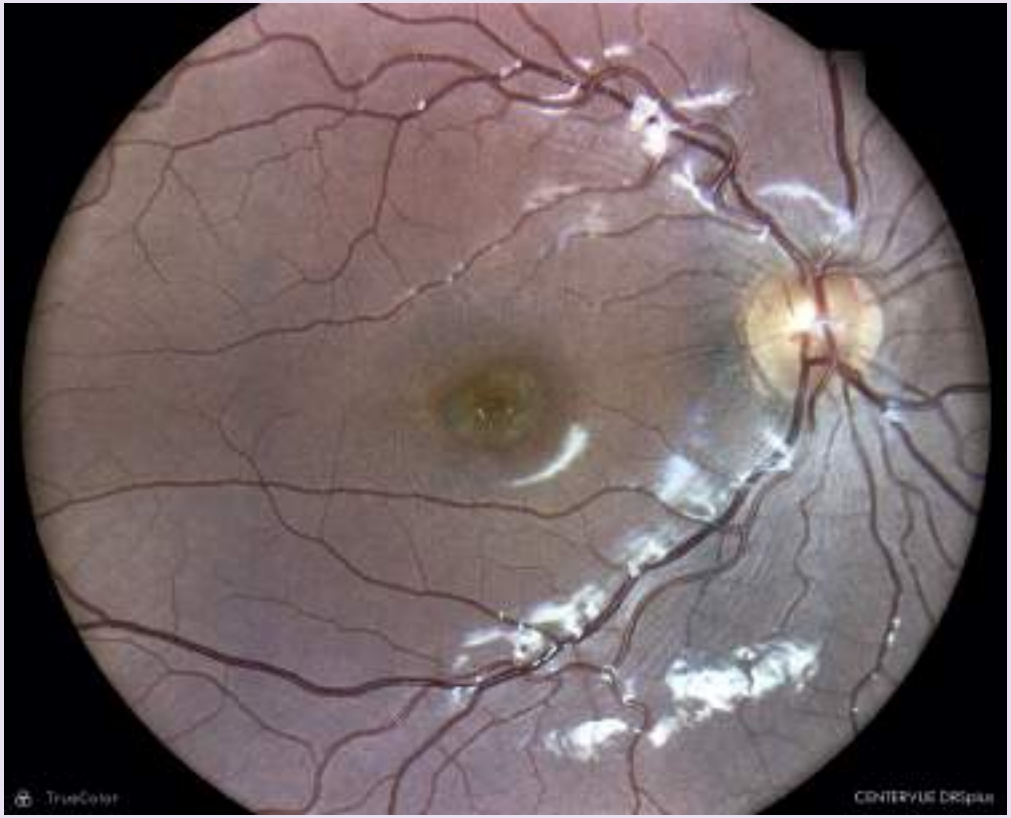

TrueColor
CENTERVUE DRSplus
TrueColor
CENTERVUE DRSplus

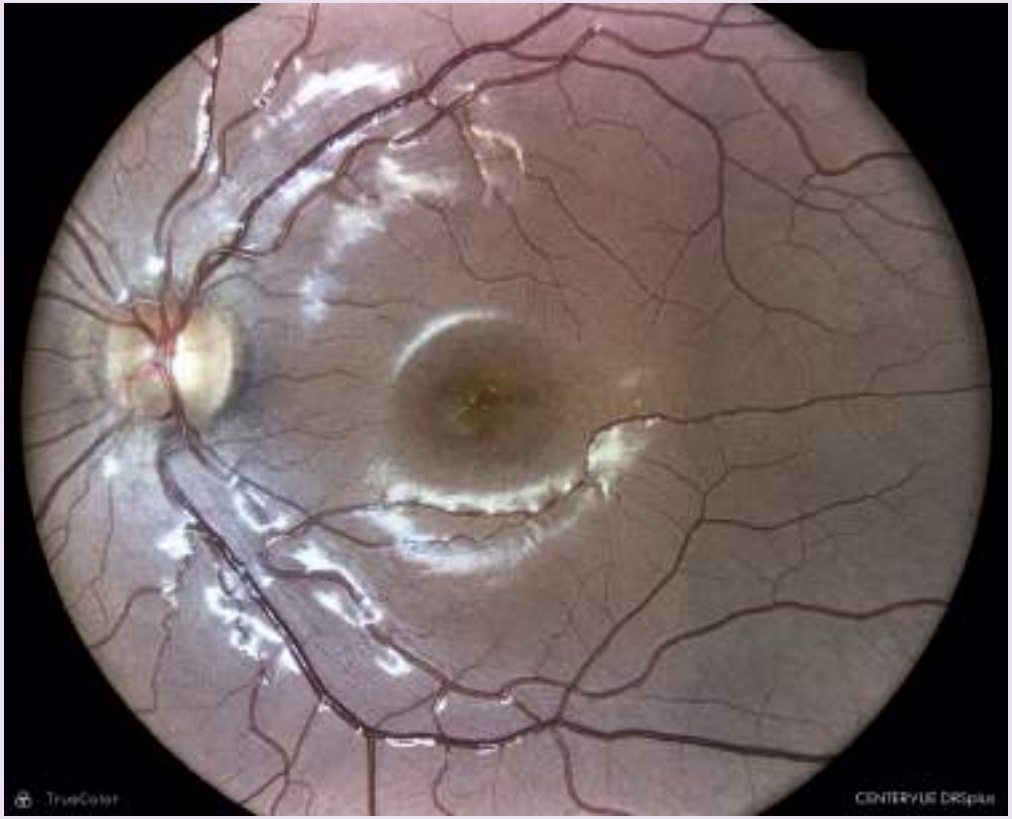
Red-Free Photography





Bull's Eye Maculopathy???



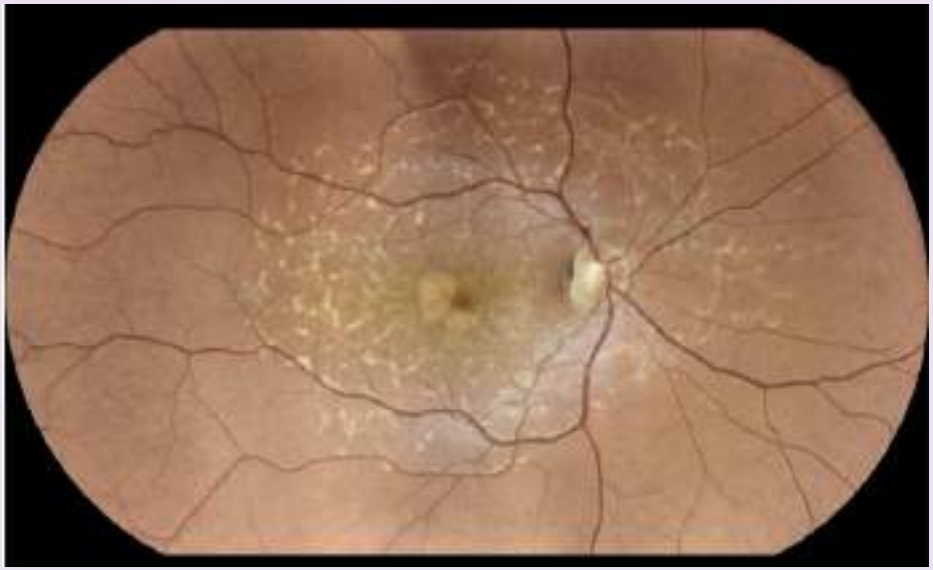


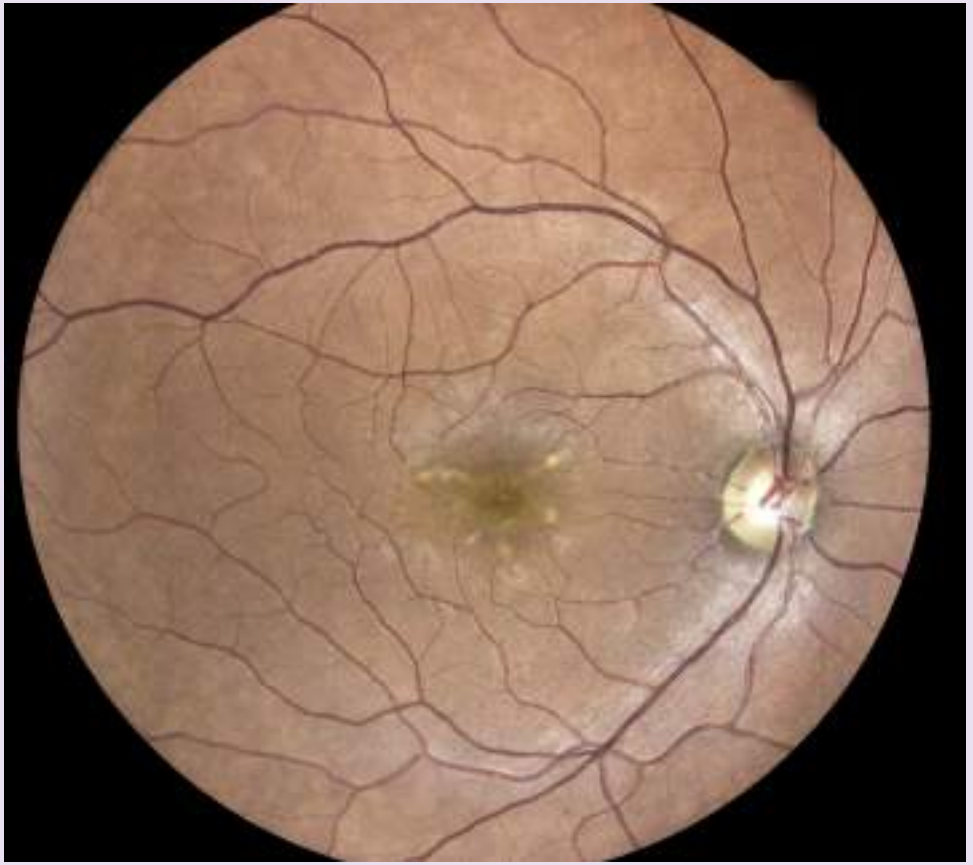
Differential Diagnosis:

1. Stargardt's Disease
2. Cone Dystrophy
3. Chloroquine Toxicity
4. Retinitis Pigmentosa?

Bull's Eye Maculopathy???

