Anterior + Intermediate Uveitis

Dr Xavier J Fagan
Ocular Immunology Clinic - RVEEH
Case Presentation

• 32yo male presents with 2 weeks of unilateral declining vision, photophobic and red eye.
What do you do now?

• History...
• Examination...
• Investigations?...
• Treatment...
Would you change anything if...

- This was the third episode in 6 months?
- There was more inflammation in the vitreous?
- There was cystoid macular oedema?
Overview

1. How we define and measure uveitis.
2. Causes of anterior & intermediate uveitis
3. Investigations for anterior or intermediate uveitis.
4. Treatment Options
5. Specific Uveitis conditions
6. Interspersed quizzes
Definitions

• Uveitis = inflammation of the uveal tract (ie, iris, ciliary body, choroid) or adjacent ocular structures (eg, retina, optic nerve, vitreous, sclera).

• Standardization of Uveitis Nomenclature (SUN)
  • Published 2005: consensus publication
  • Simplified and unified several different classification and grading systems
Note: if the patient has significant anterior uveitis + vitritis, this is anterior uveitis & intermediate uveitis, NOT panuveitis.

<table>
<thead>
<tr>
<th>Type</th>
<th>Primary Site of Inflammation</th>
<th>Includes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior uveitis</td>
<td>Anterior chamber</td>
<td>Iritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iridocyclitis</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>Vitreous</td>
<td>Anterior cyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pars planitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior cyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyalitis</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>Retina or choroid</td>
<td>Focal, multifocal, or diffuse choroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chorioretinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinochoroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroretinitis</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>Anterior chamber, vitreous, and retina or choroid</td>
<td></td>
</tr>
</tbody>
</table>

*SUN = Standardization of uveitis nomenclature.

†As determined clinically. Adapted from the International Uveitis Study Group anatomic classification in reference 1.
### TABLE 3. The SUN* Working Group Grading Scheme for Anterior Chamber Cells

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in Field(\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0.5+</td>
<td>1–5</td>
</tr>
<tr>
<td>1+</td>
<td>6–15</td>
</tr>
<tr>
<td>2+</td>
<td>16–25</td>
</tr>
<tr>
<td>3+</td>
<td>26–50</td>
</tr>
<tr>
<td>4+</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

*SUN = Standardization of uveitis nomenclature.
\(\dagger\)Field size is a 1 mm by 1 mm slit beam.

### TABLE 4. The SUN* Working Group Grading Scheme for Anterior Chamber Flare

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Faint</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate (iris and lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris and lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin or plastic aqueous)</td>
</tr>
</tbody>
</table>

Adapted from reference 12.
*SUN = Standardization of uveitis nomenclature.
Other parameters in Anterior uveitis

- Fibrin
- KPs
  - Size/shape: Granulomatous vs non-granulomatous
  - Distribution: Arlt triangle/diffuse/localised
  - Colour
- Synechiae
  - Anterior
  - Posterior
- Hypopyon
  - Mobility
- Nodules
Vitreous inflammation...

- The problem with cells
  - Remember the anterior vitreous
  - Veils
  - Posterior vitreous
- Vitreous **haze** is argued to be a better measure
- Even the SUN group couldn’t come to a consensus and referred to previous guidelines (Nussenblatt *Ophthalmology* 1985)

### TABLE 19-7. Grading of Vitreous Cells and Haze

<table>
<thead>
<tr>
<th>No. of Cells</th>
<th>Description</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>Clear</td>
<td>0</td>
</tr>
<tr>
<td>2–20</td>
<td>Few opacities</td>
<td>Trace</td>
</tr>
<tr>
<td>21–50</td>
<td>Scattered opacities</td>
<td>1+</td>
</tr>
<tr>
<td>51–100</td>
<td>Moderate opacities</td>
<td>2+</td>
</tr>
<tr>
<td>101–250</td>
<td>Many opacities</td>
<td>3+</td>
</tr>
<tr>
<td>&gt;250</td>
<td>Dense opacities</td>
<td>4+</td>
</tr>
</tbody>
</table>

*Cells are counted using a Hruby, 90- or 78-diopter lens.
Grades of haze with an indirect ophthalmoscope (Nusenblatt):

- 0: clear
- 1+: opacities without obscuration of retinal details
- 2+: few opacities resulting in mild blurring of posterior details
- 3+: optic nerve head and retinal vessels significantly blurred but still visible
- 4+, dense opacity obscuring the optic nerve head.
Other parameters in vitreous inflammation

- Snowballs: (not diagnostic, but are particularly prominent in sarcoid)
- Snow-banking
-Periphlebititis
Posterior vitreous detachment
Complications of Uveitis

