Dedicated to all our Respected Teachers who shaped our Academic career

Team MOS
Managing and Scientific Committee

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Foreword

I am extremely happy to write this foreword for a ready reckoner developed by the uveitis experts of the Maharashtra Ophthalmological Society. I have known the contributors of this booklet to be exceptionally gifted and well-trained in the art and craft of uveitis diagnosis and management. It is with great pleasure that I introduce this Ready Reckoner on Uveitis, a valuable guide tailored to address the needs of general ophthalmologists who encounter uveitis with increasing frequency.

Uveitis remains a significant challenge in the field of ophthalmology because of its complexities in clinical presentation, pathogenic mechanisms, and variable course. The need for a comprehensive, yet concise resource for general ophthalmology practitioners has long been apparent. Uveitis encompasses a broad spectrum of inflammatory eye diseases, affecting different parts of the uveal tract. This booklet is structured to help ophthalmologists understand and manage uveitis with confidence, covering topics that range from nomenclature and classification to the intricacies of immunosuppressive therapy. It provides practical insights into this challenging field. The chapters of this ready reckoner are succinct and written with a great degree of precision. The booklet starts with the fundamentals: nomenclature, classification, and targeted investigations in uveitis. It then proceeds to explore the nuances of anterior uveitis, offering you invaluable insights into the diagnosis and management of this commonly encountered condition. The chapter on cataract surgery in uveitis, offers practical tips and tricks that will be very useful when faced with the challenges presented by cataracts in uveitic eyes. Discussions include infectious uveitis and non-infectious. A unique perspective, with insights from rheumatologists on managing uveitis and scleritis in the context of systemic autoimmune diseases, emphasizes the interdisciplinary nature of uveitis management. The final chapter, Frequently Asked Questions (FAQs) for the General Ophthalmologist in Uveitis Practice, anticipates the queries you may have encountered or will encounter in your daily practice. It serves as a quick reference to address common dilemmas and concerns, offering clarity in challenging situations. I hope that this Ready Reckoner on Uveitis serves as a valuable resource for general ophthalmologists.

Amod Gupta
Emeritus Professor of Ophthalmology,
PGI Chandigarh, and Founder President of the Uveitis Society of India

Preface

Dear MOS Members

For private practitioners keeping pace with the recent developments, giving protocol-based treatments, developing treatment algorithms can be challenging.
To address this issue we thought of preparing ready reckoners as a part of presidential initiative for the year 2022-2023.

First such manual on common problems in day-to-day practice was presented to all the members when I took over as a President of MOS in October 2022. This was well appreciated by one and all and encouraged us to prepare the second one on uveitis.
Management of patients with Uveitis is always challenging due to complexities in presentations and association with systemic diseases. It requires multidisciplinary approach and we often need help of our rheumatology colleagues. We have covered all these aspects in this issue in a very concise manner. I am sure this will be an easy reference guide for institutional as well as private practitioners.

This was possible due to efforts and contribution from Dr Mayur Morekar, Dr Rohit Modi, Dr Aarti Palsule, Dr Devendra Venkatramani, Dr Samyak Mulkutkar, Dr Nikhil Beke and I thank them for their valuable inputs. I would like to specially thank Dr Aniruddha Tembe, rheumatologist from Pune for sharing his practical experience on "Role of rheumatologist" in management of uveitis.

My sincere thanks to Dr Mayur Morekar for his meticulousness and sincerity in editing and compiling the chapters.

I am grateful to Prof Amod Gupta, Emeritus Professor of Ophthalmology, PGI Chandigarh, and Founder President of the Uveitis Society of India, for his constant guidance and support in preparing this reckoner
I would also like to thank Mr Salunke from concept plus Nashik for his help in printing this manual

It gives me and my team immense satisfaction to present this second ready reckoner during our tenure from 2022-2023. I am sure this will be useful practical guide to all MOS members.

Dr Santosh Bhide
President MOS 2022-23

Foreword

While it is often said that “the eyes are the window to the soul”; we are not sure, if that may be true in every human being. Having said that, we can say with reasonable confidence that the eyes are a window to one's health and among ocular diseases, "uveitis" is the one, that is often "an open window to systemic infectious and inflammatory diseases".

Uveitis is an enigma to all us, practising ophthalmologists and i sincerely believe that there is nothing more humbling than witnessing the flaming interaction of the human body's immune system with what is foreign or what perceives as foreign; all in the 6.5-7.0 milliliter human eye. Further, trying to decode this enigma and addressing it for the betterment of our patients can be a mind-boggling experience.

The idea of trying to crystallize this enigma of uveitis and presenting it in the form of a ready reckoner was the brain child of our honourable President of Maharashtra Ophthalmological Society, Dr. Santosh Bhide and i wholeheartedly thank him for the same, and also for having me be a part of this and all the enthusiastic support and encouragement afforded by him during the making of this ready reckoner.

I thank Dr. Samyak Mulkutkar for the extensive interactions, proof reading and editing of the scientific content and also thank Dr. Rohit Modi for all the support during the making and the editing work of this ready reckoner. Our authors included young but renowned ophthalmologists from Maharashtra and i thank them; Dr. Aartee Palsule, Dr. Devendra Venkatramani and Dr. Nikhil Beke for the precise and accurate information compiled by them in the ready reckoner chapter form. Practice of uveitis is incomplete without the help of a rheumatologist; and so would have been this ready reckoner without the perspectives from our rheumatologist, Dr. Aniruddha Tembe.