Stargardt's





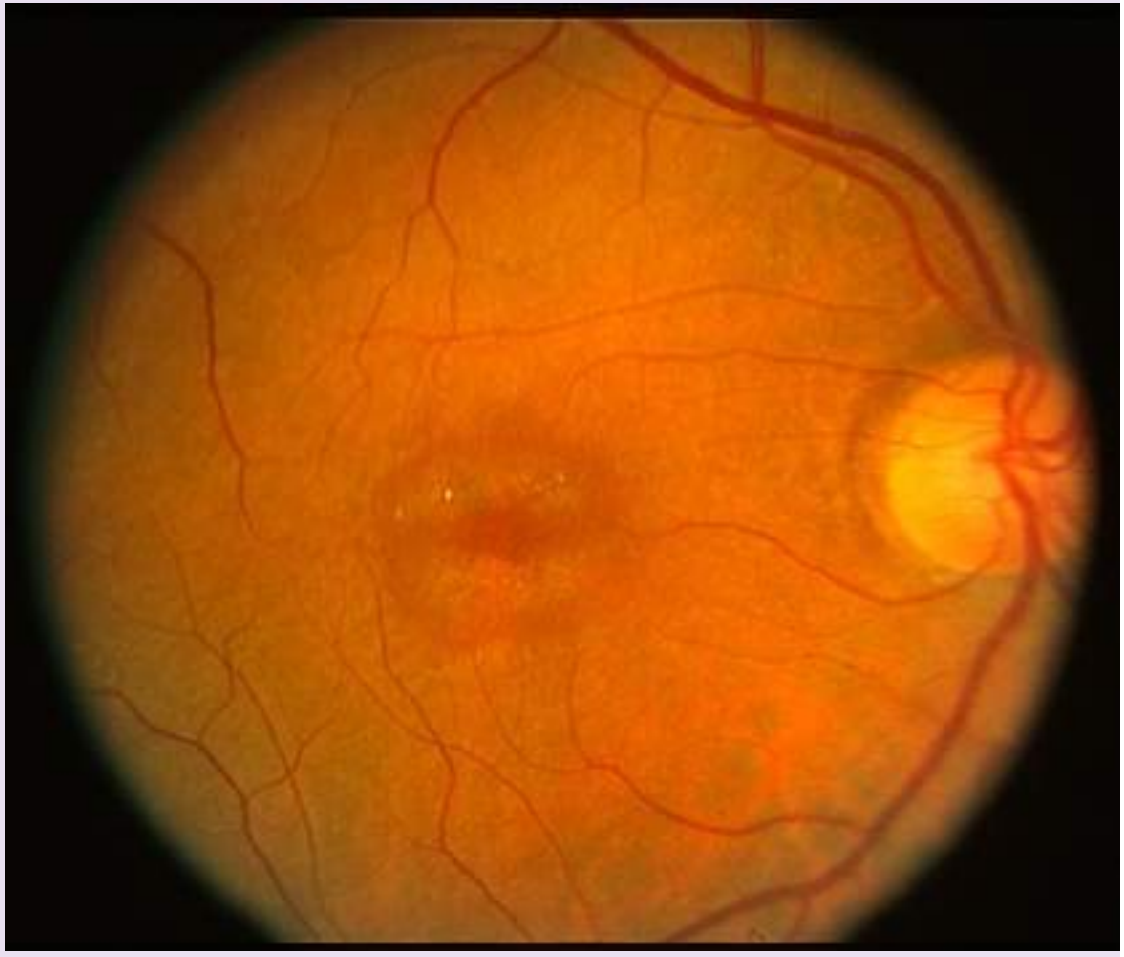
- Bilateral, decreased vision
  - Manifests in childhood or young adulthood
  - Vision loss precedes fundus findings
- Pisciform, "fish-tail" deposits
- Beaten-metal, bull's eye appearance at macula

Images courtesy of iCare

Bull's Eye Maculopathy???

Cone Dystrophy

- Slowly progressive bilateral visual loss
- Poor color vision and DAY vision
- Abnormal cone-function on ERG
- Normal fundus early with poor VA
- Bull's eye maculopathy (later)

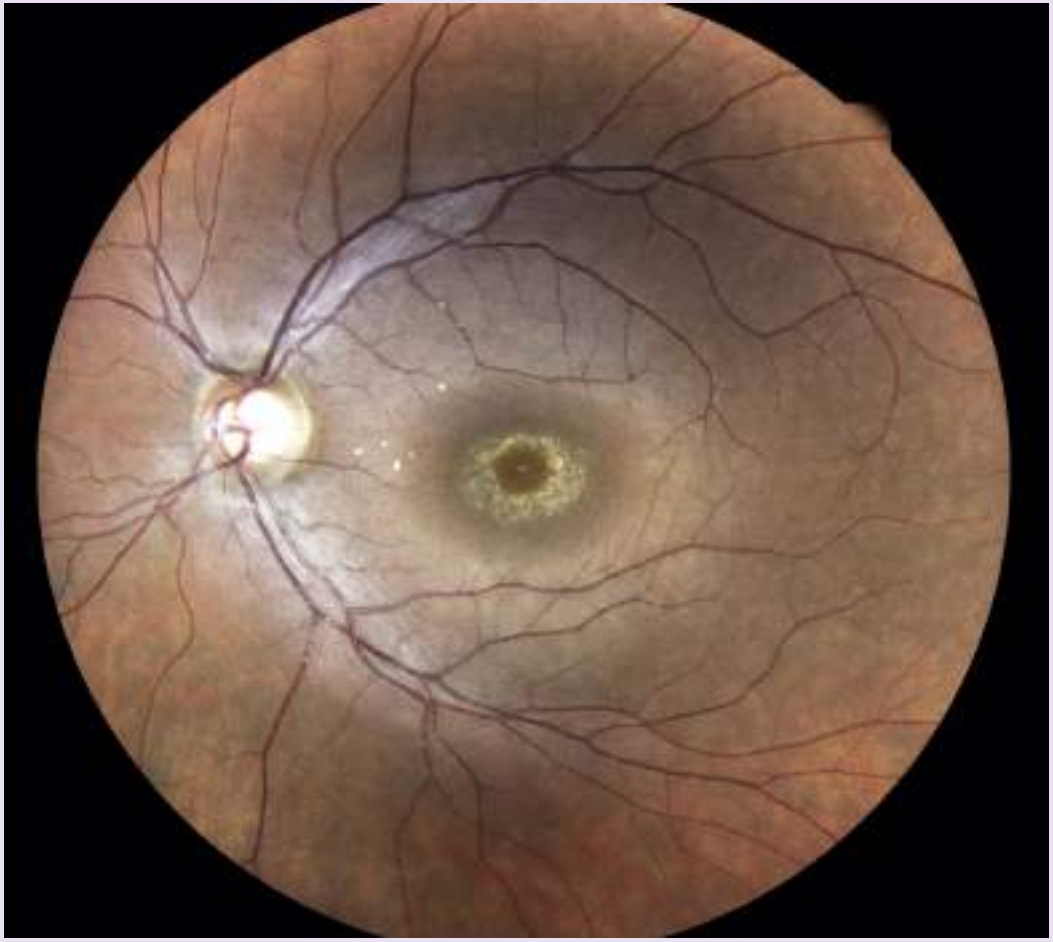


Bull's Eye Maculopathy???

Chloroquine Toxicity

- Decreased vision
- Poor color vision
- Bull's eye macula

- H/O chloroquine use!



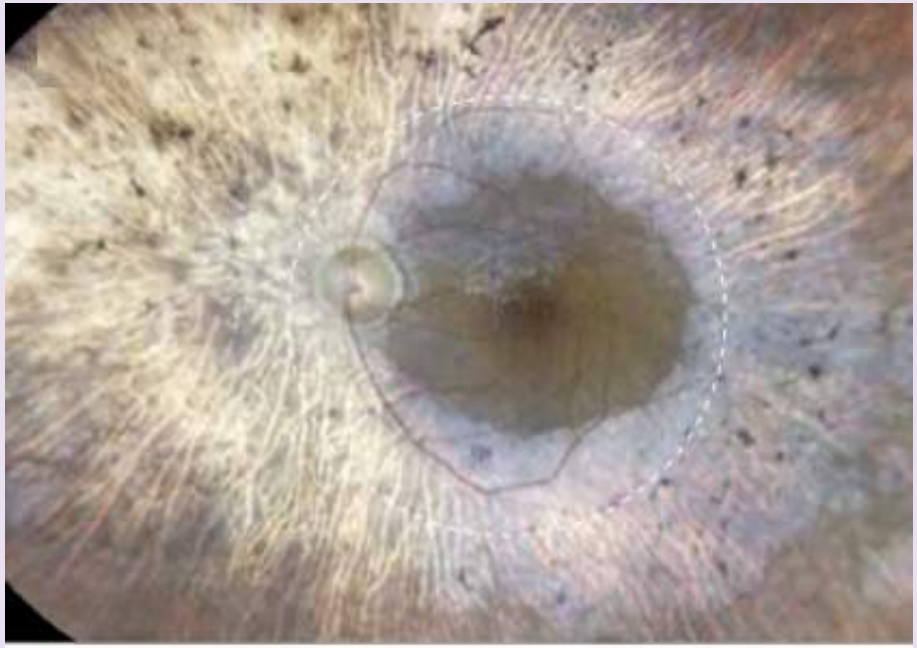
Images courtesy of iCare

Bull's Eye Maculopathy???

Retinitis Pigmentosa

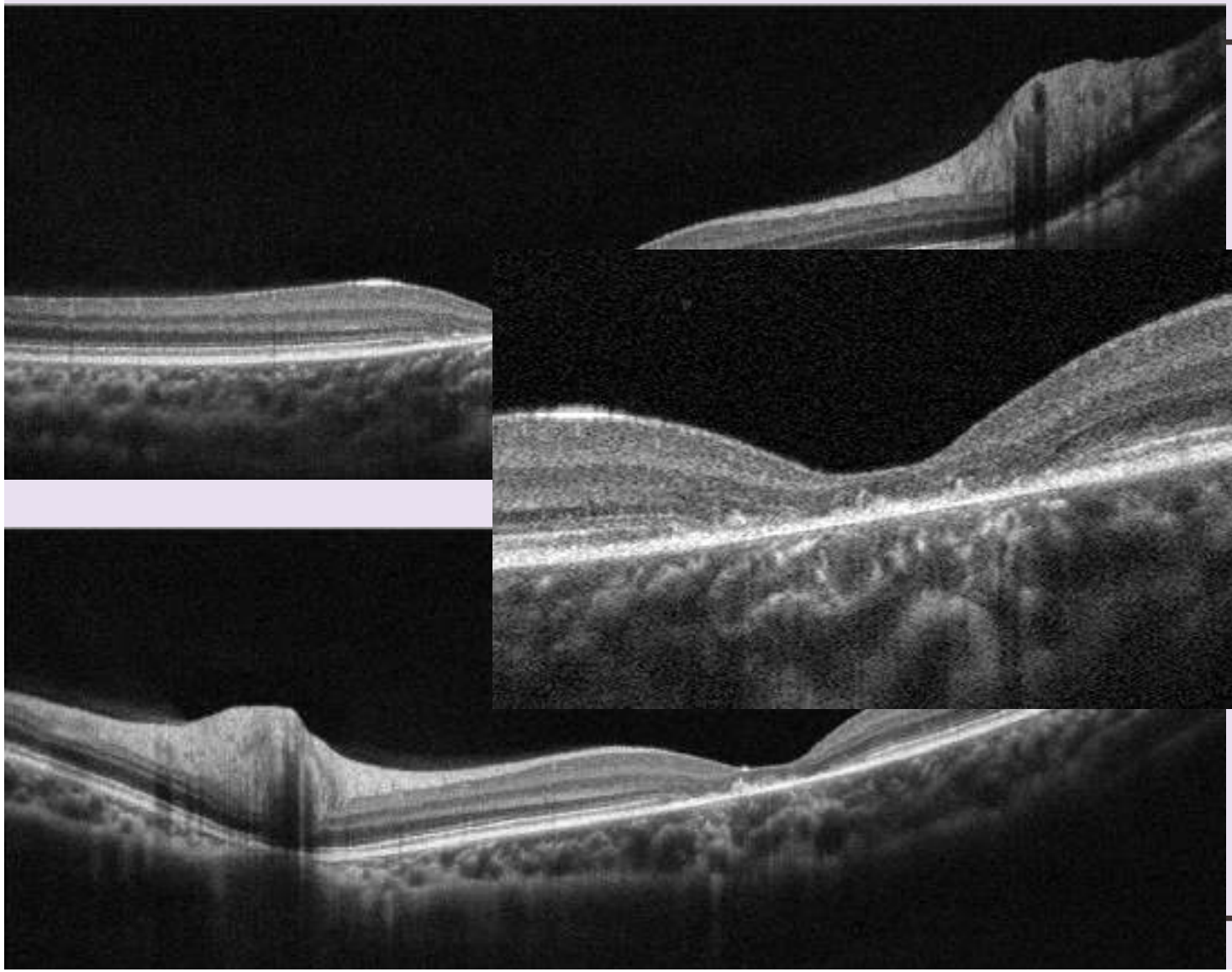
- Difficulty with night vision
- Loss of peripheral vision
- Poor central vision/CV late findings