- What are the complications of chronic and/or recurrent uveitis?
  - Anterior
    - Band keratopathy
    - Peripheral anterior synechiae
    - Posterior synechiae, iris bombe and angle closure
    - Increased IOP: pre-trabecular and trabecular causes
  - Posterior
    - Vitreous haze
    - Cystoid macular oedema
    - Disc swelling
    - Glaucomatous optic neuropathy
    - Phlebitis and ischaemia
History in Uveitis

- ‘Targeted’
- Systems review
  - Rheumatological
  - Dermatological
  - Respiratory
  - Neurological
  - Gastro-intestinal
  - Urogenital
  - Immunological
  - Others: travel, tattoo, medication/drug use

Basically, ask about everything! But some areas deserve closer attention than others.
Question...

• How do you diagnose anterior uveitis on examination?
Examination in uveitis

- Anterior uveitis is a diagnosis of exclusion
  - It is medically negligent to diagnose anterior uveitis without attempting a dilated fundus examination of both eyes

- Be systematic
  - Examine from anterior to posterior
  - Document consistently & clearly
  - Medical imaging is useful
Investigations in anterior uveitis

• Indications:
  • Unusual demographic
  • Positive systems review
  • Recurrent episodes

• Tests
  • HLA B27
  • Syphilis serology
  • CXR

• Other tests
  • ACE, QF Gold.
  • AC tap.
Investigations in intermediate uveitis

- Indications?
- Tests:
  - FBE, UEC
  - Syphilis serology
  - QF Gold & Chest X-ray
  - ACE
  - Others as directed by history + examination:
    - MRI Brain
    - Vitreous biopsy
    - Lumbar puncture

In all uveitis – aim to exclude:
1. Infection
2. Neoplasm
“Name & Mesh”

• Name the site of the location, the periodicity/chronicity.
• Compare with the known history and positive investigation findings.
• Mesh with the best known condition that fits these parameters.

Sometimes... It isn’t possible to find a neat diagnostic category for patients. This doesn’t mean we don’t treat them!
Treatments in Uveitis

• Principles:
  1. *Maximal* effectiveness with *minimal toxicity*.
  2. The more localized the disease, the more localized the treatment (ideally).
  3. Avoid irreversible treatments when you aren’t sure of the diagnosis.
  4. Steroids: treat harder early and taper faster (with some exceptions).

• Unfortunately, the most efficacious can often be the most problematic/toxic!
  • Therefore: stepwise progression from least to most efficacious/toxic.
Therapies:

- Local
  - Drops: prednefrin forte
    - 1 hourly for 1 week considered a minimum!
  - Subconjunctival injections: triamicinolone, methyprednisolone
  - Periorbital injections: sub-Tenon and orbital floor.

- Systemic
  - NSAIDs
  - Oral steroids: prednisolone
  - Intravenous steroids: methylprednisolone
  - DMARDs: methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide.
SPECIFIC ANTERIOR UVEITIS CONDITIONS

• HLA-B27
• Herpetic
• Fuch’s H1
• Lens related
• Behcet’s
HLA-B27 uveitis

- Refers to a genotype on 6p
- Epidemiology (McCluskey 2011):
  - Present in 1.4% - 8% of general population:
  - Two ways of looking at it:
    1. 25% of patients with B27 disease will get uveitis
    2. 25% of AAU is due to B27.
  - BUT only 1-2% of B27 positive patients will get systemic disease!
- Uncommon in Asians.
- Associated conditions: a little quiz...
  1. Ankylosing spondylitis: 95% B27 positive
  2. Reactive arthritis (no longer Reiter’s): 80% B27 positive
  3. Psoriatic arthritis: approx. 7% get uveitis
  4. Inflammatory Bowel Disease: 2-5% of patients get uveitis
Characteristics of B27+ Uveitis

- Flare
- Fibrin
- Recurrence
- Severity

- Previous degrees of inflammation, time to settle and treatments required are good indicators of future requirements!
- Can cause hypopyon uveitis
- MUST DILATE!!!
- Ask about other systems → refer

Quiz: What are some other causes of hypopyon uveitis?
A) Infectious
   - Endogenous
   - Post-operative
B) Inflammatory
   - Behcet’s
C) Neoplastic
D) Iatrogenic - rifabutin
Herpetic Anterior Uveitis

- HSV 1 & 2, VZV
- Characteristics:
  - History
    - Recent VZV
    - Current or previous oral HSV
    - Multiple unilateral attacks. Bilateral is rare.
  - Examination
    - ↑ IOP
    - Look for diagnostic corneal changes (new or old dendrites)
    - Anaesthetic cornea
    - Look for scars in V1 distribution (but can have HZO sine herpete)
    - Can cause scleritis as well
    - Iris changes...
Iris changes in Herpes Uveitis

- Both HSV and VZV can occur without corneal changes (Van der Lelij et al. *Ophthal* 2000 1164-70)
- Sectoral Iris atrophy – characteristic of herpetic uveitis.
  - Classically thought to represent VZV
  - But both viruses can do it & it is non virus specific
Zoster Uveitis

• As many as 43% of patients with HZO will develop irido-cyclitis (Womack *Arch Ophth* 1983) but the number is probably less than that.

