Uveitis Update 2017

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So usually when I come to an alumni meeting.

- The reviews are mainly negative
- "I came here to discuss the things that make my day exciting, not the depressing stuff…"
- "I am disappointed that the uveitis lecture did not include more discussion about the use of premium IOLs"
- But every once in a while…
- "The uveitis lecture had a fair amount of jokes about STDs and ulcers….bring him back!"

Our Goals as Ophthalmologists
What We Do Not Want

What We Do Not Want
What We Know

- Severe vision loss occurs in 25%-33% of all uveitis cases
- Repeated bouts of inflammation increase risk of severe vision loss
- High-dose corticosteroids – long term have high rates of morbidity
- Majority of physicians surveyed do not adhere to recommended guidelines to treat uveitis

Guidelines

- Active uveitis – treat with high dose of corticosteroids
- Add steroid-sparing agent if inflammation cannot be controlled with <10 mg prednisone within 3 months
- Average dose > 30 mg – maintained for average duration of 21 months
- Immunosuppressives only prescribed in 12%
But most of the time you will not see the wacky things

- So we are not going to focus on the rare posterior uveitis cases
- We are going to address the most common presentation that can give problems

What we will cover today

- Show some cool cases which highlight
- How to approach the work-up
- How to approach treatment.
- What’s my periop regimen?
- How to approach the surgery.
- Post-op inflammation?
- What signs should I worry about?
- Just in case, what’s my email address?
Case Presentation

- 50 year old caucasian female
- 4 year history of anterior uveitis mainly in the left eye
- Here for a second opinion
- Has had previous testing – all of which is negative
- Recalls negative syphilis, TB, and other inflammatory markers. States she is otherwise healthy
- Treated with local steroids (peri-ocular and intravitreal steroids)
- Last one was 1 month ago
- Vision 20/20 OD, 20/150 OS

Review of systems

- Positive for allergies and occasional wheezing
- Negative for Headaches, N/V, Arthritis, Rashes, history of STDs, Chest pain, SOB, Coughing blood, diarrhea, neuro symptoms, ulcerations in mouth or other areas.
Thoughts?

- Chronic intermediate uveitis OS>OD
- Not much on FA
- Fellow sees patient – comes out of room with
- Differential Diagnosis:
  - MS, IBD, TB, Sarcoidosis, Syphilis, Lyme disease (she is from Pennsylvania)
- Should I re-test her?
- How about treatment?
**My super nurse/research coordinator/therapist  Kim**

- Kim walks into the room and then walks out and makes the diagnosis
- What did she find?
- Audible wheezing, struggling to talk and answer questions
- Kim: “Dude, she has sarcoidosis”
- Fellow: “I thought she just had a sexy raspy voice”
- Me: Deep sigh....

**ACE – 73**

- Chest CT:
  - Multiple mediastinal and peribronchial enlarged lymph nodes, some as large as 20 mm
  - Biopsy performed – positive for non-caseating granulomas
  - Dx - sarcoidosis
Lesson

- Previous negative work-ups warrant a rethinking and possible work-up
- Sarcoidosis occurs in Caucasians
- Listen to your patient – really listen.....

Case Presentation

- 33 year old male
- 4-6 week history of blurred vision left eye
- History of Crohn’s disease
- Dx with anterior uveitis
- HLA b27 +
- Treated with topical PF
- On infliximab every 4 weeks
Case Presentation

VA OD 20/25  OS 20/70
1+ cells  4+ cells
Case Presentation

- 33 year old male
- History of Crohn’s disease
- B27+
- With Intermediate uveitis - ?posterior uveitis
- On infliximab
- Is this a common form of uveitis in IBD?
- What should we do now?
- Start prednisone?

