Uveitis: Classification, Etiologies and Clinical Signs

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Abstract

Uveitis is one of the vision threatening eye diseases. There are several conditions that can mimic uveitis. An approach to uveitis should include uveitis oriented history, ophthalmic examination, systemic evaluation, ancillary tests and laboratory investigations. Various signs and symptoms can occur in different types of uveitis. There is a new grading system of anterior chamber inflammation and vitreous inflammation by SUN working group. There is also an anatomic and an etiological classification of uveitis. New classification systems have been proposed recently for intraocular tuberculosis, ocular sarcoidosis, Vogt-Koyanagi-Harada disease, Behcet’s disease and acute retinal necrosis. This review article will update the clinical approach and various classification systems in uveitis.

Keywords: uveitis, intraocular tuberculosis, ocular sarcoidosis, Vogt-Koyanagi-Harada disease, Behcet’s disease and acute retinal necrosis

Introduction

Uveitis is one of the vision threatening ocular disorders responsible for 10% of legal blindness. It is a non-purulent endogenous or exogenous inflammation of the uveal tract primarily but contiguous structures such as vitreous, optic nerve, cornea and sclera may sometimes be involved. Standard clinical approach involves a careful history and a thorough systemic and ocular examination. Of all the cases of uveitis, around 23% of patients have a definite etiological correlation, whereas, about 77% of cases are categorized as idiopathic.

One must remember the following conditions that can mimic uveitis:

Conditions that can mimic anterior uveitis
- Conjunctivitis
- Scleritis/ episcleritis
- Acute angle closure glaucoma
- Masquerade syndrome

Conditions that can mimic posterior uveitis
- Central serous choroiretinopathy
- Posterior scleritis
- Age related macular degeneration

Conditions that can mimic panuveitis
- Endogenous endophthalmitis
- Large cell lymphoma

Any comprehensive workup of uveitis should also include relevant tests for these conditions that may rarely masquerade as uveitis.

Uveitis oriented history

Physician must enquire about the symptoms which include redness, pain, photophobia, epiphora, visual disturbances, scotoma and floaters. One must try to ascertain the onset of symptoms (sudden or insidious); course (acute, recurrent or chronic); laterality (unilateral / bilateral); any previous treatment given and response to treatment; and any associated systemic disease.

Important signs of uveitis

- Circumcorneal congestion
- Keratic precipitates
- Anterior chamber cells and flare
- Hypopyon
- Iris nodules
- Posterior synechiae
- Anterior synechiae
- Hypotony
- Secondary glaucoma
- Vitreous cells
- Snow-banking
- Retinal vasculitis
- Retinitis
- Choroiditis
- Retinochoroiditis
- Chorioretinitis
- Optic nerve inflammation

a. Keratic precipitates (KPs) (cellular deposits on the endothelium) can be classified as:

- Small, medium sized KPs are seen in non granulomatous uveitis (Figure 1)
- Large, mutton-fat KPs are seen in granulomatous uveitis (Figure 2)
- Fresh KPs are rounded, white, fluffy, with hydrated appearance
- Old KPs are shrunken, pigmented with crenated edges, faded mutton-fat

Distribution of keratic precipitates

- Inferior quadrant—base down triangle “Arlt’s triangle”
- Diffuse-Fuchs’ heterochromic iridocyclitis, Sarcoidosis, Syphilis, Keratouveitis
- Central - chronic uveitis
SUN group is presently working to establish photographic guidelines for describing KPs.

b. Anterior chamber cells and flare: (Figure 3)
To grade cells and flare, (Table 1 and 2) the slit lamp is set to maximum intensity and both the width and length of the beam at 1mm.

c. Vitreal inflammatory cells:
The SUN working group did not arrive at a consensus regarding grading system of vitreous cells. However, the NIH grading system for vitreous haze, which has now been adopted by SUN group, grades both vitreous cells and flare and may be better indicator of disease activity than cell counts alone. With this method, standardized photographs are used for comparison to ultimately arrive at the level of vitreous haze. Vitritis is seen as vitreal cellsa and vitreous strands. Small snowball opacities are more commonly seen with sarcoidosis or intermediate uveitis (Figure 4) while larger exudates over pars plana are called snowbanks. On indirect ophthalmoscopy active snowbanks have fluffy or shaggy appearance. When pars planitis becomes inactive, the pars plana appears smooth and gliotic or fibrotic.

