Review

Uuveitis – search for the cause

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Etiological diagnosis of uveitis remains a challenge in spite of all the advancement in the knowledge of uveitis. It's often a challenging task on the part of the clinician to decide which laboratory test needs to be performed. Lack of tailored approach to laboratory investigation can become huge economic burden on the patients. Investigation of uveitis is an important component in diagnosis and management of uveitis. This includes a thorough review of the patient's previous medical records and accurate assessment of the disease at each clinic visit. A complete review of the patient's medical records provides important information for planning new therapeutic approaches and guards against repeating therapies that were unsatisfactory in the past. It is required to identify specific uveitic entities like toxoplasma retinichoroiditis, to obtain diagnostic and prognostic information and to take therapeutic decision. For example in HLA-B27 positive anterior uveitis, uveitis would be recurrent and can present with fibrin and hypopyon.

There are three approaches in investigations of uveitis. First approach is to do a complete battery of the uveitis tests whatever may be the uveitic phenotypes. Second approach is no laboratory investigations, to decide treatment on the clinical examination and judgement alone. Third approach is a selective thoughtful one with tailored laboratory investigations. This approach is the best and is currently adopted by all uveitis specialists. It is important to choose wisely the laboratory investigations

Many uveitic entities have protean manifestations and one has to have a high index of suspicion, especially this become important in cases with atypical presentations. Conditions such as masquerade syndromes which mimic uveitis and can be associated with life threatening neoplasms. Multidisciplinary approach with rheumatologist, pulmonologist and infectious disease specialists often becomes necessary to establish the diagnosis.

A detailed uveitis oriented history, along with a thorough and complete ophthalmic examination becomes important, to understand and identify anatomical location and to know the extent of the primary uveitis. Subsequently a overall systemic evaluation should be done. Then the clinical characteristics of uveitis should be compared with known uveitic entities for example uveitis with arthritis, uveitis with skin lesions, granulomatous anterior uveitis, to narrow down the list of possible aetiologies. Subsequently relevant laboratory investigations should be ordered. If these tests are negative and patient is refractory to treatment, an extensive laboratory investigation will be required, which includes intraocular biopsy.

Here are a few case examples:

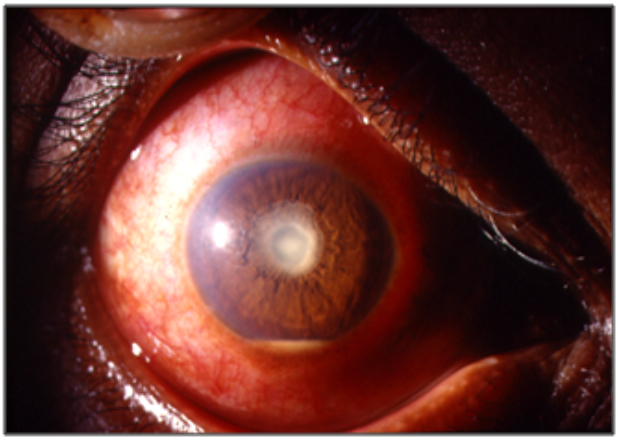

Figure 1. *Slit lamp photograph showing a case of acute anterior uveitis with fibrin and hypopyon.*

A 30 year old male presented with pain, redness and photophobia. On examination anterior chamberfibrin with hypopyon was noted (Figure 1). Fundus findings was unremarkable. In this case detailed history regarding first episode, history of recurrent episodes, response to previous treatment, systemic history regarding low backache, oral and genital ulcers becomes very important. Based on history, laboratory investigations can be tailored. Positive history of low backache and joint pains, HLA B-27 associated

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anterior uveitis can be suspected. HLA B-27 testing preferably by polymerase chain reaction should be done. Positive result indicates that patients can have multiple recurrences in natural course of the disease and should be treated promptly with topical steroid and mydriatic cycloplegic agent.

