Diagnostic and therapeutic challenges in anterior uveitis – an update

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Anterior uveitis refers to inflammation of the iris and anterior part of ciliary body. It includes iritis, iridocyclitis & anterior cyclitis. The primary site of inflammation is the anterior chamber. It is more common than posterior segment inflammation and is generally less sight-threatening and less serious, especially if treated early. Anterior uveitis usually causes reduction in vision during the acute stage but it is the sequelae of anterior uveitis which can have a long-lasting impact.

The most common causes of anterior uveitis are[1]

- Idiopathic, 37.8%
- Seronegative HLA-B27 - associated arthropathies, 21.6%
- Juvenile idiopathic arthritis, 10.8%
- Herpetic uveitis, 9.7% (Herpes simplex and Herpes zoster)
- Sarcoidosis, 5.85%
- Fuchs' heterochromic iridocyclitis, 5.0%
- Systemic lupus erythematosus, 3.3%
- Intraocular lens induced persistent uveitis, 1.2%
- Posner-Schlossman syndrome, 0.9%
- Rheumatoid arthritis, 0.9%

Syphilis, tuberculosis, phacogenic uveitis, Lyme disease and collagen vascular disease (Wegener's granulomatosis, polyangiitis, polyarteritis nodosa and relapsing polychondritis) are other causes.

Clinically, anterior uveitis can be granulomatous or non-granulomatous; acute or chronic. The control of inflammation in each form has a similar basis although differences do exist based on the underlying pathology. This article focuses on the diagnostic and therapeutic challenges that exist in the management of anterior uveitis.

Grading of Anterior Chamber Reaction

The severity of inflammation in anterior uveitis can be graded according to the scheme provided by the Standardization of Uveitis Nomenclature (SUN)[2] working group as:

CELLS IN FIELD	GRADE
<1	0
1-5	0.5
6-15	+1
16-25	+2
26-50	+3
>50	+4

For the grading of anterior chamber cells, the presence or absence of a hypopyon is recorded separately.

FLARE	GRADE
NONE	0
FAINT	+1
MODERATE (Iris and lens details clear)	+2
MARKED (Iris and lens details hazy)	+3
INTENSE (Fibrinous or plastic aqueous)	+4

Based on the type of immune reaction, anterior uveitis can be described as granulomatous or non-granulomatous. The table given below enumerates the major differences between these two clinical forms:

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	Non-granulomatous Anterior Uveitis	Granulomatous Anterior Uveitis
Onset	Acute	Insidious
Evolution	Spontaneous regression	Chronic
Keratic precipitates	Small, confluent	Mutton fat keratic precipitates
Iris	No iris nodules	Bussaca & Koeppe nodules
Flare	Intense	Mild
Pain	Severe	Mild to no pain

Investigations in Anterior Uveitis:

The first attack of non-granulomatous anterior uveitis and Fuchs' heterochromic iridocyclitis are diagnosed clinically and no investigation is warranted[3]. In other cases, suggested investigation protocol includes the following tests:

Hematological	Routine blood tests, Erythrocyte Sedimentation Rate (ESR), Serum Angiotensin Converting Enzyme (S ACE), Serum Lysozyme Assay (SLA), VDRL, TPHA, HLA-B27 assay
Radiological	Chest x-ray, x-ray of the sacroiliac joint, HRCT chest
Hypersensitivity test	Mantoux test

For any unusual presentation, an ELISA for HIV should be considered.

The cost-effectiveness of investigations ordered in anterior uveitis with respect to those recommended by the Canadian National Uveitis Survey (CNUS) has been analyzed[4]. It was found that commonly conducted tests like *complete blood counts (CBC)* [ordered in over 65% of cases] and ESR were found to be nonspecific and of limited use in the preliminary diagnosis of anterior uveitis. Similarly, rheumatoid factor (RF), though more frequently ordered, had a less positivity rate than Anti-nuclear Antibody (ANA) if juvenile rheumatoid arthritis was the cause.

Serum ACE, though considered a sensitive test for systemic sarcoidosis, was not found to be a very effective test for intraocular sarcoidosis when used alone (specificity 83%), but combining it with Gallium scan increased the specificity for diagnosis to 100%[5]. *Serum lysozyme assay* had a lower sensitivity and specificity for ocular sarcoidosis[3]. It was also found that elevated serum and urine calcium levels were of little diagnostic value in sarcoidosis.