- Waxy ONH pallor
- Arteriolar attenuation
- Bone spicules
- ERG reduced

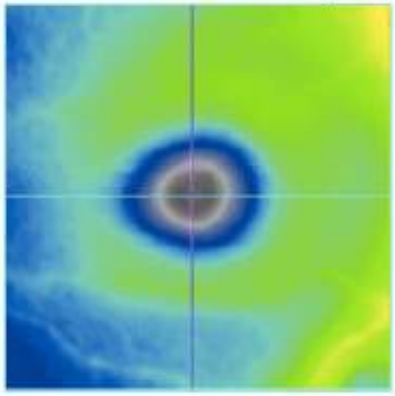


Images courtesy of iCare

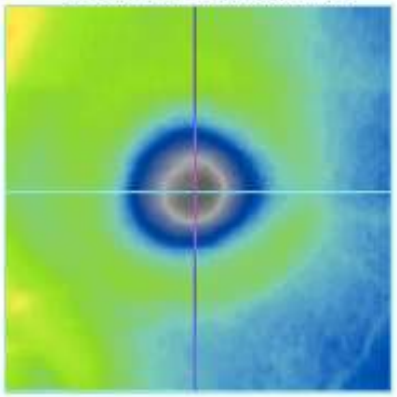
Ancillary Testing: OCT



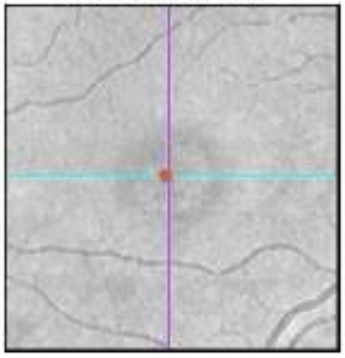
OD ILM-RPE Thickness Map



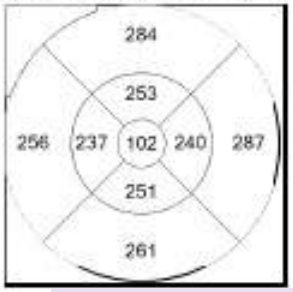
OS ILM-RPE Thickness Map



OD OCT Fundus

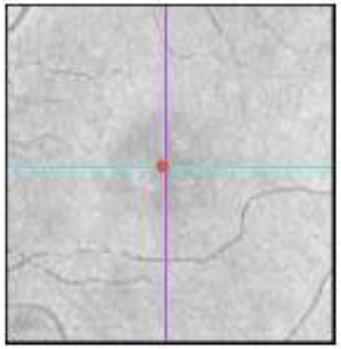


OD ILM-RPE Thickness

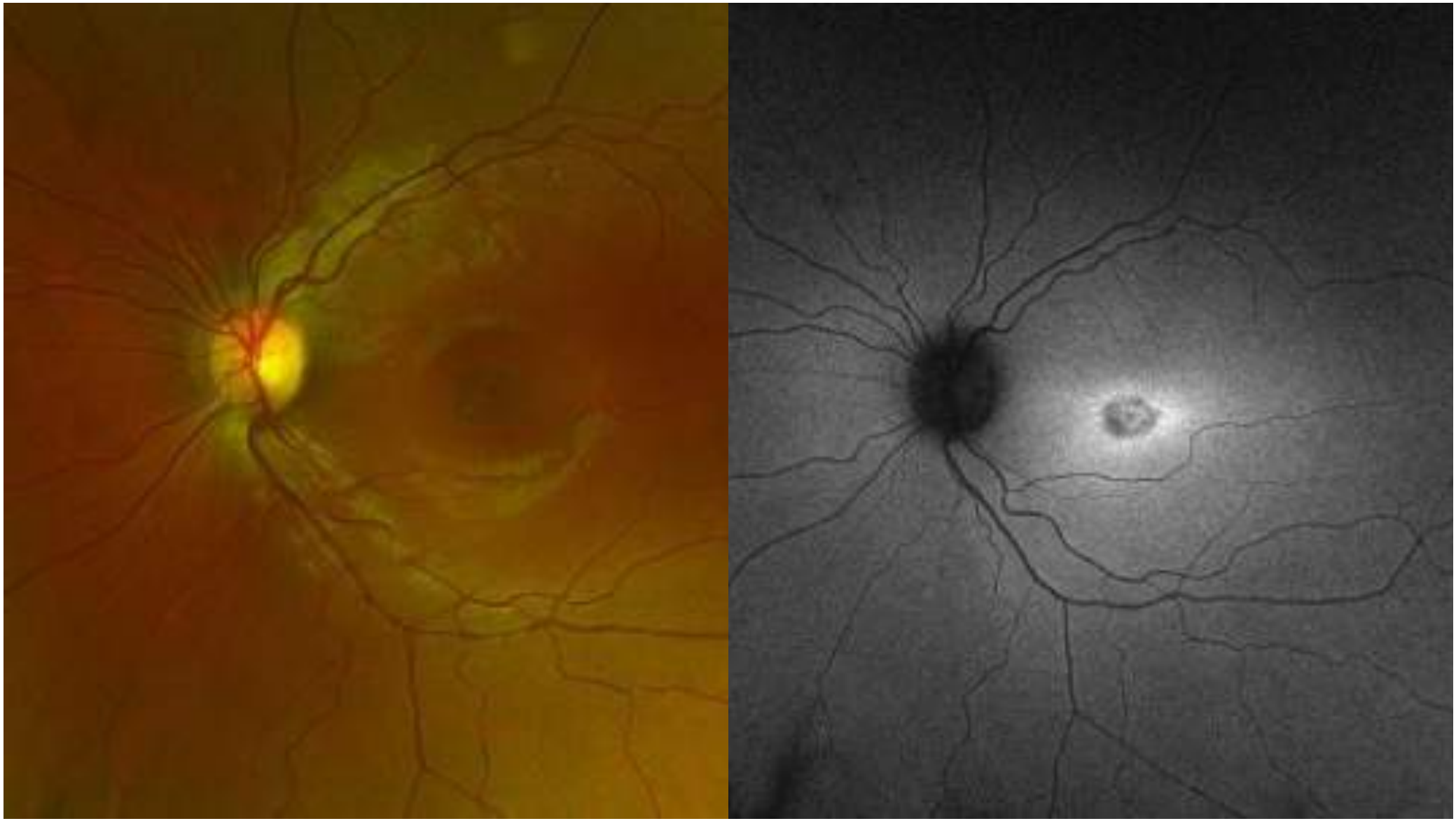


OS ILM-RPE Thickness

OS OCT Fundus

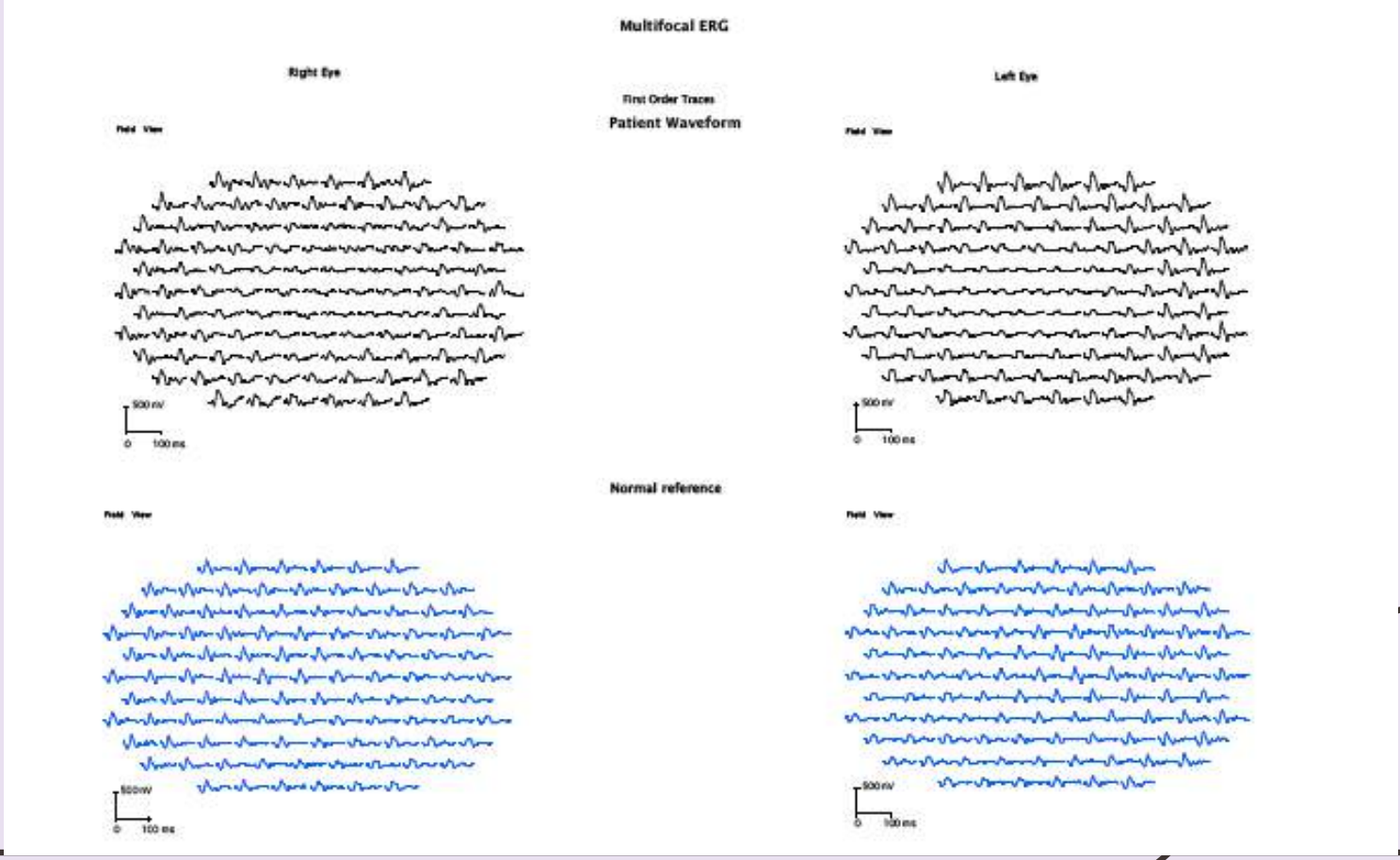


Ancillary Testing:
Fundus Autofluorescence



Electrodiagnostics: mfERG

The mfERG findings show moderate diffuse cone dysfunction in the macula area of the right and left eyes.