There can be various systemic features of uveitis. (Table 3)
Table 3

Systemic features | Diseases
---|---
Skin | Rash • Secondary syphilis
• Erythema nodosum • Sarcoïdosis
• Acne like sores, red tender nodules • Behçet’s disease
• Psoriasis • Psoriatic arthritis
• Keratoderma blennorrhagica • Reiter’s syndrome
• Lupus pernio • Sarcoïdosis
• Vitiligo • VKH syndrome and sympathetic ophthalmia

Hair | Alopecia • VKH syndrome and sympathetic ophthalmia
• Poliosis • VKH syndrome and sympathetic ophthalmia

Nails | Pitting • Psoriatic arthritis
• Dystrophy • Reiter’s syndrome

Mouth ulceration | Painful • Behçet’s disease
• Painless • Reiter’s syndrome

Arthritis | Spondyloarthritis
• Juvenile chronic arthritis
• Sarcoïdosis

Gut involvement | Ulcerative colitis
• Crohn’s disease
• Whipple’s disease

Lung involvement | Sarcoïdosis
• Tuberculosis

Urethritis | Reiter’s syndrome
• Gonorrhea

CNS involvement | VKH syndrome
• Congenital toxoplasmosis
• Behçet’s disease
• Large cell lymphoma

Classification of Uveitis

A. Anatomical Classification
1. Anterior uveitis
   • Iritis
   • Anterior cyclitis
   • Iridocyclitis
2. Intermediate uveitis: Formerly known as Pars Planitis and peripheral uveitis
3. Posterior uveitis
   • Focal choroiditis
   • Multifocal or diffuse choroiditis
   • Chorioretinitis
   • Retinochoroiditis
   • Neuroretinitis
4. Panuveitis

B. Etiological Classification
1. Idiopathic uveitis is seen in upto 30-60% of cases where a definite etiology cannot be ascertained.
2. Secondary to systemic diseases
   A. Seronegative arthritis
      • Ankylosing spondylitis
      • Reiter’s syndrome
      • Psoriatic arthritis
      • Behçet’s disease
      • Juvenile idiopathic arthritis (JIA)
   B. Gastrointestinal
      • Ulcerative Colitis
      • Crohn’s disease
      • Whipple’s disease
   C. Respiratory
      • Sarcoïdosis
      • Pulmonary tuberculosis
3. Infectious causes
   • Viral
      • Herpes zoster
      • Herpes simplex
      • Cytomegalovirus
      • Measles
      • Influenza
   • Fungal
      • Presumed ocular histoplasmosis (POHS)
      • Candidiasis
      • Coccioidoidomycosis
   • Parasitic
      • Toxoplasmosis
      • Toxocariasis
      • Pneumocystis carinii
      • Onchocerciasis
4. Lens induced
   • Phacoanaphylactic endophthalmitis
   • Phacotoxic uveitis
5. Traumatic
   • Post Surgical - Intraocular lens IOL related uveitis
   • Non surgical
6. Toxic
   • Chemical
   • Drug induced - rifabutin
C. Classification According to Type of Inflammation
Uveitis can be classified as granulomatous and non-granulomatous uveitis (Table 4). The SUN group further refined the anatomical classification (Table 5) of uveitis by also defining descriptions based on clinical onset, duration, and course. In addition, the SUN working group recommended specific terminology for grading and following uveitic activity (Table 6).

Various studies have been conducted and researchers have proposed various diagnostic criteria to classify certain uveitis-associated ocular pathologies associated with systemic conditions. These systems help to standardize the approach and diagnosis of the pathologies. The important common classifications are discussed below

Classification of Intraocular Tuberculosis (IOTB)
Recently, Gupta A et al have proposed the classification of IOTB comprising of confirmed IOTB, probable IOTB and possible IOTB. These guidelines offer a greater degree of "certainty" to diagnosis of IOTB. (Table 7)

