Clinical Approach, Investigations and Management In Infectious Uveitis – An Overview

Dr. Radha Annamalai MS ¹, Dr. Sudharshan S MS ², Dr. Jyotirmay Biswas MS ²

Uveitis is a chronic inflammatory disease. The etiopathogenesis of various uveitic conditions are varied. The distinct established entity called uveitis can be further broken up into a myriad subtypes. Several modalities of classifications exist with regard to anatomy, duration, etiology and pathology. However a more crucial differentiation ought to be made between infectious and non-infectious forms as management varies and may even be diametrically opposite. Infectious forms further encompass a spectrum comprising bacterial, spirochaetal, viral, protozoal and fungal diseases.

A description of the clinical characteristics is outlined which will enable the ophthalmologist to adopt a more prudent approach towards the diagnosis. Nevertheless several of the listed features can coexist in the same individual and need to be evaluated in detail.

In a tertiary referral eye care center, uveitis accounted for 1.5 % of new cases. Out of 1273 uveitis cases over a three year period at Sankara Nethralaya, anterior uveitis was the most commonly observed [39.28 %], followed by posterior uveitis [28.75], intermediate uveitis [17.44 %] and panuveitis [14.53 %]. The most common cause of posterior uveitis was toxoplasmosis [27.87 %]. The incidence of microbiologically proven tubercular uveitis was high as compared to other studies. A few were detected to have intraocular nematodes as the etiology for uveitis.

Clinical approach of a patient with Uveitis:
A meticulous examination of a suspected uveitis patient would involve addressing the following issues

- Establishing a diagnosis of uveitis.
- Determining the visual potential.
- Detecting an existing complication.
- Narrowing down the most likely etiology.
- Confirming the underlying systemic disease.
- Instituting appropriate treatment.

Diagnosis
Most of the infectious uveitic conditions have characteristic clinical features which can be diagnostic. One should know the typical signs and symptoms of various infective agents which would help in clinching the diagnosis. Ancillary investigations such as fundus fluorescein angiogram, indocyanine angiography may be helpful in detecting the activity of the lesions such as in choroiditis or ultrasonography in differentiating subretinal abscesses from other mass lesions.

Blood tests, especially, to detect antibodies against the infectious agents such as toxoplasma, toxocara etc. can be very helpful.
**Table 1. Classification of Infectious Uveitis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Conditions</th>
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<tr>
<td><strong>Anterior Uveitis</strong></td>
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<tr>
<td>Granulomatous Uveitis</td>
<td>Tuberculosis, Leprosy, Lyme's disease</td>
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<tr>
<td>Non granulomatous Uveitis</td>
<td>Syphilis, Herpes, Toxoplasmosis (spill over from the posterior segment)</td>
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<td><strong>Intermediate Uveitis</strong></td>
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<td></td>
<td>Tuberculosis, Toxocariasis, Lyme's disease</td>
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<td><strong>Posterior Uveitis</strong></td>
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<tr>
<td>Vasculitis</td>
<td>Tuberculosis, Toxoplasmosis, Syphilis, Cytomegalovirus retinitis (CMV Retinitis), Acute retinal necrosis, Rubella</td>
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<tr>
<td>Vitritis</td>
<td>Toxoplasmosis, Tuberculosis, Syphilis</td>
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<tr>
<td>Mild Vitritis</td>
<td>Cytomegalovirus (CMV Retinitis)</td>
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<tr>
<td>No vitritis</td>
<td>Histoplasmosis</td>
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<tr>
<td>Neuroretinitis</td>
<td>Syphilis, Lyme's disease, HIV, Cat scratch disease</td>
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<tr>
<td>Choroiditis and Retinitis</td>
<td>Toxoplasmosis, Tuberculosis, Cytomegalovirus retinitis(CMV), Herpetic uveitis</td>
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<tr>
<td><strong>PANUVEITIS</strong></td>
<td>Tuberculosis, Syphilis, Leptospirosis, Lyme's disease, Viral (herpetic)</td>
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When these investigations are non confirmatory, invasive tests such as aqueous tap, vitreous biopsy or fine needle aspiration biopsy can be done. Intraocular fluid can be subjected to special tests such as histopathology or polymerase chain reaction for detecting the genome of the organism.

**PCR in infectious uveitis**

PCR diagnosis renders it possible to detect infectious agents in situations wherein one is confronted with diagnostic dilemmas. It can help in detecting the presence or absence of the genome of various infective agents. Nested PCR is a more sensitive test while RT PCR is a more reliable test to detect the viable organisms in the specimen.