The commonly performed Tuberculin sensitivity test or *Mantoux test* was found to be non specific. The value to be taken as cut off is debatable, but in a highly endemic area like India, purified protein derivative (PPD) positivity is defined as induration of 5 mm or more in immunocompromised individuals, 10 mm or more in high risk but immunocompetent individuals including children under the age of 4 years and 15 mm or more in any person, including those who have received prior BCG vaccination[6]. Uveitis patients with induration less than 10 mm, or even erythema alone, have favorable clinical responses to oral anti-tuberculosis therapy (ATT). On the other hand, patients with proven ocular tuberculous infection can have insignificant or negative PPD skin tests[7,8].

Interferon gamma release assays (IGRA) are new immune-based in-vitro tests for detecting Mycobacterium tuberculosis (MTb) infection. They are based on the detection of interferon gamma (IFN-γ) released by sensitized T-cells by stimulation with very specific antigens like early secretory antigen target-6 and culture filtrate protein-10, both derived from a very specific region of MTb, the region of difference 1 (RD1)[9]. This segment (RD1) is deleted from all strains of BCG and the majority of environmental Mycobacteria.

The two IGRAs that are commercially available include the T-Spot TB test (based on the ELISpot technology to directly count the number of IFN-γ-secreting T cells) and Quantiferon TB Gold (QTB) In-Tube test (based on the ELISA technology, which measures the concentration of IFN-γ secretion; Cellestis Limited, Carnegie, Victoria, Australia).

Due to the high endemic nature of tuberculosis in India, QTB Gold test result should be analysed with caution. A study showed that less than 50% of respondents actually based their treatment on finding positive value for QTB gold test. However, this test had a significant association

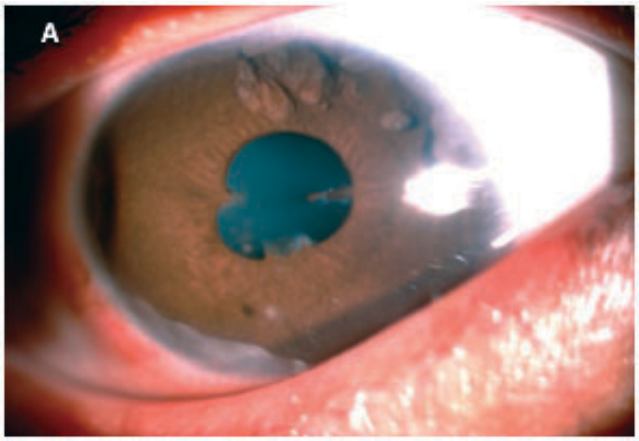

Figure 1A. Slit-lamp photograph of a 21-year old with granulomatous anterior uveitis with broad posterior synechiae and mutton-fat KPs

with serpiginous-like choroiditis and in Indian population, the test was found to remain positive even after starting ATT, though the titres had fallen[9,10].

Anterior chamber (AC) tap: With the advances made in Polymerase Chain Reaction (PCR) and flow cytometry in addition to other molecular technologies, AC tap plays an important role in diagnosis of a uveitic entity. This procedure can be done on an outpatient basis, with minimal patient discomfort and has been proved to be a safe procedure[11].

Today, PCR analysis of aqueous (Fig. 1A, 1B) collected under aseptic precautions at the slit lamp or with the patient supine, for viral DNA is the most commonly used technique to confirm the diagnosis during the acute phase[12,13]. The Goldmann-Witmer coefficient, which determines local intraocular antibody production against the virus and is generally taken to be positive when the value exceeds 3, is another useful test that may take up to 2 weeks to become positive in the acute phase, but remains positive in chronic uveitis. In the immunocompromised, PCR is more useful than Goldmann-Witmer coefficient. Combining both tests increases the sensitivity[14]. As false negatives may occur, these tests may need to be repeated and should best be done during the spike of IOP (if present), especially when suspecting viral uveitis prior to initiating therapy. Interestingly, viruses may coexist in an ocular infection. Thus, the first step of screening for viruses can be done using quantitative PCR, followed by real-time PCR to confirm the finding and to quantify the virus[13]. The purpose is twofold: first, to help to identify the virus that is causing the infection based on the viral load and second to determine the appropriate treatment. Nested PCR increases the specificity by avoiding duplication of a wrong locus. Tubercular anterior uveitis can also be diagnosed by PCR for its specific gene sequence. Resitance to rifampicin can be diagnosed by rpoB gene amplification[15].