• Data from RVEEH (Thean et al. *CEO* 2001 406-10)
  • 34 patients from RVEEH with HZO uveitis: 24 – 83 yo.
  • 32% have relapsing course of uveitis: steroid dependence.
  • 56% developed elevated IOP → of which 5 patients required trabs.

• Take home
  • See patients 1/52 & 6/52 post rash onset if normal eye exam
  • Can cause significant ocular morbidity: check IOP!
  • Some patients require chronic long term topical steroid
Pop Quiz:

• Name 5 causes of acute hypertensive uveitis:

1. Herpetic uveitis
2. Fuch’s Heterochromic Iridocyclitis
3. Toxoplasmosis
4. Posner-Schlossman syndrome
5. Less common - Phacolytic glaucoma, endogenous endophthalmitis
Fuch’s HI

• Inflammatory disorder of anterior segment and vitreous
• Rubella association (Quentin et al *Am J Ophthal* 2004 July)¹

**History**

• Often painless, white eye presenting with one of:
  1. Asymmetric visual loss: cataract
  2. Vitreous floaters
  3. Iris colour change

*95% unilateral*
Fuch’s HI

- **Examination**
- **White eye**
- Iris heterochromia:
- **Inflammation**
  - Small *stellate* KP’s scattered over entire cornea
  - Mild cells and flare
  - Iris nodules & iris crystals
  - Angle changes
- **Sequelae**
  - Cataract – esp. PSCC
  - Glaucoma
  - **Absence of**: Posterior synechiae and CMO

Diagnosis = white eye + distribution of KP’s + lack of synechiae + heterochromia
Treatment of Fuch’s HI

• Pre-Cataract Surgery: avoid steroid drops
• Post-cataract surgery:
  • often require higher dose steroid drops in immediate post-op
  • May require lifelong low frequency steroid
• Glaucoma
  • Usually well controlled with topical medications
Lens – Related Uveitis

• 3 kinds of lens related ‘uveitis’:

1. **Phacolytic** Glaucoma
   • An inflammatory glaucoma caused by leakage of lens protein through the intact capsule of a mature or hypermature cataract.

2. **Phaco-anaphylaxis**
   • (Not actually an anaphylaxis/type I HS but is labeled as such b/c of the presence of eosionphils pathologically.)
   • Granulomatous anterior uveitis in context of recent trauma

3. **Lens particle** glaucoma
   • Occurs when residual cortex obstructs the TM following surgery or trauma
Treatment

TAKE OUT THE LENS!!
Behçet’s disease

- Acute iritis with hypopyon
- Aphthous stomatitis – painful, present in 98-100% of patients!
- Genital ulceration
Behcet’s

• An idiopathic, generalized occlusive vasculitis.
• a/w HLA B51 (but this doesn’t help us!)
• Demographics:
  • Young
  • F > M (but.. Males get it worse)

Non-ocular Features
• Mucous membranes:
  • painful aphthuous ulcers (aphtha is from Latin – means small ulcers especially the white or red spots in the mouth)
  • Genital ulcers
• Skin: erythema nodosum
• Joints: non-destructive arthritis, especially of the wrists and ankles
• Neuro-Behcets: strokes, palsies and confusional states. THIS IS LIFE-THREATENING!
Formal Diagnosis Requires (Lancet 1990):
• recurrent oral ulceration + 2 of the following –

  1. recurrent genital ulceration,

  1. eye lesions,

  1. skin lesions,

  1. pathergy test (sterile needle puncture of skin, look for development of pustule or papule 1-2 days later. Approx 80% sens and spec on its own).
Behcet’s & the Eye

Anterior
- **characteristic** feature = recurrent iritis or chronic iridocyclitis that is often **bilateral** and a/w transient **hypopyon** & white eye.
- **never fibrin** (almost) content and therefore shifts according to patient head position.

Posterior
1. Primary vasculitis
2. Necrotizing Retinitis
3. Macular Oedema
4. Ischaemic optic neuropathy
Treatment of Behcets

• Systemic
  • Required for patients with:
    • Severe bilateral disease
    • Vasculitis
    • Retinitis
  • High dose oral prednisolone or IV methyprednisolone
  • Often necessitates immediate commencement of DMARD
    • Cyclosporine
    • Combined therapy
    • Biologics

• Local
  • Standard anterior uveitis treatments
  • Orbital Floor
  • Intravitreals
A reminder: Anterior Uveitis is a diagnosis of *exclusion*!