Case Presentation

- Prednisone?
- I am already on prednisone doc!
- For my Crohn’s!
- I thought you wanted to know my medications for my eyes only!
- Are you more worried or less worried now?
- Active inflammation on infliximab and prednisone
**Case Presentation**

- Labs drawn
- Toxoplasmosis IgG and IgM – negative
- Syphilis IgG positive, RPR positive 1:128
- Patient called and informed of results
- Doc, how did I get syphilis?
- Referred pt to chairman Dr. Dan Martin, world renowned expert on the process of spontaneous spirochete infection
- Syphilis = the immaculate infection

**Case Presentation**

- Treated with
- Aqueous PCN G 24U IV daily for 4 weeks
**Syphilis**

- Can present in the eye as anterior uveitis, intermediate uveitis or posterior/panuveitis
- Rank of cases in 2015
  - San Francisco, CA 516 cases, 60.5/100,000
  - Cleveland-Elyria, OH – 199 cases, 9.6/100,000

**Demographics of syphilis in US**

- Men who have sex with men only (n = 12891)
- Men who have sex with men and women (n = 1338)
- Men who have sex with women only (n = 3178)
- Men without data on sex of sex partners (n = 4140)
- Cases with unknown sex (n = 27)
- Women (n = 2298)

Image Source: Figure 40 from STD Surveillance 2015
**Syphilis Diagnosis and Treatment**

- **Diagnosis**
  - Treponemal test (FTA-Abs, Syphilis IgG) followed by non-treponemal (RPR, VDRL)

- **Treatment**
  - Neurosyphilis
    - IV PCN for 14 days or IM daily with po probenecid
  - The difference between po prednisone and intravitreal steroids
Lesson

- Even inflammatory disease patients can get infectious disease
- Patients who don’t respond to immune suppression (prednisone) – reconsider diagnosis
- Syphilis – enough said
When should I order testing

- No hard and fast rules
- Anterior Uveitis – hypopyon associated, First episode?
- Is it really anterior uveitis?
- All other types – ordering at first evaluation
- Please remember – to talk to your patient and perform a ROS.
- In our previous talk - you may need imaging to help you

What should I order?

- Think about your population and your patient (ROS), in my clinic I have a large amount of infections and sarcoidosis.
- Recurrent anterior uveitis I consider:
  - FTA-Abs/Syphilis IgG, Quantiferon Gold, ACE, CXR, HLA B27
  - Urine B-2 microglobulin for children (consider ANA in kids as well)
  - Consider AC tap for viral PCR
- For posterior/panuveitis
  - Infectious – Toxo, Bartonella depending on the presentation
  - HLA-A29 if concern of birdshot
  - Chest CT if suspicious for sarcoidosis
  - Tissue biopsy in elderly or if concerned about infectious disease
Case Presentation

- 68 year old female with h/o CNV secondary to POHS vs AMD in both eyes presents for second opinion of recurrent iritis left eye
- Gets Avastin for CNV both eyes
- Has been treated with pred forte
- Recurs every time it is stopped
- Workup negative including HLA B27, Q-gold, RPR, ACE, ANCA, ANA, CMP, CBC, Lyme
- Had previous “uncomplicated cataract surgery”
Case Presentation

- Left eye has 2+ cell, pigment diffusely on endothelium, and sectoral iris atrophy with iris transillumination defects
- On Lotemax QID because of IOP response to pred forte
- Also notes that her eye pressure has been high in the past even when she was not on steroid drops
- Other questions?
- Previous zoster infection
- Yes around the face
- AC tap – positive for VZV

Pearls for viral anterior uveitis

- Unilateral disease
- Episodes of IOP spikes
- KP or pigment on endothelium diffusely
- Iris atrophy or transillumination defects
- Iris dilation without dilating drops
- Topical antivirals don’t really help
- Systemic antivirals needed for treatment and prevention
- Chronic therapy of both anti-viral and some topical steroid
**Diagnostic Procedures**

- **Tips**
  - Prior to procedure – know who is receiving the sample
  - Recognize you have limited sample – choose your test wisely
  - Be prepared for the unexpected..