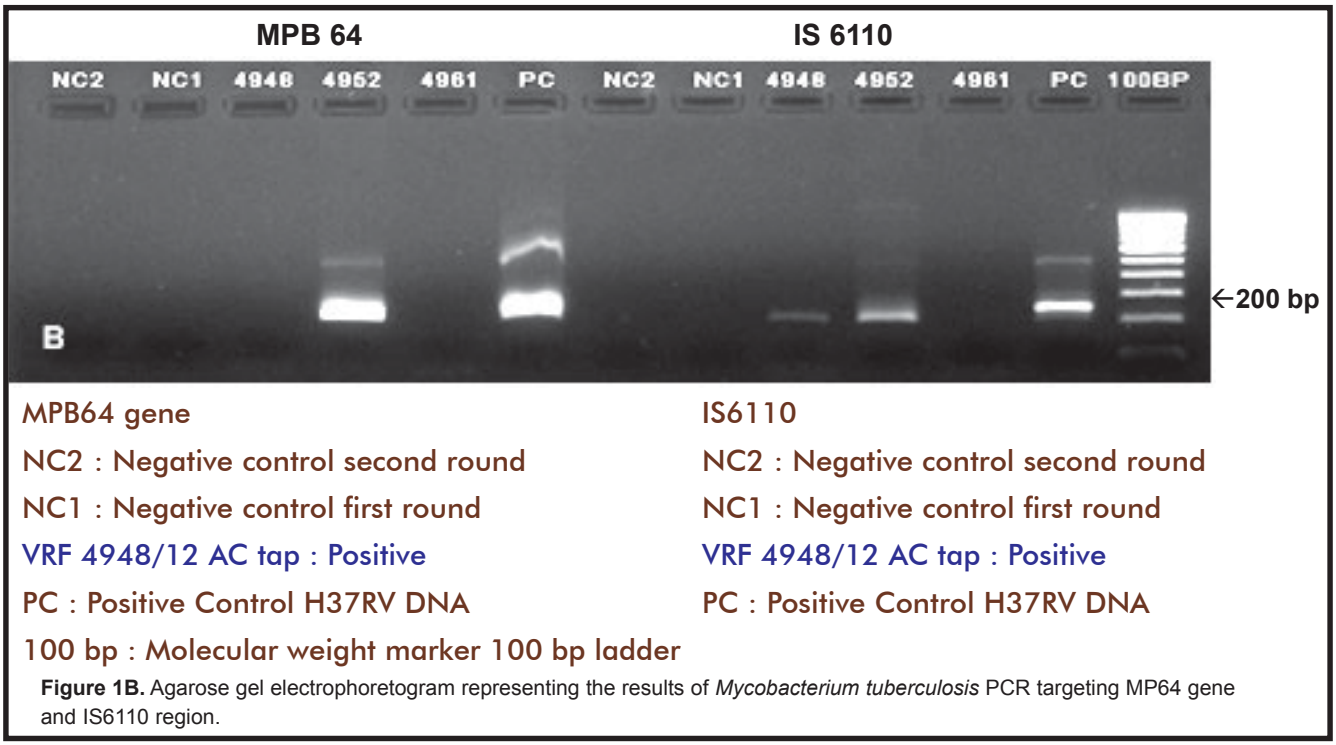

Figure 1B. Agarose gel electrophoretogram representing the results of *Mycobacterium tuberculosis* PCR targeting MP64 gene and IS6110 region.