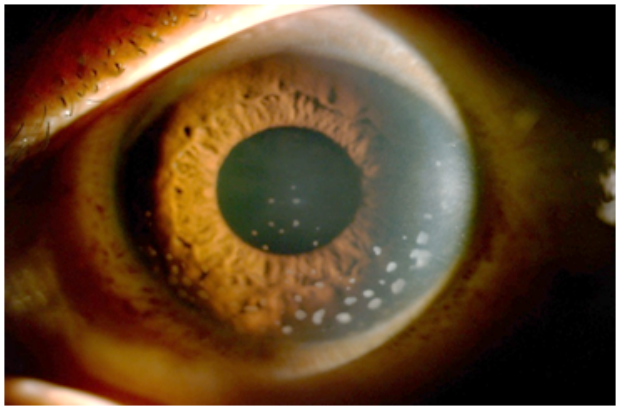

Figure 2. *Slit lamp photograph showing a case of granulomatous anterior uveitis with mutton fat keratic precipitates.*

Now, an example of another patient a 30-year-old male with complaints of mild redness and pain. Slit lamp examination revealed mutton fat keratic precipitates presenting as granulomatous anterior uveitis (Figure 2). In this case scenario tuberculosis and sarcoid associated uveitis should be first suspected. Hence patient should be advised to get Mantoux test, QuantiFERON TB gold test, chest radiograph or high resolution computed tomography (HRCT) of chest, serum angiotensin converting enzyme (ACE). Bilateral hilar lymphadenopathy on HRCT Chest, raised serum ACE and negative Mantoux test will indicate sarcoid aetiology. If these investigations are negative and patient has persisting uveitis, one can do polymerase chain reaction of aqueous by doing anterior chamber tap for mycobacterium tuberculosis DNA by nested PCR and real time PCR. Polymerase chain reaction (PCR) is a sensitive technique for identifying pathogens in small volume samples, such as from the eye. Ocular involvement in sarcoidosis occurs in 30%-60% cases and bilateral granulomatous uveitis is the most common presentation. Negative tuberculin test has been found as important bio marker for diagnosis of sarcoidosis. Serum ACE is more commonly done than serum lysozyme in routine clinical practice. However serum ACE may be raised in various other pathological conditions and children. The combined sensitivity, specificity, positive and negative predictive value of raised serum lysozyme was found much higher than serum ACE. HRCT is now the preferred choice than chest radiograph in diagnosis of sarcoidosis.

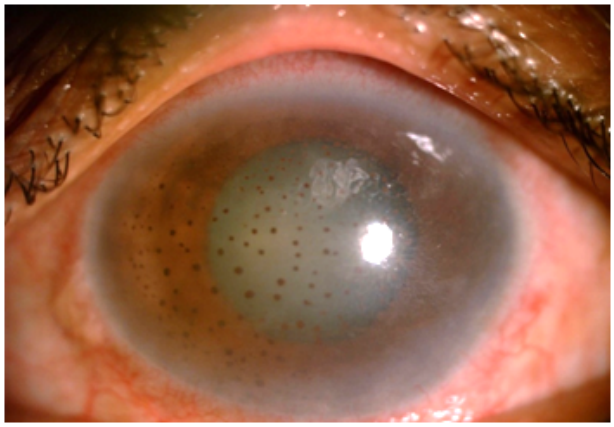

Figure 3. *Slit lamp photograph of a case of viral anterior uveitis with pigmented keratic precipitates.*

A 59-year-old known case of chronic uveitis presented with pigmented keratic precipitates, and intraocular pressure of 40 mm of hg (Figure 3). Viral anterior uveitis is to be suspected in this case. Better diagnostic approach would be anterior chamber tap for polymerase chain reaction for herpes simplex virus type 1, type 2, varicella zoster virus and cytomegalovirus by both nested and real time PCR.