(A) Bacterial

1. **Tuberculous Uveitis**

Uveitis correlates with systemic tuberculosis only in 1.39 % of patients as per our study at Sankara Nethralaya. It is believed to be predominantly a representative of an immune mediated hypersensitivity reaction in the presence of a few tubercular bacilli in the choroid or retinal pigment epithelial cells, though hematogenous dissemination can occur. Clinical features are granulomatous iridocyclitis, solitary choroidal granuloma, multifocal choroiditis, periphlebitis, and panuveitis. In a study done by Gupta V et al, out of 158 patients of intraocular tuberculosis, the commonest form of intraocular inflammation was posterior uveitis [42 %] which was consistent with our study. As high as 52.3 % of cases had posterior uveitis as the manifestation of ocular disease.

Tubercular uveitis is the most common tuberculous infection of the eye. The most common presentation of tubercular uveitis is of disseminated tubercular choroiditis (fig. 1) which manifests as choroidal tubercles. The lesions range from 0.5 to 3 mm in diameter and vary in size and elevation. The second most frequently encountered lesion is focal choroiditis (also referred to as solitary granuloma) which occurs predominantly at the posterior pole. The elevated mass may be accompanied by an overlying serous retinal...
detachment. A choroidal tubercle may progress to a sub retinal abscess (fig. 2) and may mimic a choroidal amelanotic melanoma. Periphlebitis (fig. 3) with vitreous hemorrhage occurs due to tubercular proteins and causes sudden loss of vision. A serpiginous like pattern of choroiditis is another atypical presentation in the constellation of clinical findings which may be the reason for the delay in the diagnosis. Tuberculous involvement is always associated with vitritis and perivascular cuffing which contrasts with the absence of vitritis in serpiginous choroiditis and may be instrumental in distinguishing the two diseases.

Anterior uveitis is less common and characterized by remission and exacerbation with severe anterior chamber reaction, appearance of nodules on the iris (Busacca nodules and Koeppe nodules) and mutton fat keratic precipitates of varying numbers.

Investigations: Complete blood count, Erythrocyte sedimentation rate, Mantoux, X Ray chest, CT chest may prove inconclusive and it has been inferred that polymerase chain reaction by virtue of detection of DNA for mycobacterium tuberculosis and Quantiferon gold tests are diagnostic of the disease.

Intraocular fluids such as aqueous or vitreous or a FNAC sample from the abscess itself can be subjected to PCR or histopathology testing when there is a strong clinical suspicion and if non invasive tests are inconclusive.

Newer tests such as QUANTIFERON GOLD TEST can be helpful. It is an in vitro diagnostic aid using peptide mixtures simulating early secretory proteins (antigenic target 6 and culture filtrate protein 10) in heparinized whole blood. This test measures a component of cell mediated immunity and is based on the quantification of interferon gamma released from sensitized whole blood. It detects both active tuberculosis disease and latent tuberculosis infection but however is not interchangeable with tuberculin skin test as they do not measure the same components of the immunologic process.

Treatment involves the use of Antituberculous treatment as 4 drugs [isoniazid, rifampicin, pyrazinamide and ethambutol] for an initial 2 months followed by a choice of different options of 2 drugs over the next 4 months according to DOTS (Directly Observed Treatment). Additional anti inflammatory therapy such as topical and systemic corticosteroids along with cycloplegics is required.

2. Uveitis in Hansen’s Disease

The uveal tract involvement is seen commonly in the lepromatous form and its incidence is directly proportional to the disease duration. Early and subtle signs of ciliary body involvement are autonomic dysfunction, including diminished pupillary reactions. Acute iritis may be fulminant and is caused by immune complex deposition in the uvea. Chronic iritis results from direct invasion by bacilli. A pathognomonic sign is the presence at the pupillary margin of small glistening iris pearls, which may enlarge, coalesce and drop into the anterior chamber.

Posterior segment lesions are uncommon as the bacillus has a predilection to lodge itself in the cooler parts of the body.

Treatment : Anti leprotic drugs forms the anchor of treatment in association with topical and systemic corticosteroids.
Spirochaetal Uveitis

1. Acquired Syphilis

Uveitis occurs in the secondary and tertiary stages of the disease though it may occur during any stage. Iridocyclitis occurs in about 4% of patients and is bilateral in 50% according to Western studies. The classical presentation of anterior uveitis is the presence of roseolae of iris capillaries, iris atrophy and varying degrees of vitritis.