- **When to perform**
  - When the clinical situation does not respond as expected
  - There is tissue to biopsy
  - Malignancy and/or infection is of concern

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**Be Aware of this Potential**

![Medscape](www.medscape.com)

Source: Am J Clin Pathol © 2007 American Society for Clinical Pathology
Your Biopsy - processed

FLOW CYTOMETRY

Collected Date: 01/18/2016
Received Date/Time: 01/19/2016 17:16:00
Verified Date/Time: 01/20/2016 13:38:12

Multiple necrotic cells – chronic inflammation
When should a patient start on chronic therapy?

Guidelines

- Active uveitis – treat with high dose of corticosteroids¹

- Add steroid-sparing agent if inflammation cannot be controlled with <10 mg prednisone within 3 months¹

So who should get chronic therapy?

- Those who can’t taper off prednisone
  - If you have a pt on greater than 10 mg prednisone for greater than 3 months – you need to switch
- Those who have multiple flare ups
  - My rule 3 flare ups within 12 months
- Those who you are controlling with just injections and vision is dropping
  - 20/200 ➔ IVK ➔ 20/25
  - 20/200 ➔ IVK ➔ 20/40
  - 20/400 ➔ IVK ➔ 20/60

Should I ask my patient to pay for difluprednate?

- Advantages over prednisolone acetate
  - QID therapy as effective as 8x/day pred acetate
  - Fewer pts fail
  - Faster response
- Disadvantages
  - Cost
  - IOP elevation
  - Is the endpoint the same?
**Difluprednate vs. prednisolone acetate**

**A. Grade 0 anterior chamber cells**

- **Difluprednate 0.05%, n=46**
  - Day 3: 6.4%
  - Day 7: 15.2%
  - Day 14: 25.5%
  - Day 21: 34.8%
  - Day 28: 55.3%
  - Day 35: 84.8%
  - Day 42: 80.4%

- **Prednisolone acetate 1%, n=47**
  - Day 3: 8.4%
  - Day 7: 22.5%
  - Day 14: 34.0%
  - Day 21: 55.3%
  - Day 28: 63.8%
  - Day 35: 70.2%
  - Day 42: 74.5%

**Sheppard J et al IOVS 2014**

**B. Complete clearing of anterior chamber cells**

- **Difluprednate 0.05%, n=46**
  - Day 3: 13.0%
  - Day 7: 21.7%
  - Day 14: 38.3%
  - Day 21: 52.2%
  - Day 28: 73.9%
  - Day 35: 69.6%
  - Day 42: 68.1%

- **Prednisolone acetate 1%, n=47**
  - Day 3: 21.3%
  - Day 7: 48.9%
  - Day 14: 63.6%
  - Day 21: 73.9%
  - Day 28: 69.6%
  - Day 35: 63.8%
  - Day 42: 68.1%

**Sheppard J et al IOVS 2014**
So which do I use

- I tend to use Pred acetate based on cost and coverage
- However, I often use difluprednate in those with difficulty with administering drops and/or very active
- Difluprednate has an effect on CME and retinal vascular leakage (Feiler et al 2016)
- Cycloplegia still needs to be used in anterior disease.
- I don’t use mild topical steroids

Dose Escalation

- If the patient does not respond to frequent topical quickly – I escalate therapy to oral steroids
- If I don’t think they are using it – I use oral steroids
- If I don’t think they are using oral steroids…
- I threaten them with a large bore needle into the eye
**Treatment – Systemic**

- Immunosuppressive agents
  - For chronic recurrent disease
  - For severe vision-threatening disease
  - For disease responsive only to high-dose corticosteroids

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**SITE Study**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Success at 1 yr</th>
<th>&lt;= 10 mg Pred</th>
<th>D/C within 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate</td>
<td>73%</td>
<td>55%</td>
<td>12%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>51%</td>
<td>36%</td>
<td>10%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>76%</td>
<td>61%</td>
<td>33%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>66%</td>
<td>60%</td>
<td>42%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>62%</td>
<td>47%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Biologic Agents

