

Mycobacterial Ocular Inflammation



Akbar Shakoor, M.D.

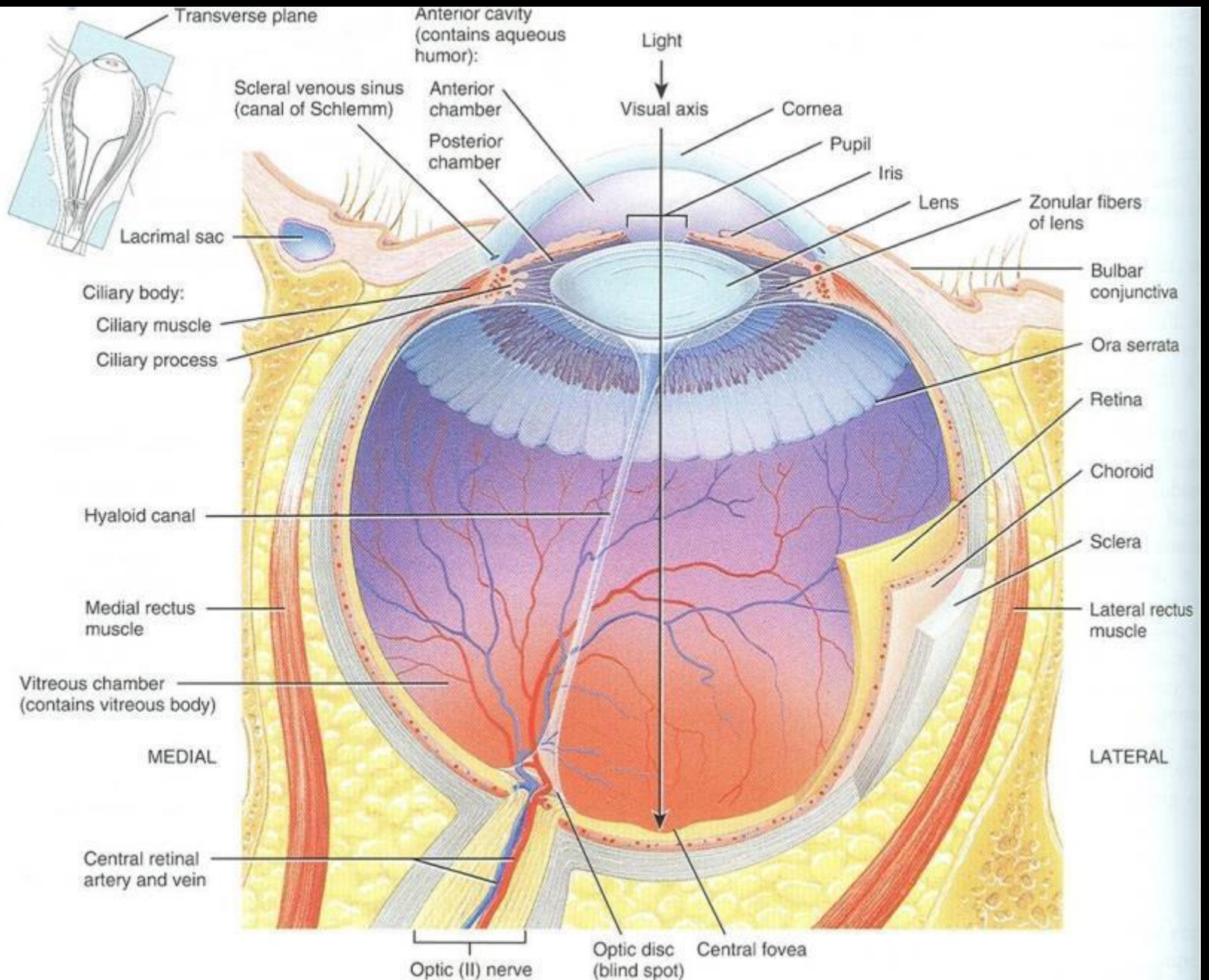
John A. Moran Eye Center, University of Utah

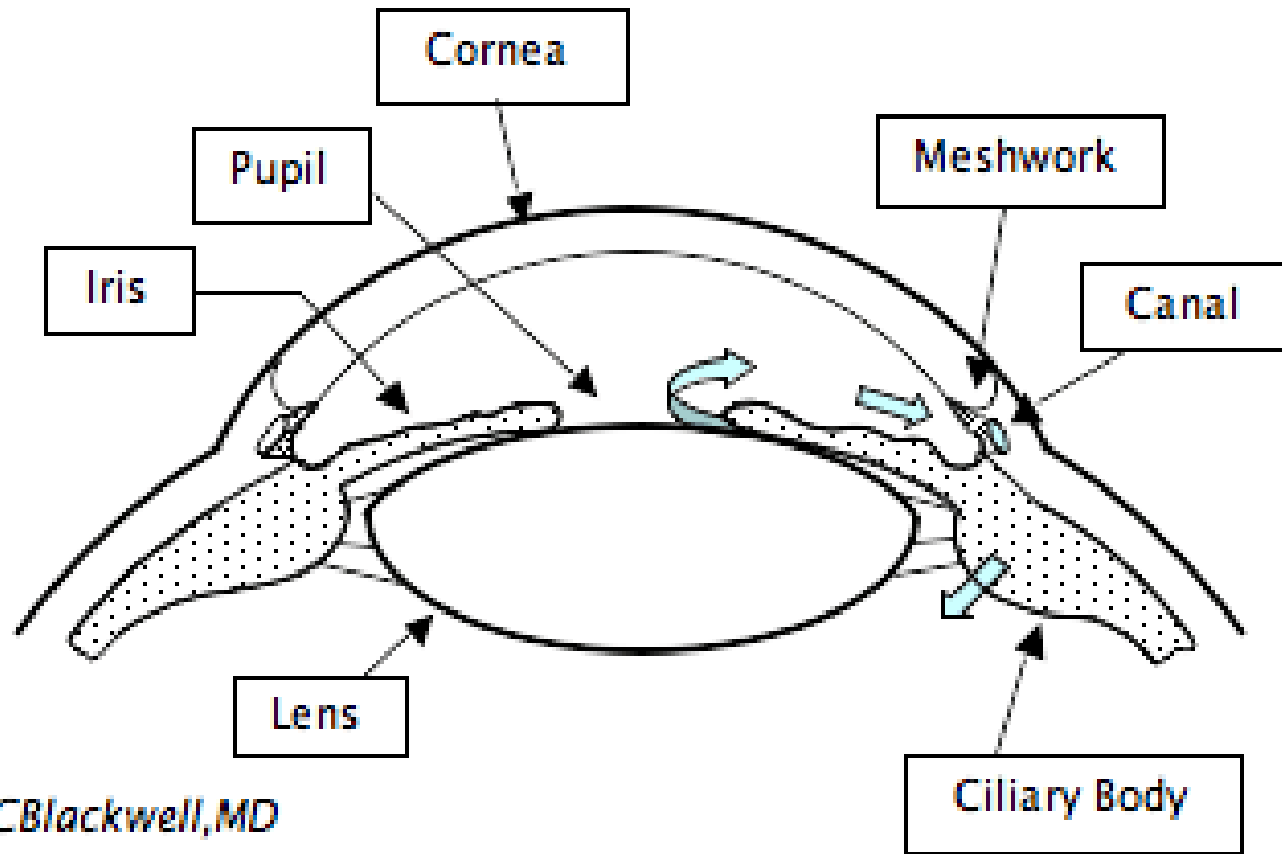
Financial Disclosure

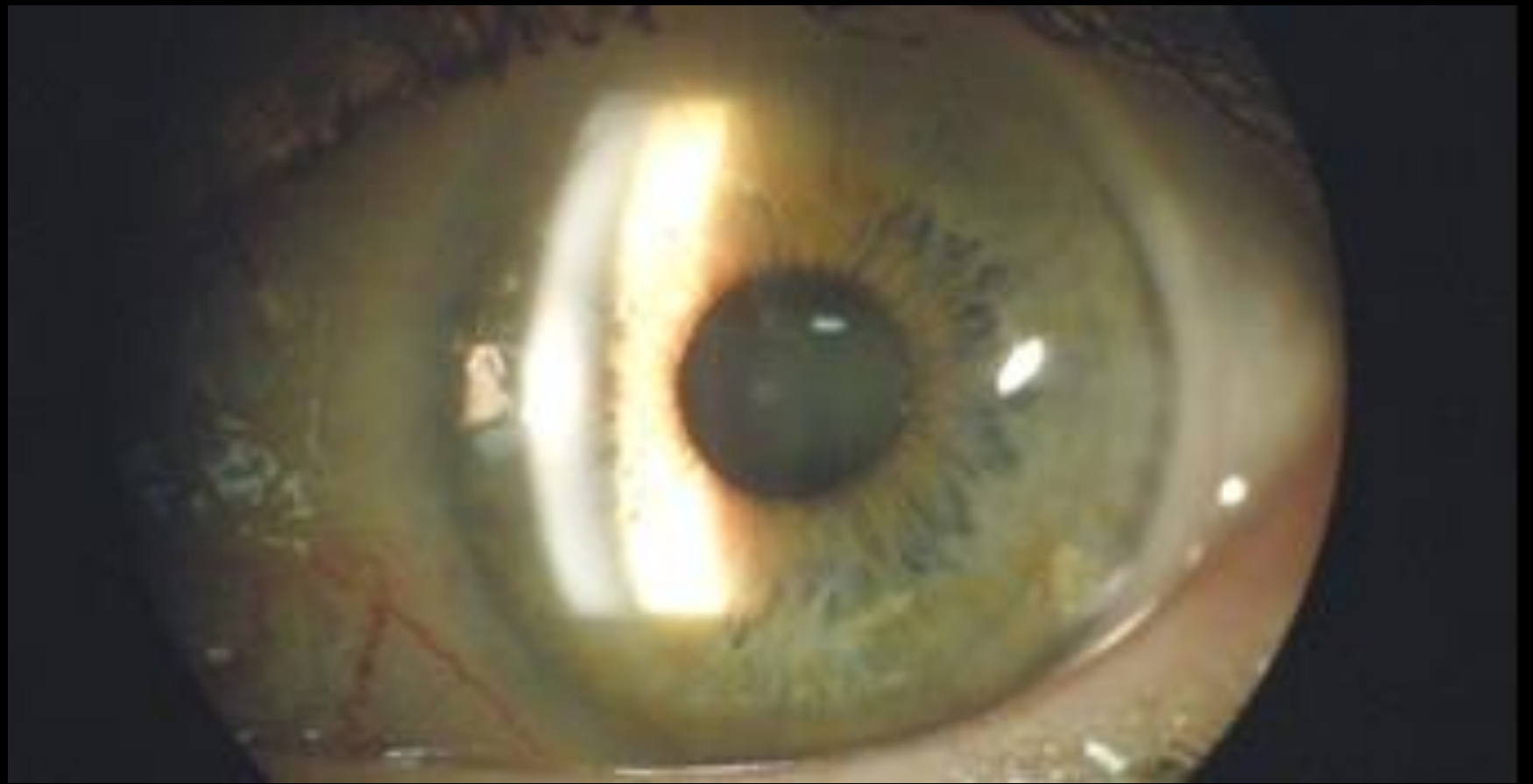
- I have no financial interests or relationships to disclose.

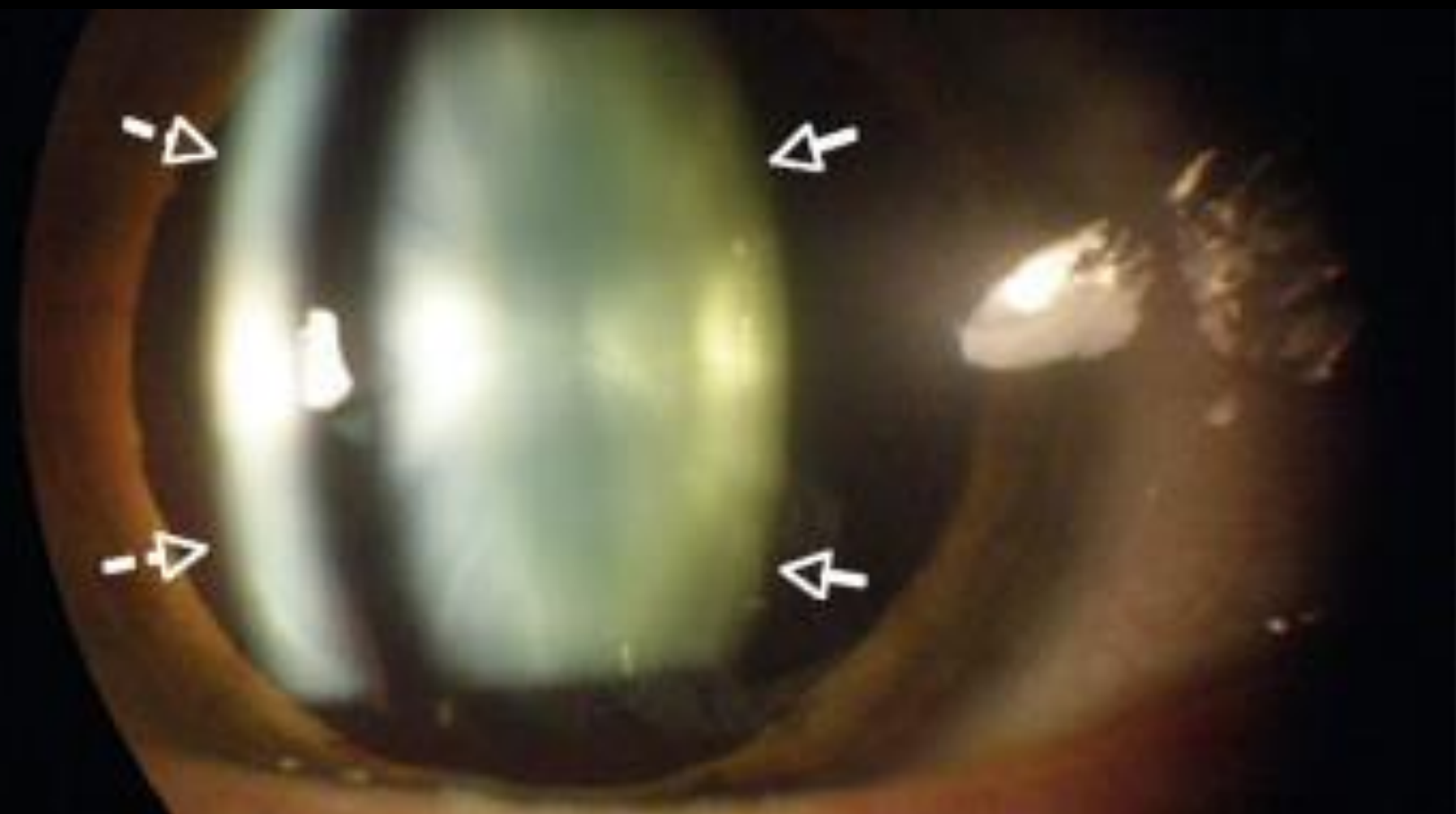
Applied anatomy

- What structures may be involved in ocular inflammatory diseases?

