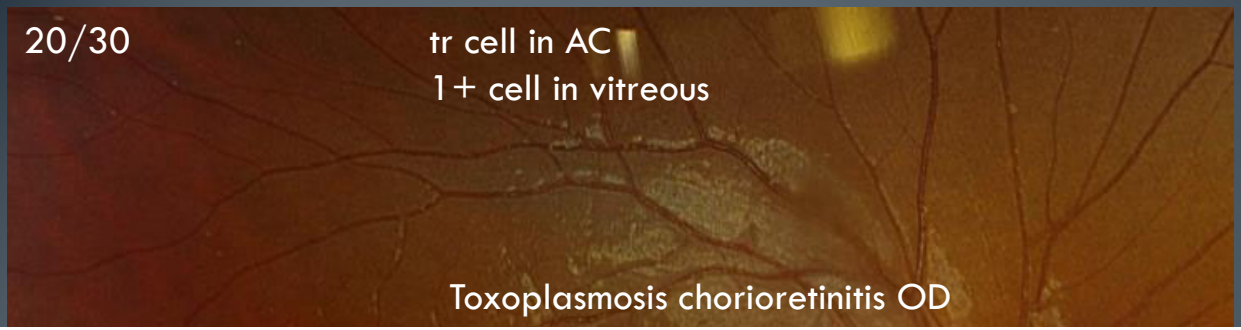
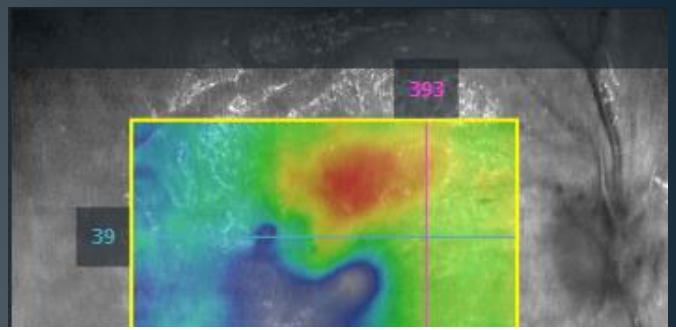
Infectious (vs noninfectious) uveitis

Phoebe Lin, MD, PhD
Uveitis and vitreoretinal surgery
Cole Eye Institute, Cleveland Clinic

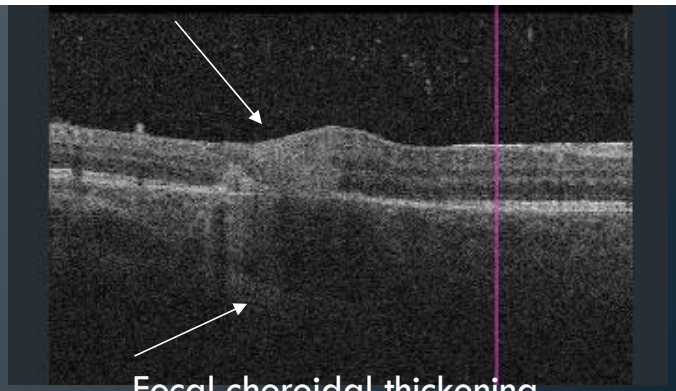
12 year old healthy F eats raw lamb (delicacy)





Component Ref Range & Units	10 d ago
Toxo IgM Qual Negative	Negative
Comment: No serological evidence of recent exposure to Toxoplasma gondii.	
Toxo IgG Qual Negative	Positive !
Comment: The result suggests recent or past infection with Toxoplasma gondii. The final interpretation should be done in conjunction with T. gondii IgM result and clinical correlation.	

Other eye normal

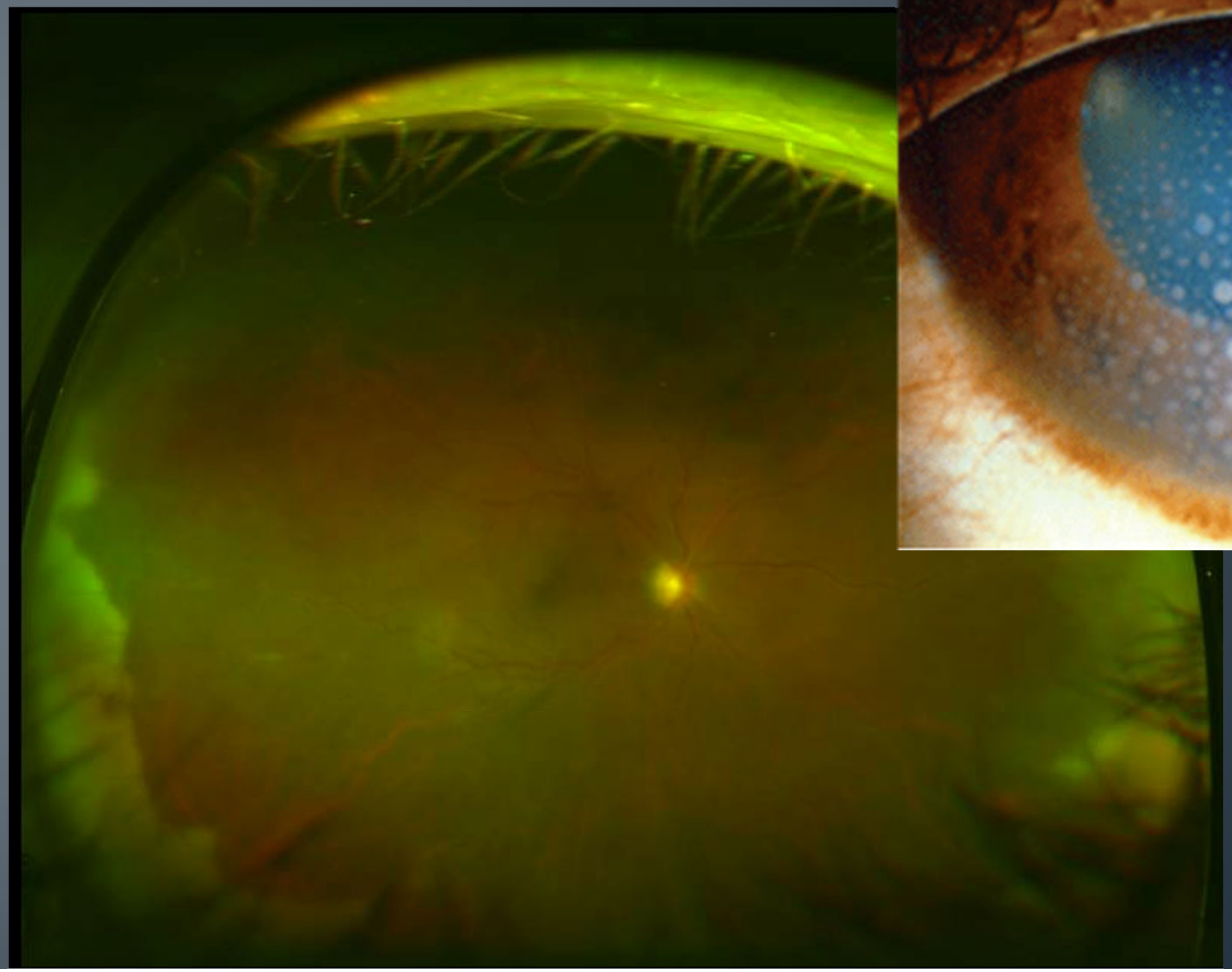


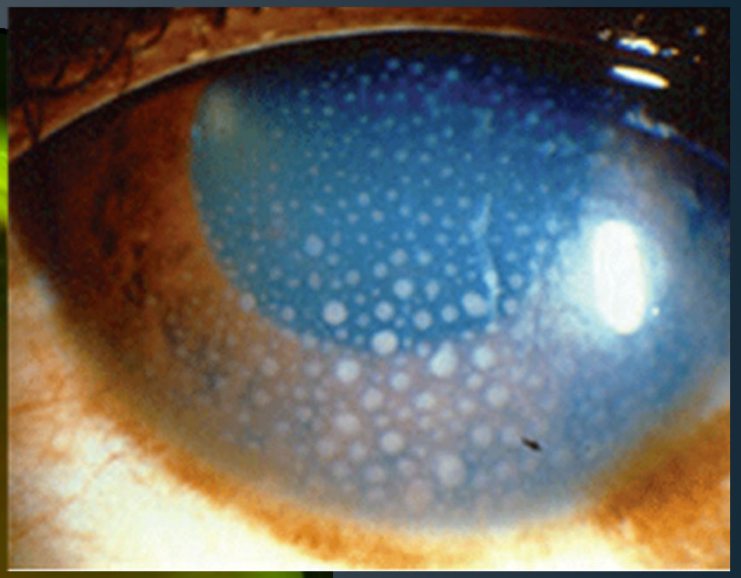
Focal choroidal thickening

42 y/o F with decreased vision OD x 2 weeks, referred for optic neuritis, consider admission for IV steroids (34 wks pregnant)

3+ anterior chamber cell
Optic nerve edema
2+ anterior vitreous cell
1+ vitreous haze

20/400 OD (nL OS)





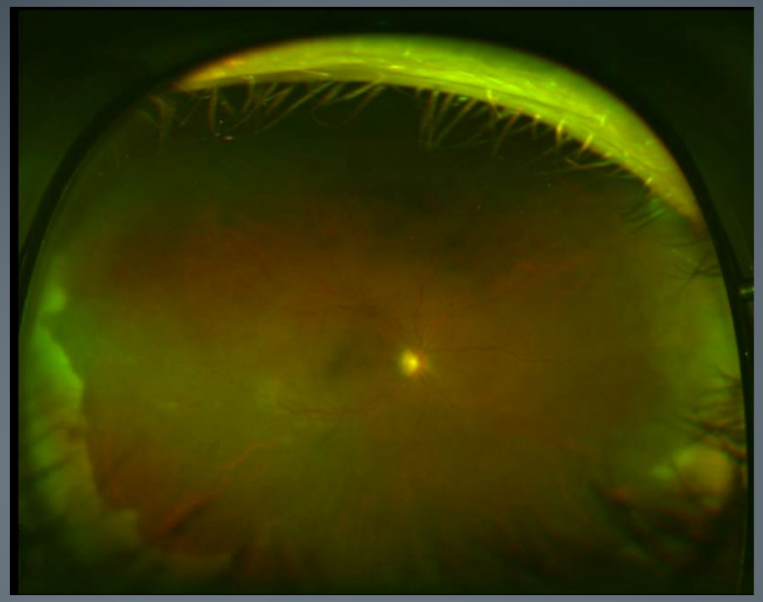
American Uveitis Society Criteria for Acute Retinal Necrosis

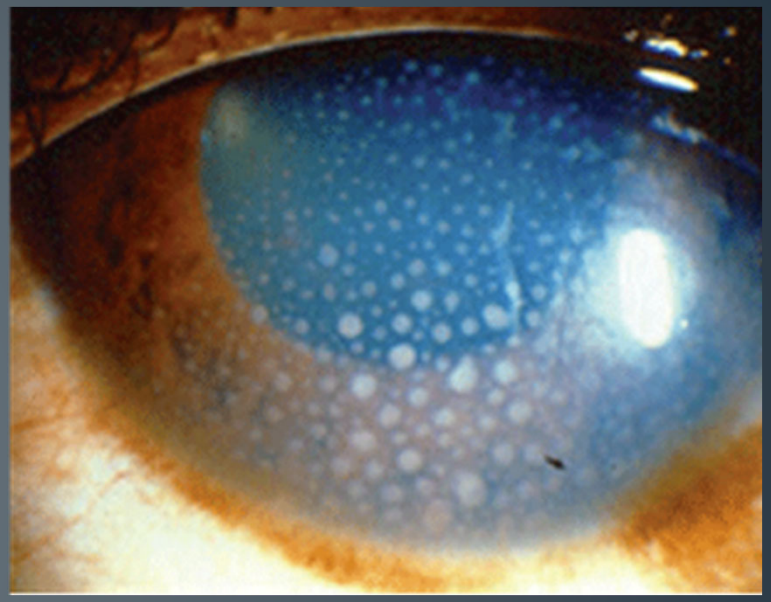
- One or more foci of retinal necrosis with discrete borders, usually located in peripheral retina Rapid progression in absence of antiviral therapy
- Circumferential spread
- Occlusive vasculopathy with arteriolar involvement
- Prominent vitritis, anterior chamber inflammation
- Optic neuropathy/atrophy, scleritis

50% due to VZV

AJO 1994;117:663-667

Back to our 42 y/o pregnant patient…





- Vitreous tap: VZV+ 800,000,000 copies/mL; CMV and HSV PCR negative
- Treated with Valtrex 2g PO TID + twice weekly intravitreal foscarnet injections

Treatment of viral retinitis

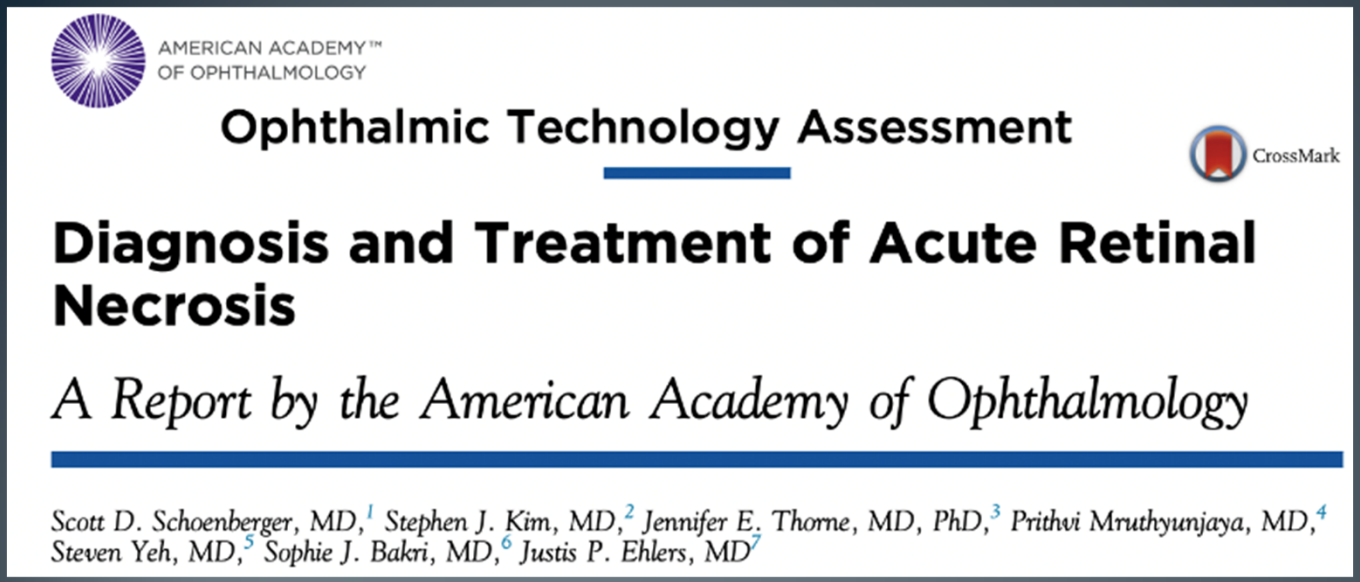
Table 1 Pharmacologic treatment of viral retinitis and uveitis

Drug	Route	Side effects	Viral coverage
Acyclovir *	Intravenous: 1500 mg/m^2/day divided Q8 h × 14 days followed by Oral: 800 mg five times a day for 6 weeks (also dose for viral anterior uveitis) Prophylactic dose: 400 mg PO BID-TID	GI symptoms, hypersensitivity reactions, renal or CNS dysfunction (requires renal dosing)	HSV-1, HSV-2, VZV, EBV ≫ CMV
Valacyclovir (prodrug)* Greater oral bioavailibility	Oral: 1 g (viral anterior uveitis)-2 g (viral retinitis) Q8 h × 6 weeks Prophylactic dose: 1 g PO BID	Similar to acyclovir	HSV-1, HSV-2, VZV ≫ CMV
Ganciclovir	Intravenous: 500 mg Q12 h × 14 days Intravitreal: 2–5 mg/0.1 mL, 3×/week Topical gel: 0.15 % Applied 4×/day × 3 months for CMV anterior uveitis Intravitreal surgical implant: lasts 8 months (no longer available)	Anemia, thrombocytopenia, granulocytopenia	HSV-1, CMV ≫ VZV, HSV-2
Valganciclovir	Oral: 900 mg BID × 3–6 weeks Prophylactic dose: 450 mg PO BID	HA, GI symptoms, bone marrow suppression, anemia, renal dysfunction	HSV-1, CMV ≫ VZV, HSV-2
Foscarnet	Intravenous: 40–60 mg/kg Q8 h × 3 weeks Intravitreal: 2.4 mg/0.1 mL every 3–4 days	HA, GI symptoms, renal or CNS toxicity uncommonly	HSV-1, HSV-2, VZV > CMV
Famciclovir (prodrug)	Oral: 500 mg Q8 h	HA, GI symptoms, rash	HSV-1 > HSV-2 > VZV

GI gastrointestinal, *HA* headache, *CNS* central nervous system, *PO* oral, *BID* twice daily, *TID* three times a day, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus

* Converted by viral thymidine kinase

Lin P Curr Ophthalmol Rep (2015) 3:170–183



Ophthalmology 2017 Mar;124(3):382-392

- Cochrane database search: 33 studies included, all retrospective
- Aqueous and vitreous PCR has good sensitivity and specificity for herpetic viral infection
- IV acyclovir or oral valacyclovir achieve equivalent plasma levels of acyclovir
- Level II and III evidence suggests that combination intravitreal foscarnet + systemic antivirals may have better therapeutic efficacy than systemic therapy alone

38 y/o F HIV+/CD4+ 30 cells/uL

20/20

HM

Bilateral CMV retinitis

CMV, QUALITATIVE BY PCR, NON-BLOOD (CSF, BONE MARROW, AMNIOTIC FLUID, OCULAR FLUID)

Status: **Final result** Dx: **Left retinitis**

Test Result Released: **Yes (seen)**

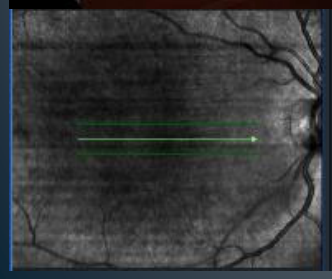
Specimen Information: **Eye, Left; Sterile Fluid/Body Fluid**

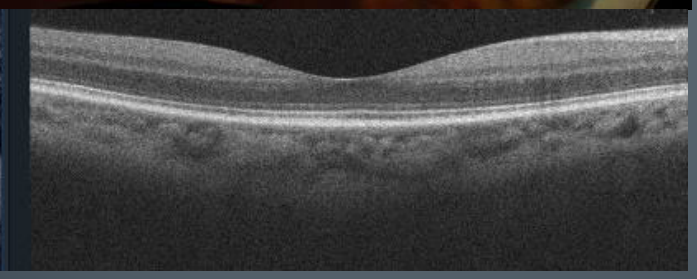
0 Result Notes

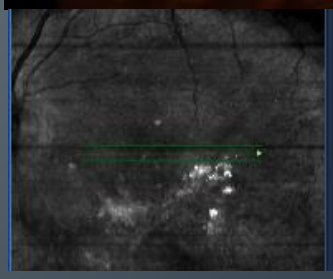
Component	1 mo ago
Specimen Source (CMVCSF)	left eye aqueous
Cytomegalovirus DNA	**Detected !**

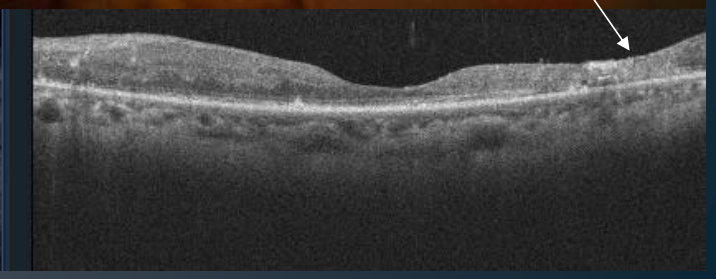
Comment: INTERPRETIVE INFORMATION: Cytomegalovirus Detection by PCR

Full thickness retinal necrosis



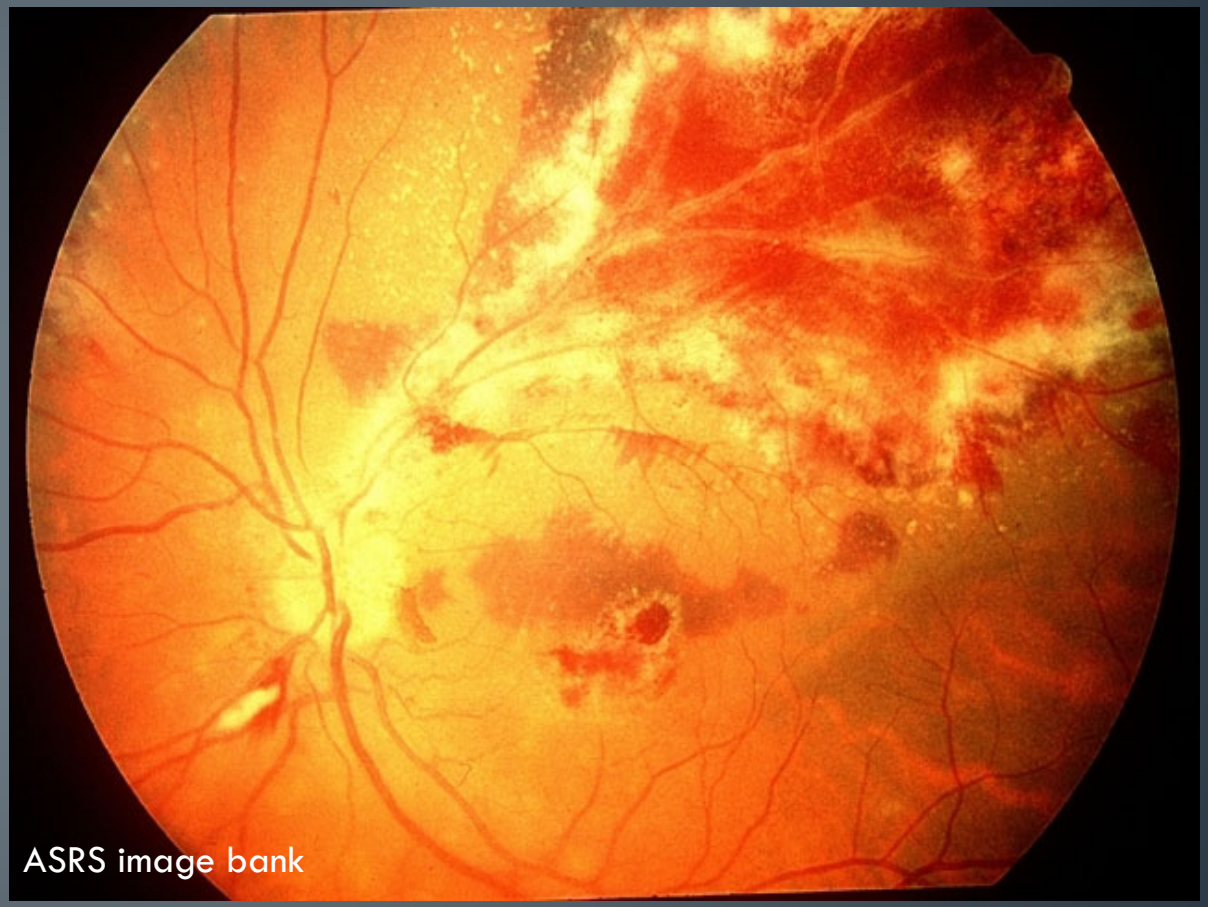






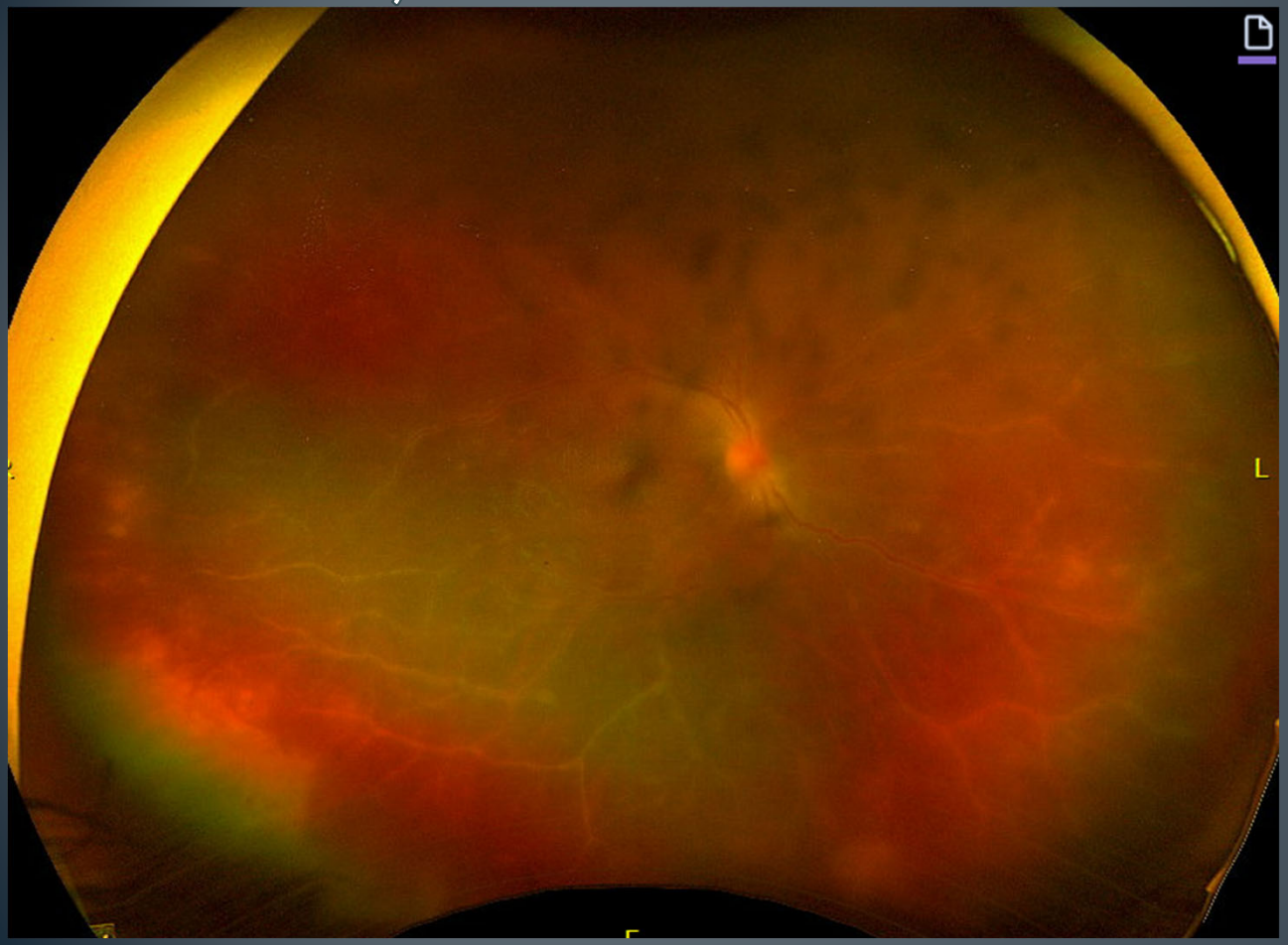
HIV positive male with decreased vision, flashes

Blood and thunder
Pizza pie appearance



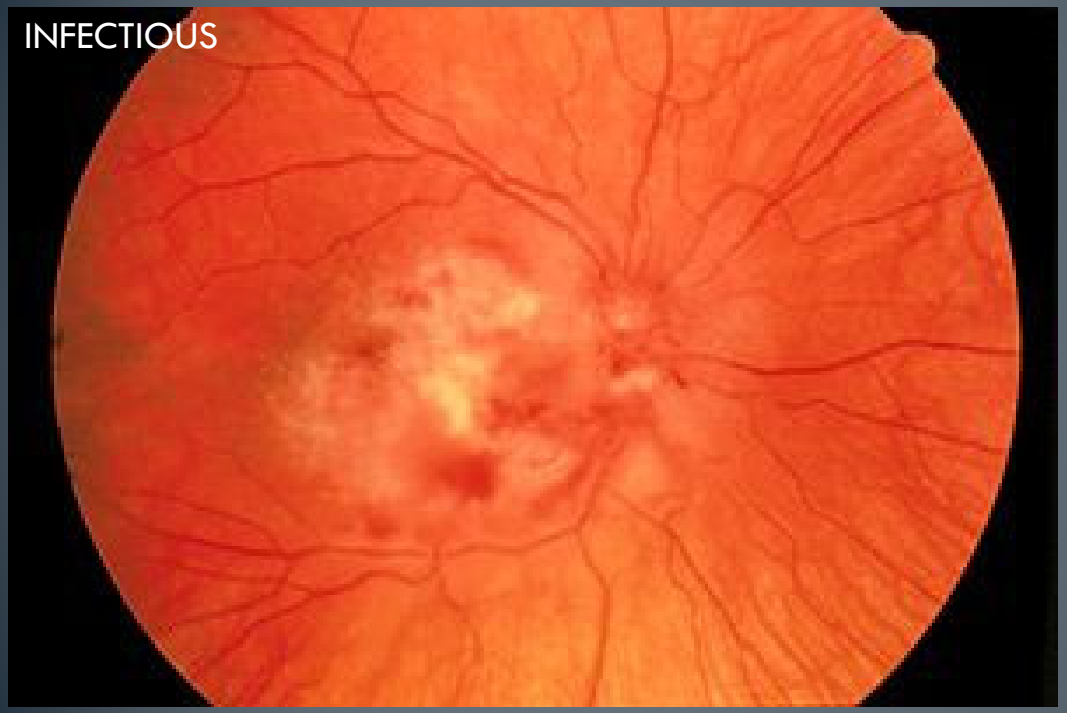
"Typical " CMV retinitis

20 y/o M monocular, referred for sympathetic ophthalmia (other eye NLP from RD)

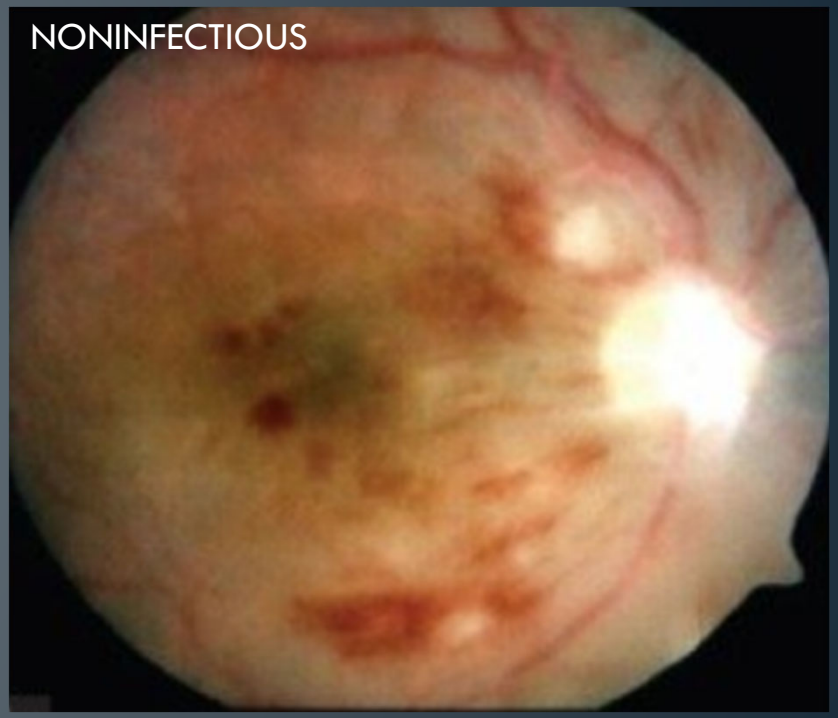


- HSV2 ARN
- HSV2 PCR + (Anterior chamber paracentesis)
- (note when history of HSV encephalitis as infant, sometimes with cerebral palsy)
- Usually reactivation of neonatal herpes acquired through vertical transmission

Infectious or noninfectious?