- Biologic Agents
  - Etanercept (Enbrel) – Anti-TNF
  - Infliximab (Remicade) – Anti-TNF
  - Adalimumab (Humira) – Anti-TNF
- Some reports of excellent response
- Now my second line agent (first line for some disease)
- Long term complications?
- Cost

RCTs in Non-infectious Uveitis: the VISUAL Program

To confirm that adalimumab is efficacious in the studied population versus placebo
Real-world design to provide insight about the safety and effectiveness of adalimumab in clinical practice

**VISUAL I**

- **Active uveitis**
  - ADA 40 mg eow or PBO
  - n=217
  - n=239

- **Controlled uveitis**
  - ADA 40 mg eow or PBO
  - n=226

**VISUAL II**

**VISUAL III**

- **Open-label extension**
  - ADA 40 mg eow
  - n=424
  - 85% of patients in VISUAL I and II
  - 85% of VISUAL I & II

ADA, adalimumab; eow, every other week; PBO, placebo

The risk of failing treatment (flare or vision loss) was reduced by almost half and the time to treatment failure was approximately doubled.

PBO | ADA
--- | ---
Median time to treatment failure | 13 weeks | 24 weeks
HR; p-value | 0.50; p<0.001 | 0.57; p=0.004
95% CI for HR | (0.36–0.70) | (0.39–0.84)

Treatment – Local Therapy

- Perioculars
- Intravitreal steroids
  - Triamcinolone
- Sustained-delivery devices
  - Fluocinolone acetonide implant
  - Dexamethasone intravitreal implant
- I use local injections as bridge therapy, for acute flares in chronic patients, for CME.
- If they need chronic therapy – fluocinolone implant or systemic
**Fluocinolone Acetonide Implant**

**Clinical Trial Results**

- Reduction in ocular inflammatory episodes
  - Average time to recurrence – 30-36 months
- Need for additional therapy
  - Systemic immunosuppression rates dropped from 44% to 8% at Year 3
- 100% cataract rate
- 70% IOP spike within 12 months, 40% glaucoma surgery rate

Sustained Local Therapy

- Patients who are good candidates
  - Recurrent posterior/intermediate uveitis
  - Ocular disease only
  - Recurrent cystoid macular edema
  - No previous history of glaucoma
  - “Pseudophakic with glaucoma tubes”
**MUST Trial**

- Multicenter Uveitis Steroid Treatment Trial
- Patients with active uveitis randomized to oral prednisone with systemic immunosuppressive agents vs. fluocinolone acetonide implantation
- Similar outcomes at year 2 between both groups
- Similar outcomes at year 5 between both groups


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**When can we safely perform cataract surgery?**
Case Presentation

- The optometrist who never refers you a patient sends you a patient!
- All of those holiday baskets finally have paid off!
- "It's an easy one"
- "I think they will need cataract surgery soon"
- "You're welcome"

Case Presentation

- 48 year old male
- Can't work now
- Uninsured
- Brother is a malpractice attorney
- Close cousin of your former long term girlfriend/boyfriend who broke up with you because "you were not serious enough"
**HPI**

- 48 Year Old Male
- Hx of scleritis
- Has been on infliximab x 2 years in past – then stopped and failed mycophenolate
- Was on Adalimumab x 6 months
- MTX 25mg weekly
- On and off PO steroids, usually 20mg but goes up to 40mg when flares
- Current meds \( \rightarrow \) on Pred 20mg

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**Initial Visit**

- Vision 20/40 OD, 20/125 OS
4 months later

- Vision 20/80 OD, 20/500 OS

Plan

- Start Cyclosporin
- Increase prednisone 40mg
Follow Up

- Becomes inactive x 3 months
- Visually significant cataracts OU
- Vision 20/200 OU

Cataract Surgery OS

- Complex with bag rupture and vitreous loss
- Vitreous to wound
- Send to Sunil.....
1 Month Post-Op

What To Do Now?