Electrodiagnostics: mfERG

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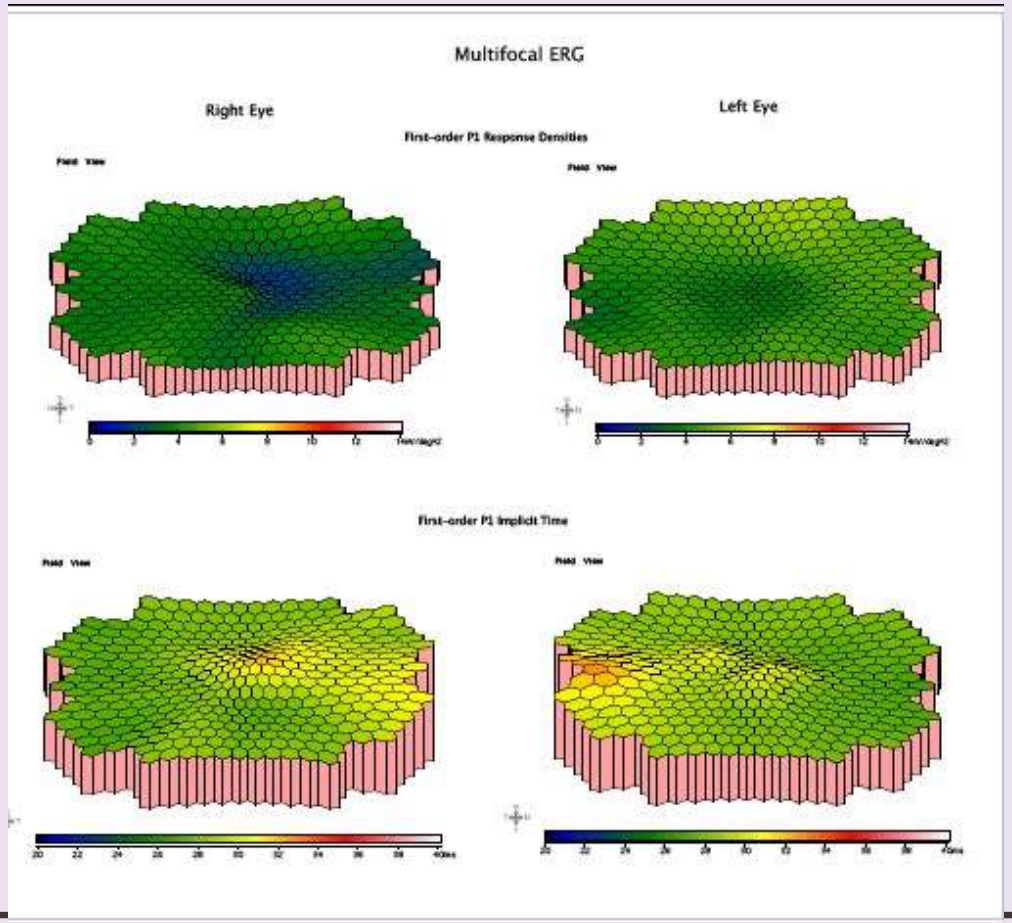


What is this??...13 y/o... we need help!!

INVITAE

INVITAE DIAGNOSTIC TESTING RESULTS

Patient name:	[redacted]	**Sample type:**	Saliva	**Report date:**	11/08/2021
DOB:	09/29/2008	**Sample collection date:**	10/12/2021	**Invitae #:**	RQ2834631
Sex assigned at birth:	Female	**Sample accession date:**	10/23/2021	**Clinical team:**	Julie Rodman
Gender:		**MRN:**			

Reason for testing

Test performed

Sequence analysis and deletion/duplication testing of the 328 genes listed in the Genes Analyzed section.

- Invitae Inherited Retinal Disorders Panel

RESULT: CARRIER

One Pathogenic variant identified in EYS. EYS is associated with autosomal recessive retinitis pigmentosa.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
EYS	c.6794del (p.Pro2265Glnfs*46)	heterozygous	PATHOGENIC
ABCA4	c.2161-6T>C (Intronic)	heterozygous	Uncertain Significance
BBS1	c.1076G>A (p.Arg359His)	heterozygous	Uncertain Significance
COL11A2	c.2682G>A (Silent)	heterozygous	Uncertain Significance
PDE6A	c.916A>G (p.Arg306Gly)	heterozygous	Uncertain Significance
PDZD7	c.244G>A (p.Asp82Asn)	heterozygous	Uncertain Significance
PEX6	c.1081A>G (p.Thr361Ala)	heterozygous	Uncertain Significance
RP1	c.4397A>T (p.Glu1466Val)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 328 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Clinical summary

A Pathogenic variant, c.6794del (p.Pro2265GlnfsTer46), was identified in EYS.

- The EYS gene is associated with autosomal recessive retinitis pigmentosa (RP) (MedGen UID: 350427).
- This individual is a carrier for autosomal recessive EYS-related conditions. This result is insufficient to cause autosomal recessive EYS-related conditions; however, carrier status does impact reproductive risk.
- Retinitis pigmentosa (RP) is a genetically heterogeneous group of inherited eye disorders characterized by progressive degeneration of the retina, typically beginning in the midperiphery and advancing toward the macula and fovea (PMID: 17296890). Abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) lead to progressive visual loss (PMID: 26835369, 26108463). Typical symptoms include night blindness followed by constriction of peripheral visual fields, which leads to tunnel vision and eventually loss of central vision (PMID: 17296890). RP is highly variable in regards to severity, clinical symptoms, and age of onset (PMID: 17296890).
- Biological relatives have a chance of being a carrier for or being at risk for autosomal recessive EYS-related conditions. Testing should be considered if clinically appropriate. The chance of having a child with autosomal recessive EYS-related conditions depends on the carrier state of this individual's partner.

autosomal recessive retinitis pigmentosa (RP)

A Variant of Uncertain Significance, c.2161-6T>C (Intronic), was identified in ABCA4.

- The ABCA4 gene is associated with autosomal recessive cone-rod dystrophy (CRD) (MedGen UID: 349030), Stargardt disease (STGD) (MedGen UID: 383681), and retinitis pigmentosa (RP) (MedGen UID: 400996). Additionally, there is preliminary evidence supporting a correlation with autosomal dominant age-related macular degeneration (ARMD) (PMID: 16880298).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

autosomal recessive cone-rod dystrophy

A Variant of Uncertain Significance, c.1076G>A (p.Arg359His), was identified in BBS1.

- The BBS1 gene is associated with autosomal recessive Bardet-Biedl syndrome (MedGen UID: 422452) and non-syndromic retinitis pigmentosa (PMID: 23143442, 27032808, 21520335).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.2682G>A (Silent), was identified in COL11A2.

- The COL11A2 gene is associated with a spectrum of related autosomal recessive conditions including nonsyndromic deafness (MedGen UID: 400602), otospondylomegaepiphyseal dysplasia (OSMED) (MedGen UID: 1617409), and fibrochondrogenesis (MedGen UID: 479768). COL11A2 is also associated with a spectrum of related autosomal dominant conditions including Stickler syndrome III (MedGen UID: 349293 and 120521), OSMED (also known as Weissenbacher-Zweymüller syndrome; MedGen UID: 341234) and nonsyndromic deafness (MedGen UID: 400917).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

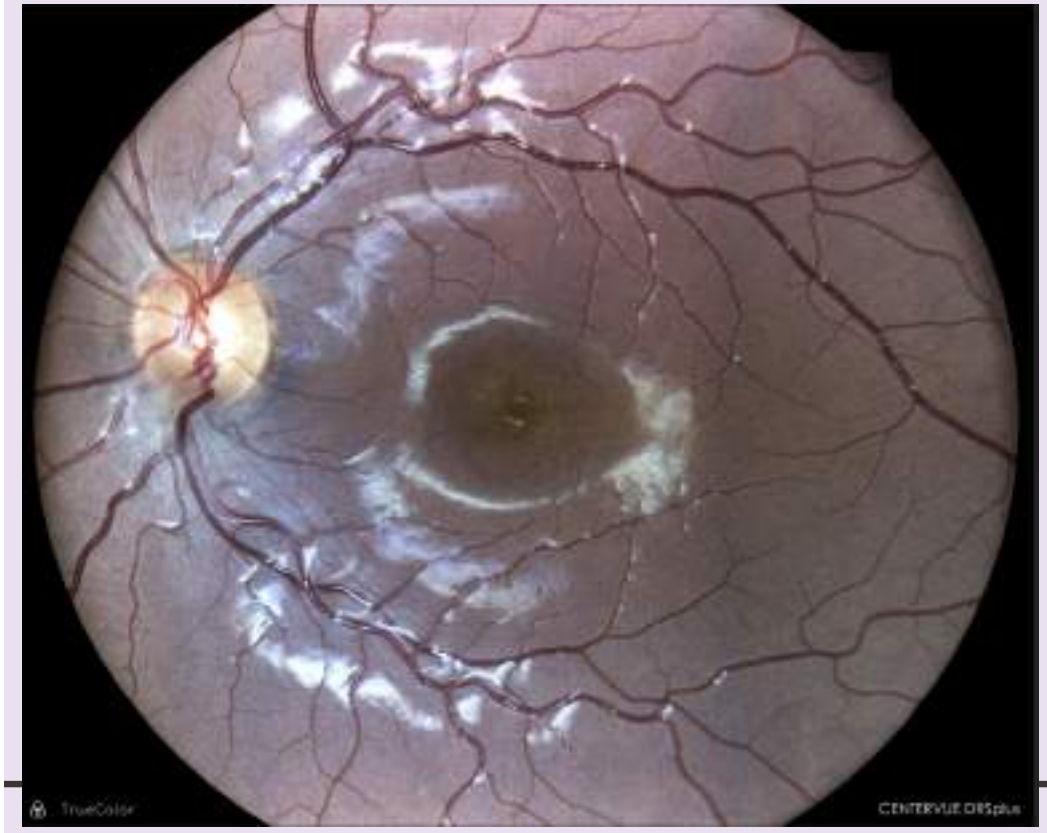
autosomal recessive Bardet-Biedl syndrome

