So I have a patient with uveitis in my chair, now what?

A targeted logical approach to the evaluation of a patient with uveitis

Disclosure Statement:
• Nothing to disclose

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Abstract

This lecture will present a targeted logical approach to evaluation of a patient with uveitis.
It will include an exploration of inflammatory conditions of the eye using case studies and discussions of history, diagnosis, laboratory testing and treatment options.
Specific entities, special situations and their challenges will be presented and discussed.

Learning objectives

• Understand the importance of history in the evaluation of uveitic conditions
• Awareness of the challenges of uveitis diagnosis
• Understand the use of the specific laboratory tests
• Exposure to treatment options and their specific challenges
• Awareness of potential complications

Case 1

68 yo WF presenting with eye redness and decreased vision in the L eye x 2 days
– trauma, flashes, floaters
POcHx – negative
PMHx – severe asthma
FHx – neg for eye diseases
Part I
The Initial Approach

Does this sound like uveitis? a review of ocular symptoms

- Pain, redness, photophobia
- Typical of anterior uveitis
- Decrease vision, flashes, floaters
- More consistent of posterior or panuveitis
- Sxs not typical for uveitis
  - Burning, tearing, dryness, mattering
  - Diplopia
  - Metamorphopsia, hemispheric vision loss, scotomas

Why the history is so important

THE FIRST EPISODE
- First episode sxs can narrow the DDx
  - Severe pain, redness, photophobia in one eye - HLA-B27 disease
  - Foreign body sensation, redness, photophobia in one eye - Herpetic

Previous episodes and treatment

- Info to gather
  - How many episodes
  - Topical, injection or oral and for how long
  - Any complications
- Info will influence treatment of current episode
  - Steroid responders
  - Need for strong topical or systemic medications
  - Recommendations for chronic systemic medication if too many episodes per year

Past medical history – meds and immune status

- Prior medical history
  - Immunosuppression (meds due to rheumatic disease, cancer tx, uncontrolled diabetes)
- Meds
  - Systemic meds can cause acute anterior uveitis (Ritubutin, Cidofovir, biphosphonates, sulfonamides, moxifloxacin)
  - Ocular meds (prostaglandins, brimonidine, metipranolol)

Trauma history

- Recent blunt ocular trauma
- Acute anterior uveitis in affected eye
- Prior severe ocular trauma (uveal prolapse or exposure)
- Sympathetic ophthalmia (uveitis in both eyes)
Social history – Travel, Pets, Sex Hx, Occupation

- Social history (EXPOSURE)
  - Travel to Africa or Tb endemic areas
  - Hunting (tick bites)
  - Cat scratches
  - HIV risk

Case 1

- 68 yo WF presenting with eye redness and decreased vision in the L eye x 2 days
- Trauma, flashes, floaters, diplopia, metamorphopsia
  - Never had an episode.
  - No prior gtts.
- POchx – negative
- PMHx – severe asthma
- FHx – neg for eye diseases
  - Medication list – includes Rifabutin.
  - New medication. Pt reports recently diagnosed HIV.
  - No foreign travel, pets.

Review of systems

- Looking for any clues at systemic diseases
  - Headaches, tinnitus, vitiligo [VKH]
  - Shortness of breath, hemoptysis [Sarcoid]
  - Joint pain (ex. lower back) [Ank. Spondylitis]
  - Rashes, skin lesions (ex. psoriatic lesions - Psoriatic arthritis, targetoid lesions-Lyme disease, oral sores-Reiter's or Behcet's)
  - Diarrhea, blood in stool [recent GI sx - Reiter's, hx UC, Crohn's dz]

Benefits of a Uveitis Questionnaire

- Gather information quickly
- Ask low yield questions without taking up visit time (ex. swollen earlobes - relapsing polychondritis)
**Other Things to Consider**