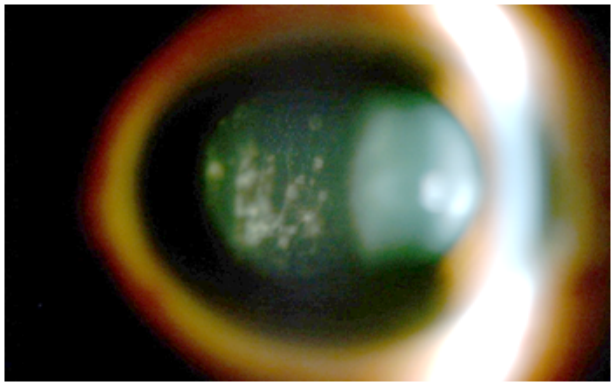

Figure 4. *Slit lamp photograph of a case of intermediate uveitis with cells and debris in anterior vitreous phase.*

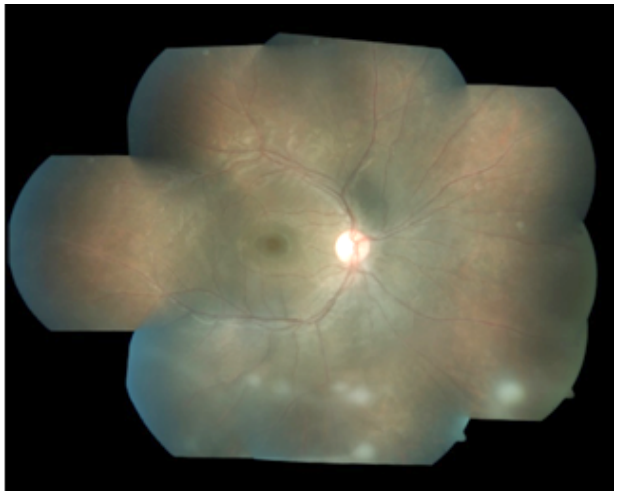

Figure 5. *Montage fundus photograph showing multiple snow ball exudates in the inferior vitreous.*

Now an example of 25 year old female with history of blurring of vision and floaters. Vitreous cell and debris (Figure 4) behind lens should be thoroughly checked. Complete fundus examination with scleral indentation becomes important to know the presence of exudates, snow ball inpars plana region (Figure 5). Positive findings will indicate intermediate uveitis. In this case too, we need to rule out tuberculosis and sarcoidosis. As tuberculosis is suspected especially in highly endemic areas, battery of tests performed are Mantoux test, QuantiFERON TB gold test, Serum ACE and HRCT. HRCT can show pulmonary tuberculosis or bilateral hilar lymphadenopathy suggestive of sarcoidosis. In TB-nonendemic areas ocular findings and chest imaging suggestive of bilateral hilar lymphadenopathy nearly always indicate sarcoidosis. However, in TB-endemic areas, bilateral hilar lymphadenopathy may be attributed to TB, and also patients with evidence of latent TB (eg, positive TST or IGRA), bilateral hilar lymphadenopathy, and uveitis could have either disease. In these situations, the only way to confirm the diagnosis is biopsy. A study of patients with uveitis and a positive IGRA in a non-endemic country suggested that when a biopsy (or bronchoalveolar lavage) is performed ~75% of these patients will have sarcoidosis and not TB.

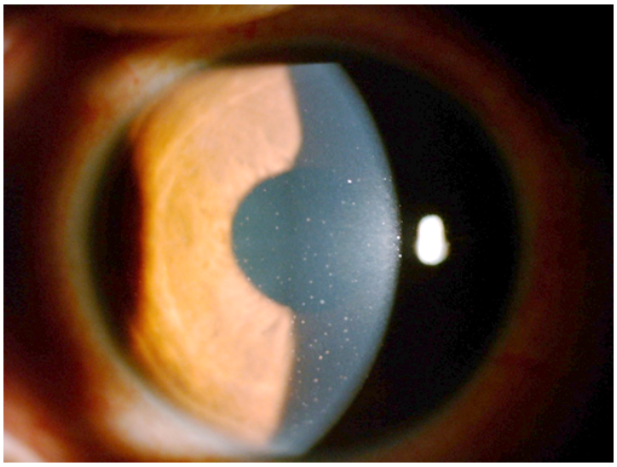

Figure 6. *Slit lamp photograph of case of Fuchs uveitis syndrome with stellate keratic percipitates.*