Posterior uveitis is seen as multifocal chorioretinitis [most common], focal chorioretinitis, neuroretinitis, isolated vasculitis and panuveitis (fig 4). The fundus in multifocal chorioretinitis displays several active, greyish yellow lesions with a preference for the posterior pole. Intermediate uveitis of Lyme’s disease or sarcoidosis may resemble syphilitic uveitis and serves as a differential diagnosis. Healed lesions assume a salt and pepper retinopathy which resembles retinitis pigmentosa.

Investigations: Diagnostic tests may be specific or non specific.

FTA-ABS is specifically directed against treponemal antigens and becomes positive during the secondary stage remaining so, for a lifetime regardless of the treatment status.

Non-specific tests such as VDRL and Treponema pallidum Immobilisation Test quantify the amount of serum antibodies directed against the antigen.

Treatment: Penicillin in either intravenous or intramuscular forms is administered.

Ocular syphilis is treated like neurosyphilis and recommendation for treatment is as follows.

Intravenous penicillin G 18 to 24 million units daily for 10 to 14 days. Further supplementation is with intramuscular benzathaine penicillin G at a dose of 2.4 million units for 3 weeks. Tetracycline (500 mg) four times daily or Doxycycline (100 mg) twice daily for 14 days is given in patients with penicillin allergy.

2. Lyme’s Disease

Uveitis may take the form of granulomatous iridocyclitis, intermediate uveitis, retinal vasculitis and rarely neuroretinitis. Recommended therapy for early disease consists of tetracycline, penicillin or erythromycin.

3. Leptospirosis

Uveitis herein is underdiagnosed as it occurs several months after the onset of the systemic disease. It can exist as two subtypes:

Acute non granulomatous uveitis which may be associated with a hypopyon.

Posterior uveitis seen as vitritis (vitreal membranes), choroiditis, vasculitis, papillitis and panuveitis.

Investigations: Diagnostic procedures are based on two principles

i) Isolation of the causative organism: ELISA

ii) Isolation of DNA: Microscopic agglutination test (MAT) Polymerase chain reaction (PCR)

Treatment involves administration of oral doxycycline 100 mg two times daily for 14 days. Cephalexin is also used as an alternative.

(C) Protozoal Uveitis

1. Ocular Toxoplasmosis

Toxoplasmosis is an ubiquitous infection with an incidence ranging from 12%-90%. On the basis of epidemiological studies, most cases of ocular toxoplasmosis are believed to result from congenital infection but may also occur due to infection acquired postnatally. The response to infection correlates with parasitic and retinal antigen levels. Active chorioretinitis is associated with anterior uveitis, which may be granulomatous or non granulomatous. A solitary
inflammatory focus of variable size [focal retinitis], adjacent to an old pigmented scar [satellite lesion] is the most common finding. Severe vitritis may impair visualization of the fundus although the inflammatory focus may still be discernable [Headlight in the fog appearance]. Occasionally vasculitis and papillitis may be seen.

A yellow white or greyish lesion is seen in the posterior pole involving the macula in a vast majority of patients (fig 5). The borders are ill defined with adjacent retinal oedema. A healed scar typically has well defined borders with central chorioretinal atrophy and peripheral pigment epithelial hyperplasia. Active lesions localized to the juxtapapillary region cause a neuroretinitis. Viral necrotizing retinopathy closely mimics toxoplasma infection in immunocompromised patients. In newborns, TORCH group of infections and others such as congenital syphilis are a major source of infection. The important differential diagnosis include other infections such as focal choroiditis due to tuberculosis and non infectious condition like macular coloboma.

Investigations : Diagnosis is based on a compatible fundus lesion and positive serology for toxoplasma antibodies. An antibody titer of raised levels of IgG and IgM are seen. ELISA is a more specific test for detection of antibodies. Polymerase chain reaction is an important tool and using this technique antibodies titres are measured in aqueous humor and serum and Witmer-Goldman coefficient is calculated. Fundus fluorescein angiography and indocyanine green angiography confirm the activity of the lesions and detect complications. Optical coherence tomography can help in detecting complications such as epiretinal membranes, vitreo macular traction, cystoid macular oedema and choroidal neovascularization.