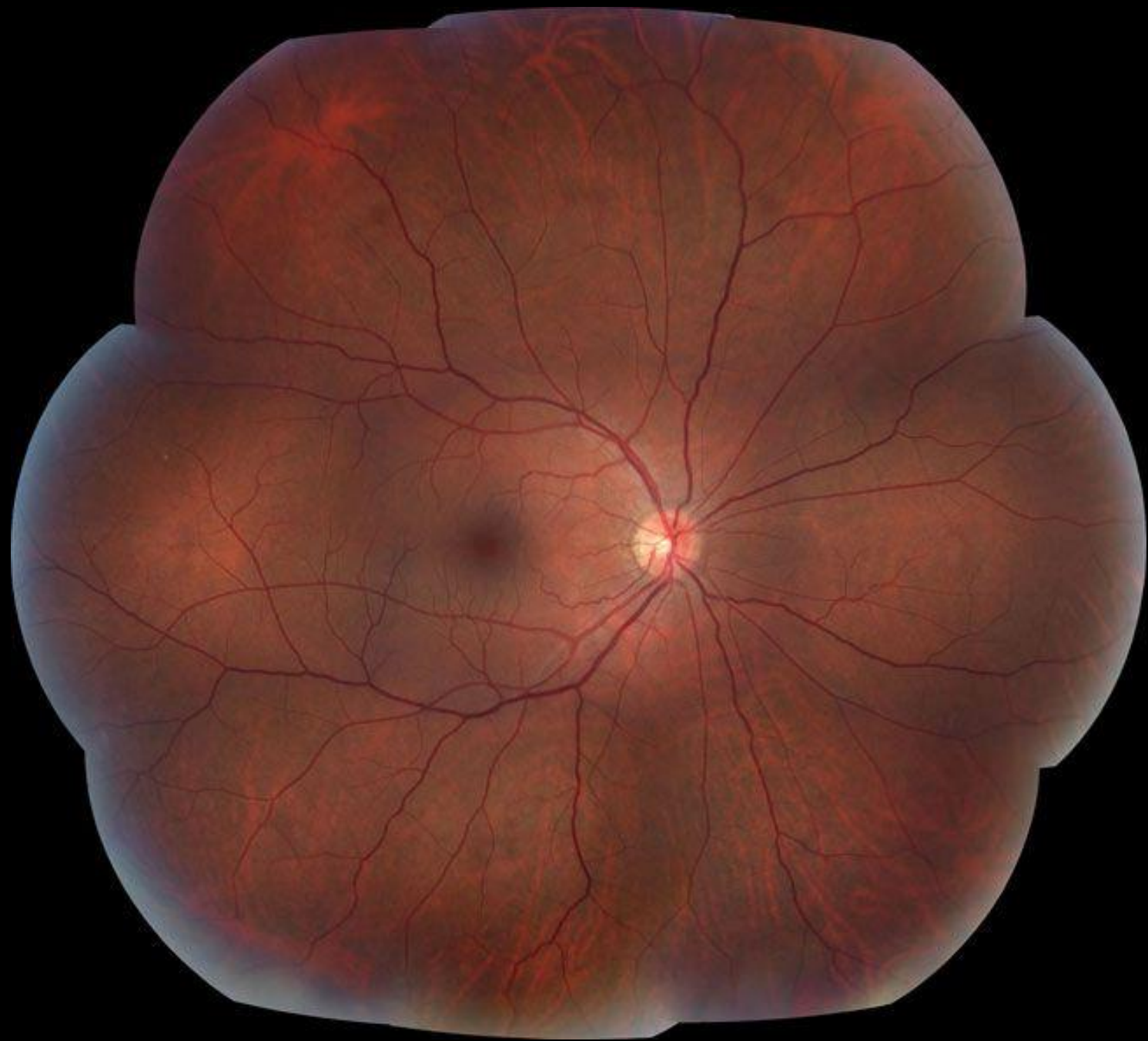


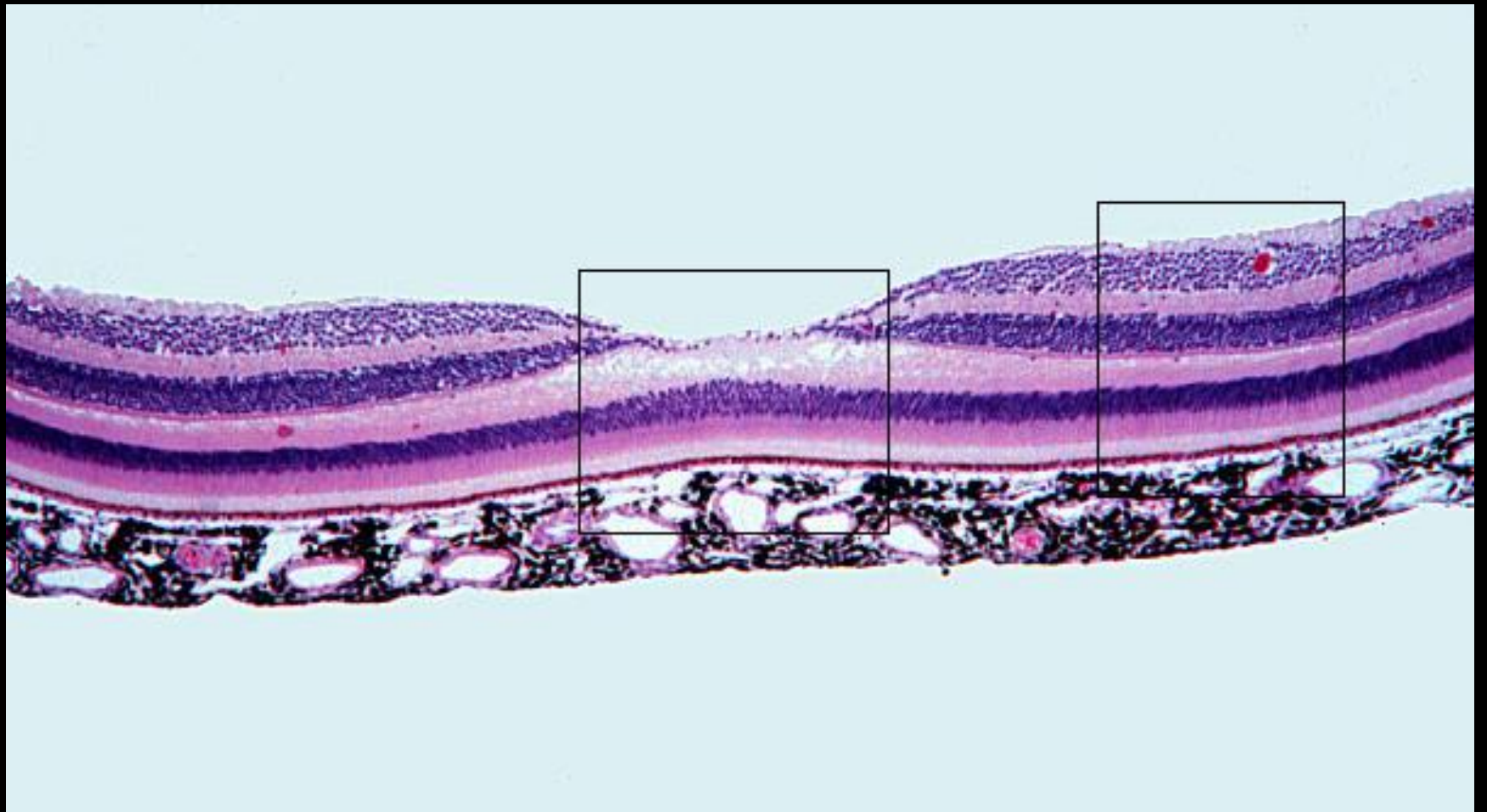


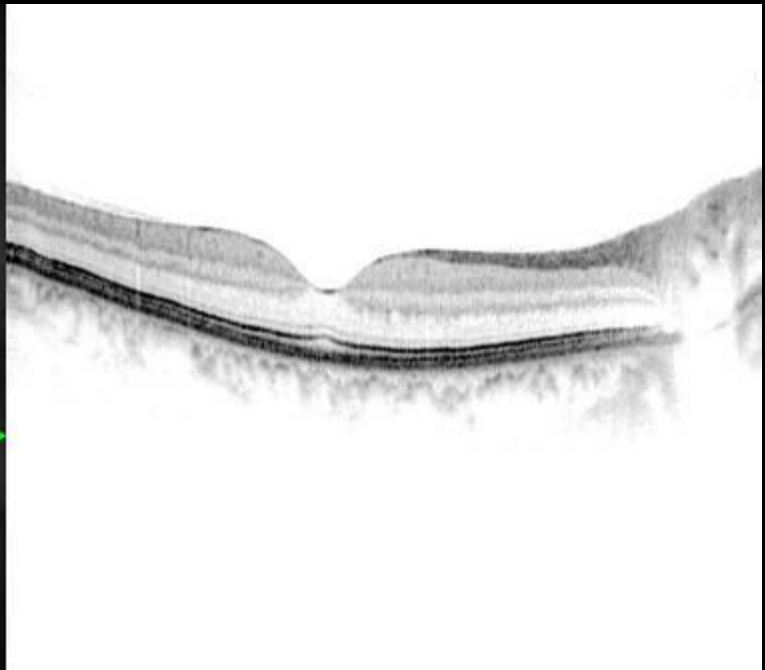
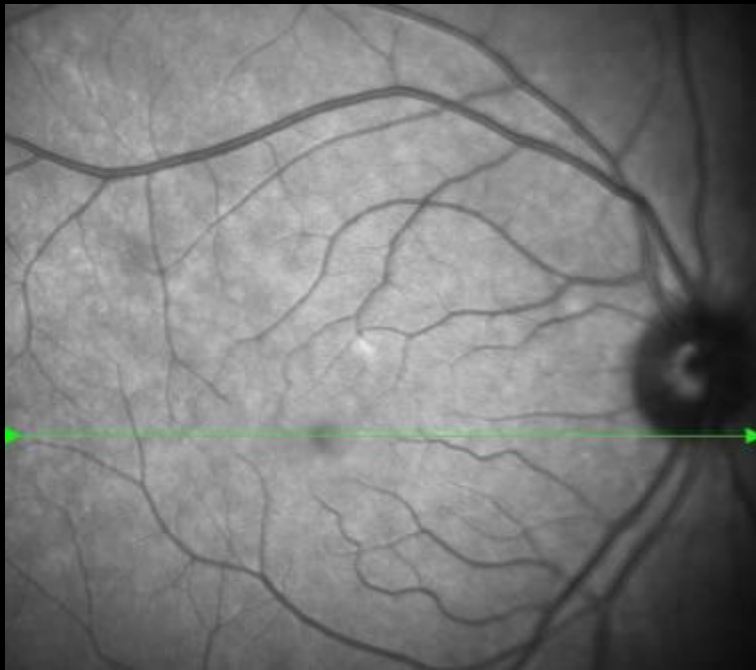




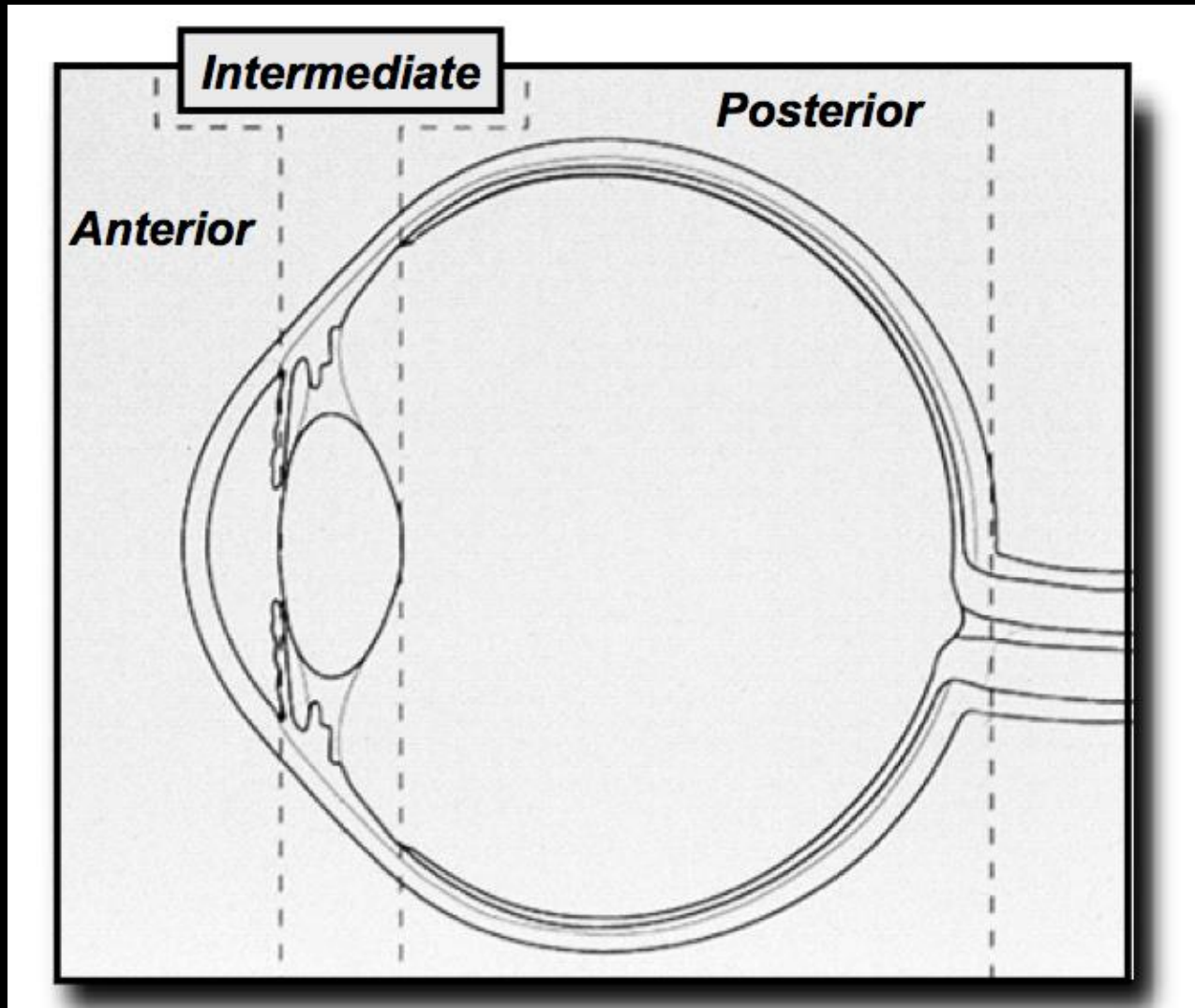








Anatomical location of inflammation



Ocular immune diseases

- Uvea - *Uveitis*
 - Iridocyclitis/iritis
 - Trabeculitis
 - Parsplanitis
 - Choroiditis
- Vasculature - *Vasculitis*
- Connective tissue
 - Scleritis
 - Orbital inflammatory disease