There are certain uveitic cases where no laboratory investigations are required. This 20-year-old male with history of no pain, redness and having few floaters. On examination, the patient had multiple fine stellate keratic precipitates all over the posterior surface of the cornea. In such cases, Fuchs uveitic syndrome should be suspected. Such patients can have raised intraocular pressure (Figure 6). They do not require further investigations. Fuchs uveitis syndrome is a chronic, typically unilateral, uveitis characterised by an asymptomatic mild inflammatory syndrome that can result in cataract and secondary glaucoma. Phacoemulsification with intraocular lens implantation is a safe procedure with good visual outcomes. Glaucoma is often unresponsive to treatment and should actively be monitored both preoperatively and postoperatively in these patients. Corticosteroid therapy, useful in other uveitis, is futile in Fuchs uveitic syndrome.

Few examples of posterior uveitis case

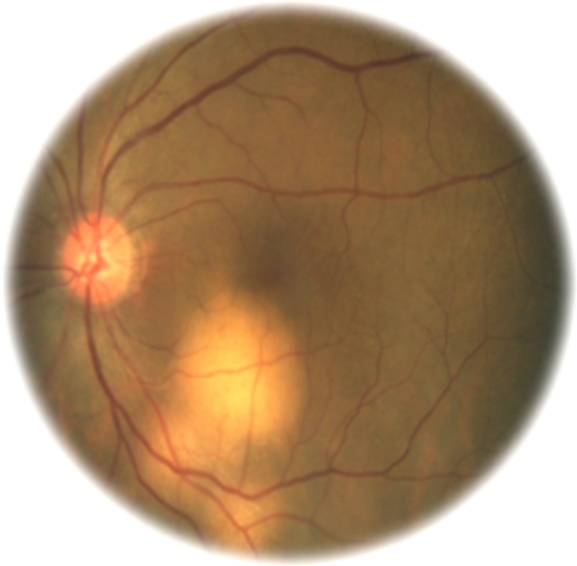

Figure 7. *Fundus photograph showing multiple choroidal nodules inferior to optic disc.*

This is an example of a 66-year-old man with a history of diminution of vision in left eye since one month. Vision in left eye was 6/18, N 18. Right eye vision was 6/6, N6. Fundus examination showed multiple choroidal nodules (Figure 7). Differentials of this case would be tuberculosis, sarcoidosis, and metastasis.

One needs to investigate for Mantoux test, Quanti FERON TB gold, serum ACE and HRCT of chest. If all the above investigations are inconclusive, further one needs to rule out metastasis by doing positron emission tomography (PET) scan. In this case routine blood investigations revealed raised erythrocyte sedimentation rate (ESR) of 38 mm in the first hour, serum ACE was 81 IU/L (reference range is 8-52 IU/L). Both Mantoux and Quantiferon TB gold test were negative. HRCT showed no abnormalities. Based on laboratory test, the patient was diagnosed as sarcoid uveitis and was treated with oral prednisolone one milligram per kilogram of body weight, which showed marked improvement of choroidal nodules lesions within six weeks. In sarcoidosis 96% of patients will have abnormal HRCT presentation, 58% have no extra-ocular manifestation. 78% of patients presented with

primary ocular involvement. Choroidal nodules can also be the presentation of ocular tuberculosis. In such scenario Mantoux test and QuantiFERON TB gold test will be positive. Characteristic HRCT Chest finding of tree in bud appearance can be seen. Tuberculosis and sarcoidosis share remarkable similarities in their clinical and radiological presentation. Both of the above aetiologies can present as anterior, intermediate, posterior and panuveitis.