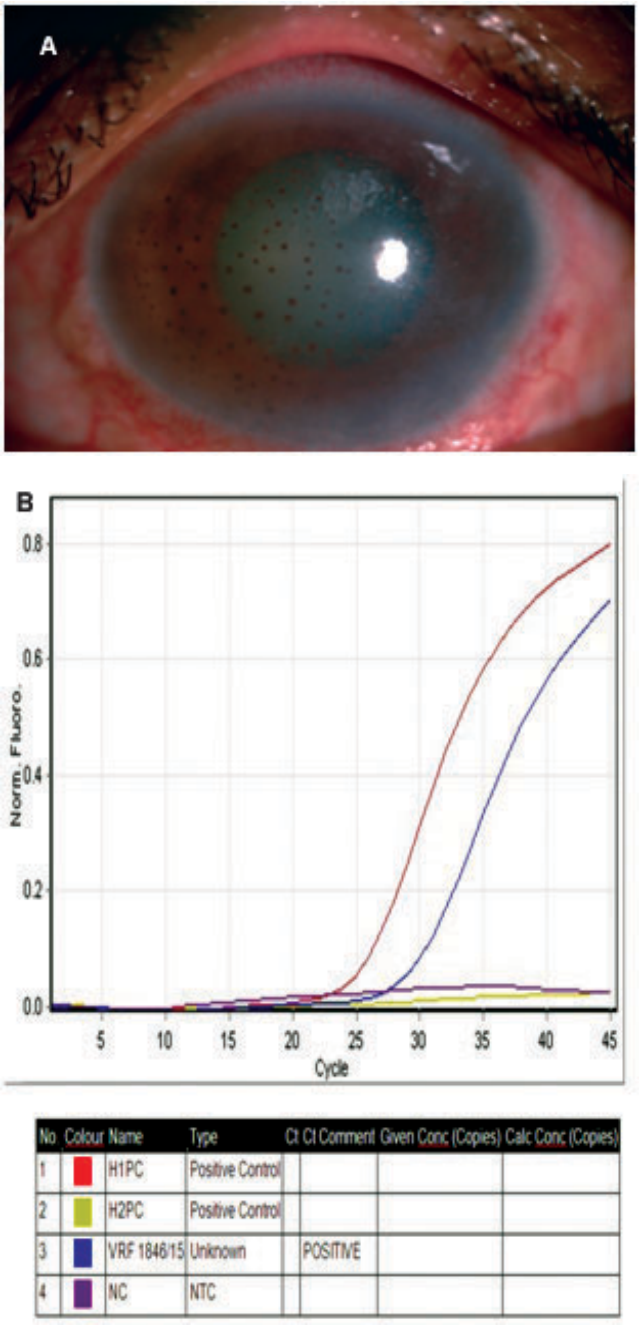

Figure 2: A. Slit lamp photograph of a 59-year old with chronic uveitis and pigmented KPs **B.** Real-time PCR for HSV 1 showing positivity

Real-time PCR is another sensitive tool to detect the presence of infections such as tuberculosis, HSV 1 and 2 (fig. 2 A, B), toxoplasmosis and cytomegalovirus from aqueous samples. In the setting of IOL-related recurrent anterior uveitis, this test may also be used to detect low-grade inflammation due to P. acnes before initiating further treatment.

Flow cytometry analysis of aqueous humor can be used to determine the CD4/CD8 ratio. It has been reported in a study that this ratio can be suggestive of the diagnosis[16]. In this study, no lymphocytes were detected in aqueous humor of controls; the CD4/CD8 ratio was < 1 in viral anterior uveitis, >1 in idiopathic anterior uveitis, presumed tubercular anterior uveitis and HLA B27 related anterior uveitis while it was >7 in patients of ocular sarcoidosis. However, aqueous ACE level is not a good diagnostic test as the value gets confounded by the ACE from the retinal vessels.

Primary intraocular lymphoma (PIOL) can rarely masquerade as anterior uveitis. Though tissue diagnosis is still taken to be the gold standard, using cytological markers for B cells, i.e. CD 19, 20, 22 has come forward as a useful supportive investigation[17]. Also, PCR analysis to detect specific IgH rearrangement is being used. Flow cytometric analysis of aqueous can provide various cytokine levels at one time. IL10/IL6 ratio of >1 showed 75% specificity for diagnosing PIOL[17,18].