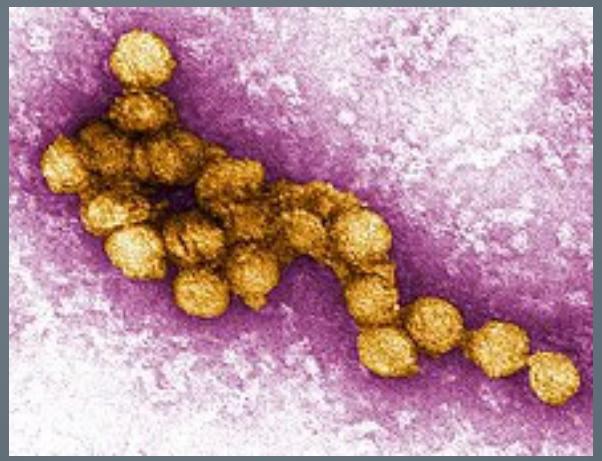
CMV retinitis

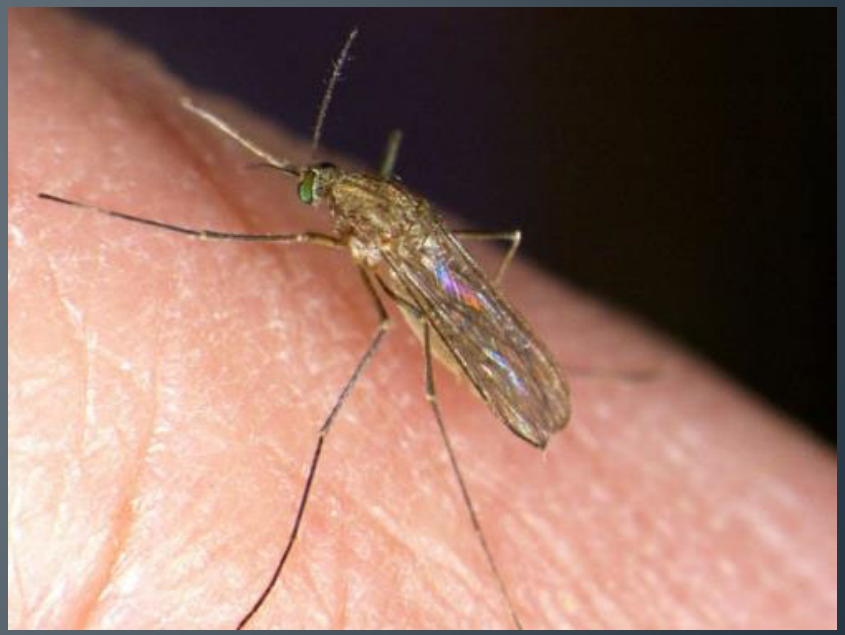


Behcet's disease

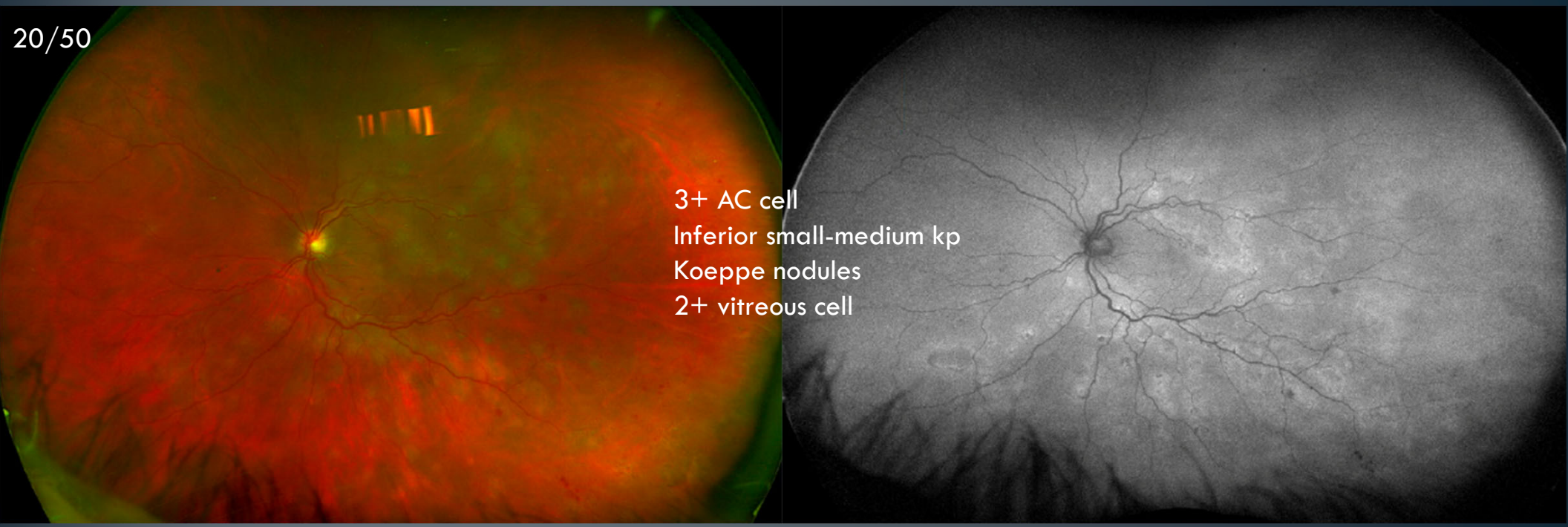
Other viruses affecting the retina

- Flavivirus

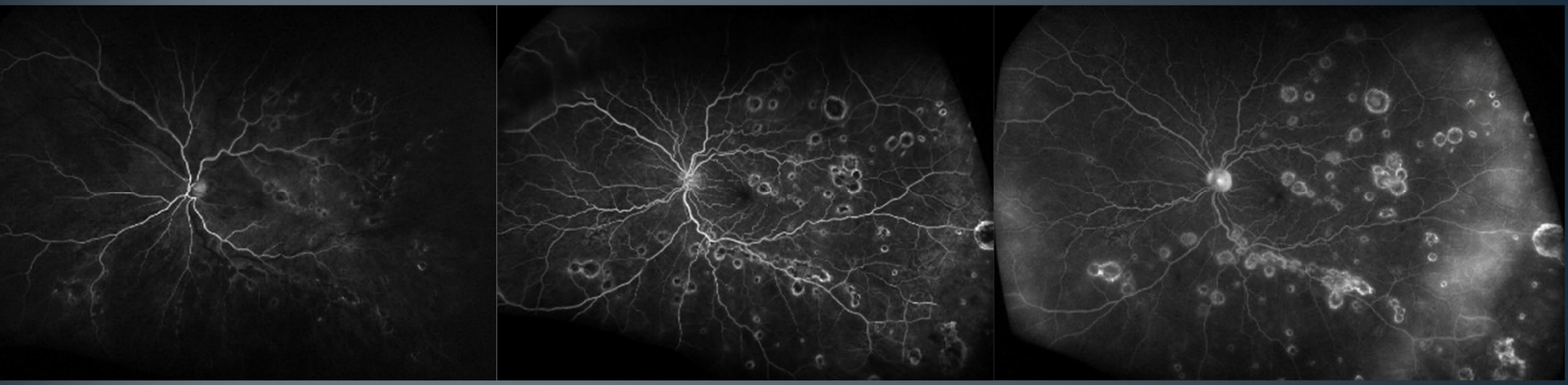


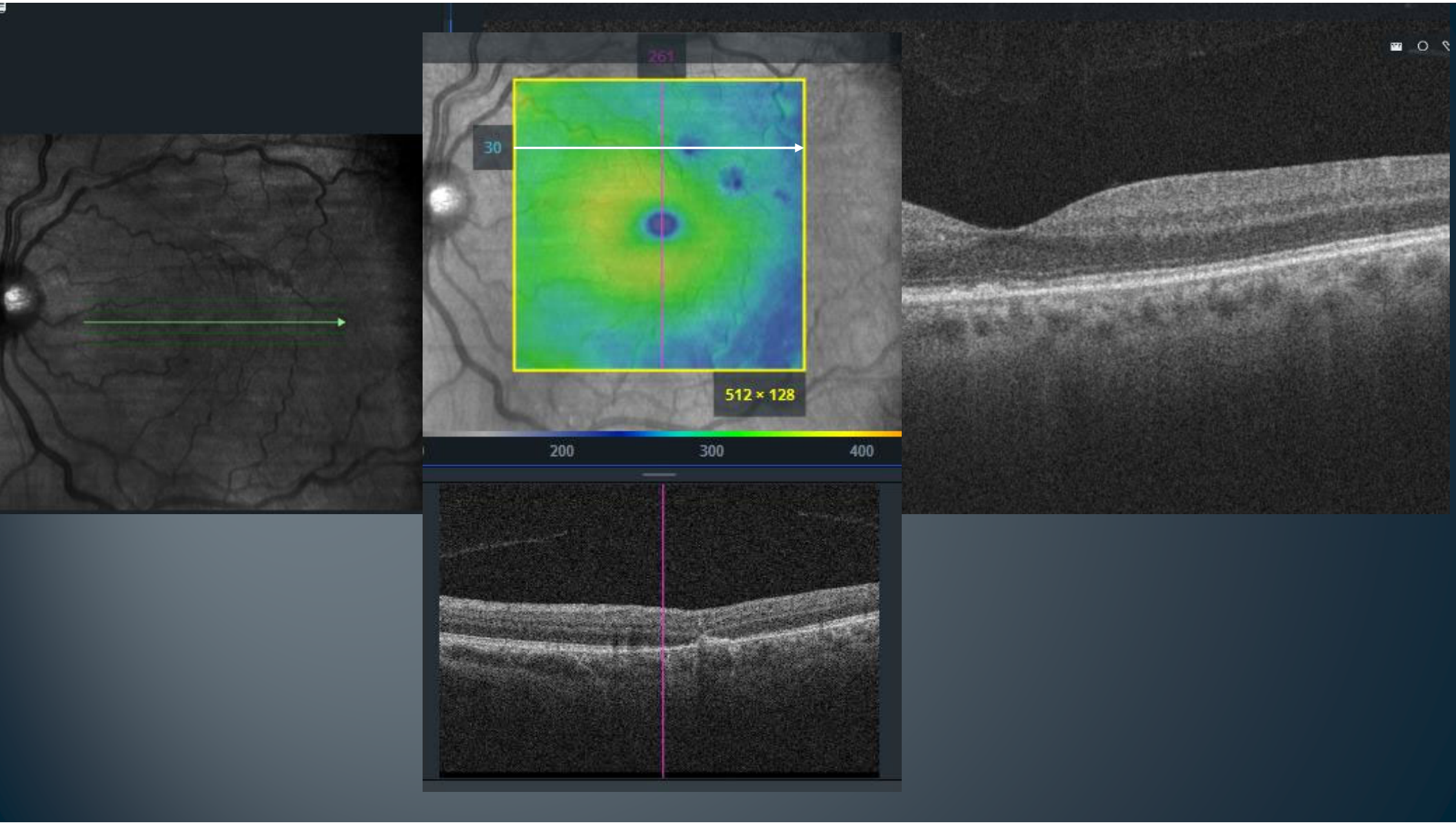


67 y/o F monocular with RA on upacitinib



Right eye lost to childhood knife trauma




261
30
512 × 128
200
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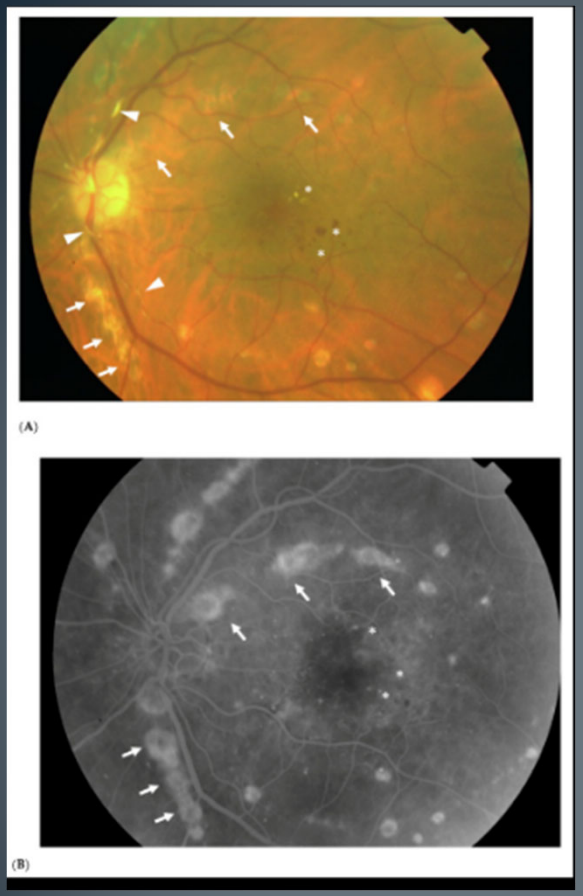
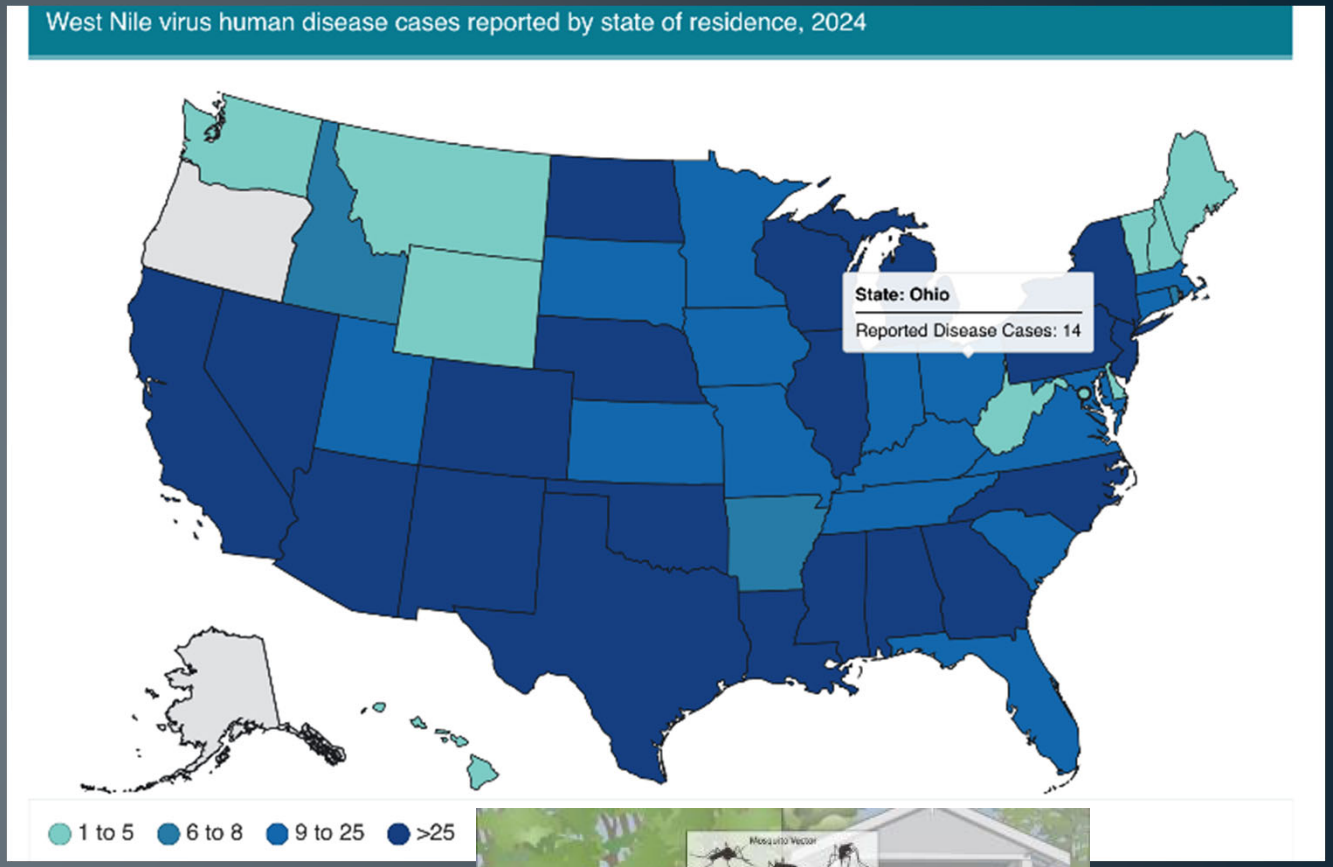
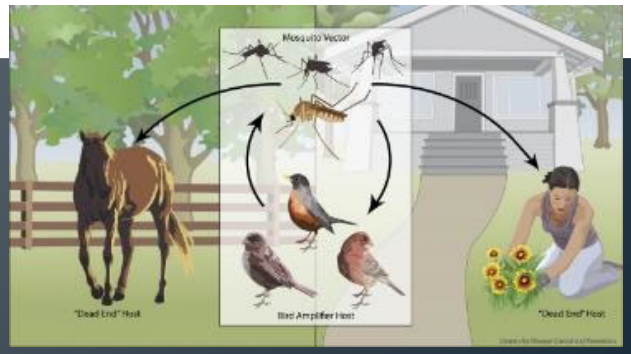


West Nile Virus (Rosseau et al Vaccines 2020)