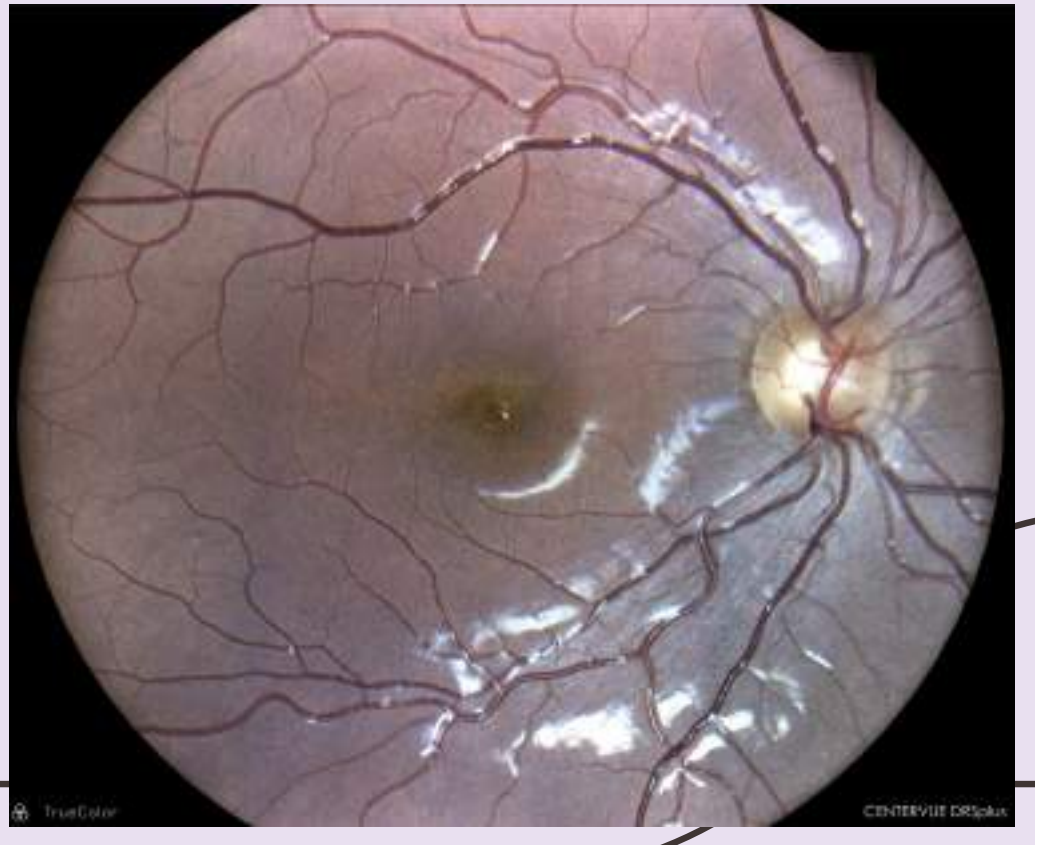
A Variant of Uncertain Significance, c.916A>G (p.Arg306Gly), was identified in PDE6A.

- The PDE6A gene is associated with autosomal recessive retinitis pigmentosa (MedGen UID: 462489). Additionally, the PDE6A gene has preliminary evidence supporting a correlation with autosomal dominant periventricular nodular heterotopia (PMID: 29738522).

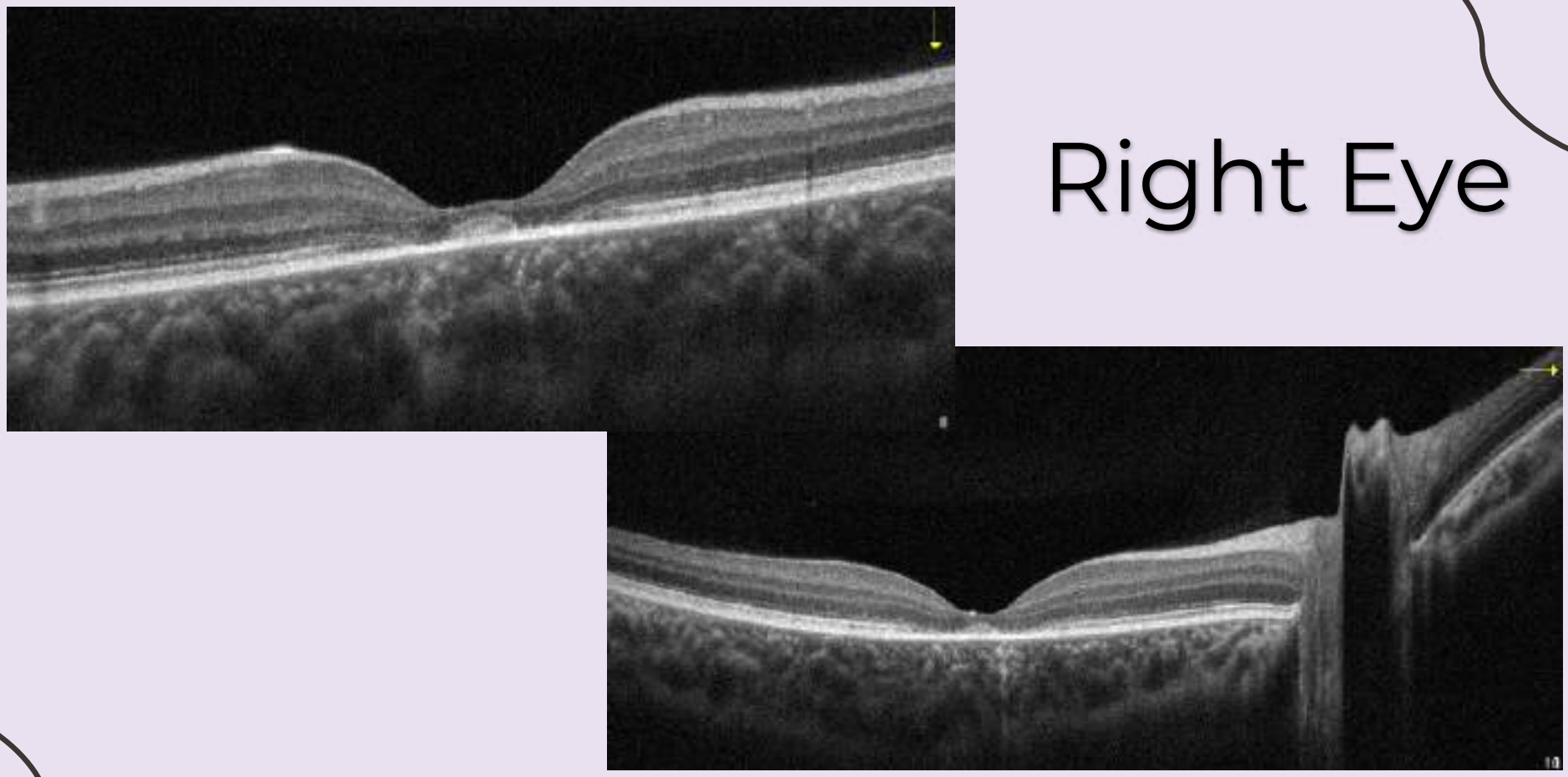
But that's not all!!!!!

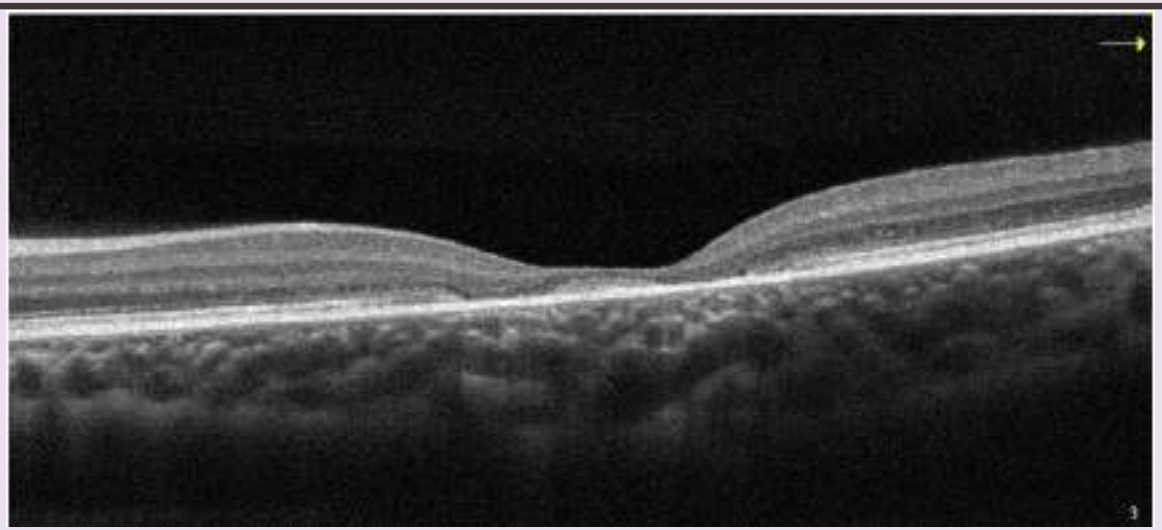
13-year-old twin sister with NORMAL vision came in for an exam also