- Begin to narrow possible uveitis entities and etiologies
  - **Age**
    - Young – idiopathic, chronic
    - Elderly – masquerades
  - **Gender**
    - Trauma – men
    - Systemic inflammatory entities – women

- **Race**
  - Ex. Sarcoidosis – more common in young AA male or elderly northern European women

- **Family history**
  - Ulcerative Colitis, Crohn’s disease

**Case 1**

- **Exam**
  - VA 20/40 R 20/200 L

- **IOP**
  - 10 R 8 L

Medication was discontinued. Tx: frequent topical steroid, dilator and low dose oral steroids

**The eye exam – what to look for**

- Visual Acuity, IOP, +/- APD
- Location of inflammation (anterior vs. intermediate vs. posterior)
- Anterior segment findings
- Vitreous findings
- Retina pathology

**Visual Acuity**

- Many factors can be involved in decreased acuity
  - Corneal opacity
  - AC cell or flare
  - Cataract
  - Vitreous haze/opacities
  - Macular pathology (CME, atrophy, ischemia)

- Evaluate best corrected visual acuity at every visit
Functional ocular exam
- IOP - by tonoapplanation
- Ensure no side effects of steroid treatment
- Monitor TM function
- APD check
- Involvement of the posterior pole
- Ocular side effects of inflammation (glaucoma)
- Uveitis etiology (MS, optic nerve granuloma)

Slit Lamp Examination
- Lid/conjunctival exam
- Granulomas
- Vesicles
- Corneal changes
  - Band keratopathy
  - Dendrites
  - Interstitial keratitis
  - Keratic precipitates

Slit Lamp Examination
Keratic precipitates
- Accumulation of inflammatory cells on the endothelial surface
- Current (white/greasy) or old (pigmented)
- Arlt’s triangle vs. diffuse distribution
- Non-granulomatous (neutrophils/lymphocytes) vs. granulomatous (+macrophages/giant cells)
- Can disappear after treatment

Grading of AC cells
0.2mm x 0.2mm directed obliquely into AC
- 0 no cells
- ½+ 1-5
- 1+ 6-15
- 2+ 16-25
- 3+ 26-60
- 4+ greater than 60
- Hypopion leukocyte layering in the inferior angle

Grading of AC flare
- 0 no flare
- 1+ faint
- 2+ moderate (iris and lens clear)
- 3+ marked (iris and lens hazy)
- 4+ intense (fibrin, plastic aqueous)

Iris Changes
- Synechiae
  - Signals recurrence, chronicity and/or severity of inflammation
  - Use dilator drop to expand pupil and prevent synechiae in small pupil configuration
Slit Lamp Examination

- Iris Nodules
- Koeppe, Busacca- indicates granulomatous dz
- Iris Atrophy
- Herpetic disease
- Fuch’s heterochromic iridocyclitis

Slit Lamp Examination

- Cataract
- Secondary to inflammation or corticosteroid use

Vitreous Findings

- Retrolental cells – spill over from anterior uveitis
- Vitreous cells
- Vitreous haze – sign used for uveitic clinical trials
- Snowbanking/Snowballs – characteristic of intermediate uveitis

Retina Pathology

- CME – most common retinal pathology in uveitis
- Infiltrates/granulomas – ex. sarcoidosis. Becomes chorioretinal scar when resolved
- Phlebitis
- Arterial occlusion – lupus, Behcet’s disease
- Serous retinal detachments – ex. VKH

Every eye exam

- Visual acuity
- IOP
- Corneal changes
- AC cell and flare
- Changes in synchiae

Very important to document

- Retina exam (frequent)
- Cataract progression
- Lid/conj changes
- APD

What should I be thinking about?

Specific entities to consider based on type and location of inflammation and other associated factors
How can I narrow this down?