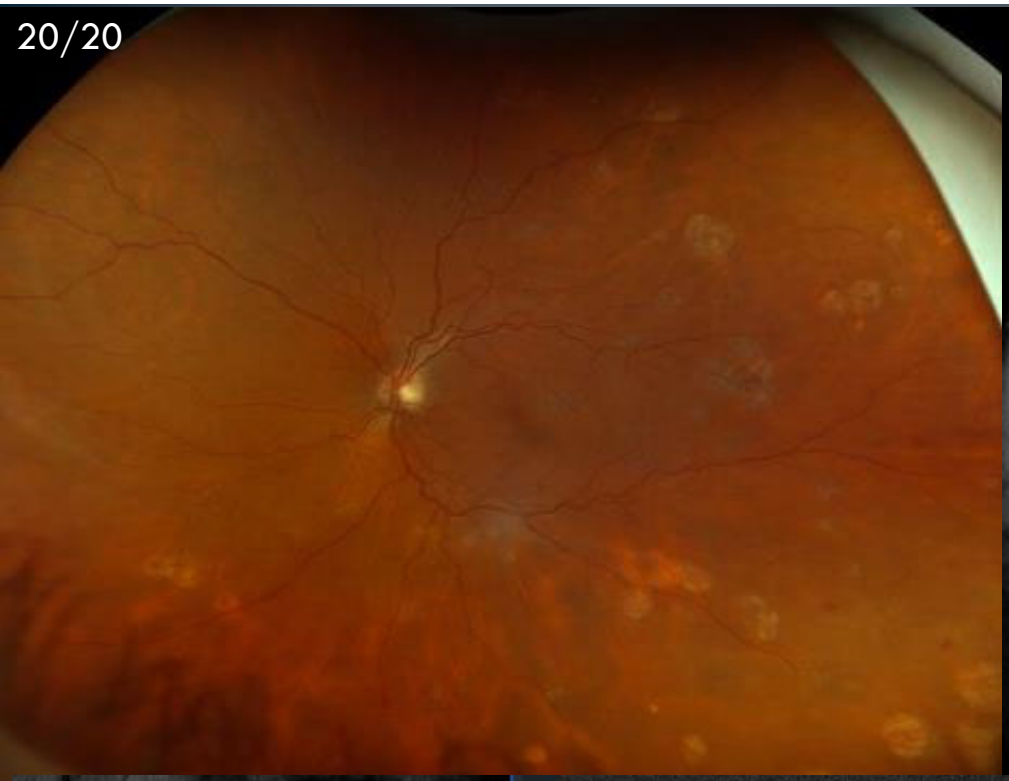


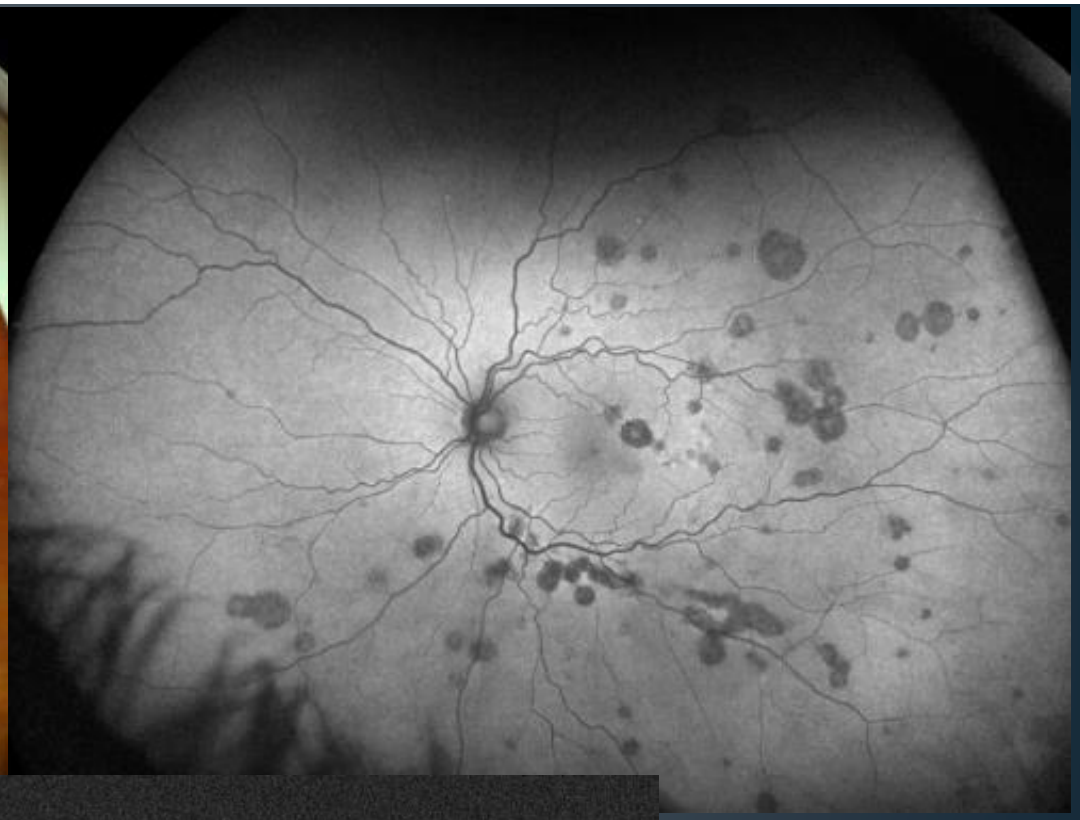
cdc.gov

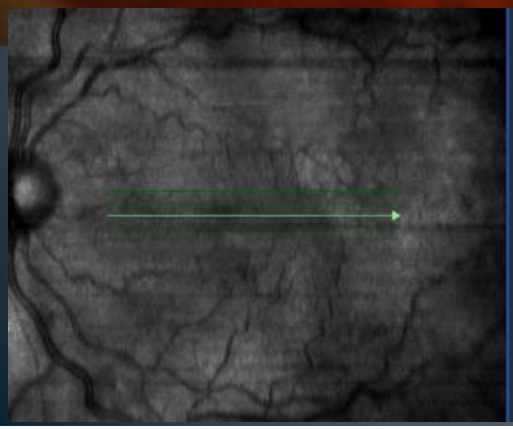
ssRNA virus, Flaviviridae family

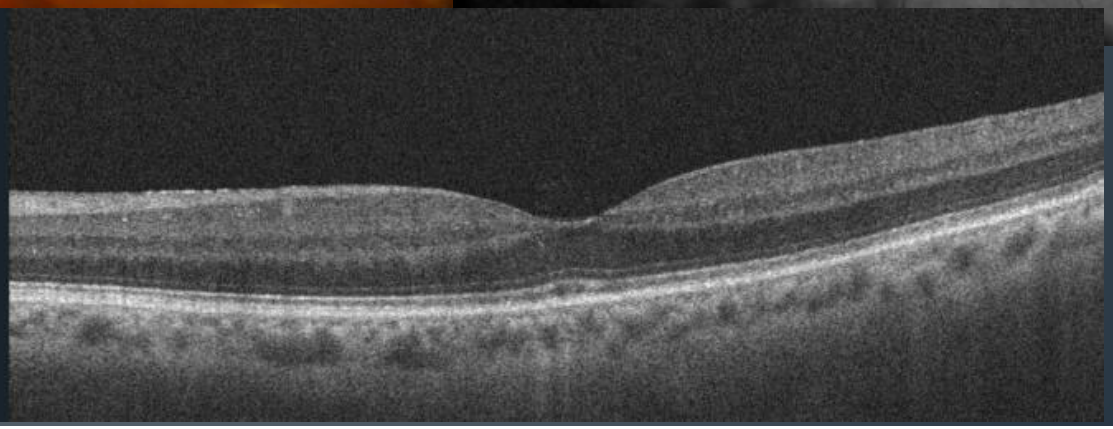


20/20

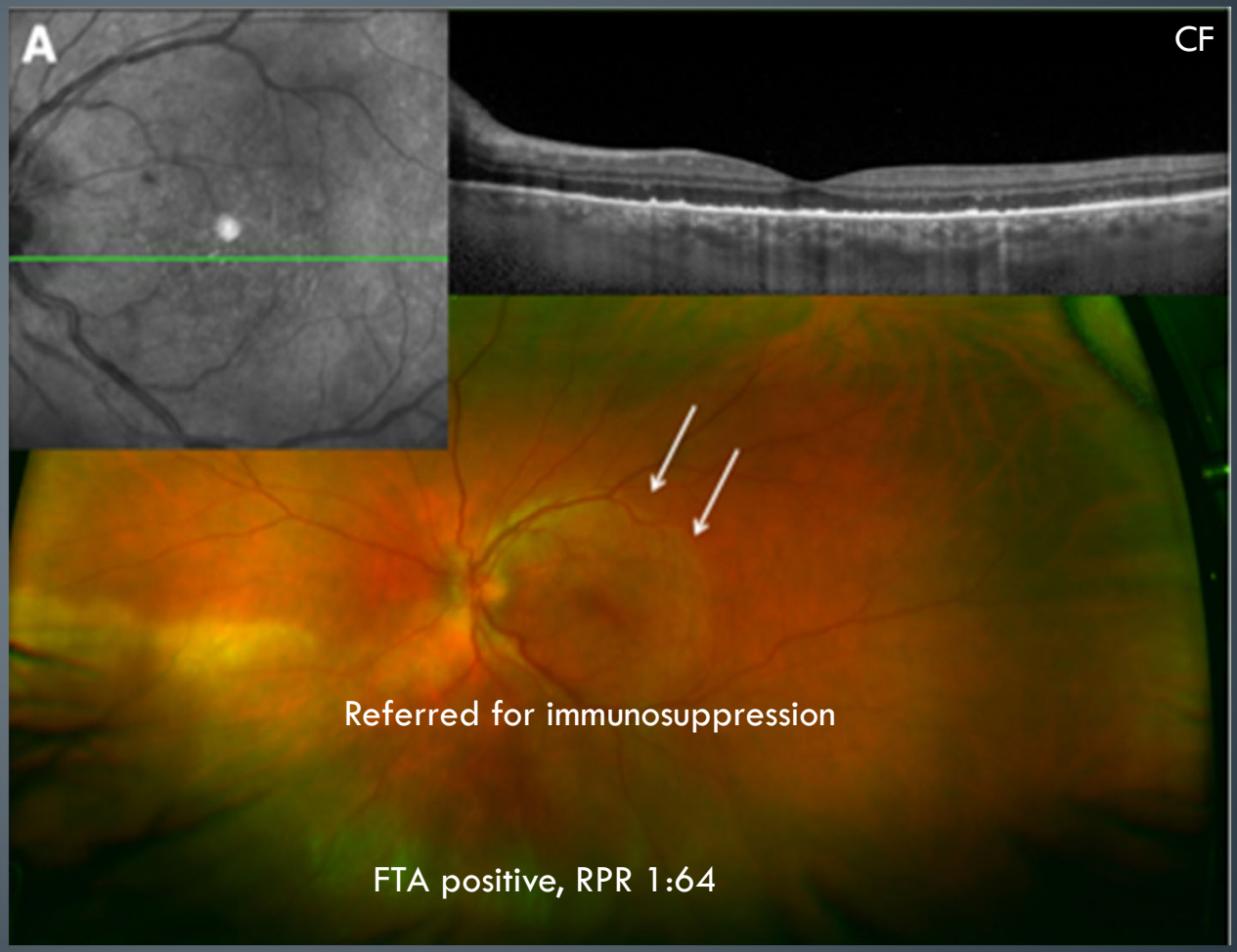








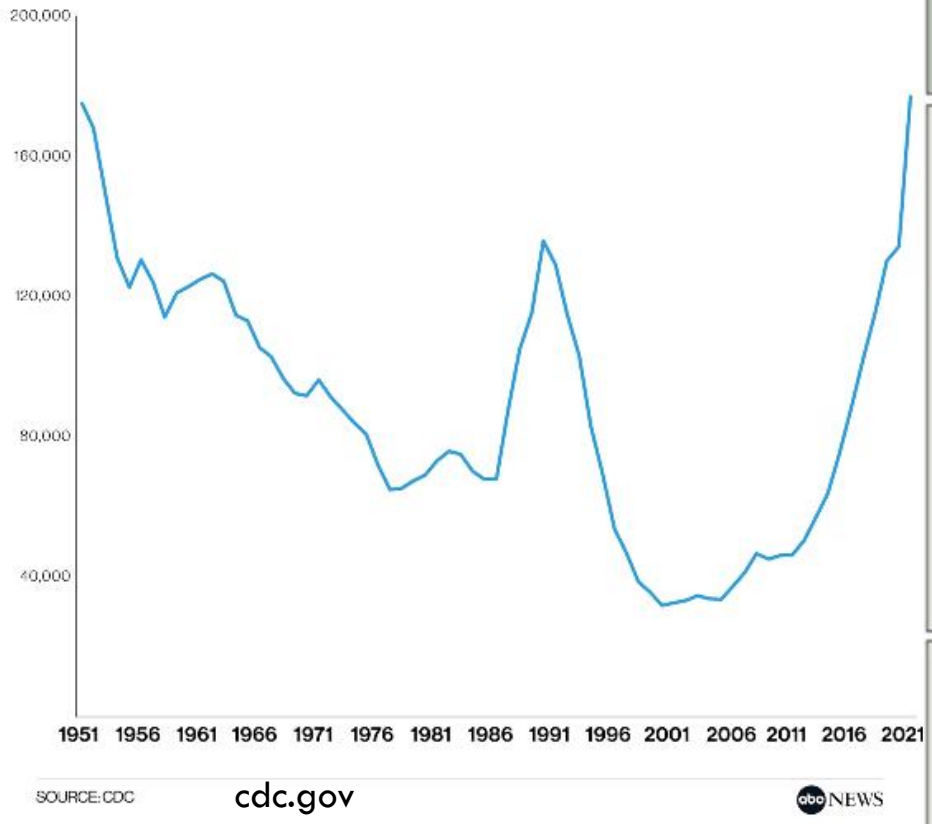
46 y/o healthy M, decreased vision OS, OD normal



Lin P, Curr Ophthalmol Rep 2015 3:170-183

Syphilis Cases in the United States

1951-2021



SOURCE: CDC

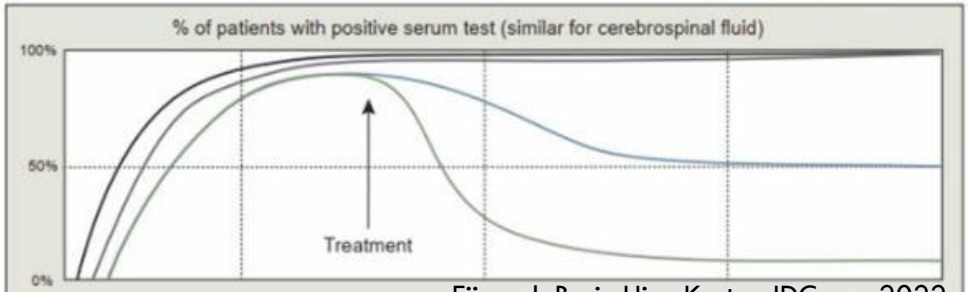
cdc.gov

abc NEWS

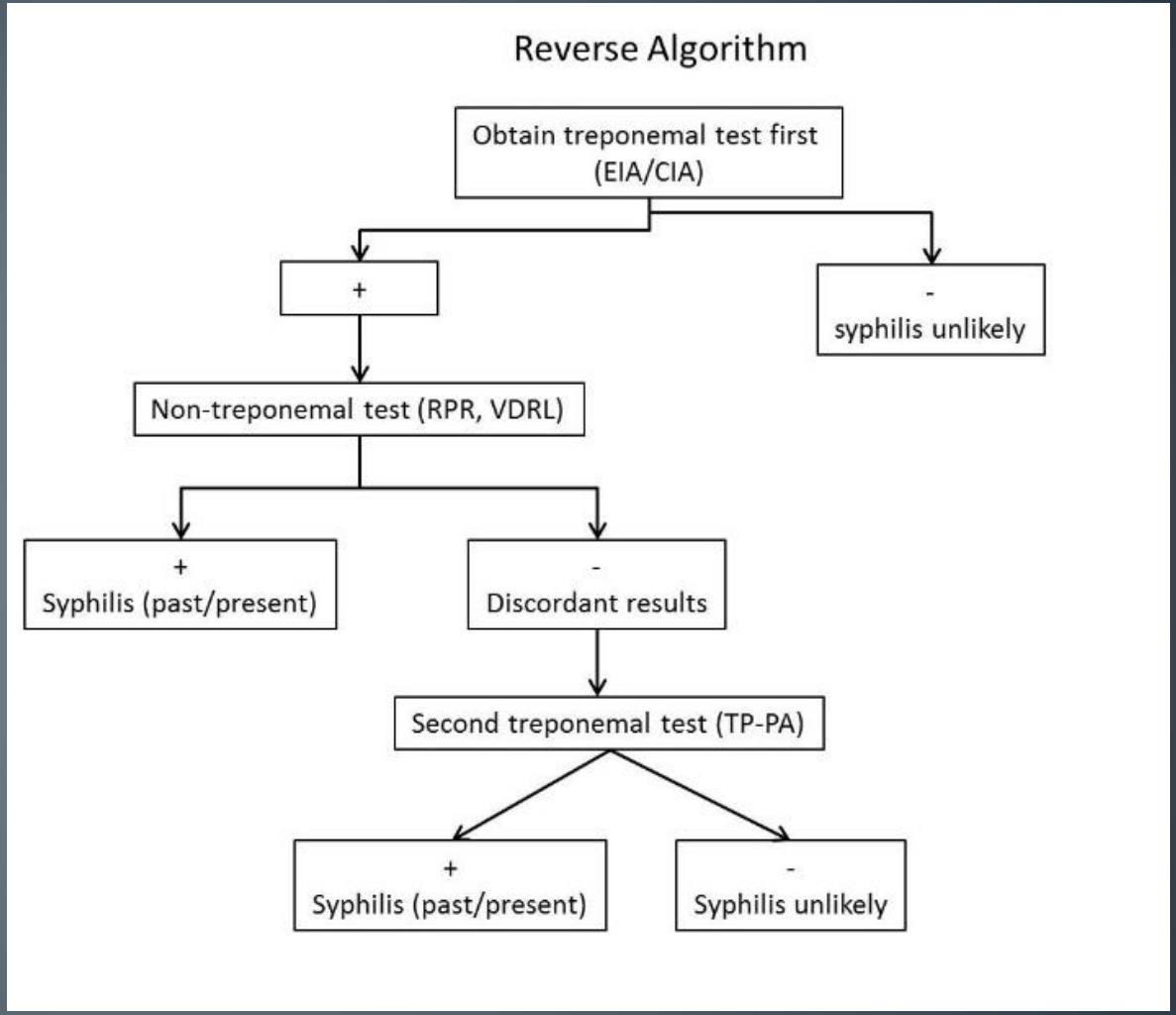
Clinical classification of syphilis infection