**EXAMPLES OF SOME THINGS THAT LOOK LIKE ANTERIOR UVEITIS IF YOU DON’T DILATE**
Acute Retinal Necrosis
Toxoplasmosis
VKH
Frosted Branch Angiitis
Take home message

• You must dilate and examine **both** eyes of a patient with uveitis.

• You can *only* say it is anterior uveitis once you have excluded posterior involvement of vitreous, retina, choroid and optic nerve.
INTERMEDIATE UVEITIS
Definition

• Where the predominant site of inflammation is the vitreous cavity (Jabs et al. AmJO 2005)
  • Presence of periphlebitis &/or CMO does not change this classification.

• Remember:
  • Look for cells in retrolental space
  • Check amount of haze in reference to standard photographs or descriptions
Pop Quiz: Common Causes of IU

1. Sarcoidosis
2. Demyelinating disease
3. Other – TB, Lyme disease, masquerade syndromes
4. IDIOPATHIC!!
Work-up

- History
- Examination
- Investigations
  1. FBE, UEC
  2. CXR
  3. ACE level
  4. Syphilis serology
  5. QF Gold

(Possible: MRI brain, lumbar puncture)
Treatment Goals

1. Identify and manage underlying systemic disorder
2. Control Ocular Inflammation
   - Stepwise approach
     - Orbital floor steroid (+ treat any concomitant anterior uveitis with drops)
     - IVTA
     - Consider oral steroid if contra-indication to local treatment or bilateral disease
3. Treat Complications of Ocular Inflammation or of treatment itself
   - CMO
   - Disc swelling
   - Cataract, glaucoma, ERM
4. Prevent recurrences
   - Long taper of steroids
   - DMARDs
MASQUERADE SYNDROMES
A word or two on masquerade syndromes

- A group of disorders:
  - That simulate chronic idiopathic uveitis
  - The primary cause is not immune mediated

- There are neoplastic and non-neoplastic causes
Examples of Masquerades:

- Adults
  - Lymphoma (esp. large B cell lymphoma)
  - Uveal malignant melanoma
  - Amyloidosis
- Children
  - Retinoblastoma
  - Juvenile xanthogranuloma
  - Acute leukaemia
- Both:
  - Retinitis pigmentosa
  - Retained intraocular foreign body
Amyloid
When to think of them...

- **Atypical features**
  - Prominent cells without inflammatory complications (posterior synechiae, cystoid macular oedema)
  - Extremes of age: very young and the elderly.

- **Atypical response** to treatments
  - Lymphoma typically responds initially to steroids but becomes progressively steroid resistant

- **Systemic disease**
  - Known systemic disease
  - Positive systems review with unusual symptoms
Primary Intraocular lymphoma

• Deserves a special mention

• Presentation
  • 50-60+
  • Floaters & ↓ VA

• Signs:
  • Vitreous
    • Diffuse cellular infiltration in sheets
  • Subretinal/sub-RPE masses
    • Yellowish-white, geographical infiltrates with overlying RPE clumps
  • Bilateral in 80-90% of cases

• Patients with Primary CNS Lymphoma: 15-25% develop PIOL

• Patients with PIOL: 60-80% develop PCNSL at around 29months

• Median survival: with CNS disease = 33months; without CNS disease at presentation = 57 months
PIOL

• Investigations
  • Ocular:
    • Vitreous tap: often inadequate cells
    • Vitrectomy: much higher yield *but only* if there are adequate cells clinically and much less likely if the patient has been on steroid recently
    • Chorio-retinal biopsy: if a subretinal/RPE lesion. Higher positive yield but more complications
  • Systemic
    • MRI Brain & Orbits with contrast
    • Lumbar puncture
    • HIV testing
    • CT C/A/P
Treatment

• PIOL with systemic involvement
  • Systemic Rx: Intravenous MTX & intrathecal chemo
    • 2nd line: rituximab; autologous stem cell transplant; whole brain irradiation (5yr survival up to 30% but lots of complications)
    • No role for brain resection
  • Ocular Rx
    • Patients with aggressive ocular treatment & systemic treatment had improved progression free survival compared to patients who only had systemic treatment: 19months vs 14 months. (Grimm et al Neuro-onc 2006)

• Isolated PIOL
  • Intravitreal Methotrexate
    • 0.4mg in 0.1mL: 2x weekly for 1month, then weekly for 1month.
    • Co-administer with folinic acid drops and tablets
  • Whole eye irradiation
    • Only if patient has poor life expectancy
Finish...