- Classification of uveitis
  - By location (anterior, intermediate, posterior)
  - By chronicity
  - By number of eyes involved
  - By granulomatous vs. non-granulomatous features

Classification of uveitis - Location

- Anterior 51%
  - Inflammatory cells in the anterior chamber with minimal spillover to the retrolental space
- Intermediate 13%
  - Inflammatory cells in the vitreous
- Posterior 19%
  - Inflammation of the retina and/or choroid
- Panuveitis 16%
  - Two or more of the above

Classification of Uveitis – Duration, Course

- Acute sudden, limited duration
- Recurrent repeated episodes, >3 mo of inactivity without treatment between episodes
- Chronic persistent >3mo, relapses < 3mo when treatment discontinued

Unilateral vs. Bilateral

- If sx unilateral – consider infectious or masquerades
- If bilateral – consider systemic immune etiologies

Unilateral acute disease – if involves either eye think HLA-B27+
Unilateral can become bilateral over time

Case

- 53yo male c/o mild pain(4/10), FBS, photophobia OD for 4 days
- (-) redness, burning or itching
- VA 20/25 OD, 20/20 OS
- One vesicle at central lid margin OD
- Unusual superficial epithelial lesions of cornea
- Dx ?Thygesson’s?
- FML tid
- RTO 1 week

Case

- 6 day f/u
- Dx with HZV two days after initial visit
- Pain around eye, tearing, photophobia
- Vesicles of the right scalp and forehead
- Continues to have superficial corneal lesions
- VA 20/40 OD, 20/20 OS
- HZ keratitis
Case

- Acyclovir and oral Prednisone and topical Emicin were Rx'd in the ER
- Change to 1% Pred Forte q4h, AT’s q1h
- Day 11 feels improvement
- Lid lesions are better
- Superficial epithelial lesions are better
- Continue Pred 1% q4h, oral pred taper, acyclovir for 2 more days

Case

- Day 18 feels good
- Facial lesions have healed well
- Superficial epithelial lesions are almost completely gone
- Finish oral pred taper, taper 1% pred over 3 weeks, AT’s q2-4h
- F/u at 5 weeks he was completely clear except for 2 small endothelial lesions
- Released for 6 months

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Anterior Uveitis

- 50% to 75% of uveitis cases
- Most are classified as idiopathic

Symptoms
- Redness
- Pain
- Photophobia
- Blurred vision

Signs
- Ciliary flush (perilimbal injection)
- Pupillary miosis
- Posterior synechiae
- Dilated iris vessels
- Peripheral anterior synechiae (PAS)

Specific uveitic entities

Fuch’s Heterochromic Iridocyclitis
- Signs
  - Iris heterochromia
  - Iris stroma atrophy
  - Fine diffuse KPs
  - Mild AC reaction
  - Mild to moderate vitritis
  - Monocular
- Symptoms
  - Pain and redness rare

Specific uveitic entities

- HLA-B27
  - As many as 50% of acute anterior arthritis may be HLA-B27 positive
  - Typical signs/sxs - hypopyon
  - Acute, recurrent
  - Association with
    - Ankylosing spondylitis
    - Reiter’s syndrome
    - Inflammatory bowel disease
    - Psoriatic arthritis

Other complications
- Secondary glaucoma
- Steroid response
- Inflammatory response
- Severe PAS
- Pupillary block
- Cataract
- Steroid or inflammatory induced
- Band keratopathy

Chronic
- Association with Rubella infection
- Complications
  - Early PSC cataract part of signs
  - Glaucoma – might be difficult to control
Anterior Uveitis
Specific uveitic entities

- Behcet's disease
  - Triad of ocular inflammation and mucosal/oral ulcerations

- Signs
  - Bilateral anterior uveitis (30% of patients)
  - Shifting hypopyon
  - Nongranulomatous KP's

- Posterior disease - vaso-occlusive
  - Macular ischemia
  - Retinal hemorrhage and edema
  - Vitritis

- Ethnicity
  - Middle eastern, hispanic

- Testing
  - HLA typing for HLA-B51
  - Skin prick test (historic)
  - Non specific screening
    - ESR, CRP, elevated WBC