Clinical stage	Primary	Secondary	Latent	Tertiary
Chronology	Incubation period: Median: 21 days Range: 3-90 days after exposure Resolves within: 2-8 weeks	Symptoms: 2 weeks - 3 months after chancre resolving Resolves within 2-10 weeks	Variable Early latent: <1 year after exposure Late latent: 1 year to >30 years after exposure	Variable 1 to >30 years Lifetime latency can occur
Symptoms & Clinical characteristics	Chancre lesion (penis, labia, peri-anal, oral mucosa) Often not recognized Hematogeneous spirochete dissemination 2-12 weeks after appearance of chancre	Typical (maculopapular) rash of palms/soles or atypical rash Mucous patches, fever, malaise, weight loss, headache, pharyngitis, arthritis, lymfadenopathy hepatitis, nephritis Condyloma lata (genital/anal warts) Early neurosyphilis Meningitis Meningovascular (CVA) Cranial nerve palsies Hearing loss Ocular syphilis / uveitis	Asymptomatic After spontaneous regression of secondary stage Recurrence to secondary stage is frequent (up to 25%)	Organ invasion "Gummata": Benign granulomatous lesions in skin, bone, brain, internal organs Cardiovascular: Aortic aneurism Coronary arteriitis Vasculitis/aortitis Late neurosyphilis General paresis Granulomatous Meningomyelitis Tabes dorsalis Cognitive dysfunction Ocular syphilis / uveitis
Diagnostics - TP IgG - THPA - VDRL treated - VDRL untreated	% of patients with positive serum test (similar for cerebrospinal fluid)			

Ocular syphilis



Ejimael, Bruin Hira Koster, IDCases 2022

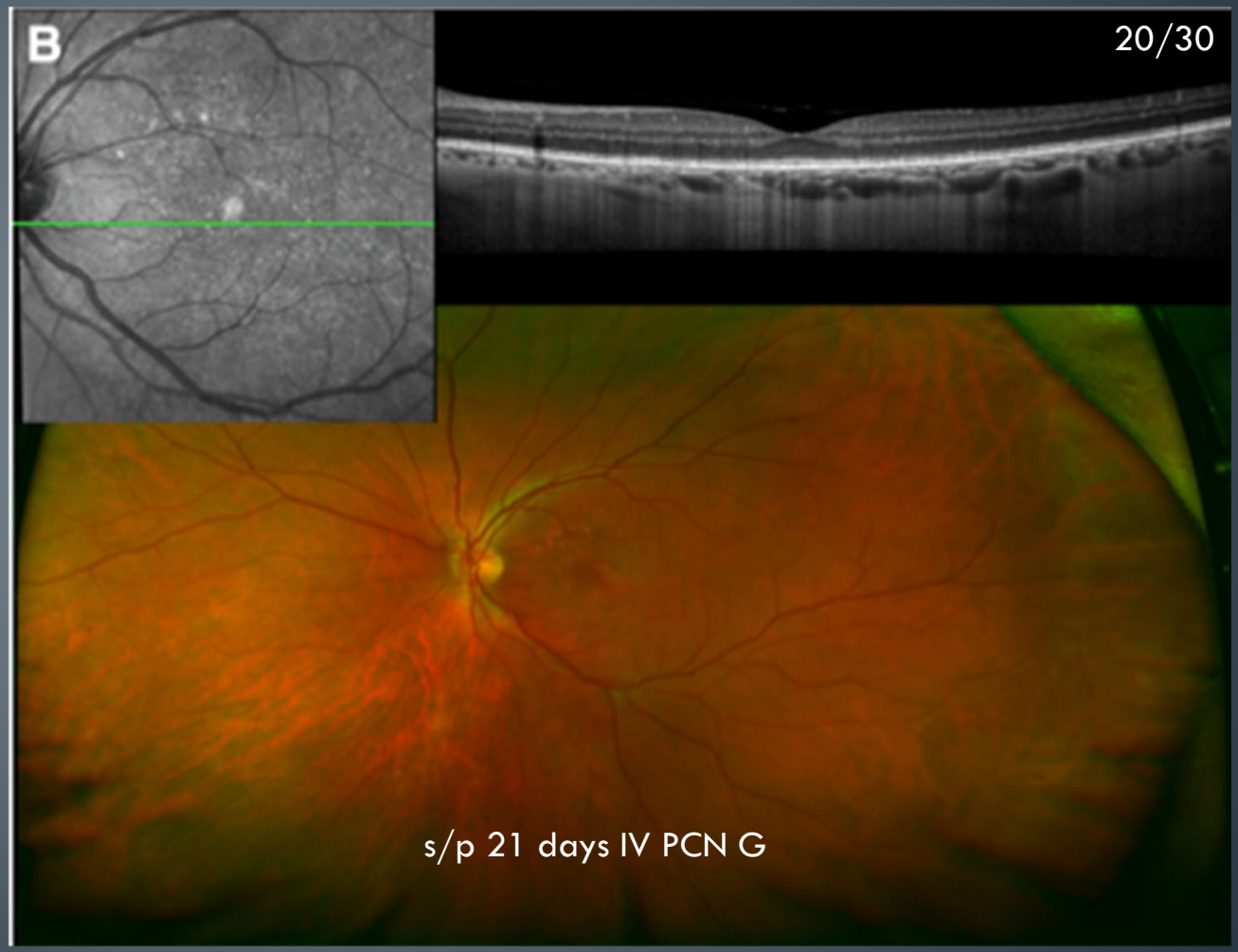


CDC recommendation since 2004

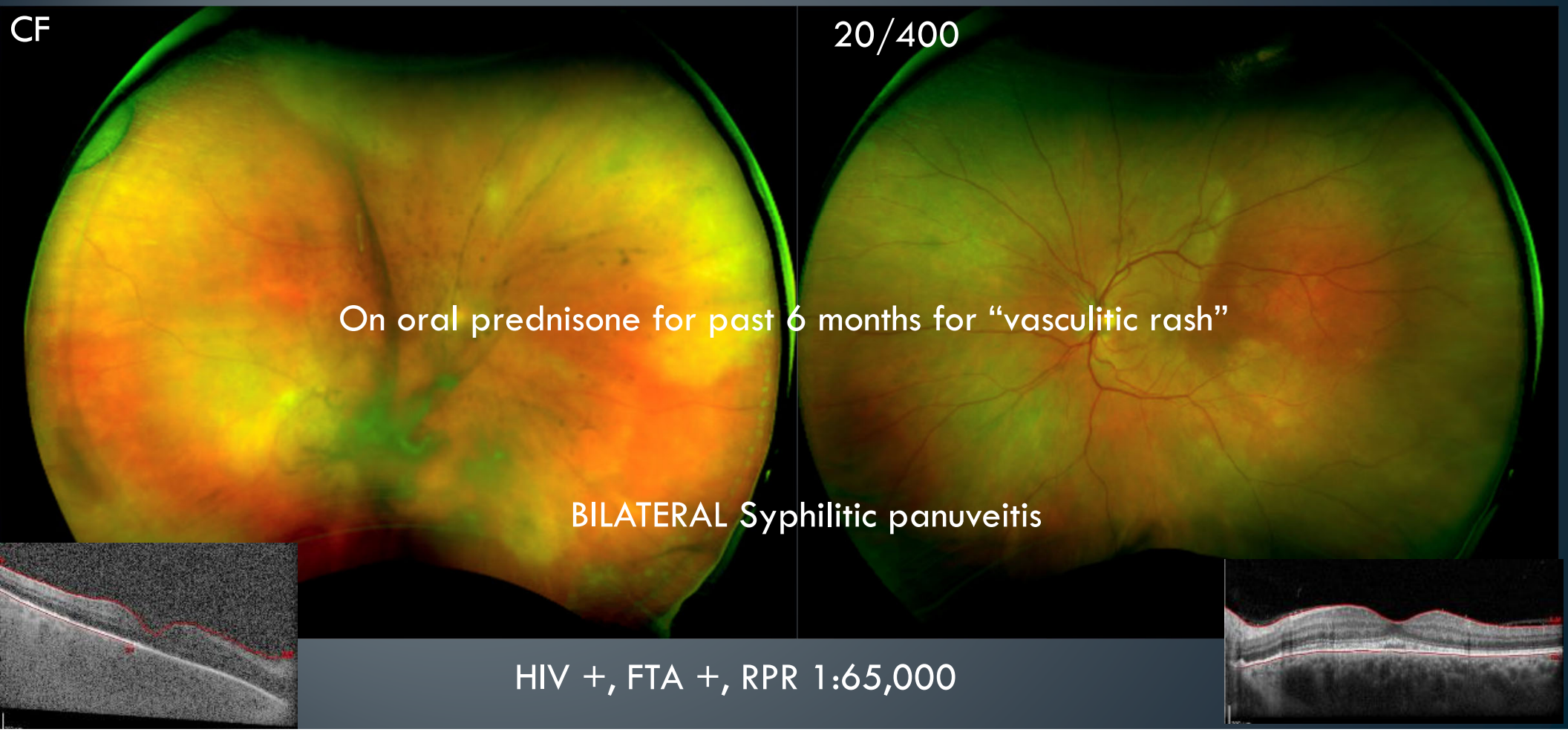
Joye and Gonzales Uveitis, Springer 2020

Treatment of ocular syphilis

- Treat like neurosyphilis: aqueous Penicillin G 18-24 million units IV daily (3-4 million units IV Q4h) x 10-14 days


B
20/30
s/p 21 days IV PCN G

65 y/o WM with referral diagnosis systemic vasculitis c occlusive retinal vasculitis OU/BRVO for initiation of systemic immunosuppression



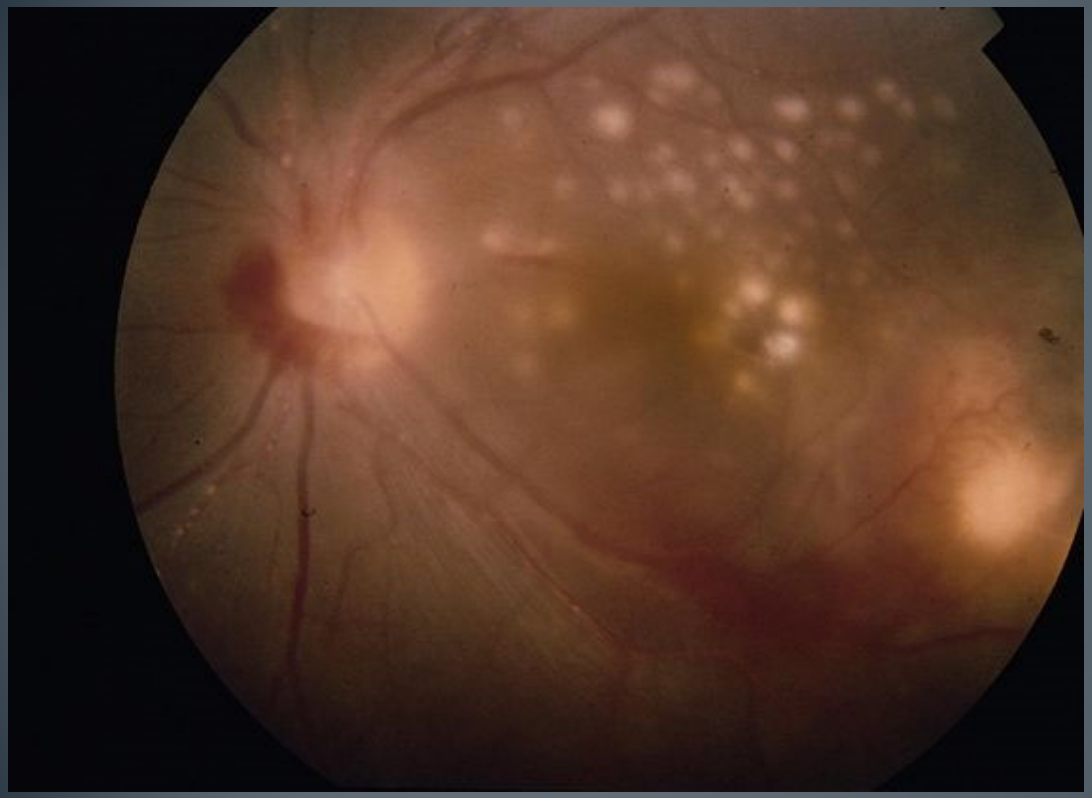
On oral prednisone for past 6 months for "vasculitic rash"