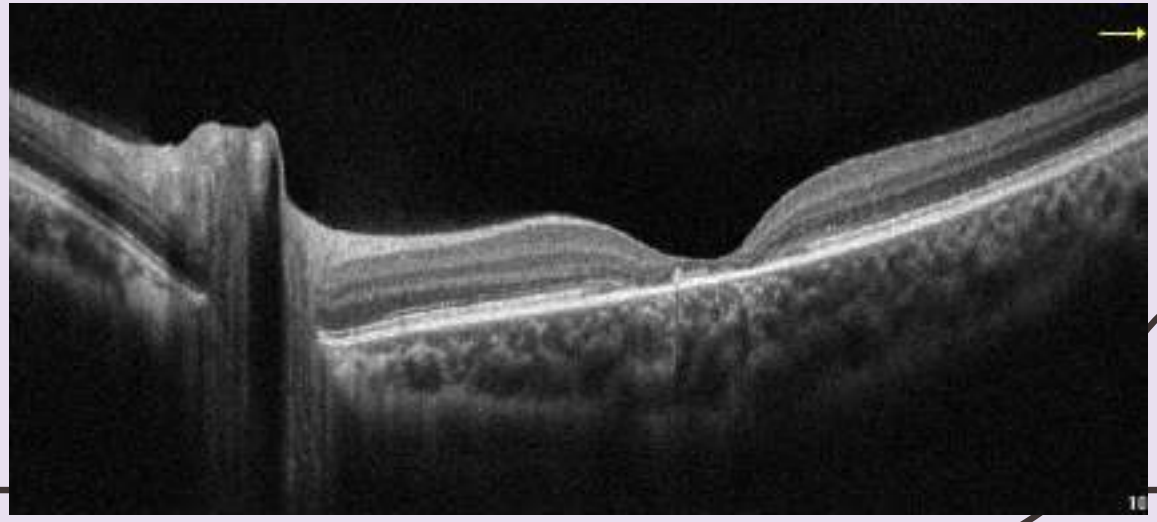


Right Eye

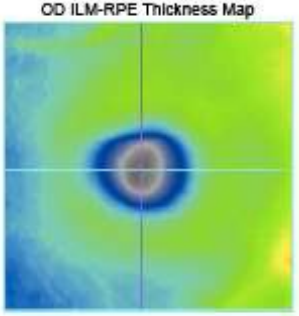


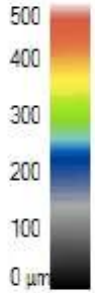


Left Eye

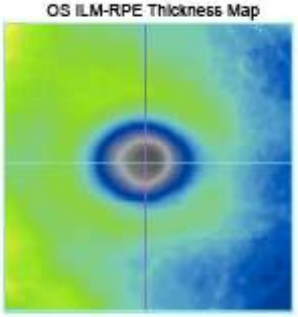


OD ILM-RPE Thickness Map





OS ILM-RPE Thickness Map

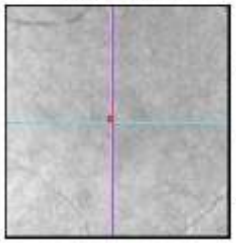


Fovea: 244, 66

Fovea: 253, 62

Normative data is not available. Patient age < 18.

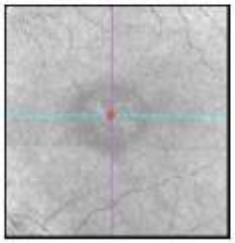
OD OCT Fundus



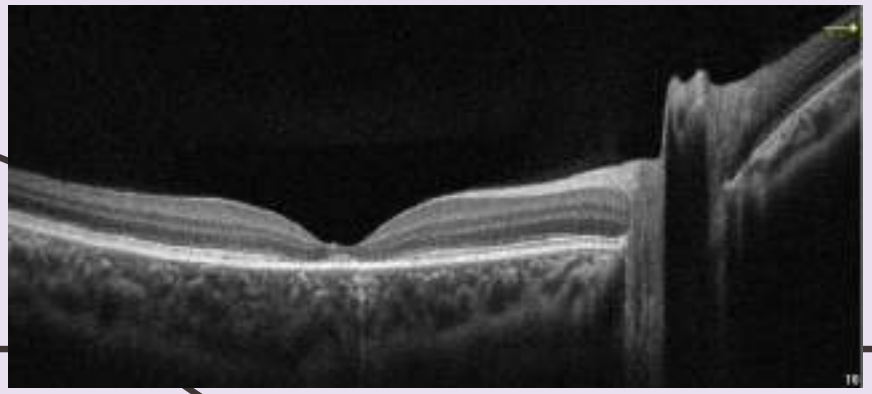
OD ILM-RPE Thickness

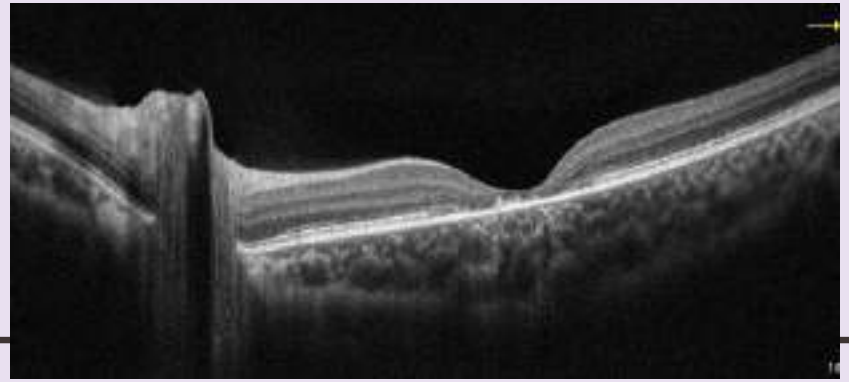
OS ILM-RPE Thickness

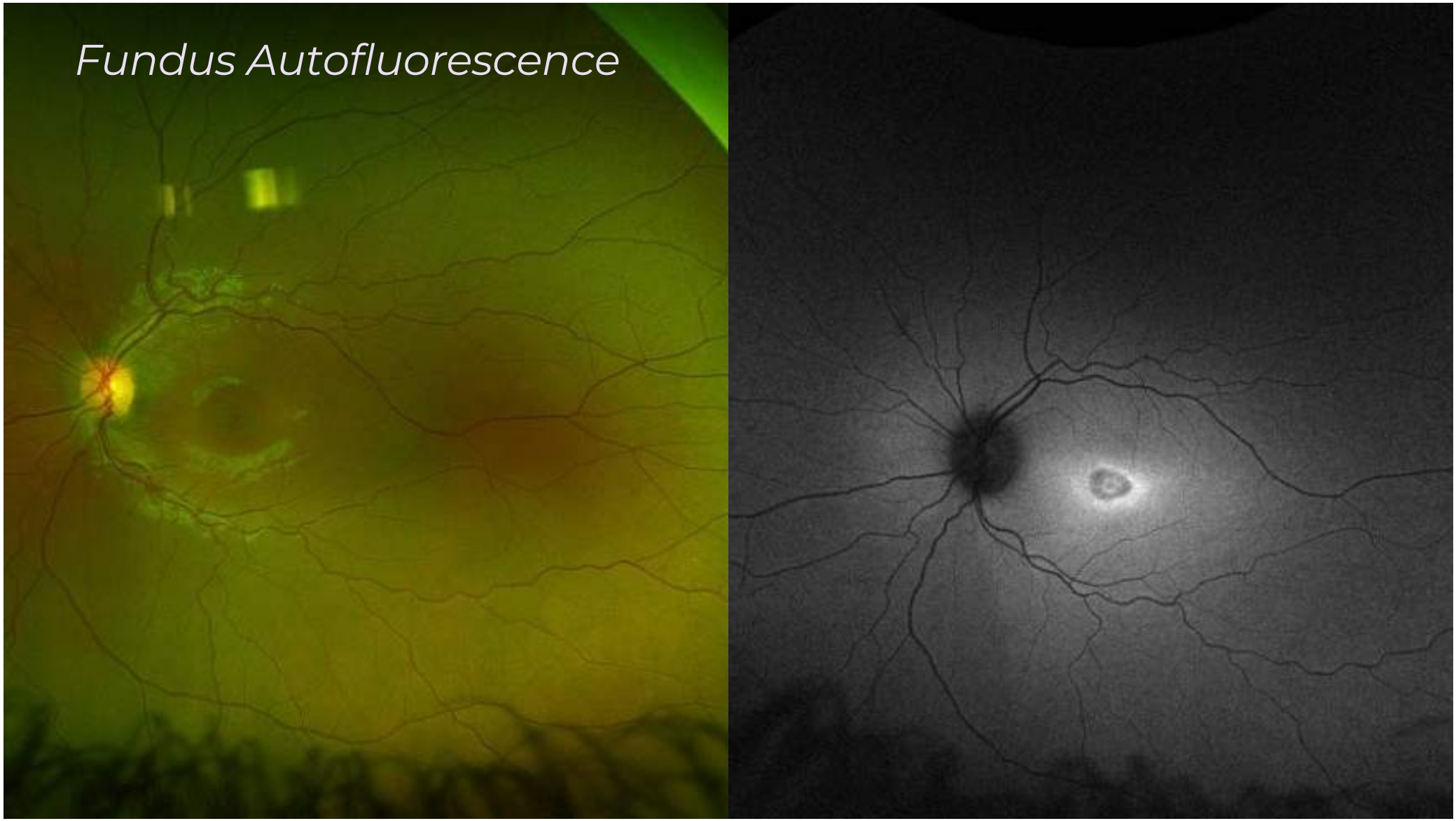
OS OCT Fundus



ILM - RPE	OD	OS
Thickness Central Subfield (µm)	117	107
Volume Cube (mm³)	9.8	9.5
Thickness Avg Cube (µm)	272	263