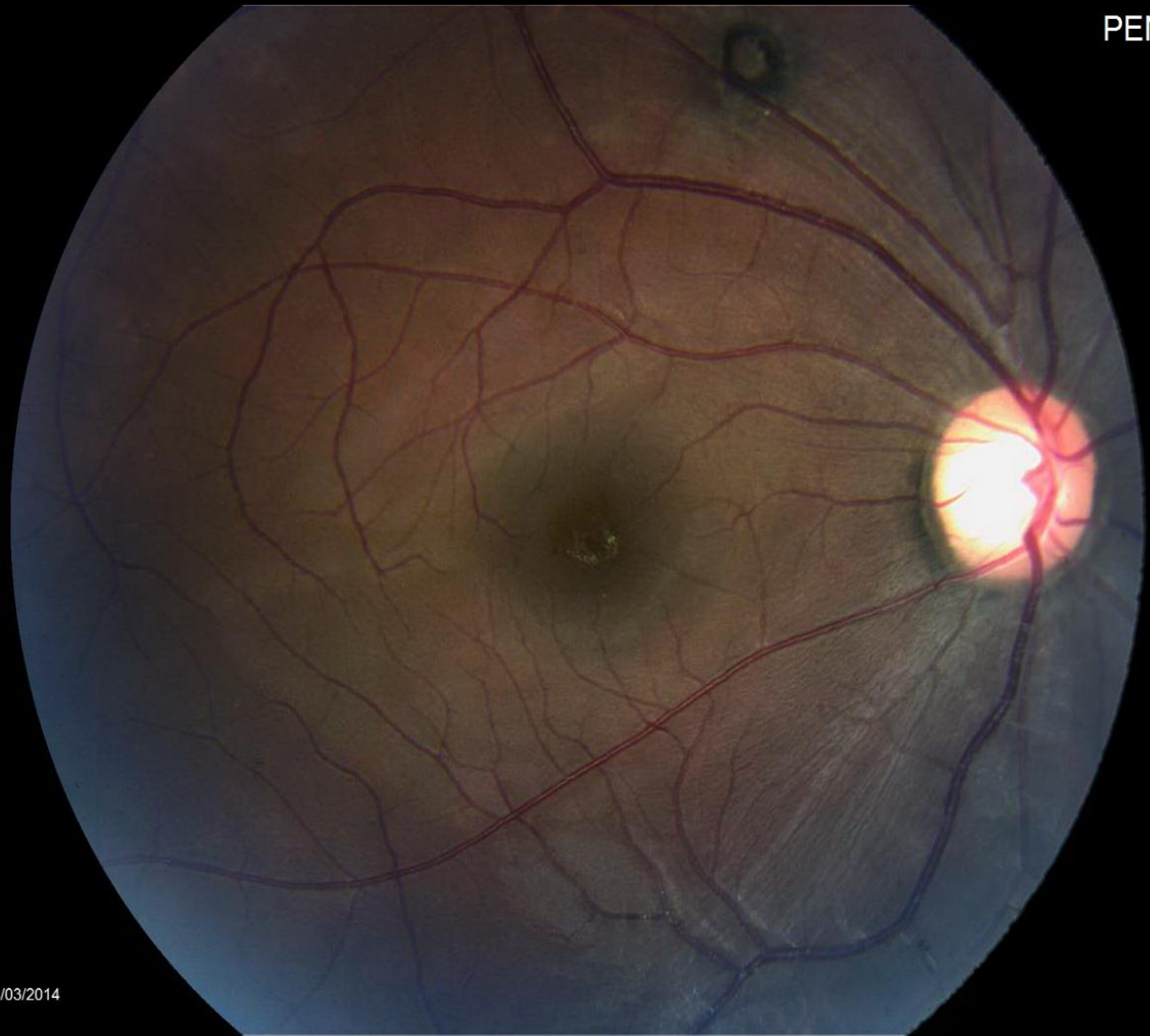
Patient CF

28 year old gentleman from Haiti

Pain and blurry vision in his left eye
for 3 months

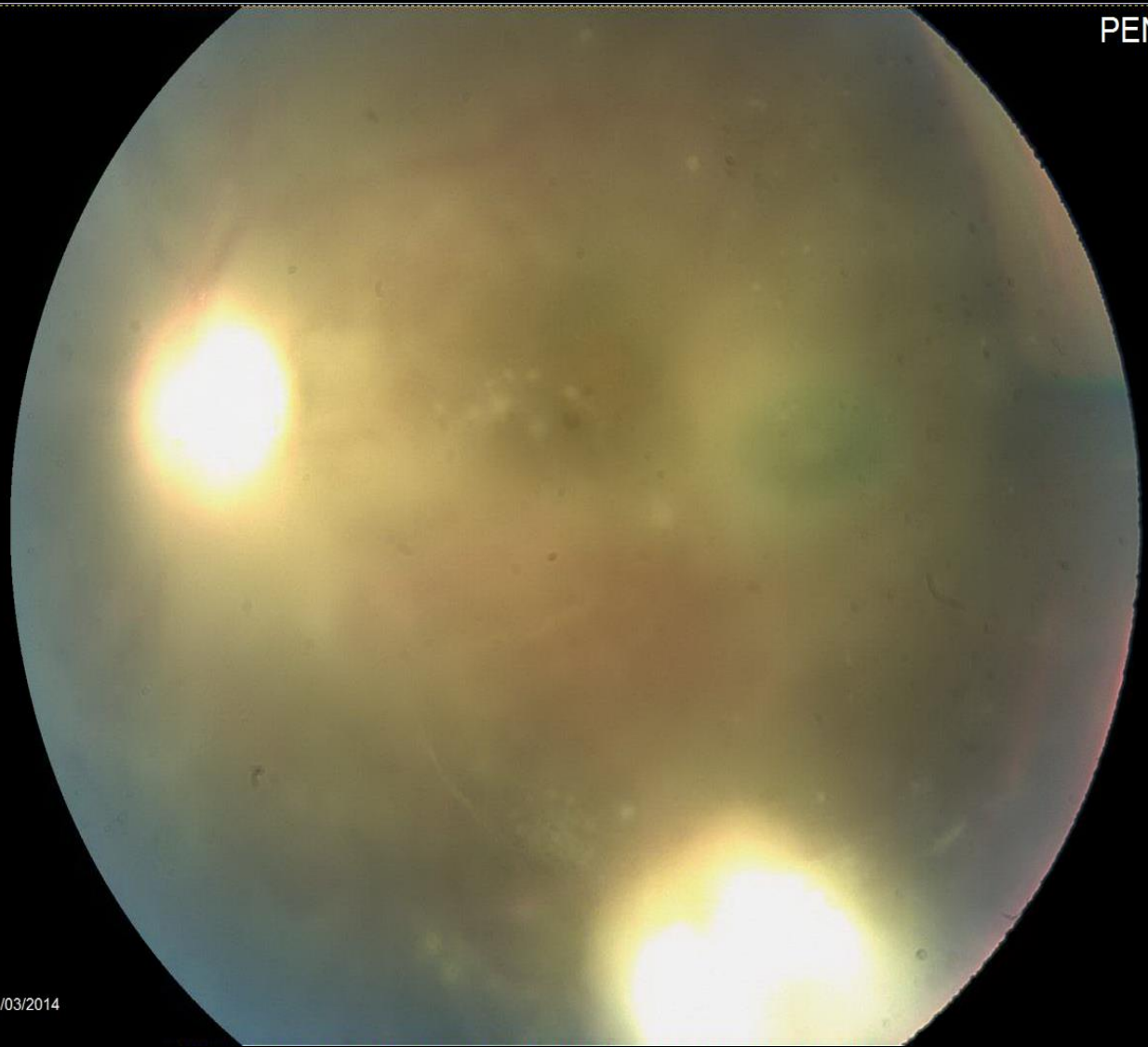
PEN

- Unremarkable right fundus photograph



04/03/2014
4

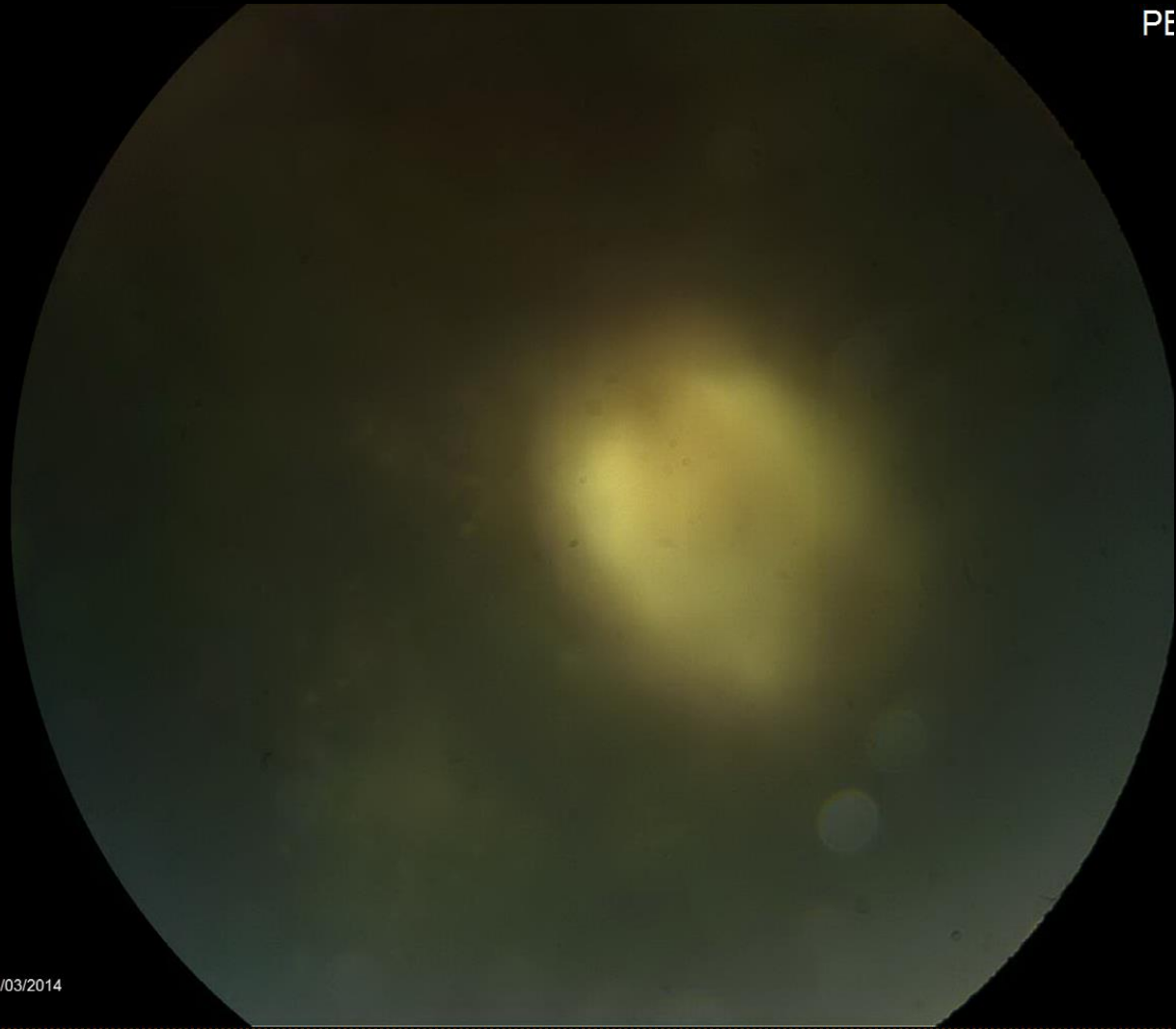
- Left fundus:
Vitreitis/ hazy
view with
significant
macular scarring
and inferior
retinochoroidal
granuloma



