Mycobacterial Ocular Inflammation

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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
Unremarkable right fundus photograph
• Left fundus: Vitreitis/ hazy view with significant macular scarring and inferior retinochoroidal granuloma
• Choroidal granuloma with overlying vitreous opacity and surrounding choroidal nodules
- 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

Courtesy Sarju Patel M.D. Cornell
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-μm 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
Biopsy of conjunctival lesions contralateral eye revealed caseating granulomas. PCR – 4 of 5 bands positive for M. TB genome.
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

Biswa 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

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

TABLE 1

Clinical Presentation in Intraocular Tuberculosis

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

*Survey of ophthalmology 2013 58(3):203-232*
60 year old Caucasian woman from Poland
Positive Quantiferon, CT chest evidence prior granulomatous disease

Note appearance of choroidal lesion
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
Diagnosis and Treatment for Ocular Tuberculosis among Uveitis Specialists: The International Perspective

Susan M. Lou, BA1*, Paul A. Montgomery, BS2, Kelly L. Larkin, MD2, Kevin Winthrop, MD, MPH2, Manfred Zierhut, MD3, and James T. Rosenbaum, MD4,5, and members of the Uveitis Specialists Study Group†

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

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

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%

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.

Case FB

- 54 year old Samoan gentleman with vascular sheathing noted on exam after cataract surgery in the left eye
- Positive Quanteferon gold TB
- Vitreous sample negative for TB by PCR
- Chest Xray unremarkable
- Started on INH and prednisone
6 weeks later returns with...
• Baysean 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
Retina. 1995;15(6):461-468
• 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

Patel, Saraiya, Tessler, Goldstein
Methods

• Inclusion criteria: at least one of the following
  – Scleritis
  – Granulomatous iridocyclitis
  – Granulomatous panuveitis
  – Serpiginous-like choroiditis

• Exclusion criteria
  – Purely non-granulomatous anterior uveitis
  – Other diagnosis to explain ocular findings
    • Behcet’s disease, other culture or biopsy proven infection
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 ≤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 reinstituted
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
Acknowledgements

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