BILATERAL Syphilitic panuveitis

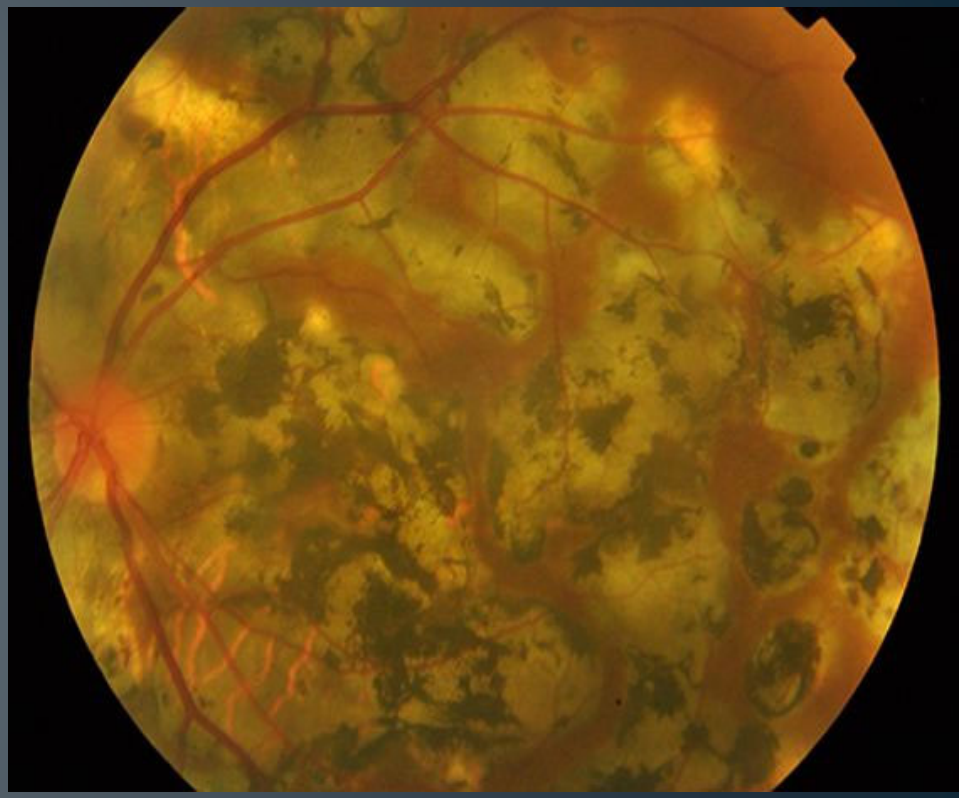
HIV +, FTA +, RPR 1:65,000

IV PCN G x 21 days

Ocular tuberculosis

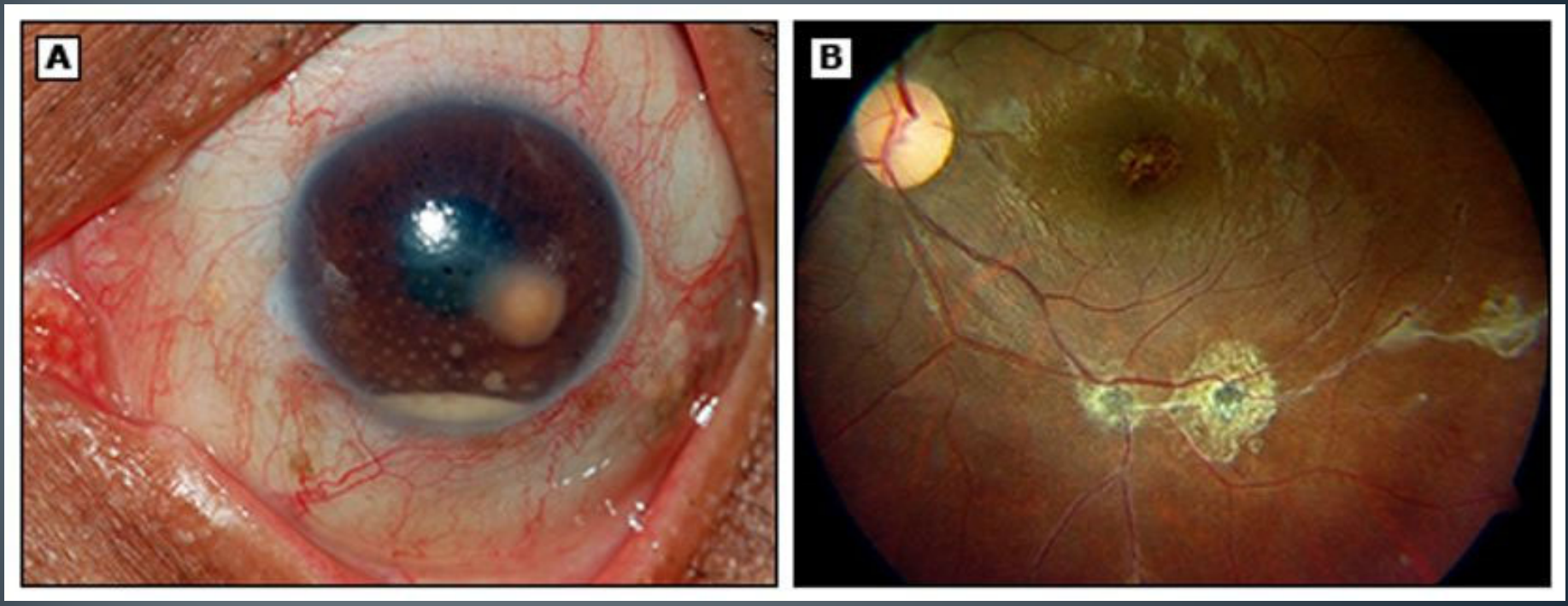


Choroidal tuberculomas



Serpiginous-like choroiditis due to TB

Ocular tuberculosis



Anterior chamber granuloma and hypopyon

Chorioretinal scars after treatment of TB

Diagnosis of ocular tuberculosis

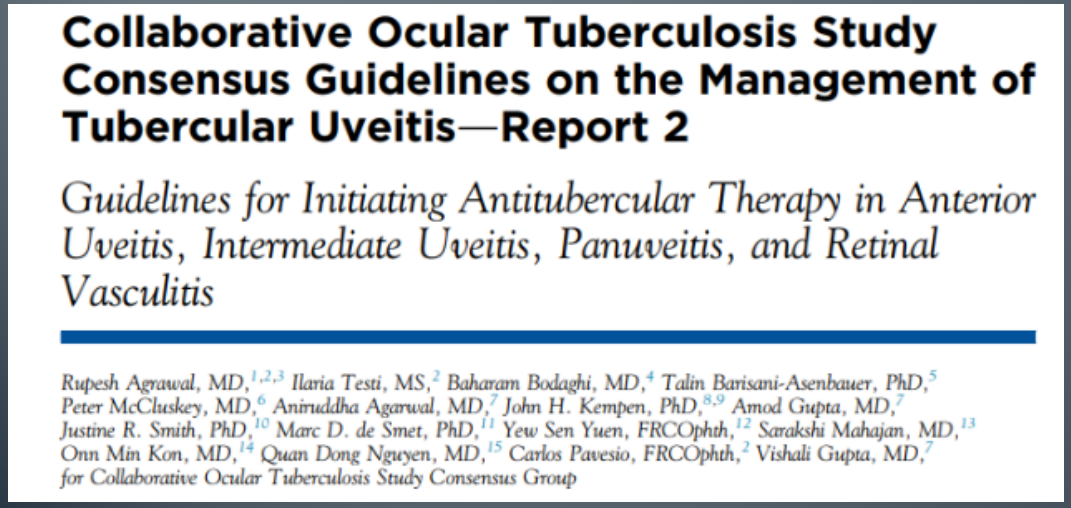
- Clinical findings + quantiferon gold positive : presumed ocular TB
- Definitive: ocular PCR (prone to false negatives), or AFB on smear or culture from ocular fluids (false negatives very high)

Treatment of ocular tuberculosis

- Treat similar to active pulmonary or extrapulmonary TB even in absence of active disease outside the eye: Rifampin, Isoniazid, Ethambutol and Pyrazinamide x 2 months → rifampin + isoniazid x 18 weeks (6 months of treatment total)

Treatment of ocular tuberculosis

- Treat similar to active pulmonary or extrapulmonary TB even in absence of active disease outside the eye: Rifampin, Isoniazid, Ethambutol and Pyrazinamide (4 drugs) x 2 months → rifampin + isoniazid x 4-7 months (at least 6 months of treatment)

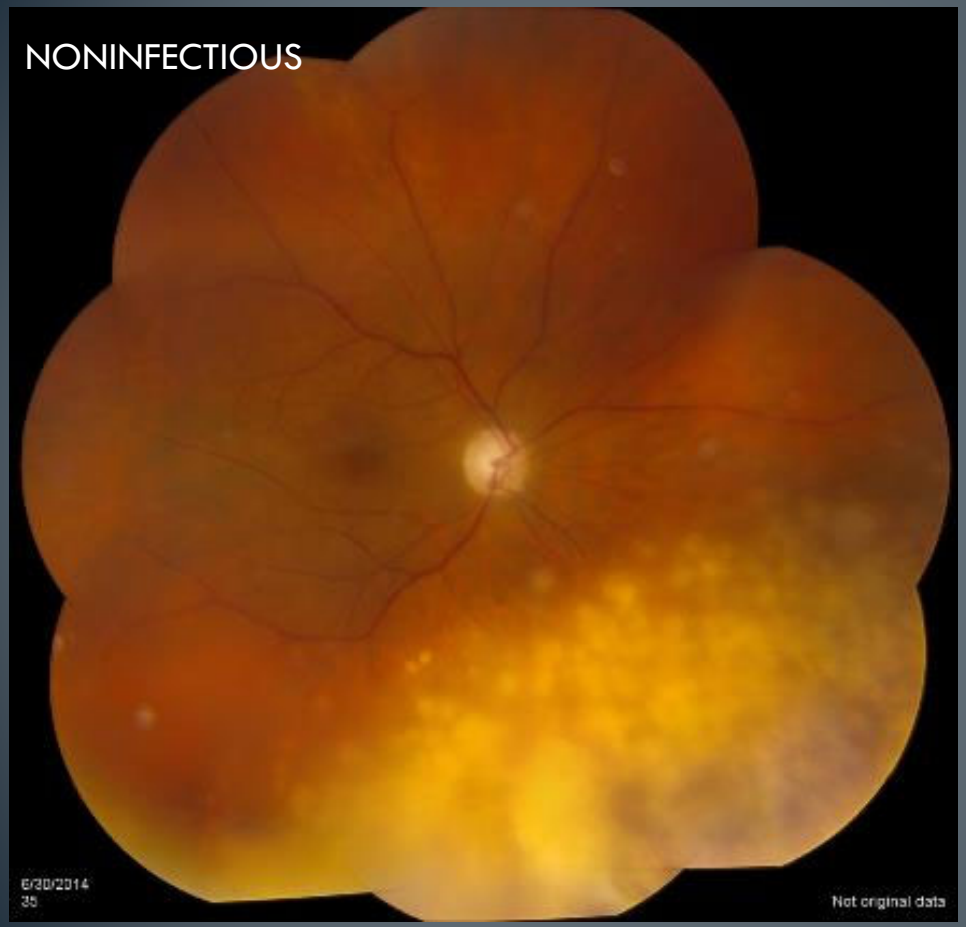


Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis—Report 2

Guidelines for Initiating Antitubercular Therapy in Anterior Uveitis, Intermediate Uveitis, Panuveitis, and Retinal Vasculitis

Rupesh Agrawal, MD,[1,2,3] Ilaria Testi, MS,[2] Baharam Bodaghi, MD,[4] Talin Barisani-Asenbauer, PhD,[5] Peter McCluskey, MD,[6] Aniruddha Agarwal, MD,[7] John H. Kempen, PhD,[8,9] Amod Gupta, MD,[7] Justine R. Smith, PhD,[10] Marc D. de Smet, PhD,[11] Yew Sen Yuen, FRCOphth,[12] Sarakshi Mahajan, MD,[13] Onn Min Kon, MD,[14] Quan Dong Nguyen, MD,[15] Carlos Pavesio, FRCOphth,[2] Vishali Gupta, MD,[7] for Collaborative Ocular Tuberculosis Study Consensus Group

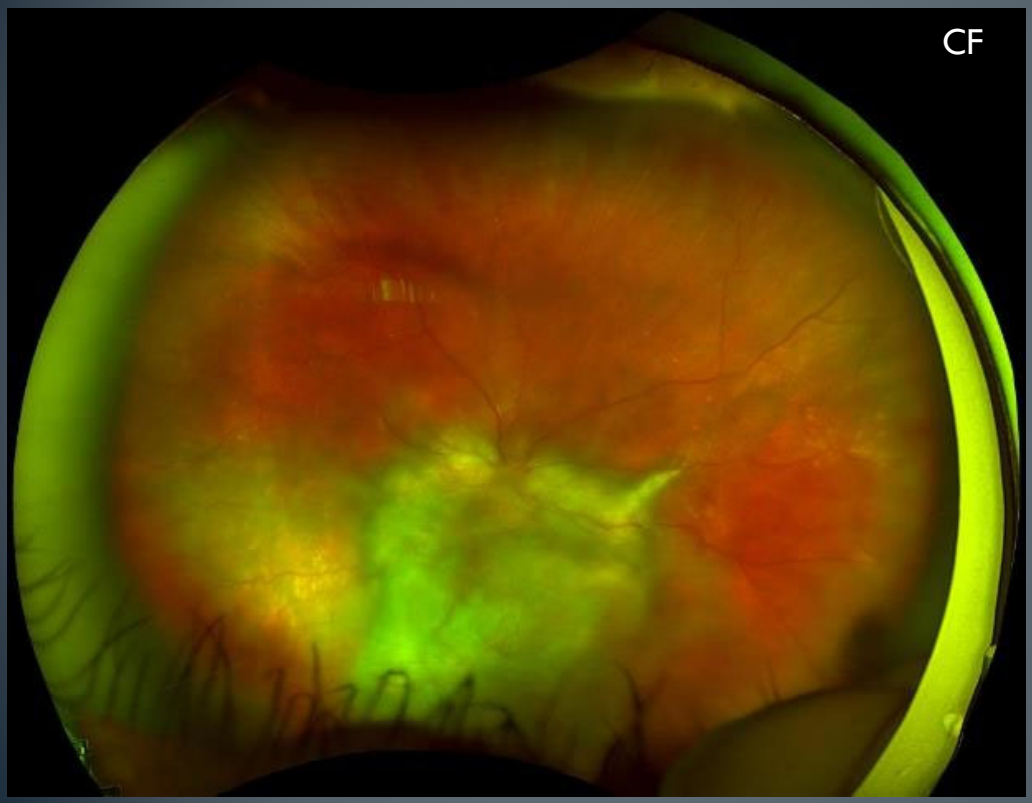
Infectious vs. noninfectious?