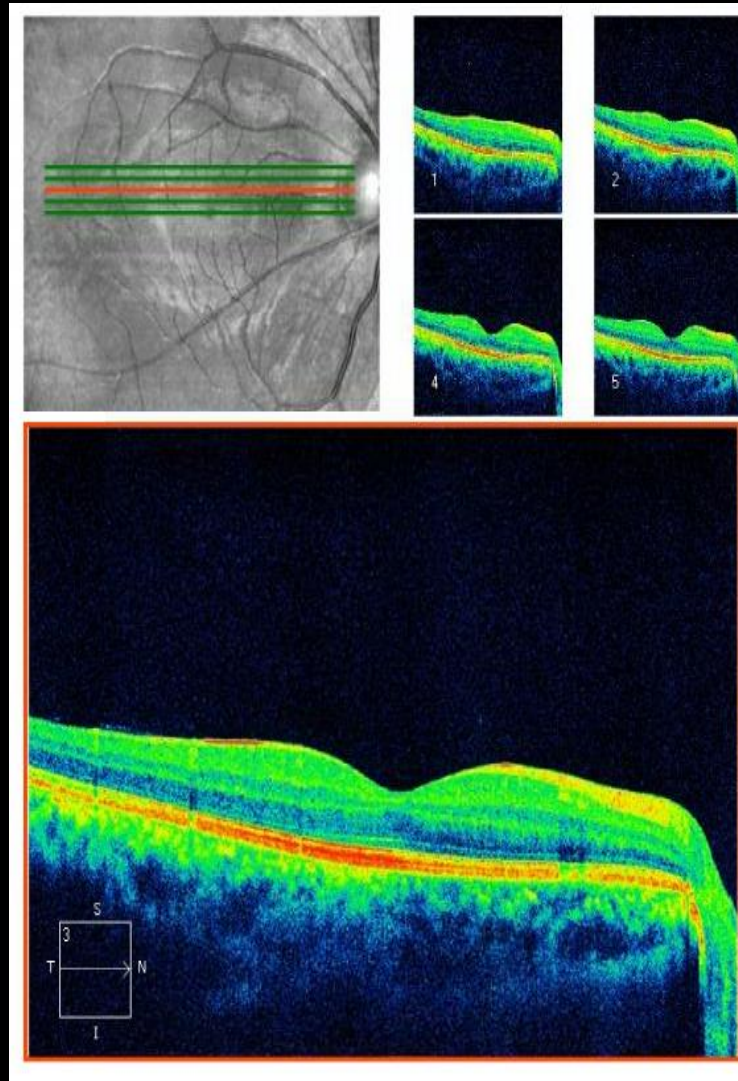
PE

- Choroidal granuloma with overlying vitreous opacity and surrounding choroidal nodules

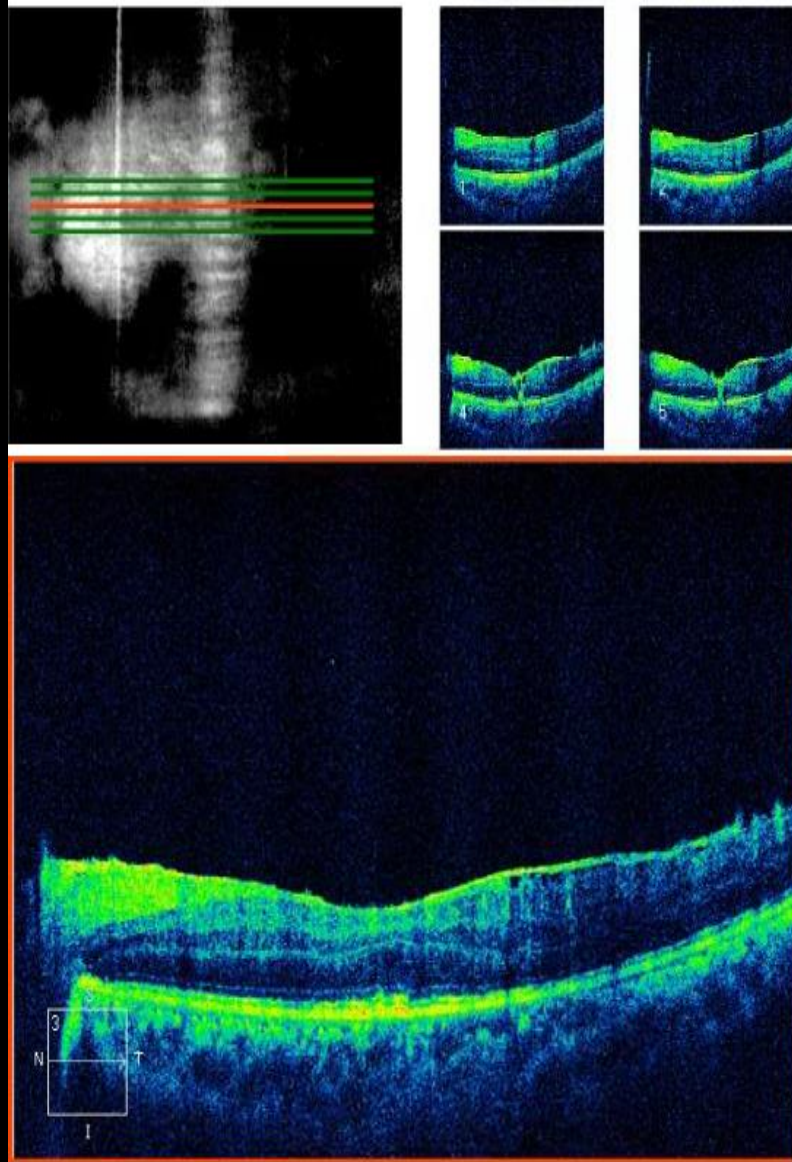
4/03/2014



- Optical coherence tomography:
Normal right macula



- Optical coherence tomography: Abnormal left macula with vitreitis and epiretinal membrane



- Vitrectomy with large volume vitreous aspirate sent for PCR
- Negative for mycobacterial DNA
- PPD positive, Quanteferon gold positive
- Good response to 4 drug therapy

Patient MS

- 54-year-old woman originally from Mexico
- Redness and pain OD for 6 months, diagnosed with nodular scleritis
- Did not improve with PO prednisone and referred in 2015
- PMH: diabetes on insulin, hypertension, hypercholesterolemia, atrial fibrillation on Coumadin

Patient MS

- Large yellow nodules consistent with infectious scleritis
- QuantiFERON positive
- CXR and CT chest bilateral hilar adenopathy



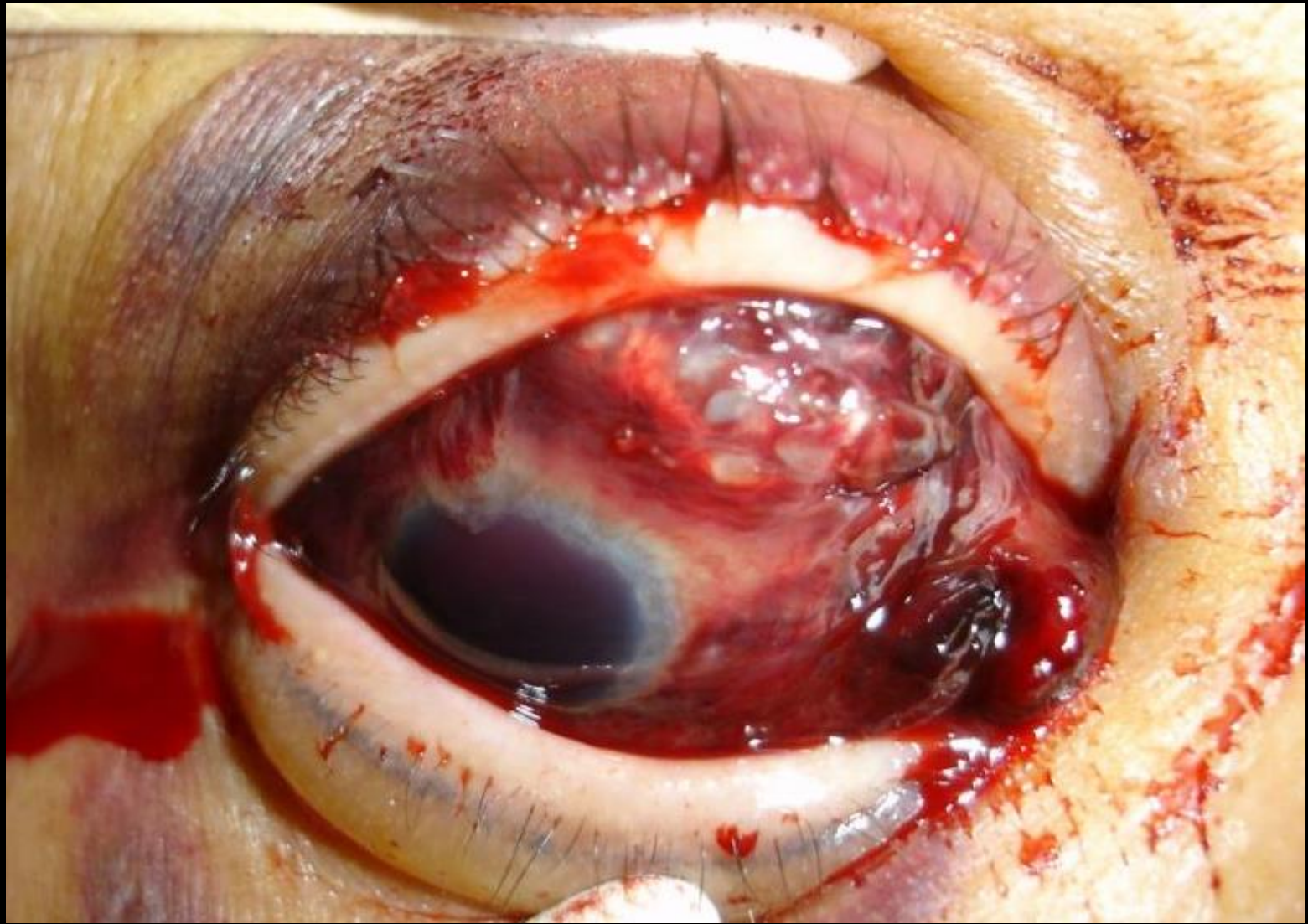
Patient MS

- Started on 4 drug therapy for TB, continued on prednisone, variable doses, MTX added
- Scleritis progressed



Patient MS

- Scleral biopsy
 - Gram stains, AFB stain and bacterial cultures negative
 - Microscopy: extensive scleral necrosis without classic granuloma formation
 - Tissue Gram stain and stains for AFB (Ziehl-Nielson and Fite stains) were negative
- On and off TB therapy and multiple IMT elsewhere
- Returned 4 months later to ER
 - Not compliant with TB meds
 - Not taking insulin
 - Still taking Coumadin but not obtaining lab tests
 - Vomiting, in DKA
 - ER noted “blood from eye”

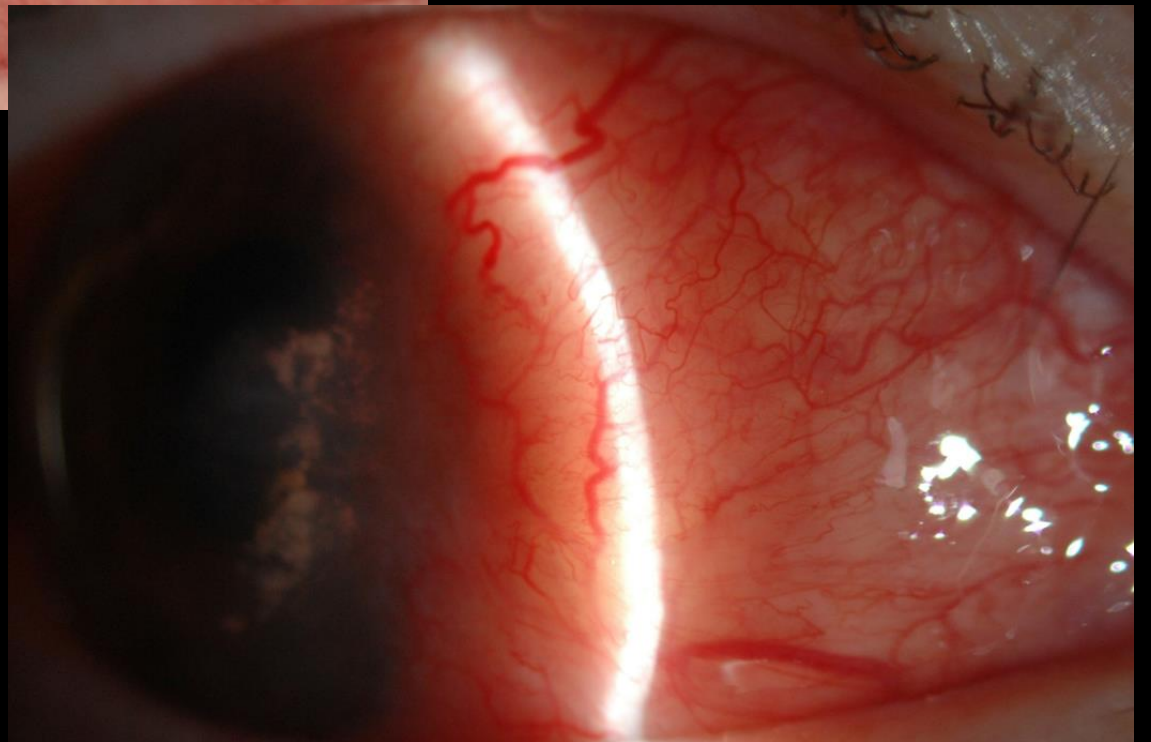
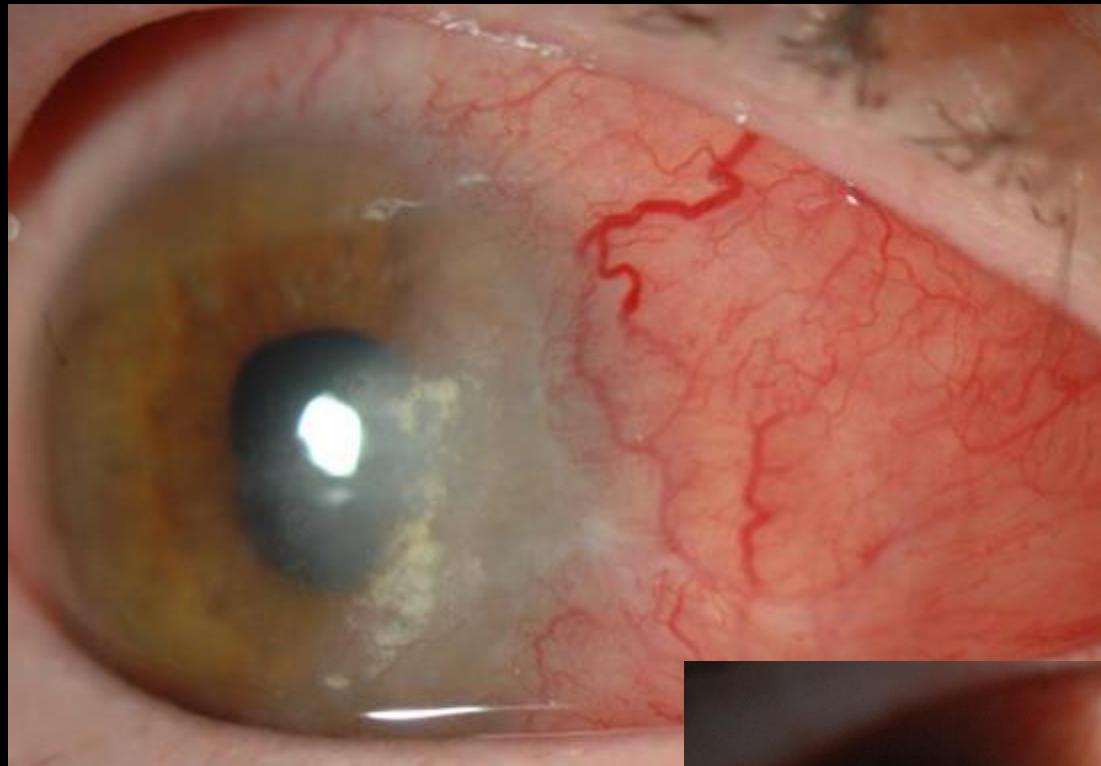