Treatment does not reduce the frequency of recurrences and only limits the size of the scar. The best combination is use of non sulphonamide with a sulphonamide and oral steroids in tapering doses. We commonly use either Clindamycin or Azithromycin with a sulfonamide in combination with systemic corticosteroids for a minimum period of 6 weeks to 3 months based on the response to therapy. It is important to specifically rule out allergy to sulpha drugs before advising those drugs.

The antitoxoplasma agents commonly in use are:

Clindamycin 300 mg 4 times daily orally for a minimum of 6 weeks.

Rarely, use of this drug may result in pseudomembranous colitis in few patients.

Pyrimethamine 50 mg daily for 6 weeks can be used. However frequent monitoring of blood counts is required. Besides oral folinic acid 4 mg three times daily should be given as supplementation. It is important to check for the tolerability of this drug by the patient. It is known to cause severe nausea, vomiting and other gastrointestinal disturbances.

Co-Trimoxazole 960 mg twice daily can be given alone or in combination.

Atovaquone 750 mg 3 times daily acts on the cystic phase.

Azithromycin and Sulfadiazine (4 gm daily in divided doses for 6 weeks) are also alternatives.

(D) Nematodes

1. Ocular Toxocariasis

This nematodal infection is seen most commonly as posterior pole granuloma and may be associated with hemorrhage. The lesion simulates a retinoblastoma, sarcoid granuloma, toxoplasmosis or focal choroiditis. Long standing masses may have choroidal atrophy, hyperplasia of the retinal pigment epithelium and choroidal neovascular membrane. Various clinical manifestations of the parasite according to decreasing preference are:

Peripheral granuloma, Posterior pole granuloma
Chronic endophthalmitis like picture
Optic nerve head involvement
Anterior segment involvement

**Investigations** reveal an eosinophilia. ELISA detects and evaluates antibodies directed against this organism.

**Treatment** is with Thiabendazole or Diethylcarbamazine. Oral corticosteroids should be used to suppress inflammation.

2. Intraocular worms – Gnathostomiasis

Gnathostoma spinigerum is an intestinal nematode. The host for human infections are domestic cats and dogs. Men can acquire the infection by eating raw meat or through skin penetration by the larva during food handling. The most common mode of presentation is anterior uveitis with or without secondary glaucoma. Iris holes may be considered a diagnostic sign. The larvae may migrate into the eye along the optic nerve or directly penetrate the sclera. Once the parasite is removed, inflammation subsides markedly with topical and systemic antibiotics.

(E) Viral Uveitis

1. Herpetic Uveitis

It is seen to occur commonly in association with active or healed keratitis. Herpetic anterior uveitis presents with fine small keratic precipitates scattered all over the endothelium with a mild anterior chamber reaction. Sectorial iris atrophy due to ischemic vasculitis, blood stained hypopyon and secondary glaucoma are characteristic features.

**ACUTE RETINAL NECROSIS** is a panuveitis which is caused by herpes simplex virus (1 or 2), varicella zoster virus and also rarely cytomegalovirus.

The characteristic triad includes moderate to severe vitritis, occlusive vasculitis involving both the arteries and veins and peripheral confluent retinal necrosis with scalloped margins.

**Investigations:** Diagnosis is usually clinical due to the typical clinical features but when in doubt, PCR testing for the viruses from the anterior chamber tap can be diagnostic.

**Treatment:** Acyclovir is given intravenously for 14 days. The dose is 750 mg loading dose and 500 mg 8th hourly for 2-3 weeks as a slow intravenous infusion. This is followed by oral acyclovir 800 mg five times daily for 3 to 6 months. Apart from its antiviral effect on the affected eye it reduces the risk of fellow eye involvement.

A newer oral antiviral drug, Valacyclovir [L-valyl ester of acyclovir], has better bioavailability and is used in the doses of 1gm three times a day for 6 to 8 weeks.

Systemic steroids are started a few days after initiation of antiviral therapy. Argon laser photocoagulation is required as prophylactic barrage in areas of potential break formation to prevent risk of RD when inflammation is under control.

(E) HIV Related Eye Diseases

The risk of developing atleast one abnormal ocular lesion for a HIV positive ranges from 52-100 %. The frequency of occurrence of opportunistic infections in HIV positive patients in India are: Cytomegalovirus retinitis, toxoplasmosis, tuberculosis, progressive outer retinal necrosis, and acute retinal necrosis due to herpetic viruses, syphilis and pneumocystis carinii. HIV uses a unique viral enzyme, reverse transcriptase to transfer the genetic code from viral RNA to viral DNA. This is then integrated into the host cell DNA. Various drugs used in the treatment of HIV target specific sites in this process. Highly active antiretroviral therapy (HAART) is a combination of any of these agents.