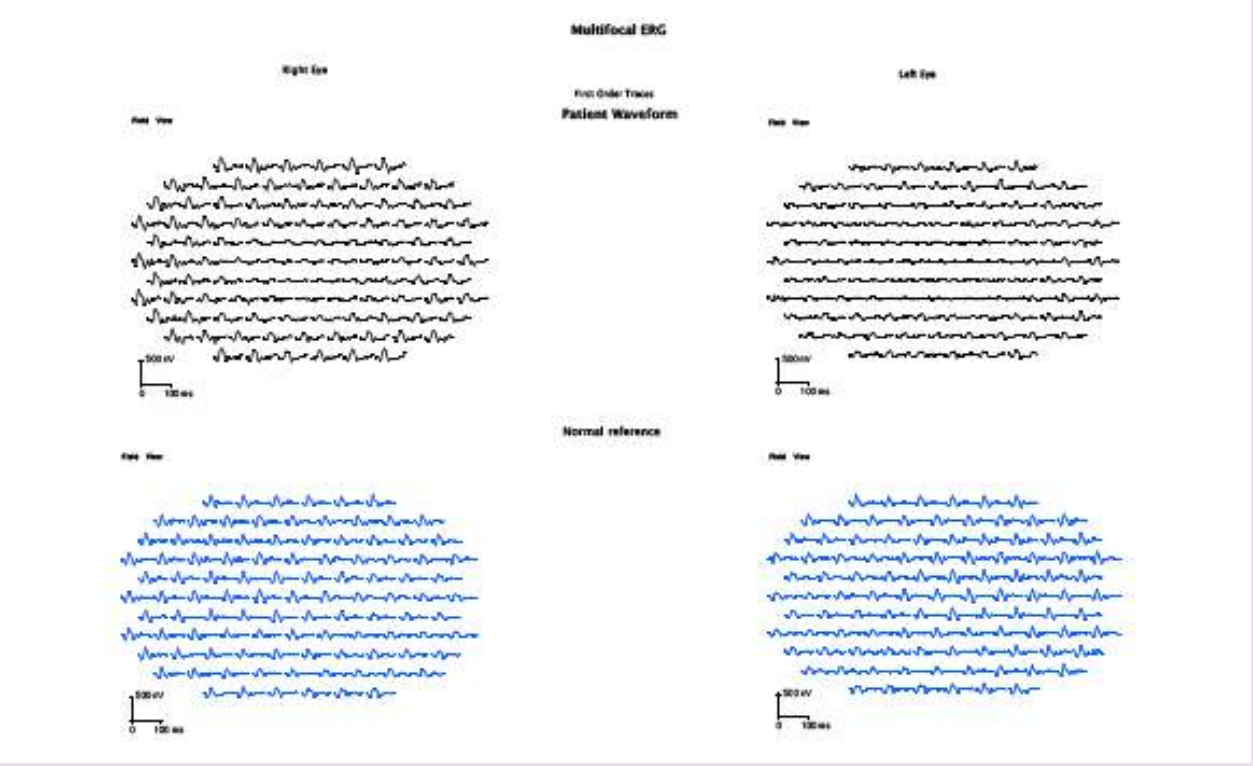





Fundus Autofluorescence

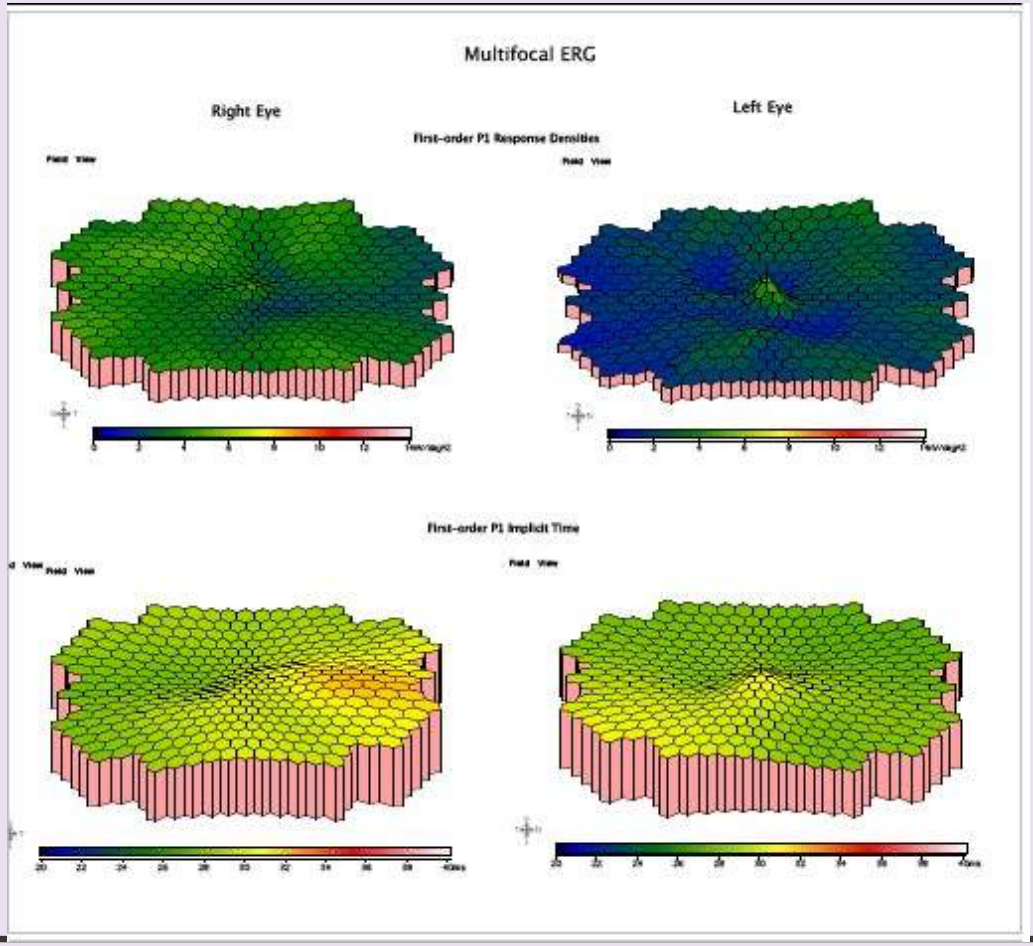
Electrodiagnostics: mfERG

The mfERG findings show moderate diffuse cone dysfunction in the macula area of the right and left eyes.



Electrodiagnostics: mfERG

The mfERG findings show moderate diffuse cone dysfunction in the macula area of the right and left eyes.



RESULT: CARRIER

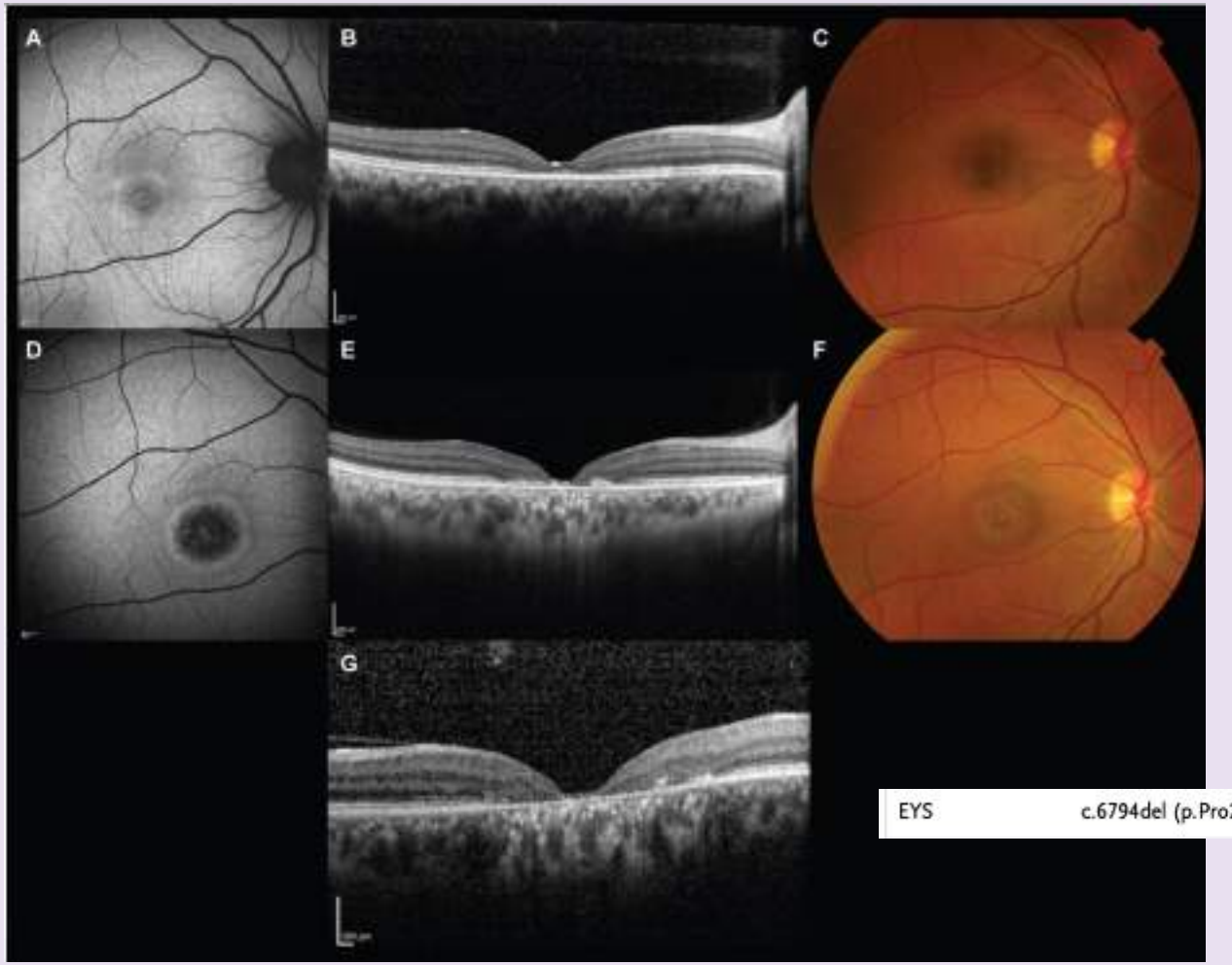
One Pathogenic variant identified in EYS. EYS is associated with autosomal recessive retinitis pigmentosa.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
EYS	c.6794del (p.Pro2265Glnfs*46)	heterozygous	PATHOGENIC
ABCA4	c.2161-6T>C (Intronic)	heterozygous	Uncertain Significance
BBS1	c.1076G>A (p.Arg359His)	heterozygous	Uncertain Significance
COL11A2	c.2682G>A (Silent)	heterozygous	Uncertain Significance
PDE6A	c.916A>G (p.Arg306Gly)	heterozygous	Uncertain Significance
PDZD7	c.244G>A (p.Asp82Asn)	heterozygous	Uncertain Significance
PEX6	c.1081A>G (p.Thr361Ala)	heterozygous	Uncertain Significance
RP1	c.4397A>T (p.Glu1466Val)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 330 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.