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| Features of granulomatous and non-granulomatous uveitis |
|----------------------------------------------------------|
| **Features**                                                   | **Granulomatous** | **Non-Granulomatous** |
| Onset       | Insidious                  | Acute                  |
| Course     | Chronic                    | Short (may be recurrent) |
| Anterior Segment |                      |                        |
| Circumcorneal congestion | +              | +++                    |
| Pain        | +                         | +                      |
| Iris nodule | +++                       | -                      |
| KP's        | Large mutton fat           | Small or medium        |
| Flare       | +                         | +++                    |
| Posterior Segment | Commonly involved | Rarely involved       |
| Vitreous    | Heavy exudates or veils    | Fine opacities         |
|             | Nodular lesions            | Diffuse involvement with edema |

| The SUN Working Group Descriptors in Uveitis³ |
|-----------------------------------------------|
| **Category**             | **Descriptor** | **Comment** |
| Onset                    | Sudden        | Insidious    | ≤3 months’ duration |
| Duration                 | Limited       | Persistent   | >3 months’ duration |
| Course                   | Acute         | Episode characterized by sudden onset and limited duration |
|                          | Recurrent     | Repeated episodes separated by periods of inactivity without treatment ≥3 months duration |
|                          | Chronic       | Persistent uveitis with relapse in <3 months after discontinuing treatment |

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Table 4: Features of granulomatous and non-granulomatous uveitis

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Table 6: The SUN Working Group Activity of Uveitis Terminology³

| Term               | Definition                                                                 | Comment          |
|--------------------|---------------------------------------------------------------------------|------------------|
| Inactive           | Grade 0 cells (anterior chamber)                                           |                  |
| Worsening activity | 2-step increase in level of inflammation (eg, anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+ | ≤3 months’ duration |
| Improved activity  | 2-step decrease in level of inflammation (eg, anterior chamber cells, vitreous haze) or decrease to grade 0 |                  |
| Remission          | Inactive disease for ≥3 months after discontinuing all treatments for eye disease | >3 months’ duration |

Table 7: The proposed classification of intraocular tuberculosis

| Clinical diagnostic group | Case definition criteria                                                                 |
|---------------------------|------------------------------------------------------------------------------------------|
| Confirmed IOTB (both 1 and 2) | 1. At least one clinical sign suggestive of IOTB (and other etiologies excluded) |
|                           | 2. Microbiological confirmation of Mycobacterium tuberculosis from ocular fluids/tissues |
| Probable IOTB (1,2, and 3 together) | 1. At least one clinical sign suggestive of IOTB (and other etiologies excluded) |
|                           | 2. Evidence of chest X-ray consistent with TB infection or clinical evidence of extraocular (EO) TB or microbiological confirmation from sputum or EO sites |
|                           | 3. At least one of the following:                                                        |
|                           | a. Documented exposure to TB                                                             |
|                           | b. Immunological evidence TB infection                                                   |
| Possible IOTB (1,2, and 3 together) OR (1 and 4) | 1. At least one clinical sign suggestive of IOTB (and other etiologies excluded) |
|                           | 2. Chest X-ray not consistent with TB infection and no clinical evidence of EO TB           |
|                           | 3. At least one of the following:                                                        |
|                           | a. Documented exposure to TB                                                             |
|                           | b. Immunological evidence TB infection                                                   |
|                           | 4. Evidence of chest X-ray consistent with TB infection or clinical evidence of EO TB but none of the characteristics given in 3 |

Clinical Signs consistent with IOTB
Presence of cells in anterior chamber or vitreous along with:  
1. Broad posterior synechiae (Figure 5)  
2. Retinal perivasculitis with or without discrete choroiditis / scar  
3. Multifocal serpiginoid choroiditis (Figure 6)
Recent Advances

Classification for Ocular Sarcoidosis (OS)

International criteria for the diagnosis of ocular Sarcoidosis (OS) proposed by the first International Workshop on Ocular Sarcoidosis (IWOS)⁵

Seven clinical signs and features were identified in the diagnosis of intraocular sarcoidosis:

- Mutton–fat KPs/ small granulomatous KPs and/or iris nodules (Koeppe/ Busacca)
- Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
- Vitreous opacities displaying snowballs/ strings of pearls
- Multiple chorioretinal peripheral lesions (active and/or atrophic)
- Nodular and/or segmental periphlebitis (+/- candlewax drippings)(Figure 9) and/or retinal macro aneurysm in an inflamed eye
- Optic disc nodule(s)/ granuloma(s) and/or solitary choroidal nodule
- Bilaterality

The laboratory investigations or investigational procedures judged to provide value in the diagnosis of OS

- Negative tuberculin skin test in a BCG- vaccinated patient or in a patient having a positive tuberculin test previously
- Elevated serum angiotensin converting enzyme (ACE) levels and/or elevated serum lysozyme
- Chest X-ray revealing bilateral hilar lymphadenopathy (BHL)
- Abnormal liver enzyme tests
- Chest CT scan in patients with a negative chest X-ray result.