Histopathology of globe

- Extensive necrotizing scleral and uveal inflammation
- Stains for AFB and cultures were negative
- Ocular Pathology Laboratory, Doheny Eye Institute (Narsing Rao)
 - Realtime PCR revealed *M tuberculosis* genome
 - 702 copies of mycobacteria in four 20- μ m histologic sections
 - “Histopathologic detection of acid fast organisms is not a sensitive method if the bacteria are few in number”

Patient MKS

- 60 year old Caucasian woman seen first 2010
- Worsening eye pain and redness OD
- Extensive prior work up negative
- Poor response to local and systemic corticosteroids



MKS

- QuantiFERON positive
- CXR normal
- ID would not treat as TB
- Progressive worsening of scleritis





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REPORT FORM

Clinical Specimen: Paraffin section of conjunctival granuloma received from Dr.Deepak Edward, USA

FINAL REPORT

Methodology : Nested Polymerase Chain Reaction targeting IS6110 region

S.no	VRF number	PCR targeting IS6110 region for the detection of <i>M. tuberculosis</i> complex genome
1	VRF 5883/10 a	Positive
2	VRF 5883/10 b	Positive
3	VRF 5883/10 e	Negative
4	VRF 5883/10 d	Positive
5	VRF 5883/10 e	Positive

Agarose gel electrophotogram showing the results of nPCR targeting IS6110 region of *Mycobacterium tuberculosis* complex genome

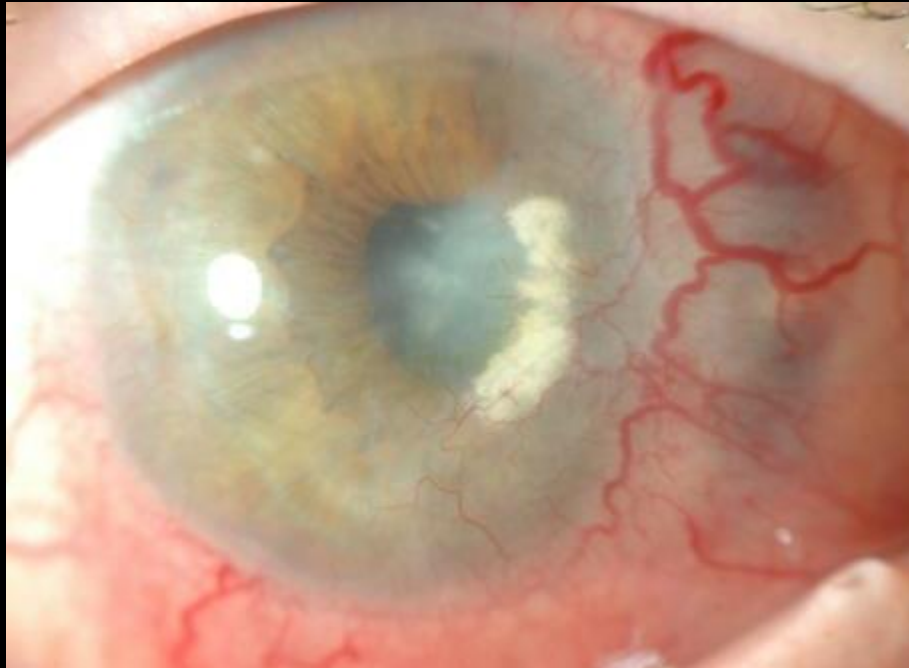
NC1 NC2 1 2 3 4 5 PC MW



NC1-NEGATIVE CONTROL 1
NC2-NEGATIVE CONTROL 2
LANE1-VRF 5883/10a(POSITIVE)
LANE2-VRF 5883/10b(POSITIVE)
LANE3-VRF 5883/10c(NEGATIVE)
LANE4-VRF 5883/10d(POSITIVE-FAINT BAND)
LANE5-VRF 5883/10e(POSITIVE)
PC-*Mycobacterium tuberculosis* H37RV
MW-MOLECULAR WEIGHT MARKER(100bp)

MKS

- 4 drug TB therapy finally started
- Prednisone, Cellcept
- Despite this, globe perforated 10 months after presentation



- Pathology: mass composed of caseating granulomas with central abscesses

Tuberculosis: Etiology/Epidemiology

- *M. tuberculosis* infection or inflammatory reaction
- Worldwide: 9 million cases 2013
 - 1.5 million TB related deaths
- USA: 9,582 active cases reported to CDC 2013
 - 3.0/100,000
 - 536 deaths 2011
- 1% to 2% systemic TB develop ocular disease
- High rates among
 - Endemic areas
 - HIV, immigrants, elderly and minority populations
 - Elderly highest non-HIV case rate

Chan et al., Clin Immunol 2004;110: 2

Munsiff et al., Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:361

Tuberculosis: Ocular Findings

- Intraocular inflammation

- Posterior uveitis (most common presentation)
- Tuberculoma (immunocompromised host)
- Multifocal choroiditis (miliary disease)
- Anterior uveitis (granulomatous/nongranulom)
- Vitritis
- Retinal vasculitis
- Panuveitis

- External disease

- Tubercles: lids/conjunctiva
- Corneal phlyctenule
- Conjunctivitis
- Scleritis
- Interstitial keratitis



Biswas et al Retina 1995;15:461

Gupta et al., 2003 Ophthalmology; 110:1744

Intraocular Tuberculosis—An Update

Vishali Gupta, MD,^{1,2} Amod Gupta, MD,² and Narsing A. Rao, MD¹

¹*Doheny Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California; and* ²*Department of Ophthalmology, Post Graduate Institute Of Medical Education & Research, Chandigarh, India*

TABLE 1

Clinical Presentation in Intraocular Tuberculosis

1. Anterior uveitis	Granulomatous, nongranulomatous, iris nodules, ciliary body tuberculoma
2. Intermediate uveitis	Granulomatous, nongranulomatous with organizing exudates in the pars lana/ peripheral uvea.
3. Posterior and panuveitis	Choroidal tubercle Choroidal tuberculoma Subretinal abscess Serpiginous-like choroiditis
4. Retinitis and retinal vasculitis	
5. Neuroretinitis and optic neuropathy	
6. Endophthalmitis and panophthalmitis	

Eales disease is considered by some to reflect tuberculous infection/hypersensitivity.

Multifocal Serpiginous Choroiditis

- M (70%)> F
 - Middle age (mean 33 yrs.)
- Evidence ocular or non-ocular TB
 - PPD, QuantiFERON gold
 - CXR, PCR (AC, vitreous)
- Non-contiguous multifocal choroiditis
diffuse plaque-like choroiditis
 - Bilateral (60%)
 - Vitritis (80%)
- Treatment
 - ATT and corticosteroids
 - IMT for progression

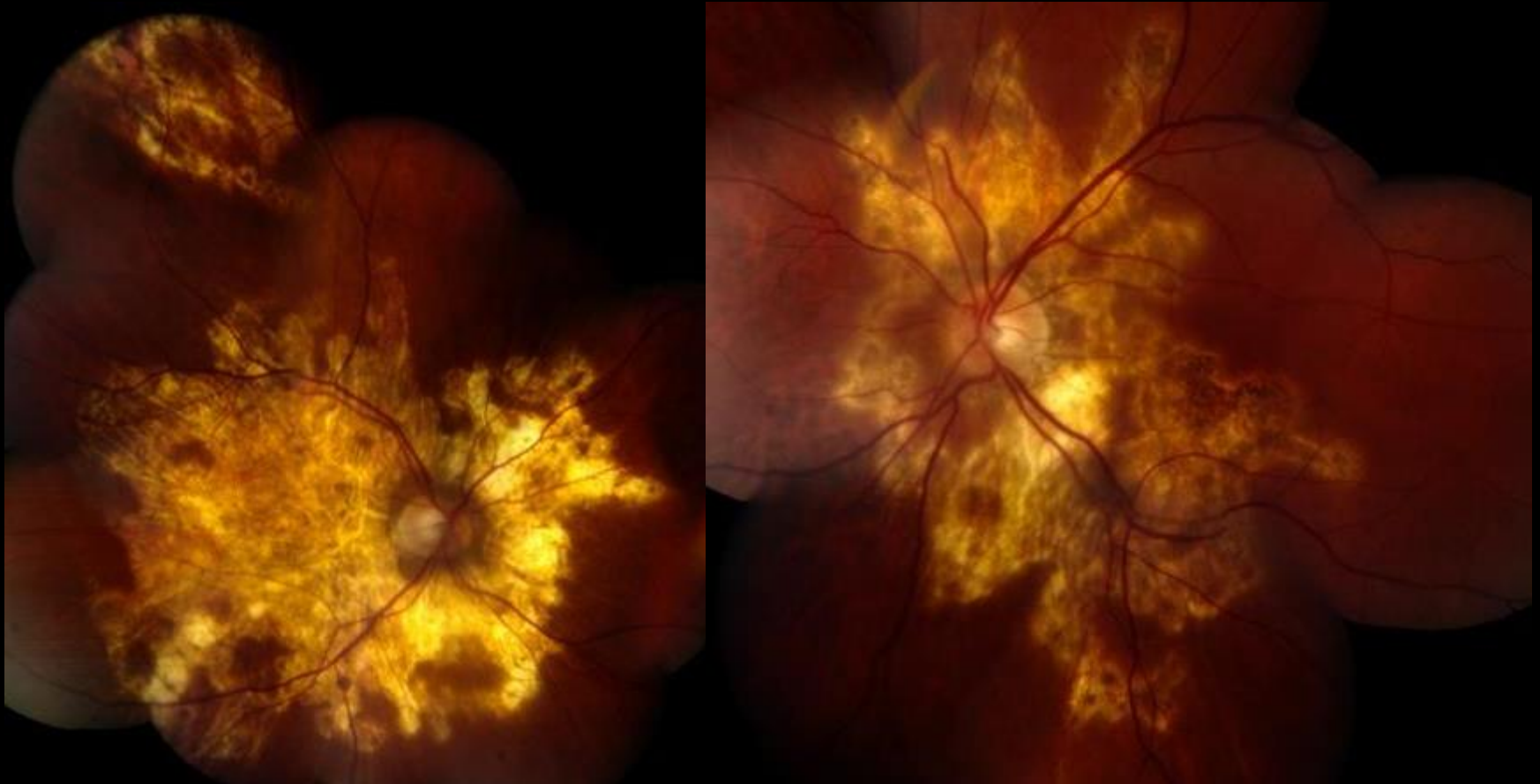


Courtesy Narsing Rao,
MD

Bansal R, et al. Ophthalmology 2012;119; 2334

*Khanamiri NH, Rao NA. SurvOphthalmol.
2013;58:203*

Multifocal serpiginoid choroiditis

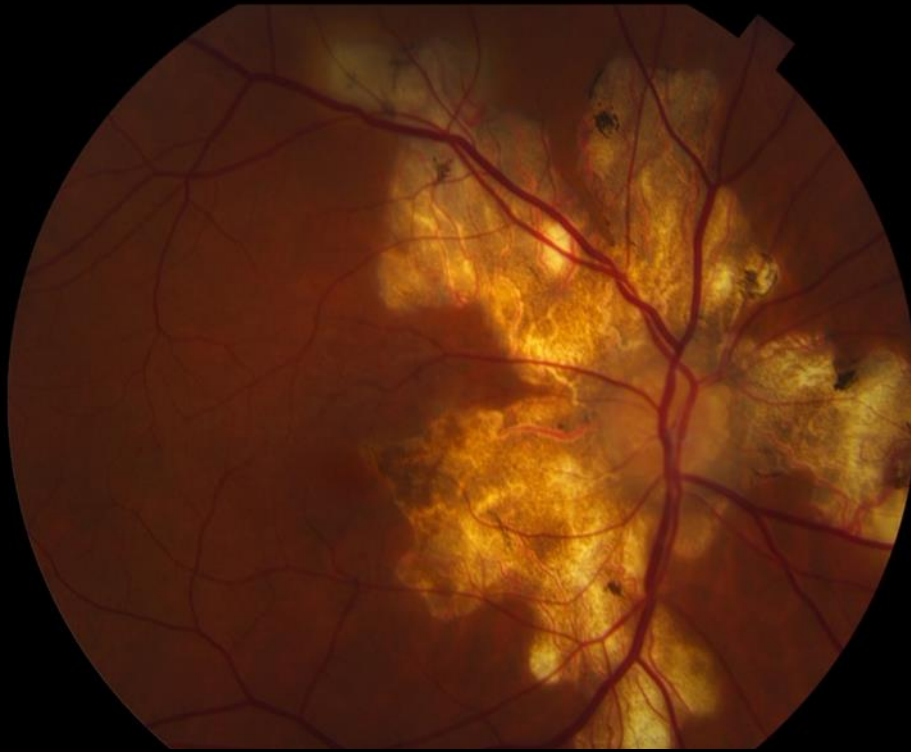


62 year old male referred with worsening serpiginous after two years prednisone and IMT.