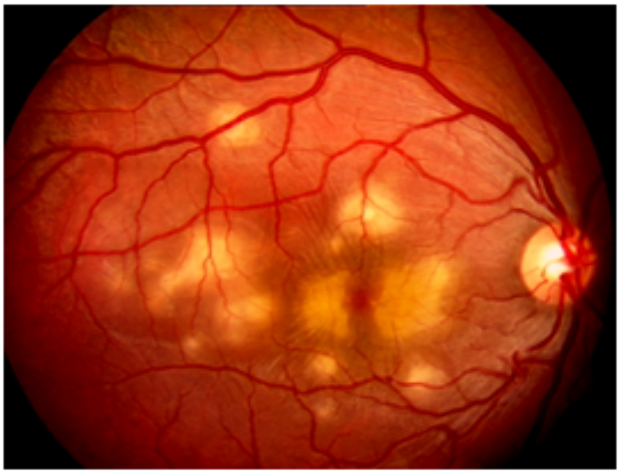

Figure 8. *Fundus photograph showing multiple placoid lesions in the choroid.*

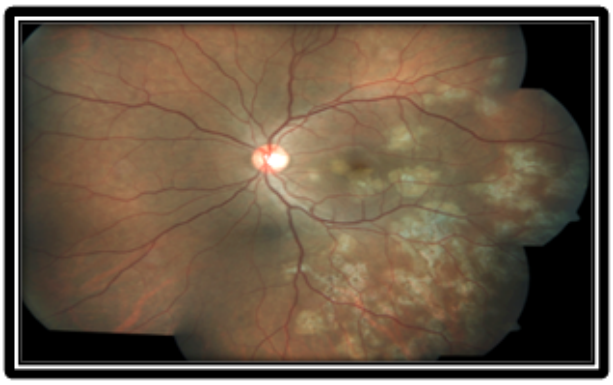

Figure 9. *Montage fundus photograph showing multifocal serpinginoid choroiditis.*

In cases of multifocal choroiditis (Figure 8) differentials of ocular tuberculosis, ocular sarcoidosis, acute posterior multifocal placoid pigment epitheliopathy, multifocal serpiginoid choroiditis (Figure 9), and lastly syphilis should be kept. Along with the battery of tests done for tuberculosis and sarcoidosis, treponemal test like Treponema pallium haemagglutination assay (TPHA), fluorescent treponemal antibody absorption assay (FTA-ABS) and non treponemal test like rapid plasma regain (RPR) or venereal disease research laboratory (VDRL) are to be done to rule out syphilis. World Health Organisation (WHO) has recommended both treponemal and non treponemal test for screening and diagnosis of syphilis. Currently multifocal serpiginoidlike choroiditis is thought be of tubercular etiology.

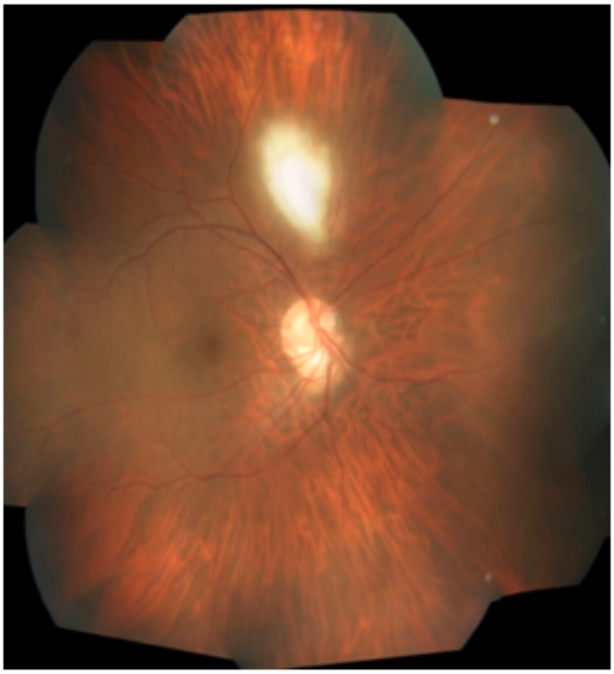

Figure 10. *Montage fundus photograph showing focal retinitis due to toxoplasmosis.*

In patients presenting with retinitis, lesions appear whitish in colour, ill-defined margins associated with retinal oedema and localised vitreous haze (Figure 10), and sometimes they look like head light in fog appearance. Such patients will require screening for toxoplasma primarily; ELISA for toxoplasma is preferred. If ELISA turns out to be negative and there is strong suspicion specifically for human immuno-deficiency virus positive cases, polymerase chain reaction of intraocular fluid for toxoplasma should be done.