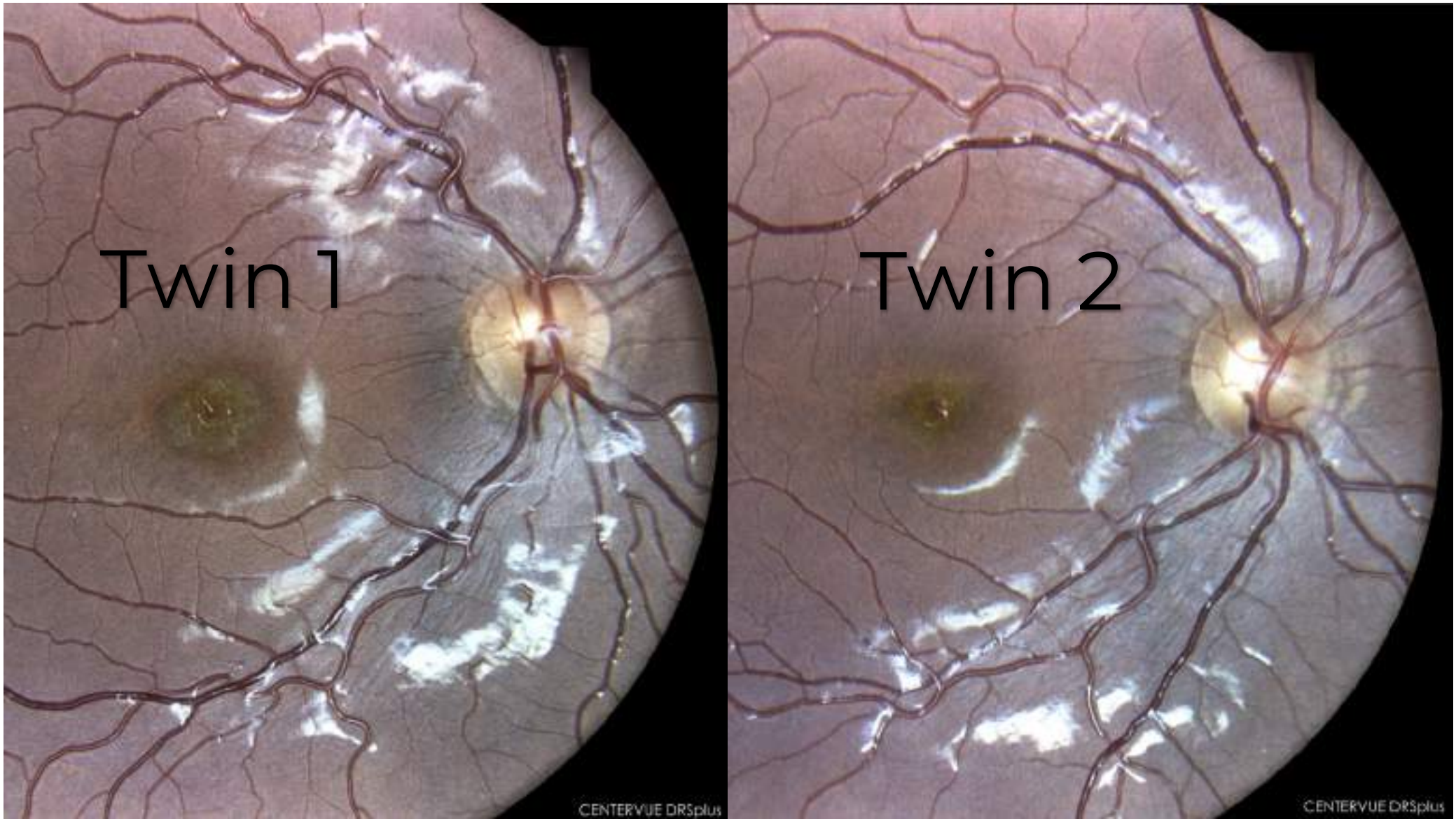
EYS mutations are one of the most common causes of autosomal recessive retinitis pigmentosa in Asia and Europe.

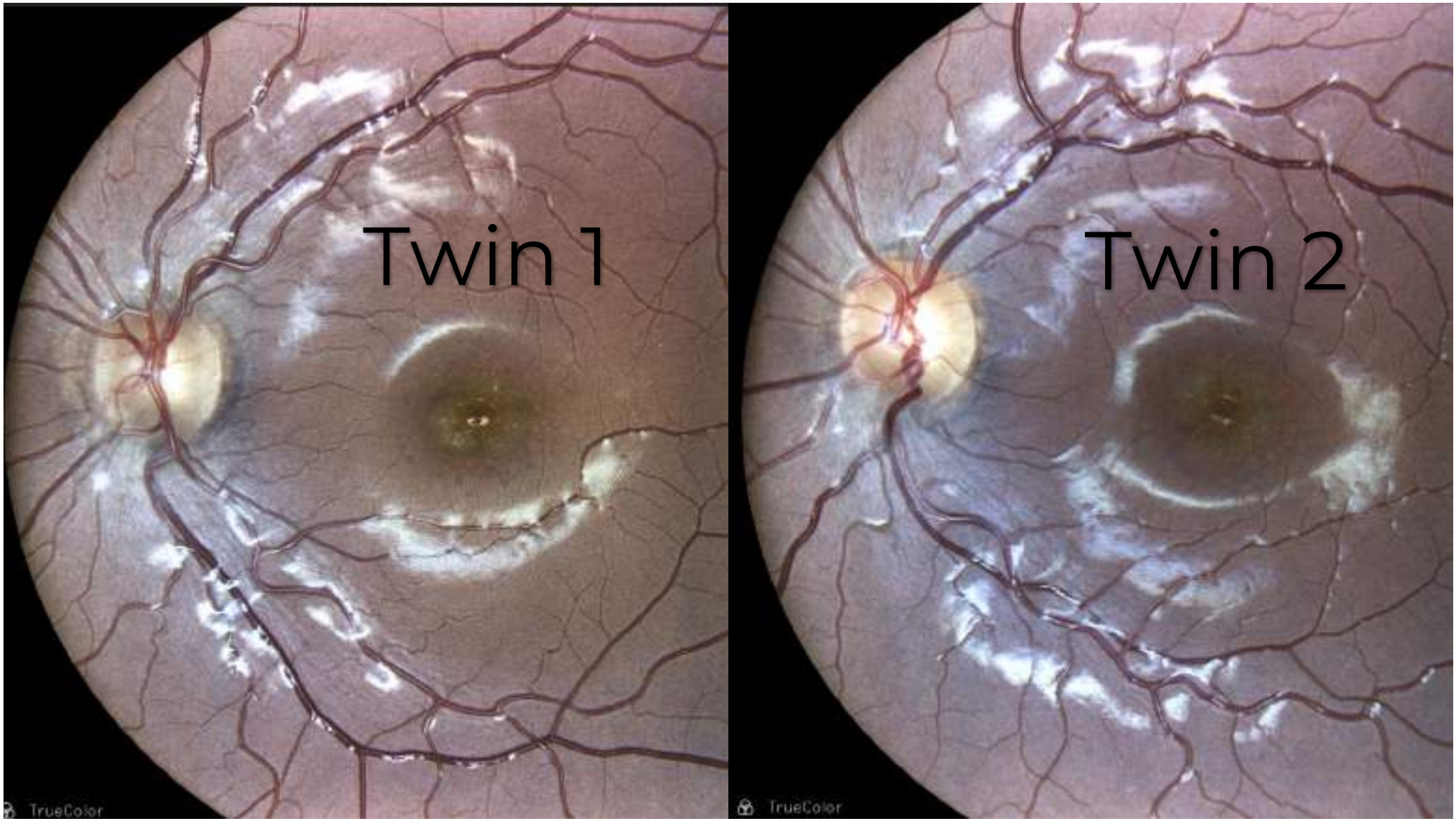
Novel findings include the presence of homozygous *EYS* mutations in Cone Rod Dystrophy patients and compound heterozygous *EYS* mutations in patients with macular dystrophy.

EYS	c.6794del (p.Pro2265Glnfs*46)	heterozygous	PATHOGENIC

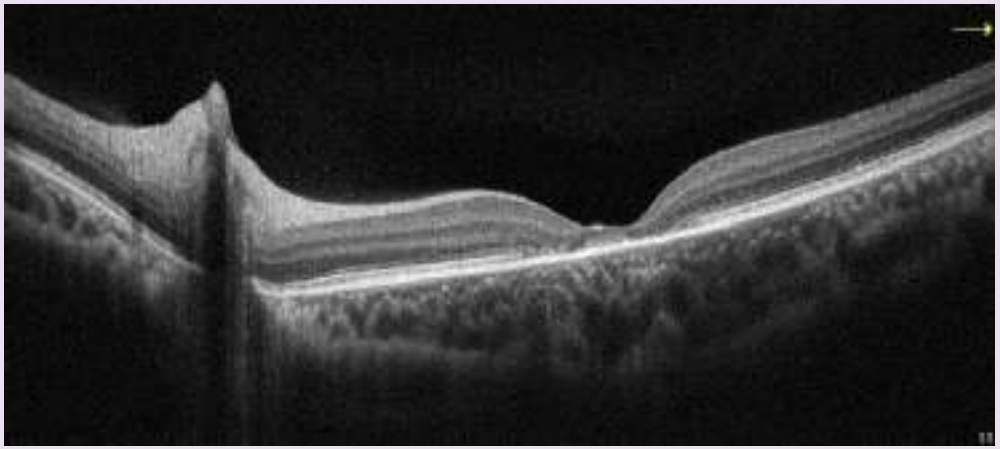
Disease progression of EYS-associated macular dystrophy

Comparison Between Twins

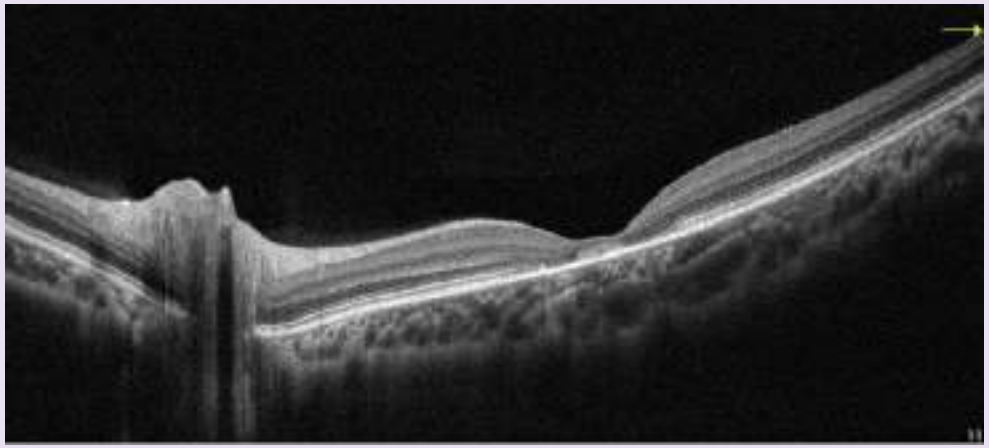

Twin 1
Twin 2
CENTERVUE DRSplus
CENTERVUE DRSplus


Twin 1
Twin 2
TrueColor
TrueColor

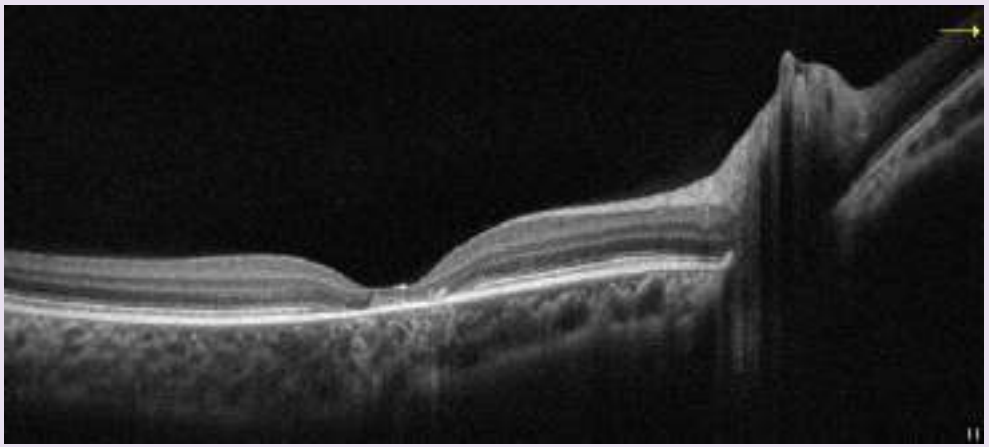
Twin 1



Twin 2



Twin 1



Twin 2