Had subtle interstitial keratitis right eye
PPD positive. Note peripheral lesions

Serpiginous choroiditis vs infectious multifocal serpiginoid choroiditis

- Features suggesting TB (Narsing Rao)
 - Endemic area
 - Multifocality of lesions
 - Unilaterality of lesions
 - Vitreous or AC reaction
 - Early lesions are macular rather than peri-papillary
 - Response to ATT

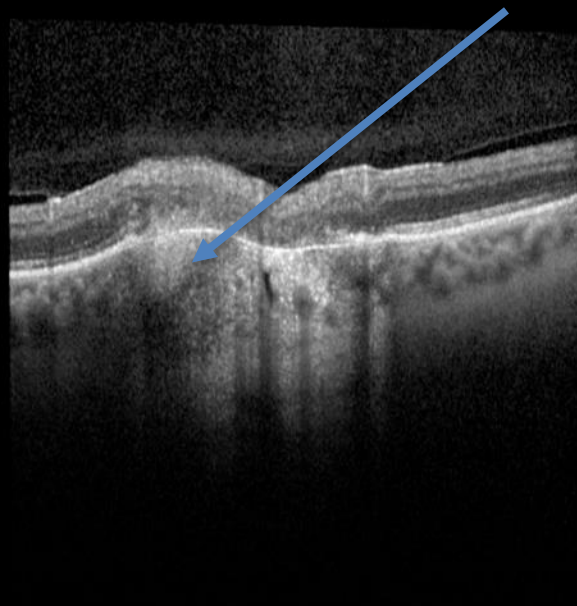
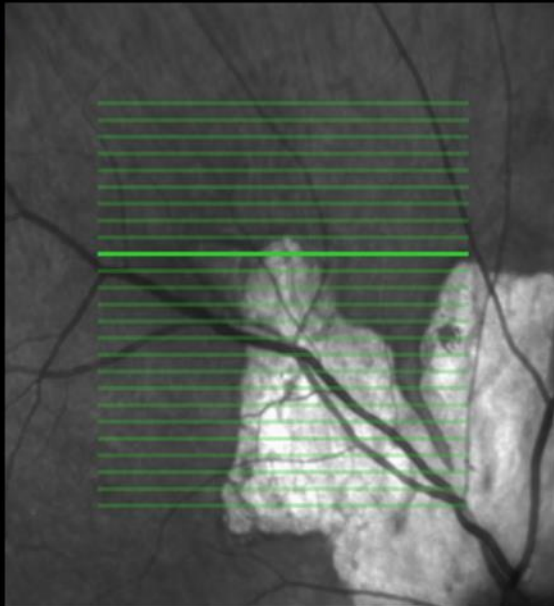


60 year old Caucasian woman from Poland
Positive Quantiferon, CT chest evidence prior granulomatous disease

Note appearance of choroidal lesion

Oct 09, 2013 (OU) ▾

OD Volume (11339) ▾



Tuberculous Uveitis

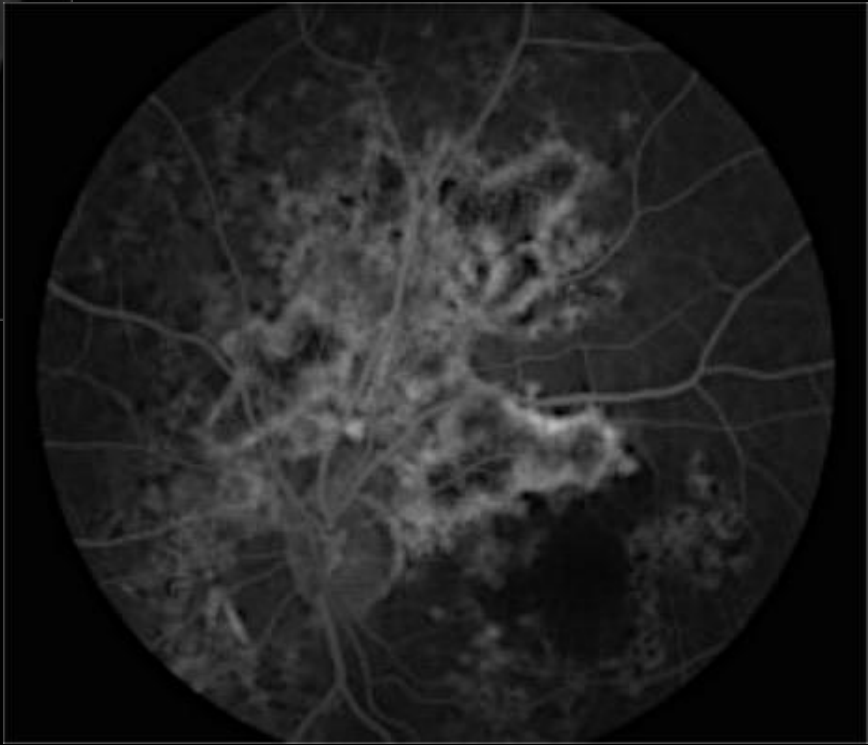
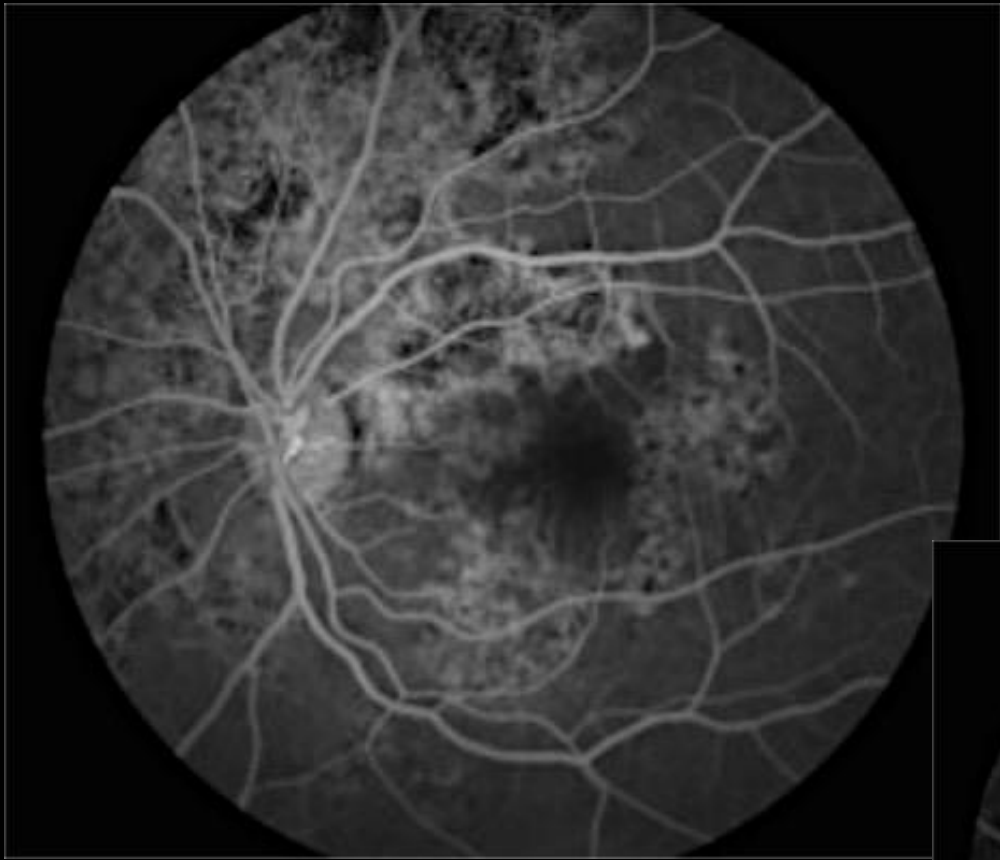


Photograph courtesy of Narsing A. Rao, MD

Patient SA

- 32 year old physician
- Unilateral choroidal lesions
- Painless loss of vision 1 week prior to presentation

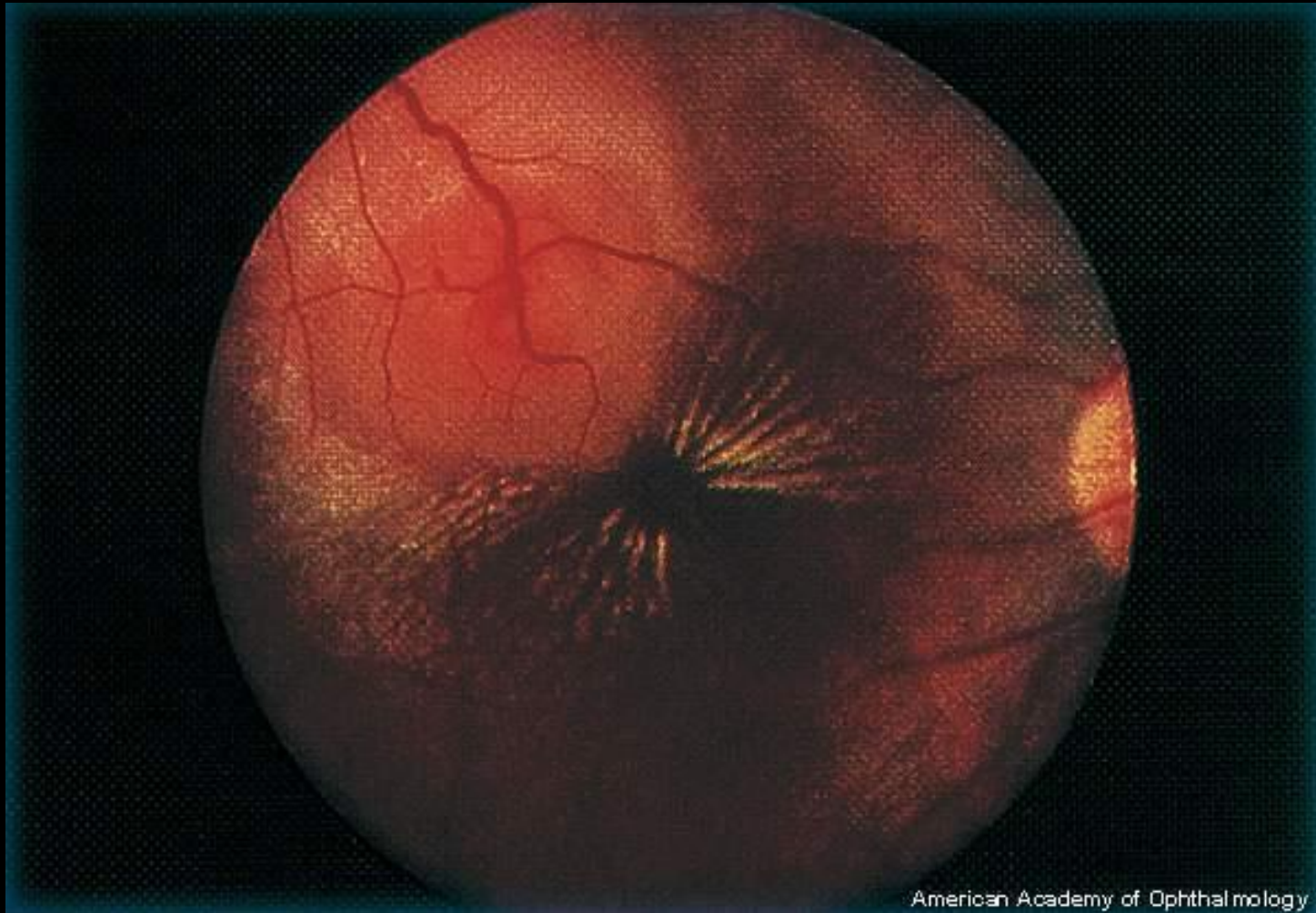




Tuberculous Uveitis



Tuberculous Uveitis



Tuberculous Uveitis

- Multiple presentations
- No consensus thus far on classic features
- Can affect all tunics of the eye

ORIGINAL ARTICLE

Diagnosis and Treatment for Ocular Tuberculosis among Uveitis Specialists: The International Perspective

Susan M. Lou, BA^{1*}, Paul A. Montgomery, BS¹, Kelly L. Larkin, MD², Kevin Winthrop, MD, MPH², Manfred Zierhut, MD³, and James T. Rosenbaum, MD^{4,5}; and members of the Uveitis Specialists Study Group†

¹Oregon Health & Science University, Portland, Oregon, USA, ²Department of Ophthalmology, Oregon Health & Science University, Portland, Oregon, USA, ³Centre of Ophthalmology, University of Tuebingen, Tuebingen, Germany, ⁴Departments of Ophthalmology, Medicine, and Cell Biology, Oregon Health & Science University, Portland, Oregon, USA, and ⁵Devers Eye Institute, Legacy Health System, Portland, Oregon, USA

TABLE 2. Comparison of uveitis workups for case 1 (no TB risk factors) between physicians who practice in developed and developing countries.

Test	Developing countries	Developed countries	p value
CBC with differential	56 (88%)	57 (72%)	0.0250
CMP	22 (34%)	36 (46%)	0.1752
RPR	52 (81%)	77 (97%)	0.0012
Chest radiograph	42 (66%)	68 (86%)	0.0039
Chest CT	38 (59%)	11 (14%)	<.0001
TST	62 (97%)	45 (57%)	<.0001
Interferon-gamma release assay (IGRA)	46 (72%)	36 (46%)	0.0016
Other	21 (33%)	29 (37%)	N/A
Other: serum ACE levels	12 (19%)	24 (30%)	0.1111
	N = 63	N = 79	

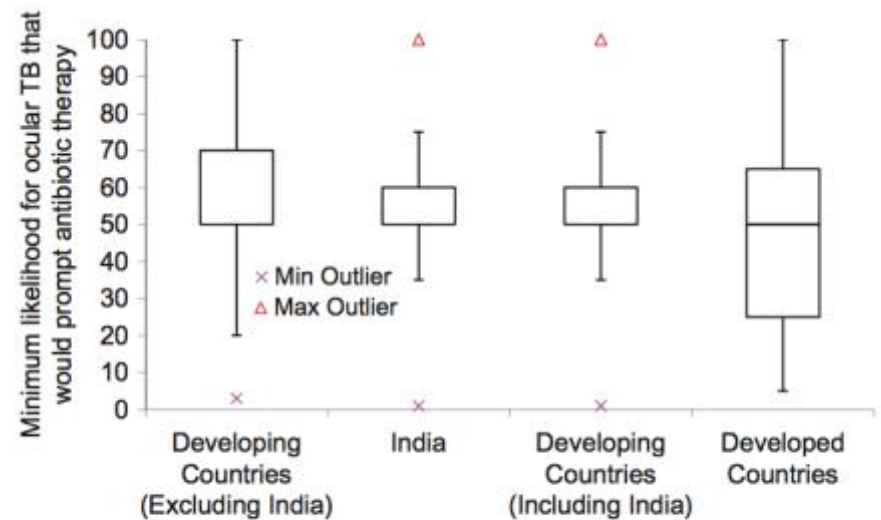


FIGURE 1. Box-and-whisker plot representing the minimum likelihood of ocular TB required for physicians to begin antibiotic therapy.