Approach in a case of necrotizing retinitis

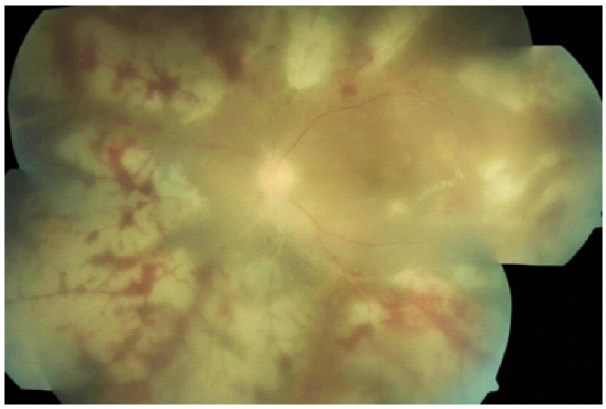

Figure 11. *Montage fundus photograph showing peripheral necrotising retinitis with haemorrhage in acute viral retinitis.*

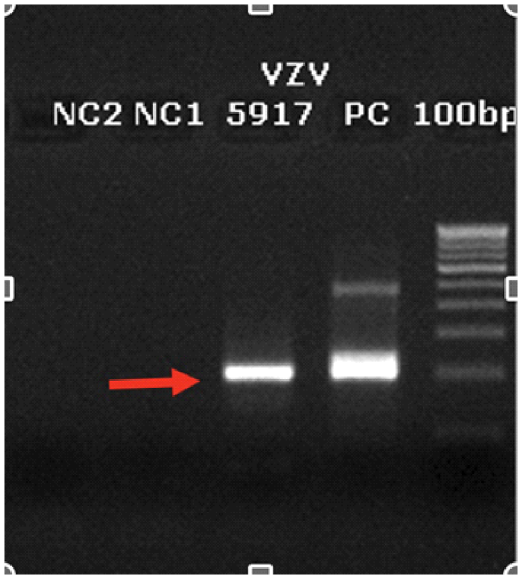

Figure 12. *PCR gel photograph showing amplified varicella zoster virus DNA.*

A 34-year-old female had history of marked loss of vision, Fundus examination revealed peripheral necrotising retinitis with haemorrhages (Figure 11). Preferred approach should be anterior chamber tapor vitreous biopsy for polymerase chain reaction for herpes group of viruses (herpes simplex type 1, herpes simplex 2, herpes zoster and cytomegalovirus). In this case varicella zoster virus DNA was found (Figure 12). In unusual presentation like vitiritis, subretinal precipitates, syphilis should be suspected, so careful history of high risk sexual exposure is to be taken. Test for treponemal and non treponemal should be done. In retinal vasculitis we have to rule out collagen vascular diseases, tuberculosis and sarcoidosis.

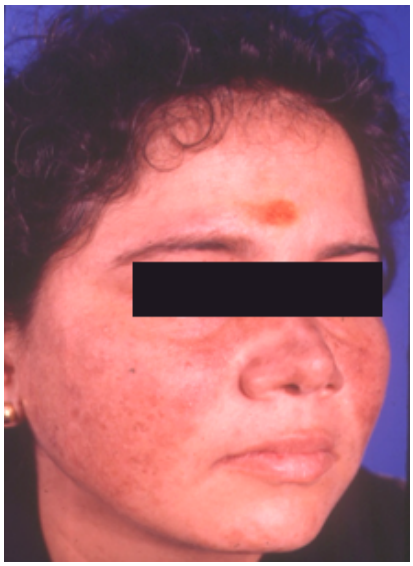

Figure 13. *External photograph of patient with systemic lupus erythematosus showing bilateral malar rash.*

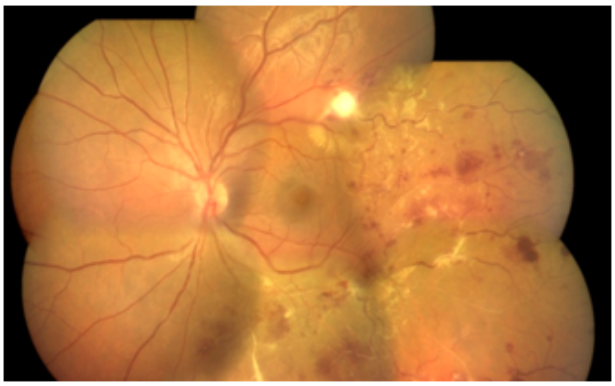

Figure 14. *Montage fundus photograph of systemic lupus erythematosus showing cotton wool spots, retinal vasculitis with haemorrhage.*