- Complications
  - Retinal atrophy, optic atrophy

- Lens-induced uveitis
  - Non-penetrating traumatic anterior uveitis
    - Signs similar to acute anterior uveitis

- Post-surgical uveitis
  - As part of the normal response to intraocular surgery
  - CONSIDER ENDOPHTHALMITIS

- Drug-induced uveitis

- Traumatic uveitis
  - Non-penetrating traumatic anterior uveitis
  - Signs similar to acute anterior uveitis

- Post-surgical uveitis
  - As part of the normal response to intraocular surgery
  - CONSIDER ENDOPHTHALMITIS

Anterior Uveitis
Specific uveitic entities

- Glaucomatous cyclitic crisis (Posner-Schlossman Syndrome)
  - Signs/sxs
  - Fine KP's
  - Elevated intraocular pressure - responds to steroids
  - Hazy cornea
  - Monocular
  - Responds well to steroids

- Complications
  - Progression to glaucoma

- Lens-induced uveitis
  - Signs
  - Fine KP's
  - Elevated intraocular pressure - responds to steroids

- Hazy cornea
  - Monocular
  - Responds well to steroids

- Complications
  - Progression to glaucoma

Anterior Uveitis
Specific uveitic entities

- Herpes zoster ophthalmicus
  - Early
    - Lesions in distribution of CN V1
    - Pseudo-dendritic lesions of the cornea
  - Later
    - +/- Stromal keratitis
    - Anterior uveitis (diffuse KP's, iris atrophy, synechiae)
    - ALWAYS EXAMINE THE POSTERIOR POLE FOR RETINITIS

- Treatment
  - Consider antivirals early in the disease
  - Slow steroid taper

- Complications
  - K scars
  - Neurotrophic cornea

Anterior Uveitis
Infectious uveitic entities
Anterior Uveitis

Infectious uveitic entities

- Herpes Simplex Uveitis
  - Signs
  - Stromal involvement or endothelialitis, but can occur with corneal epithelial lesions, rarely.
  - Recurrence without corneal involvement
  - DILATE EYE TO EXAMINE FOR RETINITIS

Other viruses
- West Nile virus
- HTLV-1
- Measles
- Mumps
- Epstein-Barr
- Influenza

Intermediate Uveitis

Sxs
- Floaters, flashes and blurred vision
- No pain, redness or photophobia

Signs
- Mild AC signs: cells, KPs, posterior synechiae
- Vitreous cells are main diagnostic sign
- 25% of patients with phlebitis (venous sheathing)

Possible etiologies
- Pars planitis: contains yellowish white aggregates in the pars plana. May become confluent. Do not resolve completely with treatment. No etiology by definition.
- Sarcoidosis
- Multiple sclerosis – up to 15% of IU
- Infectious

Infectious etiologies
- Lyme disease
  - Hx exposure, targetoid lesion, Lyme titer
- Tuberculosis
  - Hx exposure, check PPD/chest X-ray/Quantiferon Tb

Diagnosis
- ROS
- Clinical ophthalmic exam
- Tests
  - CBC
- Laboratory to rule out infectious and above etiologies (ACE, lysozyme, FTA-ABS or TPPA, Lyme titers, Quantiferon Tb or PPD)
**Posterior Uveitis**

- Inflammation affects the retina and/or choroid
  - Retinitis - Fluffy white retina lesions with vitritis
  - Choroiditis - Yellow or grey retinal elevation with demarcated borders and no vitritis

- Auto-immune
  - White dot syndromes
  - Systemic inflammatory disorders

- Infectious
  - Viral (Herpetic)
  - Fungal (POHS)
  - Protozoal (Toxo)

**White Dot Syndromes**

- Group of heterogeneous disorders
- Multiple white-creamy lesions in the retina, RPE and/or choroid