- Inflammation now significantly worse
- What should we do team?
- My plan:
  - Send to Angela....
  - Admit for 3 days IV Solumedrol
  - Also started on IV cytoxan
  - After 3 days Solumedrol placed on Prednisone 60mg
Exam 2 Weeks Later

It Took Angela and I A Long Time….

- Cyclophosphamide
- Steroids
- Adalimumab
- Cyclophosphamide again
  - Infliximab 10 mg/kg monthly
  - 1 year later off of all steroids
  - Now…
Cataract OD
When is okay to do surgery?

- Historically
  - Wait for 3 months of inactivity
  - Multiple papers report improved outcomes
- Is it because:
  - Peri-op management
  - Better phaco surgery
  - Better IOLs

Now

- 3 months of quiescence desirable
- But, we operate when there is minimal activity and uveitis is controlled
- Operate during the window of opportunity
- Aggressive peri-op management
**Perioperative management?**

- **Why?**
  - Reduce complication risk
  - Recurrence (as high 53%)
  - Post-operative fibrin formation (up to 30%)
  - CME (5-40%)
  - IOL deposition (10-20%)
  - PCO? (50-90%)

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**Classic regimen**

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<th>Maintenance Regimen</th>
<th>Peri-op Regimen</th>
</tr>
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<td>Inactive anterior uveitis</td>
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<td>Topical Steroids</td>
<td>Pred drops 6x/day 1 week prior +/- po steroids 30-60 mg</td>
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<td>Immunosuppressive +/- Topical +/- Prednisone</td>
<td>Pred drops 6x/day + PO steroids (at least 30 mg)</td>
</tr>
<tr>
<td>Chronic Panuveitis Uncontrolled</td>
<td>Immunosuppressive +/- Topical +/- prednisone</td>
<td>Pred Drops q1-2 hour + high dose po steroid</td>
</tr>
</tbody>
</table>
**My Perioperative Approach**

- In quiet eyes with no history of recent inflammation – preop topicals
- In chronic anterior uveitis – Preop topicals + 1 week prior dexamethasone implant vs intraop triamcinolone vs po steroids
- In posterior disease – combination of topical, intravitreal and po steroids.
- If I am not sure if there is an infectious cause – I DO NOT INJECT STEROIDS
- Scleritis patients - I avoid intravitreal injections, I use po steroids +/- periocular steroids.
- Taper slowly topicals and po.

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**Classic regimen Plus Intravitreal**

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<td>Topicals +/- IVT or dex 1 week prior</td>
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</table>
**What’s My Surgical Technique for CE/IOL?**

- I am a retina surgeon who has healthy relationships with my anterior segment colleagues so I stay away from cataract surgery
- In general
  - Control of iris – try to minimize iris manipulation if possible. Iris hooks and Malyugian rings are used often in our institute for post synechiae
  - Stain capsule
  - Acrylic IOLs
    - I do not recommend prophylactic vitrectomy/posterior capsulectomy for adults

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**Scleritis and cataract**
Postop Pic

Back to our original patient

- Heavy topical therapy pre-op
- Unable to get ozurdex approval
- Intravitreal triamcinolone at time of surgery
- PO steroids 5 days prior
- Does great
- 20/30 1 year out
- No postop inflammation
- Kept on topicals x 3 months…. 
What about post-op inflammation?