Human Leucocyte Antigen (HLA) typing: Although routinely performed, especially for seronegative arthropathies, the positive predictive value is low (< 0.50), indicating the limited usefulness of routinely applied HLA typing as a diagnostic test. HLA-B27 testing, however, may be of value in identifying a previously undiagnosed or misdiagnosed spondyloarthropathy among patients with recurrent acute anterior uveitis as this test has a relative risk ratio of 69.1[13].

Treatment of anterior uveitis:

Treatment of anterior uveitis focuses on:

- Relief of pain and photophobia
- Elimination of inflammation
- Prevention of structural complications such as synechiae, secondary cataract and glaucoma
- Preservation or restoration of good visual function.

The management of an acute attack of anterior uveitis still follows almost the same protocol, i.e. topical corticosteroids and cycloplegics being the mainstay of treatment[3].

Corticosteroids:

They act by modifying and decreasing the inflammatory response in the eye. They inhibit both the cycloxygenase pathway and lipoxygenase pathway of inflammatory response. *The usual rule is to treat aggressively and taper quickly.* However, if topical steroids alone are inadequate, periocular and systemic administrative routes should be considered.

The choice of topical steroid is based on the severity of uveitis; in cases with severe AC reaction, a topical steroid with strong potency such as prednisolone acetate should

be preferred whereas in cases with mild anterior uveitis, a weaker topical steroid may be used. *In steroid responders one should try and avoid steroid as far as possible and can use topical non-steroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen or weak steroids or steroids with least propensity to raise IOP such as rimexolone 1% or flurometholone acetate 0.1%.* Another recently approved steroid is difluprednate (0.05%) (difluoroprednisolone butyrate acetate). It is a synthetic fluorinated prednisolone derivative. This has greater glucocorticosteroid receptor binding activity than prednisolone acetate. This is due to fluorination at C6 and C9 positions and replacement of C-17 hydroxyl group with butyrate ester, which increases its specificity for the glucocorticoid receptor. Greater corneal penetration is achieved by the addition of acetate ester at position C-21. A consistent dose uniformity is achieved with difluprednate ophthalmic emulsion 0.05% when compared with branded and generic prednisolone acetate ophthalmic suspensions 1%. Foster et al., have inferred from their studies that a four times daily dosing of difluprednate ophthalmic emulsion 0.05% is as effective as eight times dosing with prednisolone acetate 1% ophthalmic suspension in the treatment of endogenous anterior uveitis[19]. Reports on its use post cataract surgery show potency equivalent to prednisolone acetate[20]. Elevation of IOP in patients with uveitis, especially in children treated with topical difluprednate has been reported in the literature[21].

Periocular steroids, though more effective in treating cystoid macular edema and intermediate or posterior uveitis, have recently been shown to be effective in managing refractory anterior uveitis as well[22]. A periocular injection may be an appropriate addition to topical corticosteroids in non-responsive and severe uveitis. Although some systemic absorption does occur, it is much less than when corticosteroids are given systemically.

Systemic corticosteroids are indicated when the anterior uveitis is not responding to topical drugs alone or if the disease is recurrent and bilateral[3]. If there is any component of posterior uveitis, one may need to start oral corticosteroids earlier. Indications of systemic steroids include:

- Anterior uveitis resistant to topical therapy
- Occasionally prior to surgery
- Posterior or intermediate uveitis with spillover anterior uveitis

Iontophoresis: Iontophoresis is a non-invasive method of application of low current to an ionizable substance (drug) to increase its mobility across a surface by electrochemical repulsion. Phase 2 trials have been conducted on delivery of dexamethasone phosphate by ocular iontophoresis in noninfectious anterior uveitis[23]. Dexamethasone phosphate (40 mg/ml, EGP-437) is a prodrug and is a good candidate for iontophoresis delivery, as it possesses two acidic protons (pK values of 1.9 and 6.4), making it a highly water-soluble formulation with a high buffering capacity. In addition, it has well-characterized safety and efficacy profiles for ophthalmic use. To deliver dexamethasone phosphate, which is an anion at physiologic pH, a cathodic delivery is used to produce hydroxide ions, which drive the dexamethasone phosphate anions into the ocular tissues, by electrochemical repulsion. Also, these hydroxyl ions (OH) increase the pH of the drug solution, shifting the equilibrium towards the ionized state, thereby increasing the efficiency while buffering the formulation.