Ocular Tuberculosis: Diagnosis

- Presumptive
 - No pulmonary/systemic disease
- Tuberculin skin test (PPD)
 - ≥ 5 mm HIV +
 - ≥ 10 mm health care worker
 - ≥ 15 mm everyone else
- QuantiFERON gold assay
 - Latent disease
- Chest x-ray
 - Normal 50% patients with ocular TB
- Ocular tissue, intraocular fluid analysis
 - Acid-fast bacilli
 - Culture more sensitive
 - PCR (AC, vitreous)
- Diagnosis in response to empiric TX alone

Ocular TB

- Uncommon
 - Biswas reported ocular morbidity in only 1.39% of 1005 patients with active pulmonary and extrapulmonary TB in southern India
- Definitive diagnosis difficult
 - Acid-fast smear, tissue culture, PCR from ocular tissues
 - May be negative because of low bacterial load
 - Natural inhibitors of Taq polymerase in vitreous decrease yield of PCR
 - Sensitivity of PCR in vitreous samples 33.3% -46.9%

Int Ophthalmol. 1995-1996;19(5):293-298

Ophthalmology. 2009;116(7):1391-1396.

Tuber Lung Dis. 1999; 79(4):229-233

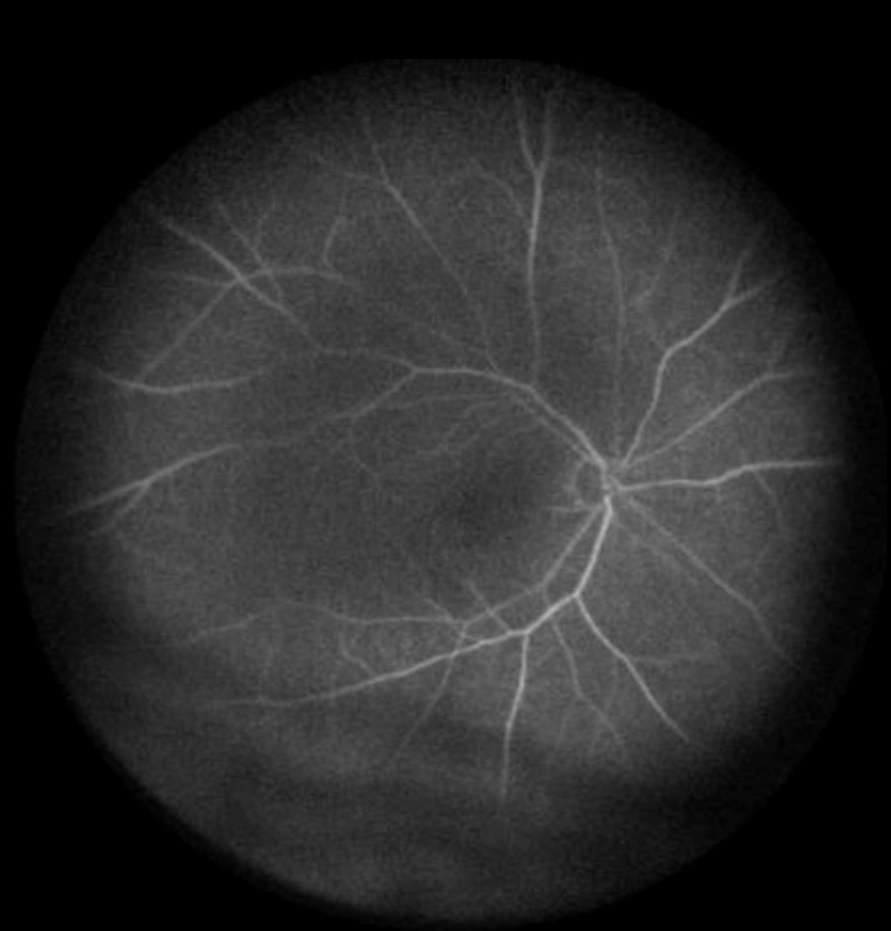
PCR diagnosis

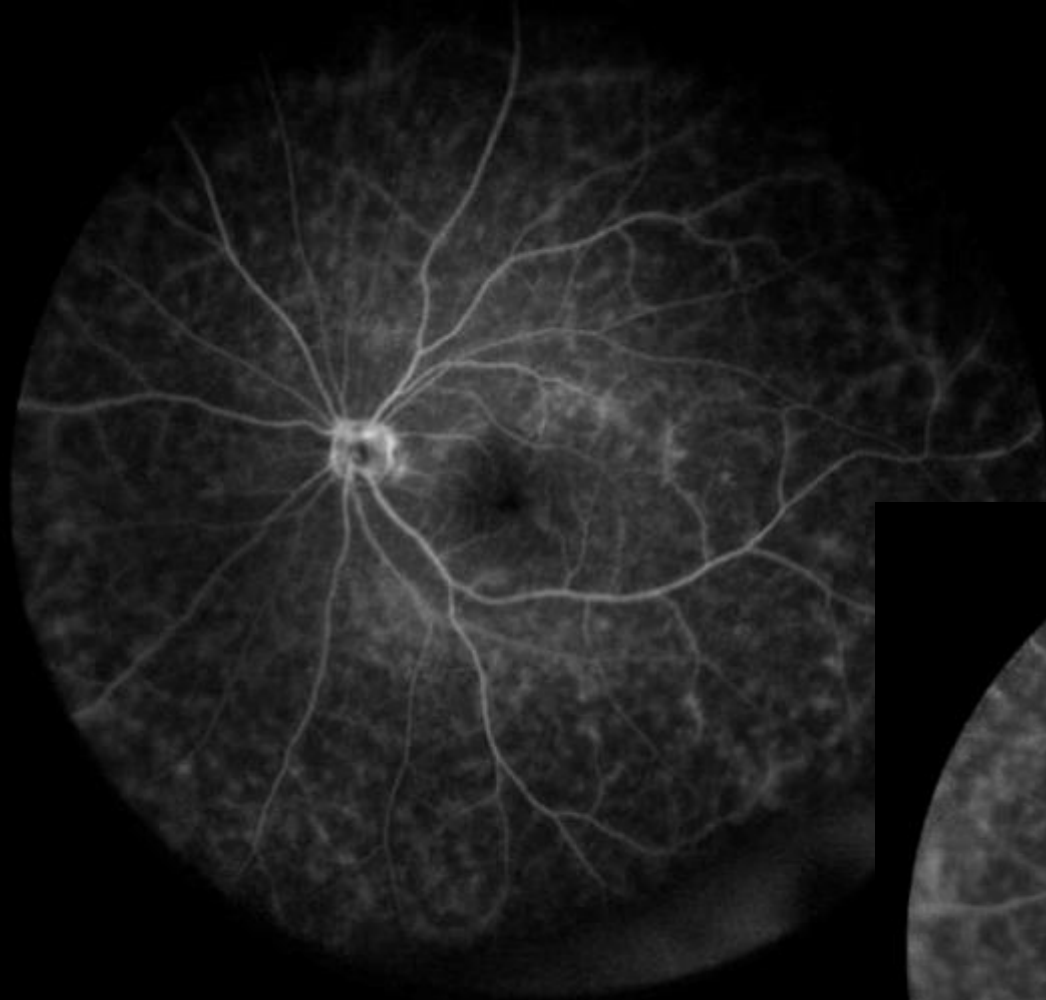
- PCR on aqueous samples from eyes with granulomatous uveitis
- Twenty out of the 53 samples (37.7%) in the study group were positive
- One sample out of 17 in the disease control group (5.7%) showed a weakly positive band.
- No sample from the healthy control group showed a positive PCR.

Arora SK, Biswas et al. Diagnostic efficacy of polymerase chain reaction in granulomatous uveitis. Tuber Lung Dis. 1999;79(4):229-33.

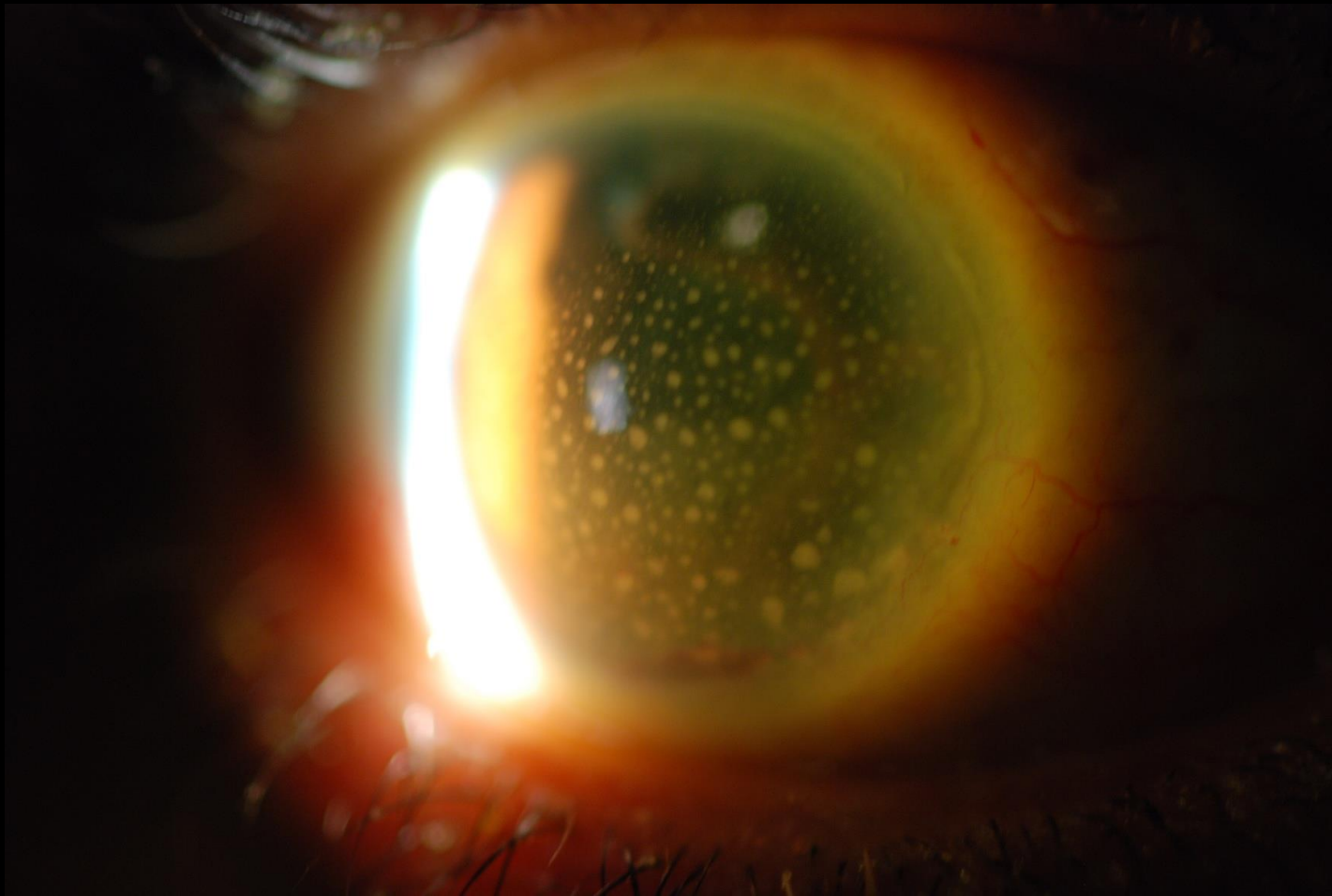
Case FB

- 54 year old Samoan gentleman with vascular sheathing noted on exam after cataract surgery in the left eye
- Positive Quantiferon gold TB
- Vitreous sample negative for TB by PCR
- Chest Xray unremarkable
- Started on INH and prednisone





6 weeks later returns with...



To Be or not TB?

James T Rosenbaum

Relative t
gists deal **BMJ**

course, every patient requires advice, grant population and the study provides a TB endemic area; a history of incarceration or homelessness; a history of intra-

test, my preference is to not obtain the test. The treatment, usually with four antibiotics, has undesirable features that include expense, inconvenience, and most of all, toxicities including hepatic injury. I am more likely to order the test if I note

Rosenbaum JT. *Br J Ophthalmol* August 2014 Vol 98 No 8

- Bayesian analysis of TB testing in uveitis
- Positive predictive value is higher in endemic areas
- It makes sense to exclude patients with syndromic uveitis
- Pre immunosuppressive TB testing

- Should we be testing all comers with ocular inflammatory disease for TB?
 - Non syndromic uveitis
 - Atypical features
 - Endemic regions
 - Granulomatous disease

But ocular TB is really tough to treat...