- Entities
  - Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
  - Birdshot chorioretinopathy
  - Diffuse unilateral subacute neuroretinitis (DUSN)
  - Multiple evanescent white dot syndrome (MEWDS)
  - Multifocal choroiditis with panuveitis (MFC)

- Signs
  - Blurred vision, photopsias, nyctalopia, floaters and visual field disturbances

- Systemic Inflammatory Disorders

- Disorders affecting the retina
  - Systemic lupus erythematosus
    - 10% can have eyes affected
  - Vasculitis (cotton-wool spots, exudates, hemorrhages)
  - Severe cases can develop retinal infarction and NV
  - Wegener's granulomatosis
  - Polyarteritis nodosa

**Infectious**

- Acute Retinal Necrosis
  - Caused by HSV-1 or 2, VZV
  - Blinding disease
  - Age 20s and 50s (bimodal distribution)
  - Sxs of decreased vision, floaters, eye redness

- Signs:
  - Mild anterior uveitis
  - Epi/scleritis
  - Retinitis (necrosis)
  - Vasculitis
  - Vitritis
  - Optic neuropathy

**Posterior Uveitis**

**White Dot Syndromes**

**Systemic Inflammatory Disorders**

**Infectious**

**Posterior Uveitis**

**White Dot Syndromes**

**Systemic Inflammatory Disorders**

**Infectious**

**Posterior Uveitis**

**Infectious**

ALWAYS DILATE EYE IN EVERY UVEITIS CASE.
Posterior Uveitis
Infectious
- Other viruses that can affect eye
  - EBV
  - Rubella
  - CMV
    - HIV/AIDS, immunocompromised patients
    - Sxs, signs similar to ARN from HSV
    - Needs prompt treatment to avoid permanent blindness

Posterior Uveitis
Infectious
- Uveitis due to fungal disease
  - Ocular Histoplasmosis Syndrome
    - Triad of peripapillary atrophy, punched out CR lesions and macular choroidal neovascularization
    - No vitritis
    - Sxs: visual loss, metamorphopsia
    - Complications - CR scars from neovascularization

Posterior Uveitis
Infectious
- Uveitis due to fungal disease
  - Toxoplasmosis
- Non-infectious
  - Sarcoidosis
  - Sympathetic Ophthalmia
  - Vogt-Koyanagi-Harada Disease
- Infectious (Panuveitis vs. posterior uveitis)
  - TB
  - Lyme
  - Toxoplasmosis
  - Syphilis
  - Endophthalmitis

Panuveitis
Non-infectious
- Sarcoidosis
  - Multisystemic granulomatous disease (every organ), eye involvement in 25%
  - Epidemiology:
    - Young AA: 82 per 100,000
    - Easter European: Ex. Sweden 64 per 100,000
  - Signs:
    - Anterior chamber inflammation (mild-mod)
    - Moderate to severe vitritis
    - White-yellow lesions in retinal periphery
  - Signs:
    - Prevention: enucleation of injured eye
    - High dose steroids (1 to 1.5mg/kg/day), slow taper after response (<3months)
Special Situations

The Pediatric Patient
Masquerade syndromes
The immunocompromised patient

Case
- 57 yo white female c/o "smeary" vision,
- Looks like dots or a glass of dirty water
- No pain, no redness
- Floaters in OS preceding OD by six months
- h/o Non-Hodgkin's lymphoma 3yrs earlier
- s/p chemo, rad
- Recent head and orbit MRI was normal
- Lyme, RPR, FTA-Abs all negative
- Meds: colase, estrogen cream
- Va 20/30 OD, 20/20 OS

Case
- Normal findings except mild NS and cellular debris in the vitreous
- Diagnosis of vitritis, ?secondary to lymphoma recurrence?
- Retinal consult for diagnostic vitrectomy
- Large B-cell Lymphoma
- Tx with 5 cycles of high dose Methotrexate
- Whole brain and ocular radiation (26gy)
- Six years lymphoma free