This is a case of 24 year old female presented with bilateral malar rash (Figure 13). On fundus examination retinal vasculitis with cotton wool exudates was noted (Figure 14). Patient should be investigated for anti double standard DNA (anti - ds DNA) to rule out systemic lupus erythematosus. In the presence of specific symptoms and signs determination of IgG isotype of ANA using indirect immunofluorescence using human Hep2 cells as a substrate is gold standard and initial step in diagnosis of systemic lupus erythematosus. Thorough comprehensive eye examination and multidisciplinary approach with rheumatologist is essential. Patients with SLE on systemic immunosuppression with complaints of sudden diminution of vision cytomegalovirus retinitis, varicella zoster retinitis, nocardial, tubercular choroidal abscess should be ruled out apart from lupus retinopathy.

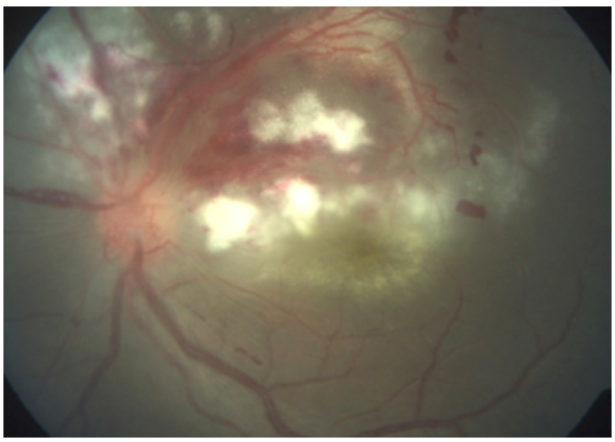

Figure 15. *Fundus photograph of case of post fever retinitis, with multiple retinal exudates with neuroretinitis.*

This is a case of post-fever retinitis. Ocular examination of the patient revealed retinal exudates, disc oedema suggesting neuroretinitis (Figure 15). In such cases dengue, rickettsia, typhoid, chikungunya should be ruled out by ELISA and polymerase chain reaction.

It has been described post fever retinitis is associated with viral, protozoal, and bacterial systemic infections like chikungunya, dengue, West Nile fever, rickettsiosis, rift valley fever, typhoid and rubella. The onset of the ocular symptoms on an average 4 weeks (2-8 weeks) following an episode of fever, hence proper history regarding fever, duration and treatment should be taken. The delay in the onset of post fever retinitis from the initial systemic symptoms is attributed to the corresponding phase for antibody production, immune-complex and autoimmune antibody formation.