The Eye Gate II Delivery System (EGDS, Eye gate Pharmaceuticals, Inc., Waltham, MA) is a novel ocular iontophoresis system designed to deliver substantial levels of drug non-invasively into the anterior segments of the eye while minimizing systemic distribution.

Cycloplegics/ Mydriatics:

All cycloplegic agents are cholinergic antagonists that work by blocking neurotransmission at the receptor site of the iris sphincter and ciliary muscle.

Cycloplegics serve four purposes in the treatment of anterior uveitis[3].

To relieve pain by immobilizing the iris

To prevent adhesion of the iris to the anterior lens capsule (posterior synechia), which can lead to iris bombé and elevated IOP

To stabilize the blood-aqueous barrier and help prevent further protein leakage (flare)

To break the already formed synechiae

The cycloplegics commonly used are listed below:

Short acting cycloplegics:

Tropicamide (0.5 and 1%) has a duration of 6 hours

Cyclopentolate (0.5 and 1%) has a duration of 24 hours

Long acting cycloplegics:

Homatropine 2% has a duration of up to 2 days

Atropine 1% is the most powerful cycloplegic and mydriatic with duration of up to 2 weeks.

Cyclopentolate is not favoured as it can cause disruption of blood aqueous barrier, increasing the inflammation.

Non-steroidal anti inflammatory drugs (NSAIDs):

They are used for reduction of ocular pain and inflammation following cataract surgery and in scleral inflammation[23,24]. They are potent inhibitors of the cyclooxygenase (COX)-2 enzyme and have a highly lipophilic molecule that rapidly penetrates to produce early and sustained drug levels in all ocular tissues.

Bromfenac ophthalmic solution 0.09%: It can be used (twice daily dosage) as either monotherapy or as an adjunct therapy to steroids.

Nepafenac 0.1%: It is a prodrug. It penetrates the cornea six times faster than diclofenac. It is converted to amfenac in ocular tissues. It has been approved for thrice daily dosage beginning one day prior to cataract surgery.

Immunosuppressive agents:

They are usually not used in acute anterior uveitis except in a few cases like JIA-associated iridocyclitis. The immunosuppressives commonly used are methotrexate (MTX) and azathioprine (AZA)[23]. Low dose, once a week MTX has become the therapeutic agent of choice for children with JIA who fail to respond adequately to NSAIDs. In these selected patients with chronic active uveitis low dose MTX is effective and well tolerated. Several authors have reported a favourable response of JIA associated uveitis to treatment with low dose MTX[25]. In low doses MTX is less toxic than most immunosuppressants including corticosteroids. Immunosuppressive therapy must be started in conjunction with the internist. Patients need to be educated about the side-effects of immunosuppressives and should be strictly advised regular blood and systemic examinations.

Biological agents:

They are not used commonly as first line treatment in anterior uveitis, but recent reports have come into vogue supporting their efficacy in treatment of underlying systemic dieases, thereby preventing recurrences. Infliximab, a tumour necrosis factor (TNF) α inhibitor has been successfully used in treating HLA B27 associated anterior uveitis[26] and recurrent anterior uveitis in the paediatric age group, especially that associated with JIA which can otherwise be resistant even to immunosuppressive therapy[27].

Monitoring

Monitoring of response to treatment is of prime importance in the management of anterior uveitis and should include visual acuity and anterior chamber reaction grading. The schedule of follow-up should depend on the severity of initial inflammation, potential for sequelae and type of therapy instilled. Patients should be carefully monitored for side-effects of treatment. A careful and detailed history including systemic medication cannot be overlooked in view of presentation of anterior uveitis as a drug-induced complication, especially with newer ATT drugs like Rifabutin and patients on Cidofovir as part of the HAART regimen[28].

Once the patient's condition has stabilized, follow-up should be every one to six months. The longer the eye is quiet, the longer can be the interval between follow-up visits.

Conclusion:

Although routine blood tests and the use of corticosteroids and cycloplegics are the mainstay in the treatment of anterior uveitis, newer and more specific investigations and treatment modalities in the form of immunosuppressives and biological agents are now available to treat the disease and prevent uveitis-related complications.

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