The pediatric patient
- Juvenile idiopathic arthritis (JIA)
- Tubulointerstitial nephritis and uveitis syndrome (TINU)
- Pars planitis
- Toxoplasmosis/Toxocara

Masquerade Diseases
- Chronic Retinal Detachments
- Retinal Degenerations
- Ocular Ischemic Syndrome
- Endogenous Endophthalmitis
- CNS Lymphomas
Masquerade Diseases

- Metastatic cancers
- Systemic lymphomas and leukemias
- Solid tumors such as lung and breast
- Ocular Tumors
- Uveal melanomas, retinoblastomas

Patients that are immunocompromised:

- PORN
- CMV retinitis
- Fungal
- Other Viral
- Immune-recovery uveitis

What can I do to help figure this out?

- Workup for the uveitis patient
- Labs
- Imaging
- Biopsy

Biopsy

- Helps to distinguish inflammatory processes from neoplasms
- Sarcoïdosis, lymphoma

Imaging

- Chest X-ray / CT chest
- R/O tuberculosis, sarcoidosis, Wegener’s granulomatosis

Imaging

- MRI
- R/O multiple sclerosis, lymphoma
**Imaging**

- OCT
- FA

**Laboratory Testing**

- Complete Blood Count (CBC)
- Rule out any underlying systemic disease
- Antinuclear Antibodies (ANA)
- Found in multiple autoimmune diseases
- SLE
- Angiotensin Converting Enzyme (ACE)
- Sarcoidosis
- Serum Lysozyme
- Use in conjunction with ACE
- Lyme Titer
- Be aware of false positives
- Confirm positive titers with western blot

**Laboratory Testing**

- HLA typing
  - HLA-B27
- RPR/VDRL/FTA-ABS
  - Practically all patients with uveitis should be tested for syphilis.
  - FTA-ABS has a specificity and sensitivity of 99%
  - VDRL has a sensitivity of 70%
- Erythrocyte sedimentation rate (ESR)
  - Non-specific marker of inflammation
- C-reactive protein
  - Acute phase protein used to monitor response to inflammatory disorders
- Purified protein derivative (PPD)
  - Skin test for tuberculosis

**What is best for treatment?**

- Degree and Location drive treatment
- Time must be given for therapies to be effective and successful
- Time must also be given for tapering of steroids

**The need for cycloplegics**

- Mydriasis and Cycloplegia
  - Helps prevent or breaks posterior synechiae
  - Reduces pain and photophobia
  - Cyclopentolate is not recommended, due to its chemoattraction for leukocytes

- 5% Homatropine
  - (2% in pediatrics)
- 0.25% Scopolamine
- 1% Atropine
- Only Atropine is commercially available at this time
Corticosteroids

- Topical
- Subtenon
- Intravitreal

Intraocular inserts
- Oral
- Intravenous

Essential considerations:
• Monitor side effects:
  • IOP (glaucoma causes BLINDNESS)
  • Cataract formation – avoid steroids in children
  • Infections – keratitis with chronic steroid use

Topical Steroids

- 1% prednisolone acetate suspension
- 0.05% difluprednate emulsion (Durezol)

Topical Steroids

Dosing
• Depends on severity
• Err on the side of more rather than less
• Q1-2h while awake
• Failure may be due to infrequent dosing strategy
• Give the therapy time to work
• Taper slowly

When to consider oral treatment with steroids

• Need for more aggressive therapy
• Start with 0.5-1.5mg/kg/day of prednisone
• Maintain high doses until beneficial effect
• Then start long taper
• Consider ranitidine 150mg once or twice/day
• Significant side effects to long term use

Secondary complications to watch for. Don’t let your patient lose vision due to these if you can help it!

• Glaucoma
• Synechiae
• Cystoid Macular Edema
• Cataract
• Epiretinal Membrane
• Retinal Detachment
• Choroidal Neovascularization
• Vitreous debris