- Most chronic post-op CE/IOL inflammation is not uveitis
- Most is due to surgery and genetics
- Not enough topical therapy or not for long enough
- Also your cataract surgery wasn’t perfect (its okay I won’t tell anyone)
- But some can be concerning and warrant work-ups
- So first – increase topical therapy frequency (real topical steroids)
- Then if not quiet – add po steroids – if not better - refer

Post surgery inflammation

- Consider
  - Infection
  - IOL touch of iris
  - Was there intraoperative manipulation of iris
- Tissue sample
  - Vitreous or anterior chamber tap/inject
  - IOL removal/PPV
**Case Presentation**

- **CC:** Recurrent uveitis, Left Eye

- **HPI:** 62 year-old man
  - Presented with redness, blurred vision OS one month ago
  - Improved with drops but 2 recurrences on taper, last one 10 days ago

- **Past Ocular Hx:**
  - CE OS 1 year ago, OD 10 months ago
  - Amblyopia OS

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**Exam**

- **OD 20/30 OS 20/70**
- **SLE**
  - OD: Quiet
  - OS: 2-3 + AC cell, Mutton Fat KP, PCIOL, 2+ Vit Cell and 2+ Haze
Assessment

- Unilateral Panuveitis, Left Eye
- Two episodes in past 6 weeks
- Started 1 year after phaco – related to cataract surgery?

Plan

Labs

CBC, CMP, ACE, HLA-B27, Syphilis IgG, quantiferon

Start Difluprednate, po steroids
Case Presentation

- Increasing anterior chamber cell over next few visits despite topicals
- Plan?
- Another injection?
- Restart oral prednisone?
Persistent 2+ AC cell on topical QID
### Assessment

- Chronic endophthalmitis
- AC tap – P. acnes
- What now?
- Inject vs IOL explant?
- Receives injection of vancomycin with plan for PPV/explant

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### Surgical Video
What signs should I worry about?

- When things don’t respond the way I expect
  - High dose prednisone should quiet most inflammatory diseases
  - Retinal whitening that appears out of nowhere
  - Infections that progress on therapy
- Necrosis of the retinal, scleral melts
- Diffuse hemorrhage and diffuse vascular sheathing
- Anyone referred to me with worsening vision after intravitreal/periocular steroids
- Hypopyon that I can’t explain

Last Case

- Let’s put it all together
- And show you
- Why ophthalmology is awesome….
Case Presentation

- 32 year old male
- Transferred from outside hospital for ophthalmology intervention
- 3 week history of progressive painful swallowing, diagnosed with candida esophagitis
- Unable to eat – losing weight, on TPN
- While on TPN – develops sudden floaters and vision loss
- Diagnosed with candida endophthalmitis
- Anti-fungals changed, but progressive worsening of vision
- Transferred – ophtho resident called

- Vision 20/200 OD 20/20 OS
- Tr AC cell
- DFE: see photos
- But first – I will show you his mouth
So my resident thinks......

- This does not make sense
- What would Sunil do?
- Recheck everything...
Resident thinking...

- Multiple ischemic areas
- Looks like artery occlusions
- Can systemic fungal infection give you artery occlusion?
- Maybe but rare, and no lesions OS, and no full thickness lesions
- But inflammatory disease can.
- Let me look at his mouth again
So...

- Mouth ulcer, multiple artery occlusions
- ?Behcet's
- What else should he have?
- Yup – lets check you everywhere
Success!

- Oral ulcers, genital ulcers, retinitis = Behcet's
Case Presentation

- Started on IV Solumedrol
- Eating in 2 days
- Esophagus lesions determined to be ulcers – resolved within 5 days
- Gains weight back
- Started on IV infliximab
- f/u vision 20/30 OD, 20/20 OS
- Ophtho resident – saves this patient’s life.
Lessons learned

- Take the outside history with a grain of salt
- If clinical picture does not fit – re-examine diagnosis
- Sometimes the eye exam needs to be done without your clothes off.

Summary

- We have answered some questions
- When to work-up and how to work up a patient
- Treat patients with chronic therapy when they display chronic disease
- Periop management/ Post-op inflammation management
- Watch out for the bad signs
- Be observant and constantly question the supposed “truth”
- Just in case: srivass2@ccf.org