- A Delay in diagnosis and institution of treatment is associated with increased morbidity
- Therapy reported to be effective in only 40% - 70% of published cases
- Enucleation rates of up to 30%

Eye (Lond). 2011;25(4):475-480

Am J Ophthalmol. 2008;146(5):772-779

Retina. 1995;15(6):461-468

Mycobacterial Ocular Inflammation

Delay in Diagnosis and Other Factors Impacting Morbidity

Sarju S. Patel, MD, MPH, MSc; Nehali V. Saraiya, MD; Howard H. Tessler, MD; Debra A. Goldstein, MD

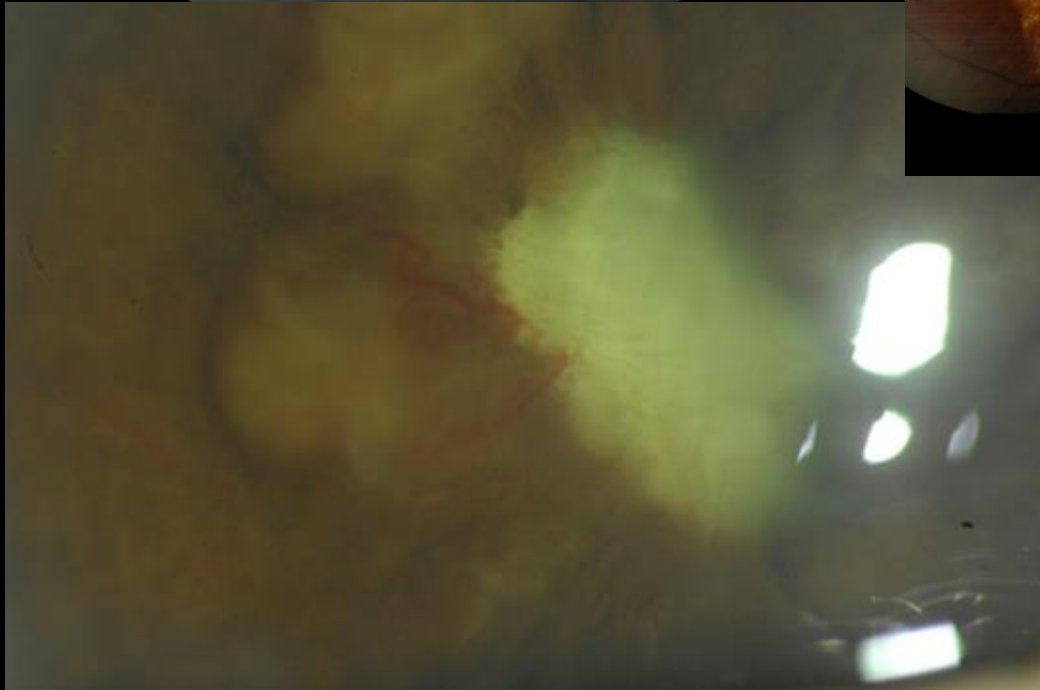
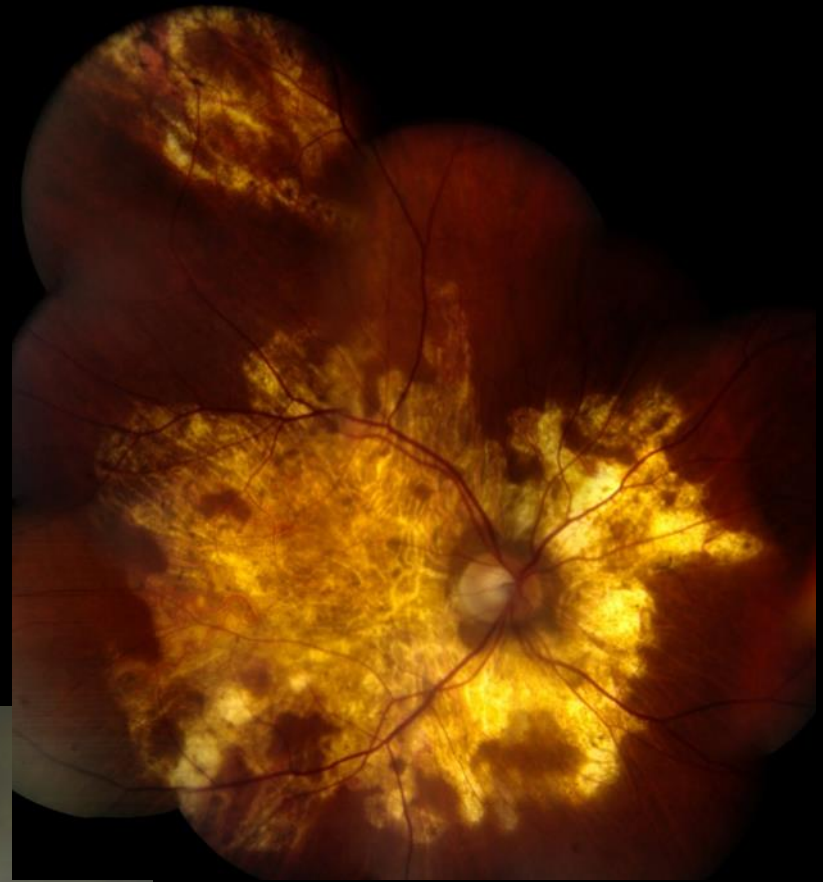
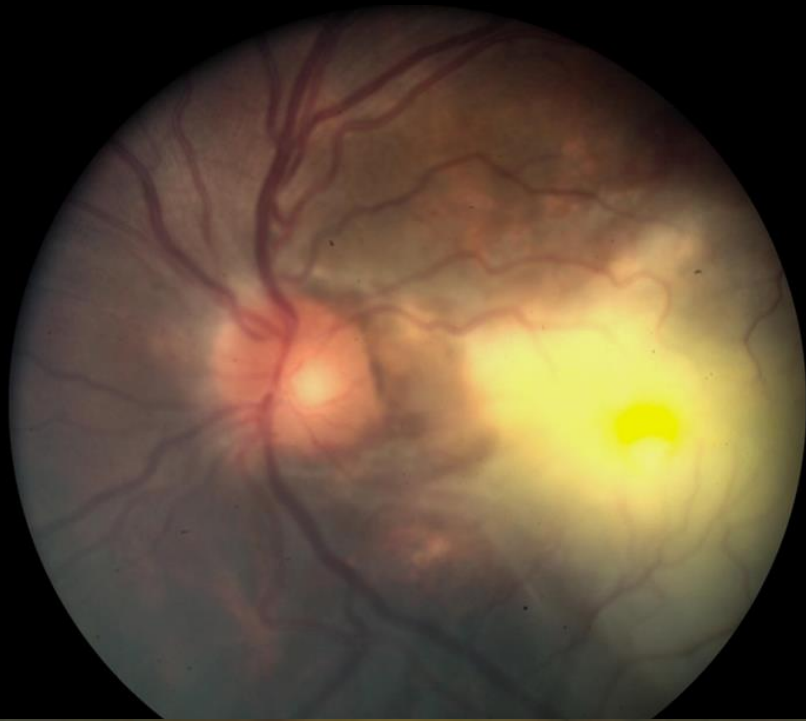
- Largest case series from North America
- 17 patients included with definite ocular TB

Mycobacterial Ocular Inflammation

- Retrospective study
- Inclusion criteria
 - Positive screening test (TST and/or QuantiFERON) AND response of eye disease to anti-TB therapy
 - Clinical/radiographic evidence of TB elsewhere in body AND response of eye disease to anti-TB therapy
 - Positive biopsy/culture diagnosis elsewhere in body AND response of eye disease to anti-TB therapy
 - Positive culture, PCR or histologic diagnosis from ocular tissue, regardless of response to therapy

Methods

- Inclusion criteria: at least one of the following
 - Scleritis
 - Granulomatous iridocyclitis
 - Granulomatous panuveitis
 - Serpiginous-like choroditis
- Exclusion criteria
 - Purely non-granulomatous anterior uveitis
 - Other diagnosis to explain ocular findings
 - Behcet's disease, other culture or biopsy proven infection



Courtesy Sarju Patel M.D. Cornell
Deborah Goldstein M.D. NWU

Results

- 17 patients included in the analysis
 - 14 *M tuberculosis* infection
 - 3 nontuberculous mycobacterial infection
 - African American: 7 (41.2%)
 - Hispanic: 5 (29.4%)
 - White, non-Hispanic: 3 (17.6%)
- 8/17 patients (47%) were born in the United States
- 12 patients (71%) had a history of possible TB contacts
- 5 patients (29%) had no identifiable exposure risk

Results

- 17 patients, 9 (53%) had bilateral disease
- 26 eyes
 - 4 scleritis (15%)
 - 2 granulomatous anterior uveitis (8%)
 - 11 posterior uveitis (42%)
 - 9 panuveitis (35%)
- Posterior uveitis tended to be bilateral ($P = .001$)
- All scleritis was unilateral

TB testing

- 12 of 13 (92.3%) available TST results were positive
- 7 of 8 (87.5%) QuantiFERON-TB Gold were positive
- 13 of 15 patients (86.7%) had at least one positive test
- 2 patients with negative screening test results had localized nontuberculous mycobacterial infection diagnosed with biopsy

Chest imaging

- 4 of 15 (27%) with available results had CXR consistent with tuberculous disease
- 5 of 9 (56%) had positive CT chest
- 7 of 15 patients (47%) had any chest imaging consistent with current or prior granulomatous disease

Systemic infection

- 13 of 17 patients (76%) had isolated ocular disease
- Only 4 (24%) had evidence of systemic TB
 - 1 miliary tuberculosis (TB), 2 lymphadenopathy, 1 active pulmonary TB

Delay in referral

- Average delay in referral to the uveitis service 755.3 days (range, 7-3017 days)
- Race was associated with delay in referral to a uveitis specialist on bivariate analysis
 - All non-Hispanic Caucasians were referred after 3 years of symptoms
 - Asian patients from endemic countries were referred within 6 months ($P = .045$)
- Posterior uveitis was associated with longer delays till referral
 - 1587 days vs 478 days for other manifestations

Delay in diagnosis

- Delay in diagnosis was associated with negative CT chest
 - The 5 patients with CT chest findings c/w TB were diagnosed on average 241 days from symptom onset
 - vs. 989 days for the 4 patients with negative imaging ($P = .03$; $r^2 = 0.61$)

Visual loss

- Ten eyes (39%) of 8 patients (47%) had irreversible vision loss secondary to TB with best-corrected visual acuity of $\leq 20/200$
 - Four of the 13 patients (31%) with disease controlled with antimycobacterial therapy had irreversible profound vision loss
 - All 4 with uncontrolled disease had vision loss ($P = .03$)
- Profound visual loss was associated with delay in diagnosis
 - Patients diagnosed and treated after 500 days were more likely to have vision loss than those diagnosed earlier (OR, 20.0; 95% CI, 1.41-282; $P = .03$).
 - Those with profound irreversible vision loss were diagnosed in 1260 days on average, compared with 475 days for those without irreversible visual loss

Disease control

- Average time to control of disease (in those patients for whom disease could be controlled) was 137.8 days (42-252 days) after initiation of ATT
- Five cases took more than 200 days to achieve control
- Supplemental use of steroids to control inflammation after initiation of ATT was not associated with shorter periods until control of disease

Disease relapse

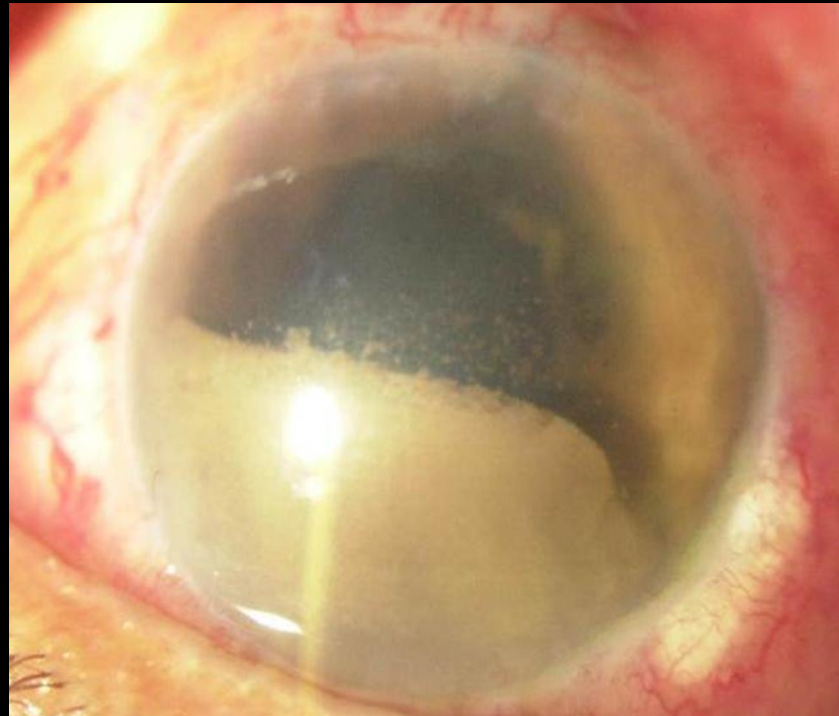
- Ten eyes (39%) of 6 patients (35%) had relapsing course
- Only 2 patients relapsed after a complete course of therapy both of whom had multifocal serpiginous-like choroidopathy
 - 1 after 8 months of isoniazid and rifabutin
 - 1 after 9 months of RIPE
 - Both responded to reinstatement of ATT alone
- Three patients with multifocal choroiditis relapsed with decrease in ATT between 1 and 4 months but responded when multidrug therapy was reinstated

Disease relapse

- Relapsing course
 - 80% of patients with posterior uveitis
 - 17% of other patients including panuveitis ($P = .03$).
- Relapse was associated with supplemental steroid use
 - Those treated with supplemental oral steroids after instituting ATT were 10 X more likely to relapse compared with those not so treated (univariate analysis (OR, 10.1; 95% CI, 1.60-64.0; $P = .01$))
 - No correlation between relapse rate and cumulative dose or duration of steroid treatment (data not shown)

Loss of the eye

- 3 eyes enucleated
 - 2 after spontaneous perforation from uncontrolled necrotizing nodular scleritis
 - 1 panuveitis in heart transplant patient



In summary

- Think about TB
- The prognosis for mycobacterial ocular disease is still not great
- Longer therapy usually required than for systemic disease
- At least for patients with scleritis, perhaps we should be considering local therapy

Conclusions

- Ocular mycobacterial infection is uncommon
 - 0.5% of 3606 new uveitis referrals seen at a US tertiary referral uveitis service over 15-years met study inclusion criteria
- Ocular TB typically occurs without clinically apparent systemic disease
 - **Absence of pulmonary TB should not delay or prevent anti-TB therapy**

Conclusions

- **Consider the diagnosis of TB, even in patients who are not from or have not been to endemic countries, regardless of race**
 - Caucasians in this series had significant delay in diagnosis, which clearly correlates with increased morbidity

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