**Cytomegalovirus Retinitis in HIV**

CMV retinitis develops in 15-40 % of HIV positive patients. It is the most common ocular infection in AIDS. It runs parallel to the existing CD4 count wherein less than 50 cells /mm³ is associated with the disease. It is seen as a fulminating retinitis with vasculitis and mild vitritis. The opacification extends alongside the retinal blood vessel in a characteristic “brushfire like” fashion. In the earlier stages the retina shows white granular patches with regular margins and variable overlying haemorrhage. The perivascular distribution gives rise to “Cottage cheese with tomato ketchup” or “pizza pie” appearance (fig 6). Severe vascular sheathing gives rise to “frosted branch angiitis” (fig 7) which is seen in about 6 % of patients. Retinal detachment occurs in 30 % of healed cases.
**Treatment** may be administered individually or in combination.

Ganciclovir is the drug of choice to treat this infection. It is given intravenously as 5 mg/kg every 12 hours for 2 weeks followed by 5 mg/kg once daily as maintenance as slow infusion. Oral drug Valganciclovir, Intravitreal ganciclovir and biodegradable ganciclovir implants are also very effective. Valganciclovir, is a prodrug of ganciclovir and achieves blood levels comparable to intravenous ganciclovir. Induction therapy involves 900 mg twice daily for 21 days followed by 900 mg once daily as maintenance therapy.

**Toxoplasmosis in HIV:** Ocular toxoplasmosis is seen in 1-2% of AIDS patients. Retinochoroiditis lesions are more extensive (fig 8) and multifocal with broad areas of necrosis rendering a hard indurated appearance to the retina. There is more severe visual impairment and serological diagnosis is often difficult due to depressed antibody response. Anterior chamber tap for PCR testing may be helpful.

**Varicella zoster virus in HIV:** Progressive outer retinal necrosis is caused by a variant of VZV and is among the most common opportunistic infections occurring in advanced stages of AIDS. The posterior pole (macula) is involved in the early stages and hence visual prognosis is poor. The outer retinal layers are principally involved with rapid confluence of inflammatory foci leaving large areas of retinal necrosis. The scant or absent involvement of retinal vasculature renders the characteristic “cracked mud” appearance of the fundus. (fig 9)

**Ocular syphilis**

About 1-2% of HIV positive patients are found to have ocular syphilis. Ocular findings include chorioretinitis, optic neuritis, papilloedema. An unusual manifestation of syphilis is acute necrotizing retinopathy and may

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<th>COMPARISON OF VIRAL RETINITIS</th>
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<tr>
<td><strong>CMV RETINITIS</strong></td>
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<tr>
<td><strong>Organism</strong></td>
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<td><strong>Presentation</strong></td>
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<td><strong>Vision</strong></td>
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<td><strong>Anterior uveitis</strong></td>
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<tr>
<td><strong>Vitreous</strong></td>
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<td><strong>Retinal necrosis</strong></td>
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<td><strong>Characteristic appearance</strong></td>
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<td><strong>Complications</strong></td>
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mimic ARN. In HIV positive ocular syphilis a neurological abnormality is found to be more common. The other ocular infections that may coexist in patients with HIV are: Ocular Tuberculosis in AIDS, HIV retinopathy, Atypical Mycobacterial infection, Cryptococcus neoformans, Candida, Molluscum contagiosum and Pneumocystis choroidopathy.

(F) Fungal Eye Diseases

Usually present with endophthalmitis and has to be treated with intravitreal and systemic anti fungi followed by vitreoretinal surgery if not responding.

Conclusion

Crucial facets to be addressed are the complications associated with uveitis such as complicated cataract. Besides, the ideal time to initiate corticosteroid therapy [to suppress associate inflammation] as an adjunct to treatment directed against the infective agent needs to be tailored to the patient’s response. The diagnostic procedures and tests are trimmed according to the various suspected infections.

If the etiology remains undetermined: CBC, ESR, Mantoux, VDRL, X-ray chest, Motion for ova/cyst, Urine for albumin/sugar is ordered as part of a routine work up.

Intra ocular fluid testing is very helpful in cases of diagnostic dilemma. The ophthalmologist needs to concur with the dermatologist, dentist, physician, rheumatologist and STD clinic. Working in tandem will orient more precise and efficient management.

References

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