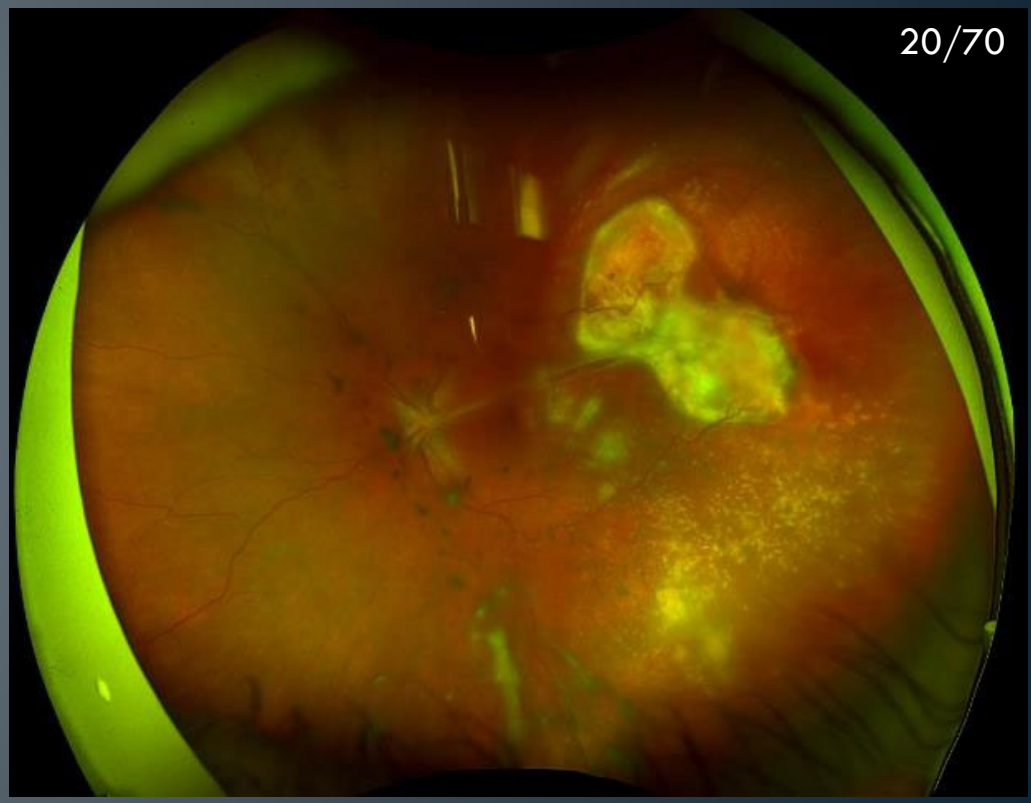


SARCOIDOSIS

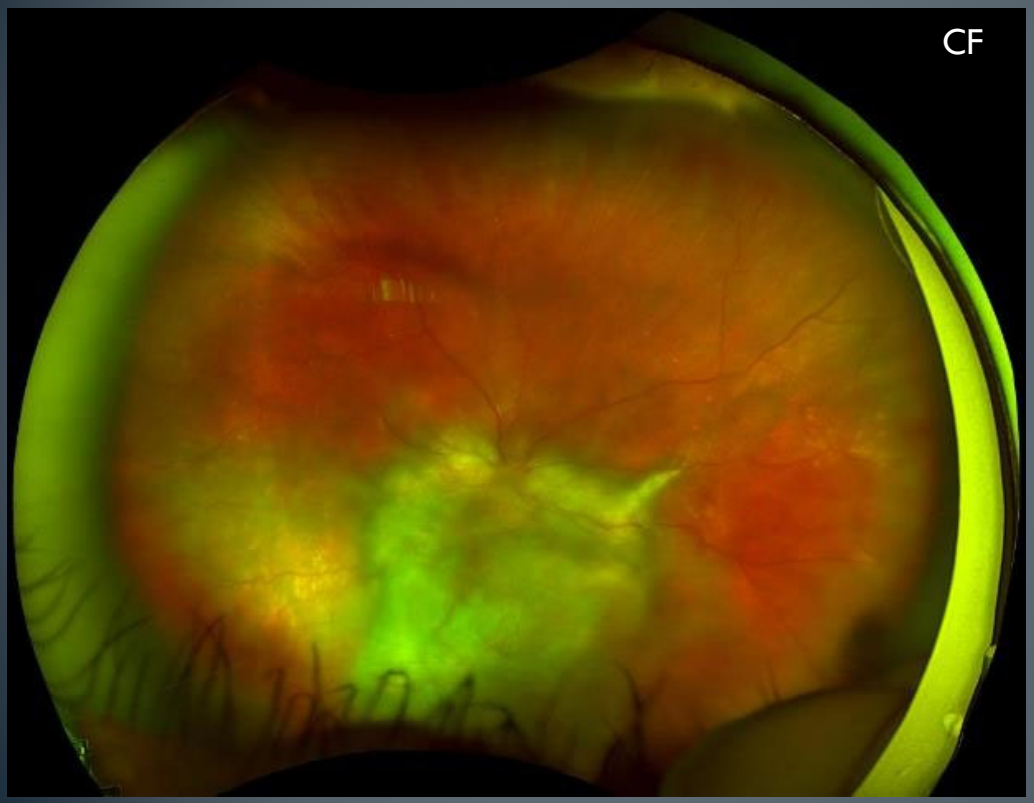
OCULAR TUBERCULOSIS

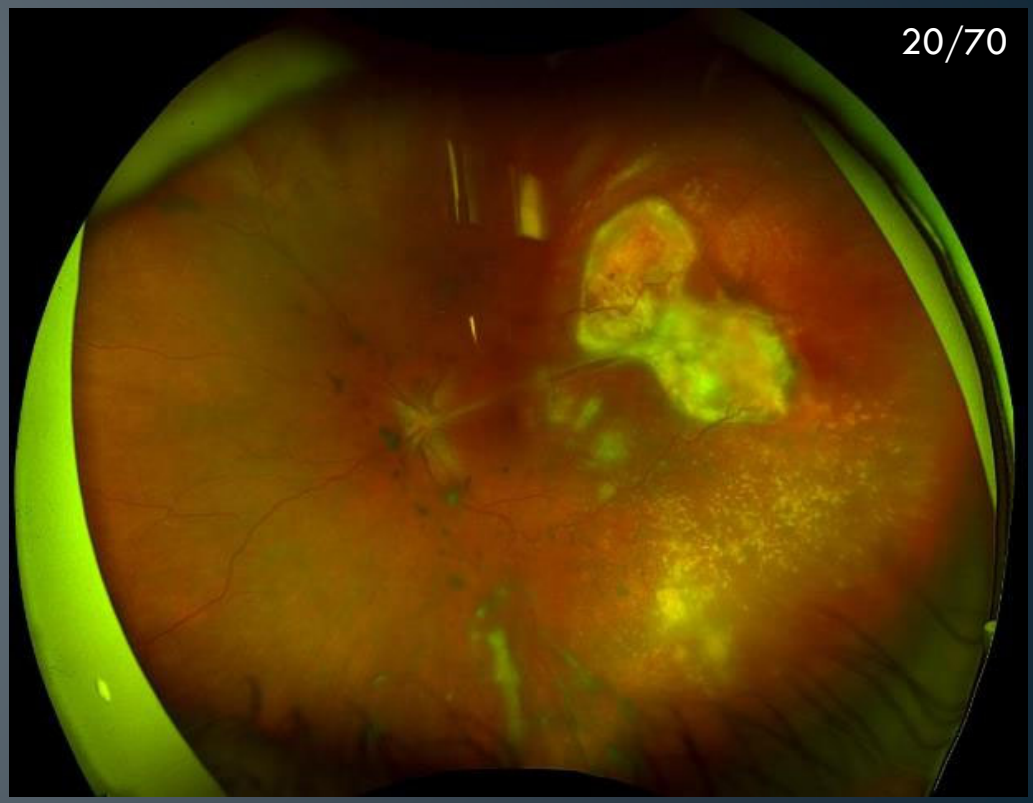
22 y/o autistic F with lupus





+ prednisone 80 mg, s/p rituximab for lupus nephritis



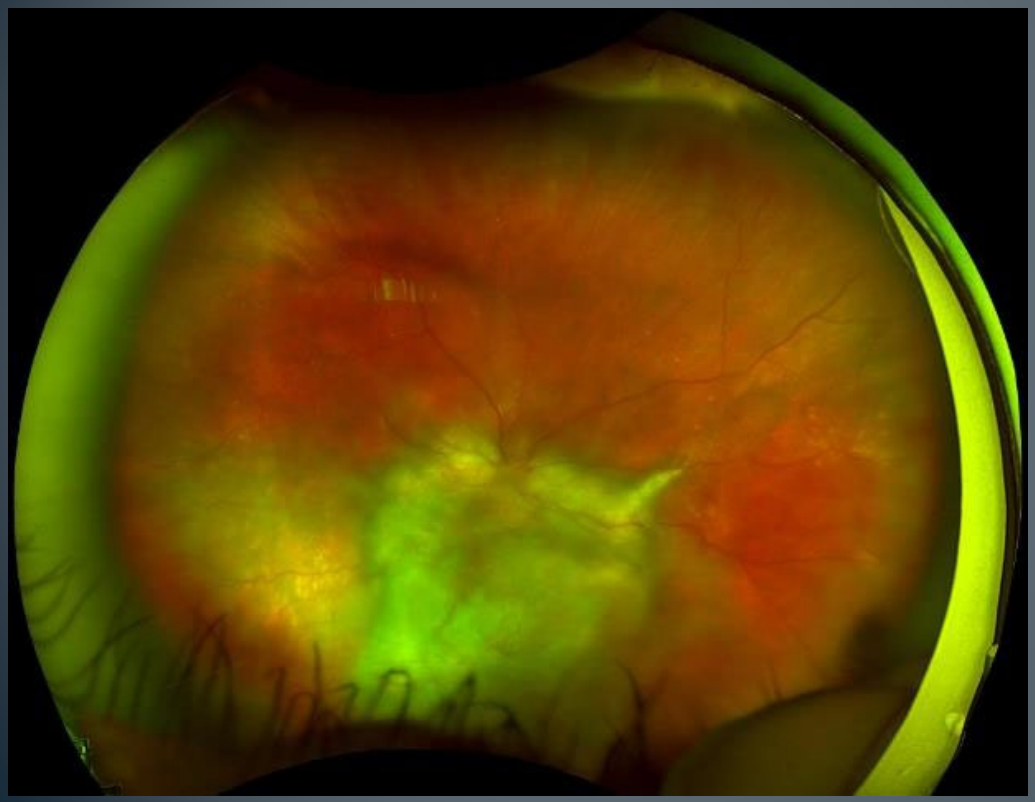


NOCARDIA cyriacigeorgica: disseminated in lung, brain, spine, retina 1 year prior
Active despite 6 months IV ceftriaxone, PO linezolid + Bactrim

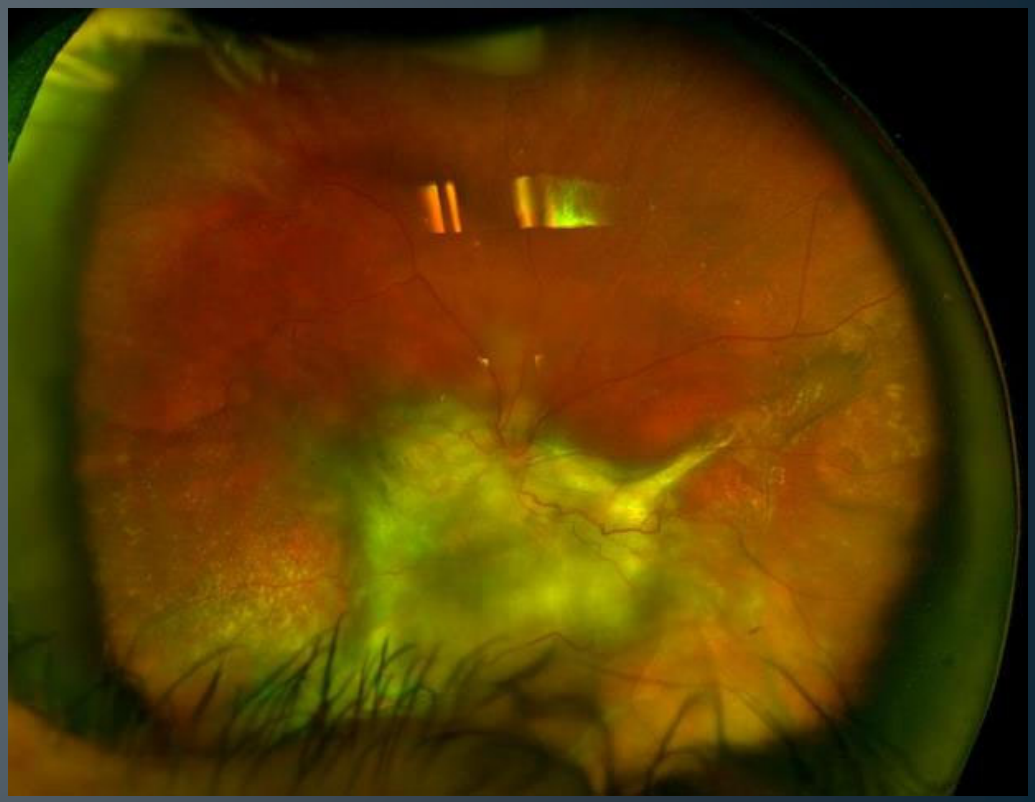
Nocardia endophthalmitis

- Soil-based aerobic, weak gram positive, partially acid-fast rod-shaped bacteria that can form branching filaments
- Difficult to diagnose: culture, PCR
- Difficult to treat: obtain sensitivities as strains vary
- Immunosuppressed individuals

s/p switch from IV ceftriaxone to IV meropenem + 4 weekly intravitreal amikacin



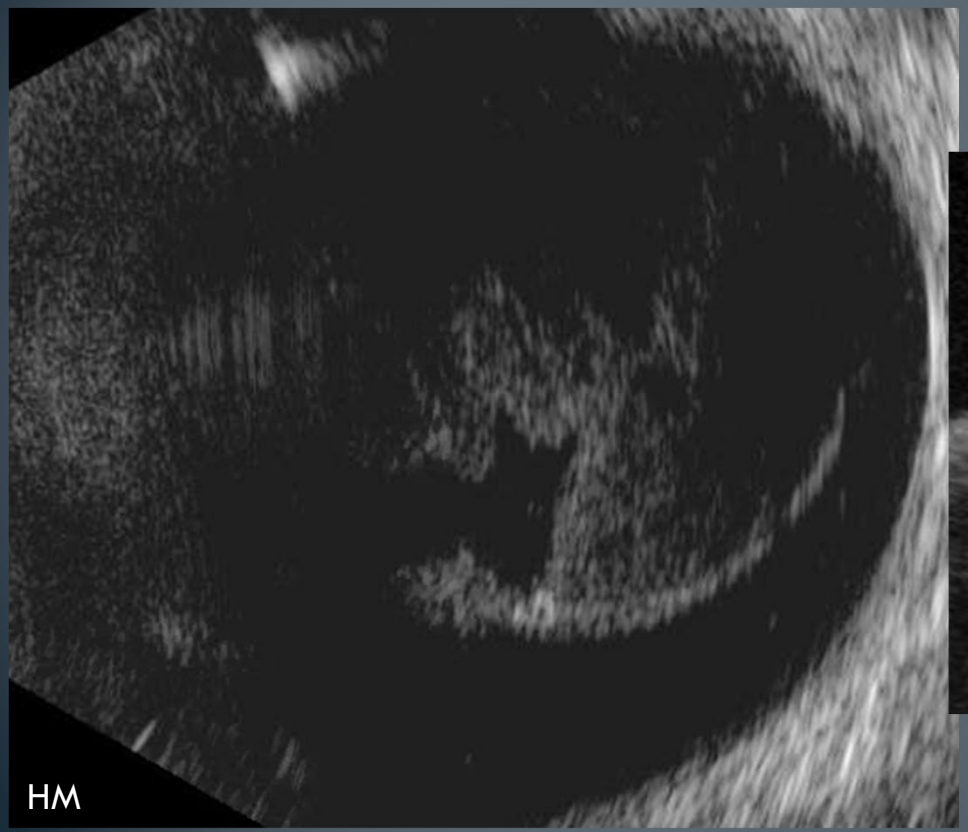
9/22/23



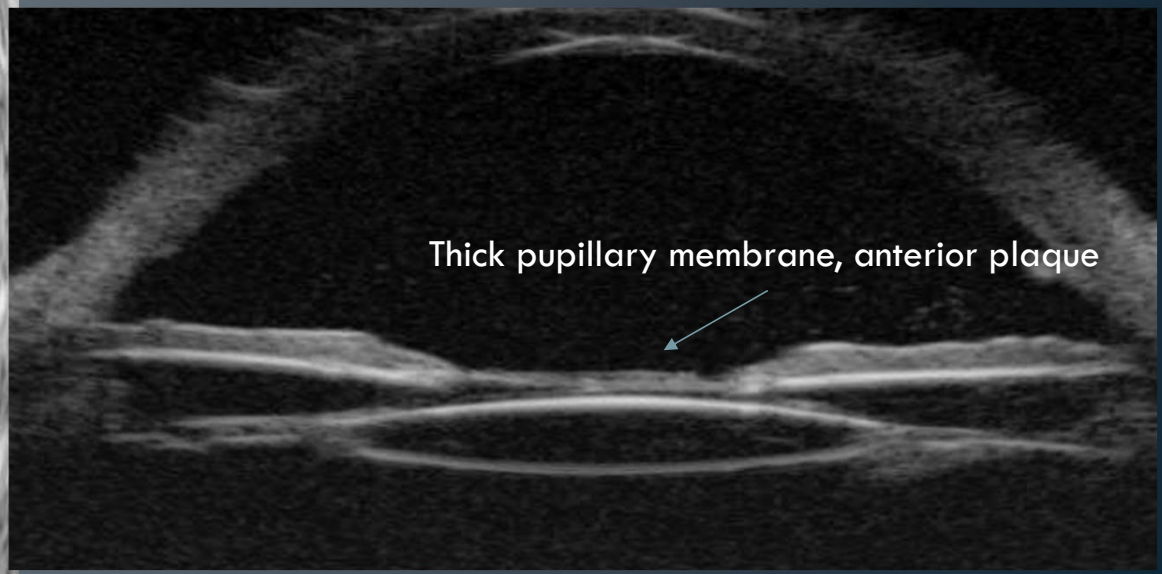
10/23/23

74 y/o F chronic unilateral hypertensive anterior uveitis x 1 year for treatment of viral anterior uveitis

Cataract surgery took place 8 years prior

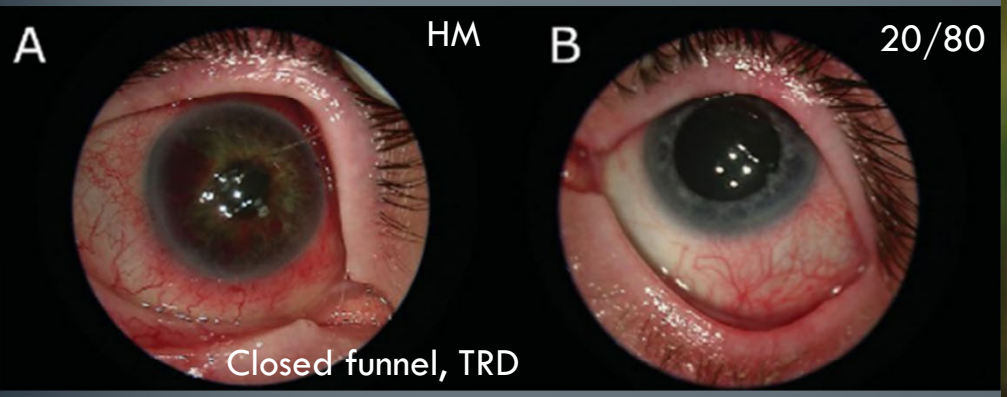


FTA, Quantiferon negative
Aq PCR: HSV, VZV, CMV negative



Vitreous culture: negative
Universal bacterial PCR: +Cutibacterium Acnes (prev P. acnes)
IOL/capsule removed, injection of ceftazidime, final BCVA 20/25

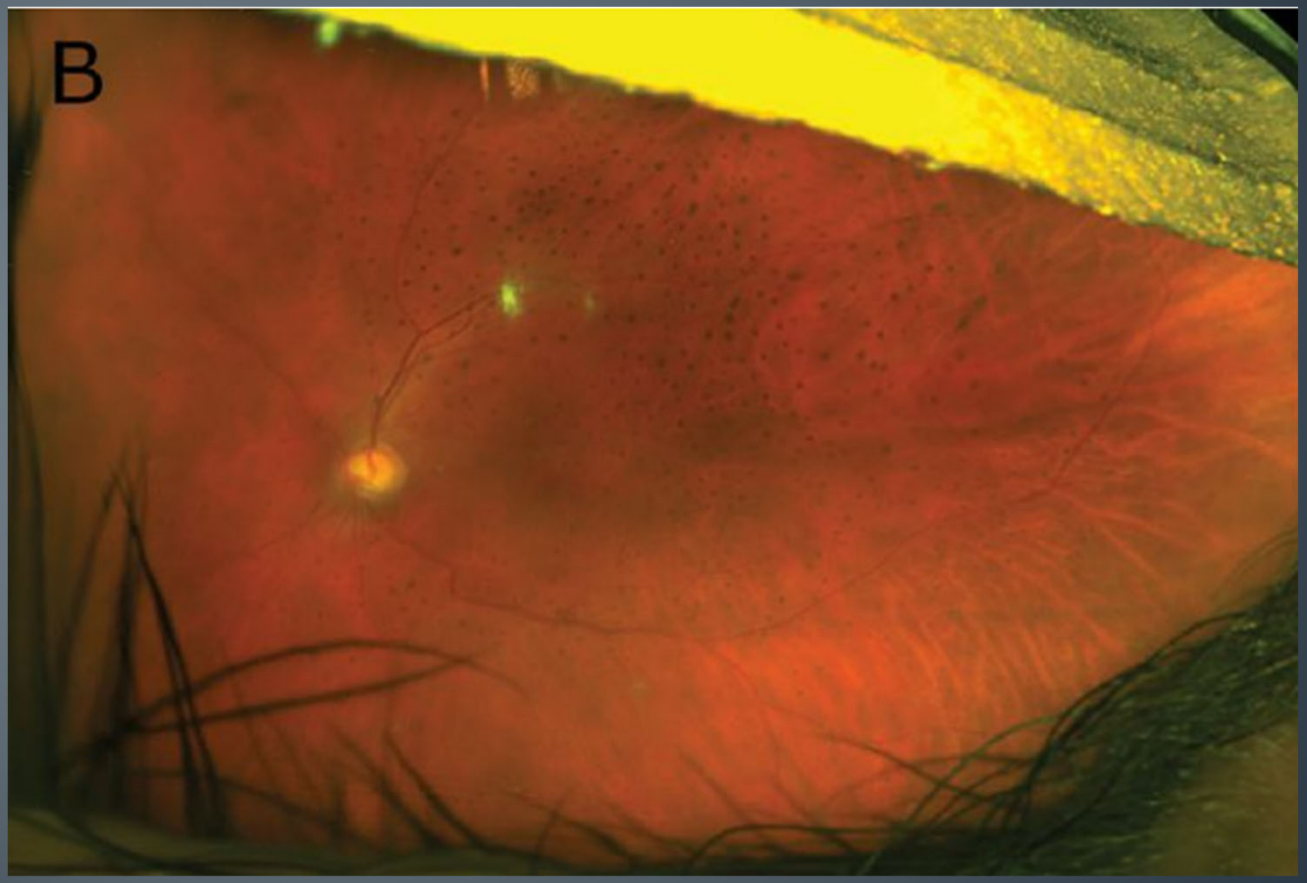
49y/o previously homeless man in a home for advanced dementia