Four levels of certainty for diagnosis of OS (diagnostic criteria) were recommended in patients in whom other possible cause of uveitis have been excluded:
Definite ocular sarcoidosis
- Biopsy supported diagnosis and compatible uveitis

Presumed ocular sarcoidosis
- Chest X-ray positive, showing BHL and compatible uveitis, if biopsy is not done

Probable ocular sarcoidosis
- Presence of 3 intraocular signs and 2 positive laboratory tests, if biopsy is not done and chest X-ray is normal

Positive ocular sarcoidosis
- Presence of at least 4 intraocular signs and 2 positive laboratory investigations, if lung biopsy was done and negative

Diagnostic criteria for Vogt-Koyanagi-Harada (VKH) disease
(2001 Revised diagnostic criteria for VKH disease)

The following 5 criteria are noted in establishing the diagnosis of VKH as follows:
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis.
2. No clinical or laboratory evidence suggestive of other ocular disease entities.
3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined).
   a. Early manifestations of disease
      i. There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as one of the following:
         (i) Focal areas of subretinal fluid (Figure 10 A) or
         (ii) Bullous serous retinal detachments.
      ii. With equivocal fundus findings; both of the following must be present.
         (i) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, (Figure 10 B) large placoid areas of hyperfluorescence, pooling within subretinal fluid (Figure 10 C), and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography, and
         (ii) Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography.

Figure 9: Candle wax drippings of sarcoidosis

Figure 10 (a): Serous detachments with subretinal fluid in VKH syndrome

Figure 10 (b): Fundus fluorescein angiography picture of multiple pin point hyper fluorescence in early phase in VKH Syndrome

Figure 10 (c): Fundus fluorescein angiography picture of pooling of dye in late phase in VKH syndrome
b. Late manifestations of disease.
   i). History suggestive of prior presence of findings from 3a, and either both (2) and (3) below, or multiple signs from (3);
   ii). Ocular depigmentation (either of the following manifestations is sufficient):
      (i) Sunset glow fundus
      (ii) Sugiura sign;
   iii). Other ocular signs:
      (i) Nummular chorioretinal depigmented scars, or
      (ii) Retinal pigment epithelium clumping and/or migration, or
      (iii) Recurrent or chronic anterior uveitis.
4. Neurological/auditory findings (may have resolved by time of examination).
   a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus), or
   b. Tinnitus, or
   c. Cerebrospinal fluid pleocytosis.
5. Integumentary finding (not preceding onset of central nervous system or ocular disease).
   a. Alopecia, or
   b. Poliosis, or
   c. Vitiligo

Complete VKH Criteria 1 to 5 must be present
Incomplete VKH Criteria 1 to 3 must be present with either 4 or 5
Probable VKH Isolated ocular disease without systemic involvement i.e., only Criteria 1 to 3 must be present

Diagnostic system for Adamantiades Behçet’s disease
(International study group for Behçet’s disease)
Recurrence oral ulcers (Figure 12) (at least 3 or more times per year plus 2 of the following) criteria:
1. Recurrent genital ulcers (Figure 13)
2. Ocular inflammation
3. Skin lesions
4. Positive cutaneous pathergy test

American Uveitis Society Criteria for Diagnosis of Acute Retinal Necrosis (ARN) Syndrome (Figure 11)
1. One or more foci of retinal necrosis with discrete borders located in peripheral retina (macula lesions do not exclude diagnosis in the presence of peripheral retinitis)
2. Rapid progression in absence of anti viral therapy
3. Circumferential spread
4. Occlusive vasculopathy with arteriolar involvement
5. Prominent vitritis, anterior chamber inflammation
6. Optic neuropathy/atrophy, scleritis, pain supportive but not required.

Figure 11: Confluent areas of necrosis with hemorrhages seen in acute retinal necrosis

Figure 12: Oral ulcers in Behcets disease

Figure 13: Genital ulcers in Behcets disease
**Summary**

The physician must first ascertain whether the patient is presenting with a uveitic or non uveitic entity. Secondly, which part or parts of uvea is involved. After comparing the clinical characteristics with known uveitic entities, one can shortlist etiological possibilities, advice tailored relevant investigations and then finally initiate therapy. This is followed by modification of treatment if necessary, monitoring the therapy for possible side effects and then assessment and treatment of complications due to uveitis, if any. The above discussed classification systems assists an ophthalmologist to assess a patient with uveitis properly and allow to classify, stage and monitor uveitis.

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