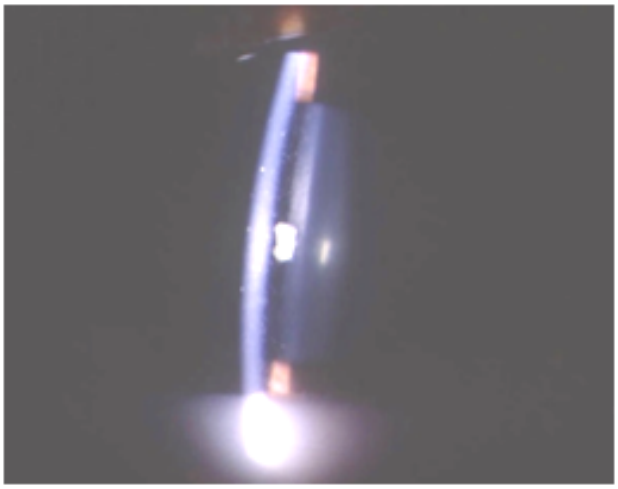

Figure 16. *Slit lamp picture showing persistent hypopyon in a 8 year old girl.*

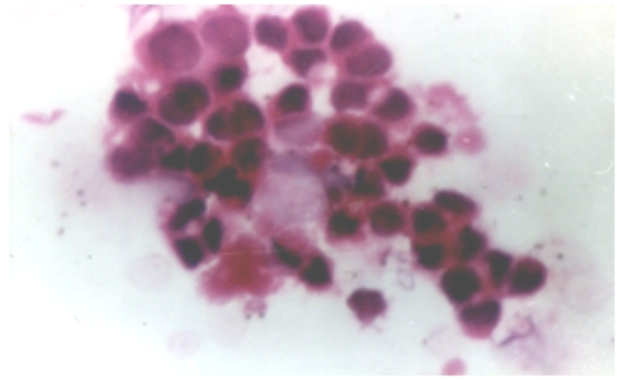

Figure 17. *Cytology image showing multiple basophilic cohesive tumour cells suggestive of retinoblastoma.*

Sometimes non-uveitic entity can masquerade uveitis, any uveitis in children or elderly masquerade syndrome should be kept in mind. This is an 8 year-old-girl presented with persistent hypopyon, not responding to topical and systemic steroid (Figure 16). B mode ultrasonography revealed normal study. Retinoblastoma was suspected. Anterior chamber tap was done and sent for cytology. Cytology study showed multiple basophilic cohesive tumour cells with high nuclear cytoplasmic ratio confirming retinoblastoma (Figure 17).

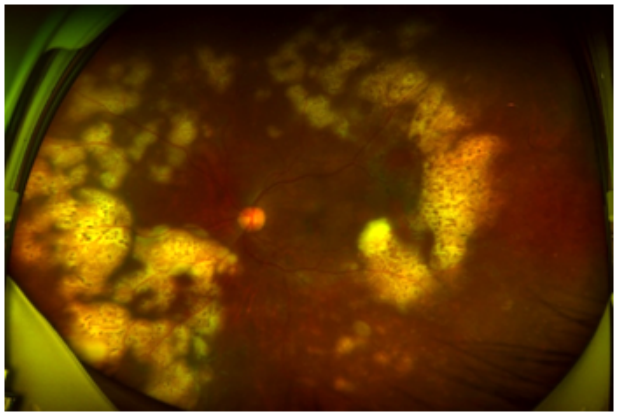

Figure 18. *Montage fundus photograph showing multiple coloured plaque like lesion in a case of primary vitreo-retinal lymphoma.*

This is a 55-year-old female who presented with diminution of vision in right eye since five months. Fundus showed multiple cream coloured lesions with leopard skin like appearance (Figure 18). Ultrasound B scan and optical coherence tomography were suggestive of choroidal lesion. The patient was suspected to have primary vitreo-retinal lymphoma. Vitreous biopsy showed atypical large lymphocytes. Cell block preparation showed atypical large lymphoid cells with necrotic background confirming the diagnosis of vitreo-retinal lymphoma. Fine needle aspiration biopsy or chorioretinal biopsy are sometimes needed to diagnose primary vitreous-retinal lymphoma.

Summary

Searching a cause for uveitis, needs a good uveitis oriented history. A thorough systemic and ocular examination should be performed to determine the anatomical location, extent of the uveitis. Subsequently a short differential diagnosis should be made and then tailored laboratory investigations should be done in a step wise approach. If routine tailored battery of tests are inconclusive, then intraocular fluid or tissue specimen should be subjected for cytopathology, microbiology and molecular biological testing. Ancillary tests like like fundus fluorescein angiography, indocyanine angiography, fundus auto fluorescence, optical coherence tomography, aids in diagnosis, disease activity and prognosis of disease entities. It is important to establish a diagnosis in all uveitic cases to start prompt and appropriate therapy to salvage the vision[1].

Reference

1. Dutta Majumder P, Palkar A, Annamalai R, Biswas J. Laboratory investigations in uveitis: current practice and future directions. *Can J Ophthalmol.* 2018; **53**(3): 193-8. doi: 10.1016/j.jcjo.2018.02.003.