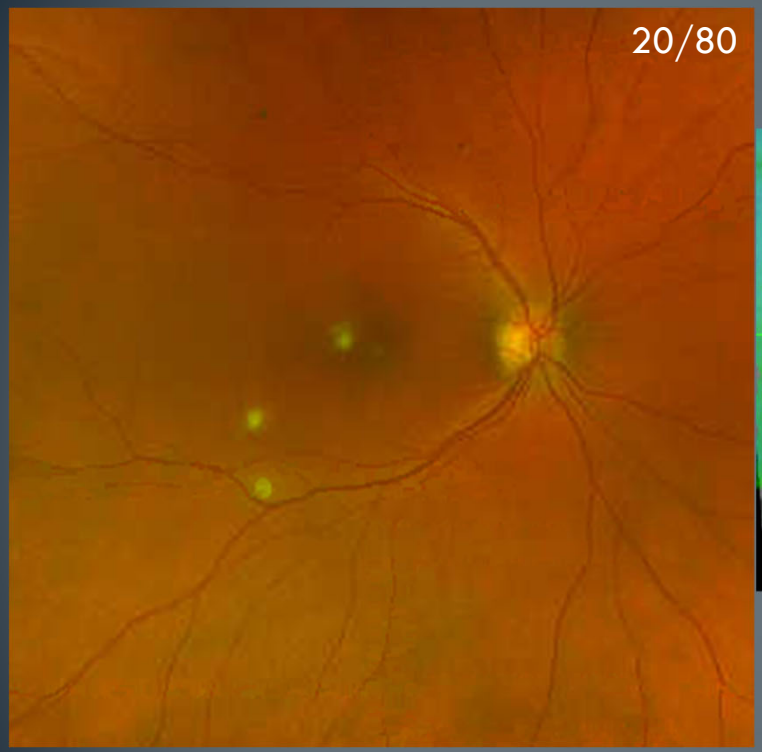
Gensure R and Flaxel CJ New Retinal Physician Oct 2022

Universal PCR: *Tropheryma whipplei*; EM: consistent

s/p Bactrim + Rifampin x 6 months



38 y/o F s/p cholecystectomy of gangrenous gallbladder; remote IVDU; now denies, unilateral vision loss OD



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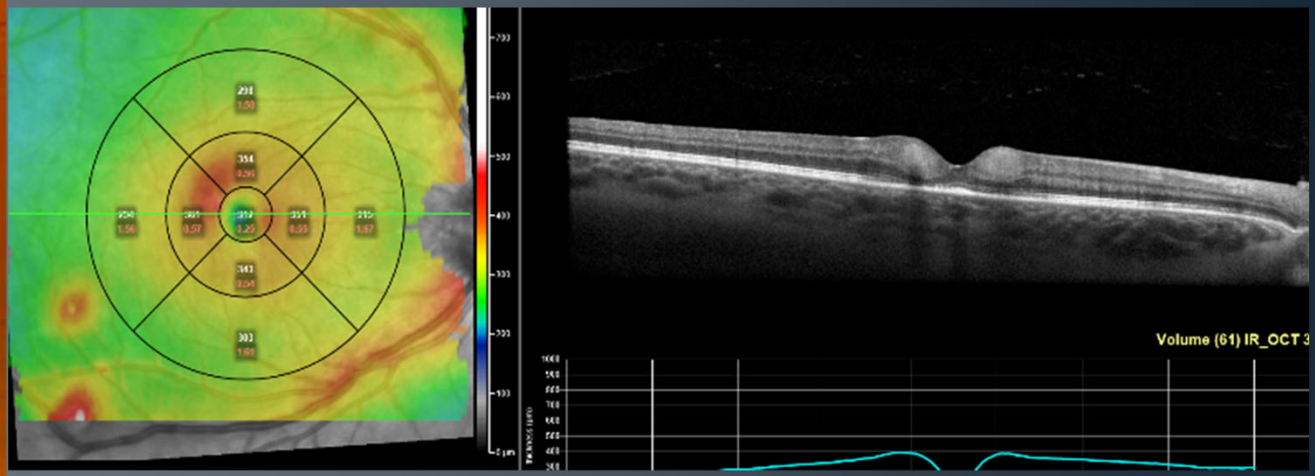
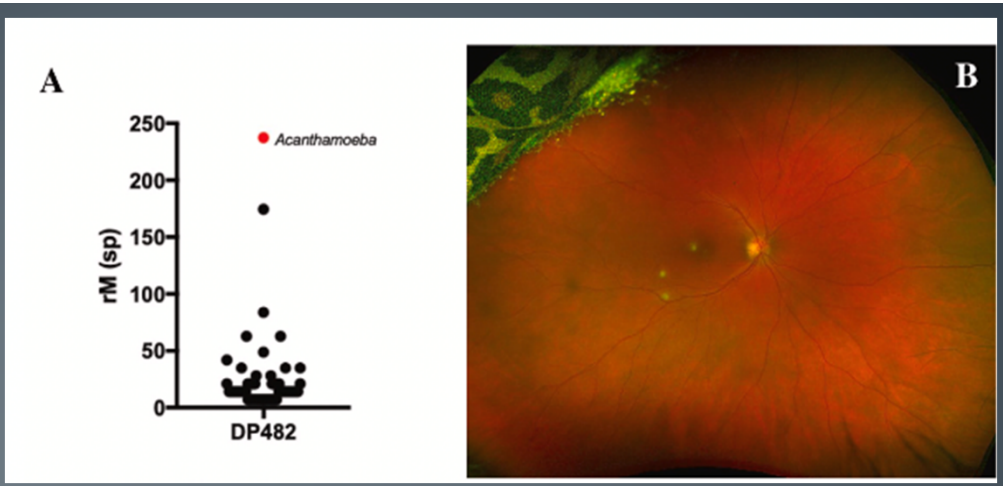
Minimal vit cell, no AC cell; OS normal
FTA and Quantiferon negative; blood cultures negative

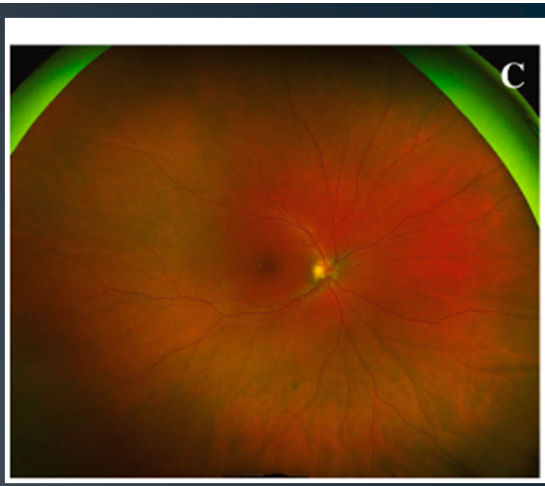


Vitreous tap x 2 negative by culture (bact/fungal)
PCR: negative fungal universal; few reads16S PCR (bacterial universal); negative Toxoplasmosis, MTB, ATM
CT-chest: 8 mm LLL nodule
Slow response to intravitreal voriconazole x 3
Prednisone PO course→ worsened

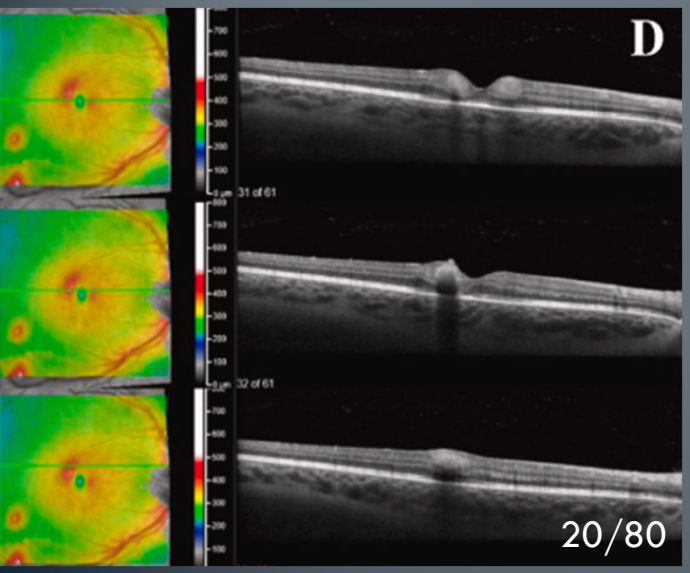
Metagenomic Deep Sequencing (Thuy Doan, MD, PhD, UCSF): many reads for Acanthamoeba

Acanthamoeba retinitis

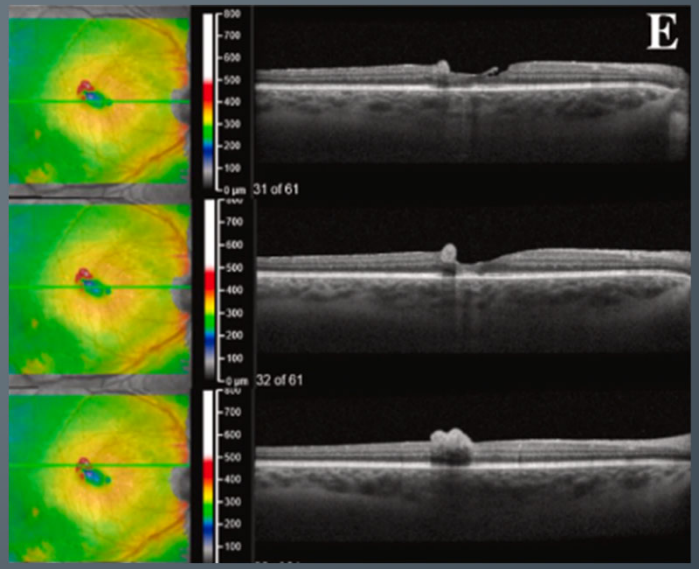




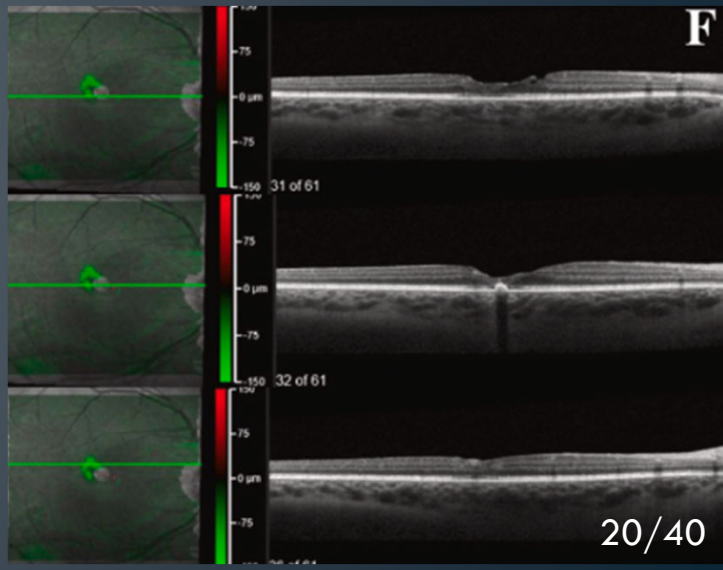
Initial presentation



1 month (s/p intravitreal voriconazole weekly)



5 months PO Bactrim + PO Voriconazole



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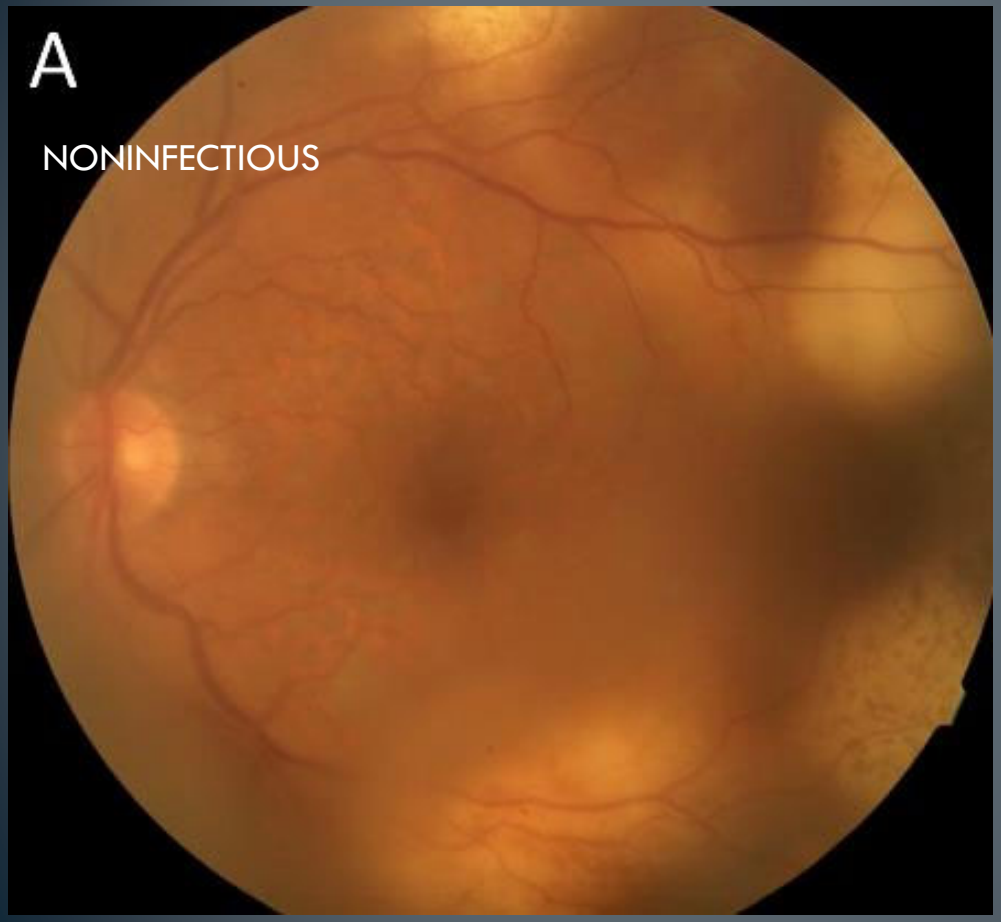
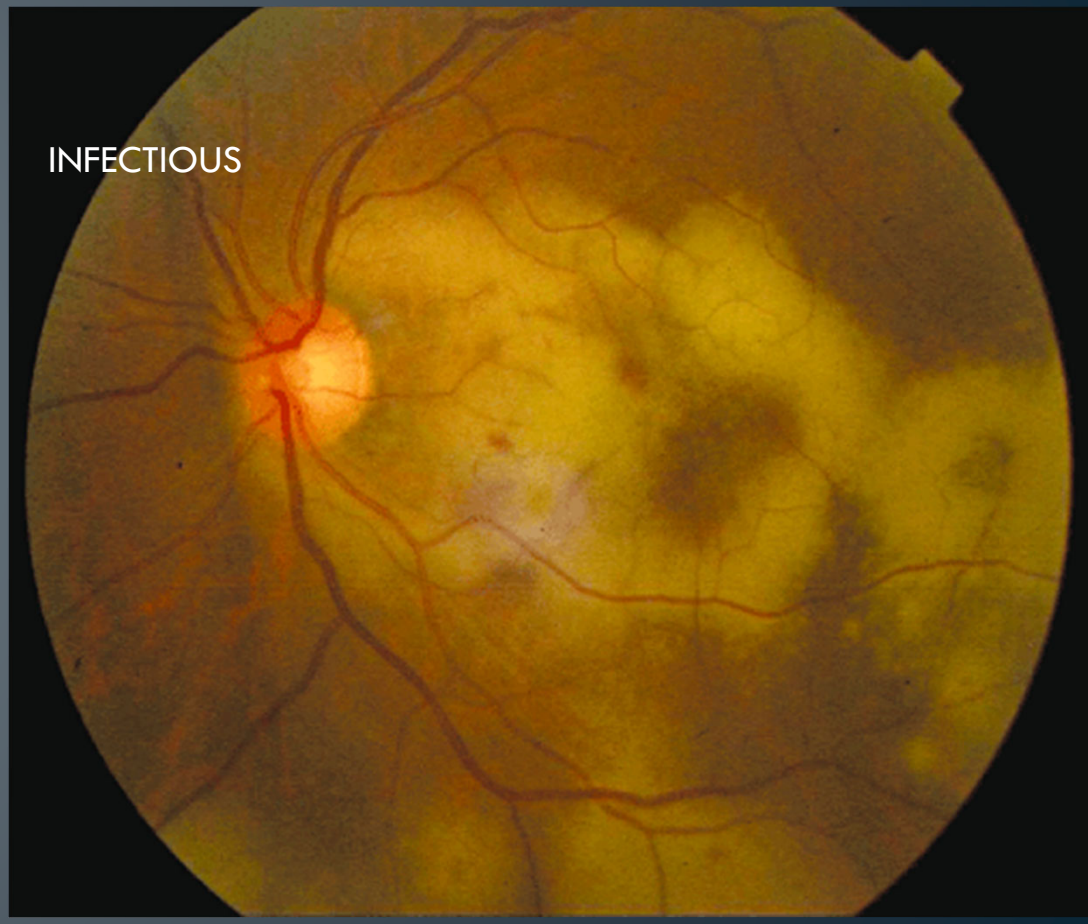
Infectious vs. noninfectious?



Vitreoretinal lymphoma



Progressive outer retinal necrosis in HIV+ pt with VZV retinitis

Pearls on how NOT to miss infectious uveitis

- Do NOT succumb to referral diagnosis: perform *de novo* examination/review of systems/medical & medication history
- Maintain high suspicion
- Maintain low threshold for testing (Aq tap→ vitreous tap→ diagnostic vitrectomy)
  - Culture, directed PCR, universal PCR, metagenomic deep sequencing (research)
- Infectious uveitis is NOT always unilateral and not always full thickness retinal necrosis
- Viral retinitis, Toxoplasmosis, syphilis, syphilis, syphilis, tb …other (whipples, C. acnes, acanthamoeba!)

Thank you!

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