All of us wholeheartedly thank our under graduate, post graduate and fellowship teachers of ophthalmology; from whom we have learnt the science and art of practice of ophthalmology and uveitis. My sincere acknowledgements to one the leading uveitis experts and the teacher of teachers, Prof. Amod Gupta Sir for affording our ready reckoner an apt forward.

Uveitis as a disease entity can be overwhelming to the most astute of ophthalmologists; which makes it almost mandatory that we thank all our patients and their families for all their interactions with us always.

A show is incomplete without it's audience...a book is unviable without it's readers... So, a very special thanks to all the esteemed members of Maharashtra Ophthalmological Society and i do hope this shall be a pleasant read and reckoner for all of us.

Wishing all a great festive season, a Happy Deepawali and a Prosperous New Year.

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01. Nomenclature, classification, and targeted investigations in uveitis

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Introduction

Uveitis is a multifaceted inflammatory condition affecting various structures within the eye. Accurate classification and targeted investigations are pivotal for effective management.

The Standardization of Uveitis Nomenclature (SUN) Working Group has developed a classification system that assists in understanding the anatomical and etiological aspects of uveitis.

This chapter delves into the SUN classification system and explores tailored investigations to identify the underlying causes.

Section 1: The SUN Classification System

The SUN classification system combines the anatomical location (A), etiology (E), and syndrome (S) of uveitis to create a comprehensive classification. Let us break down the components:

1. Anatomical Location (A):

- **Anterior Uveitis (AU):** Inflammation primarily affects the iris and anterior chamber.
- **Intermediate Uveitis (IU):** involves inflammation in the vitreous and ciliary body.
- **Posterior Uveitis (PU):** Affects the choroid and retina.
- **Panuveitis (PAN):** Inflammation encompasses all anatomical segments.

2. Etiology (E):

- **Infectious (INF):** Caused by microorganisms like bacteria, viruses, fungi, or parasites.
- **Non-Infectious (NI):** Includes autoimmune, systemic, or idiopathic causes.
- **Masquerade Syndrome (MS):** Conditions mimicking uveitis, such as lymphomas.

3. Syndrome (S):
   - When a specific syndrome is recognized, it can be added to the classification (e.g., HLA-B27-associated acute anterior uveitis).

The SUN*Working Group Anatomic Classification of Uveitis

Type	Primary Site of Inflammation*	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vireous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

* SUN= Standardization of uveitis nomenclature.

The SUN* Working Group Descriptors of Uveitis

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	<3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment >3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

* SUN= Standardization of uveitis nomenclature.

The SUN*Working Group Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field*
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

* SUN= Standardization of uveitis nomenclature.

* Field size is a 1 mm by 1 mm slit beam

Understanding this classification aids in precise diagnosis and treatment planning.

Section 2: Tailored Investigations for Uveitis

Identifying the underlying cause of uveitis is essential for appropriate management. Tailored investigations depend on the clinical presentation and classification of uveitis.

a) Detailed Medical History:

- A thorough medical history helps identify potential triggers, recent infections, or medication use that may be linked to uveitis.

b) Complete Eye Examination:

- A comprehensive eye examination evaluates the severity, location, and complications of uveitis, providing valuable clinical insights.

c) Laboratory Tests:

- **Blood Tests:** Depending on clinical suspicion, a range of blood tests may be recommended, including:

- Complete Blood Count (CBC) to assess for anaemia or infection.

- Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) to gauge inflammation.

- Autoimmune markers like Antinuclear Antibodies (ANA) for systemic

autoimmune diseases.

- HLA-B27 testing for conditions like ankylosing spondylitis-associated uveitis.

- Infectious Disease Serology: Specific serological tests for infections such as syphilis, tuberculosis, or

Lyme disease are vital in cases of infectious uveitis.

d) Imaging:

- Optical Coherence Tomography (OCT) and Fundus Fluorescein Angiography (FFA) provide detailed visualization of retinal and choroidal involvement, aiding in diagnosis and monitoring.

e) Aqueous or Vitreous Sampling:

- In cases of diagnostic uncertainty or infectious uveitis, obtaining samples of aqueous humor or vitreous fluid can provide microbiological cultures or cytokine analysis, respectively.

f) Systemic Evaluation:

- Collaborating with a rheumatologist or infectious disease specialist may be necessary for a comprehensive systemic evaluation, especially in non-infectious uveitis cases associated with systemic diseases.

Conclusion:

Uveitis is a complex ocular condition that necessitates a systematic approach for diagnosis and management. The SUN classification system helps standardize the nomenclature and classification of uveitis, making it easier for clinicians to communicate and plan treatment strategies. Tailored investigations, based on this classification, aid in identifying the underlying causes and guide appropriate therapy. Accurate classification and targeted investigations are fundamental steps towards ensuring optimal care and outcomes for patients with uveitis.

Interpretation of commonly ordered investigations in uveitis

A. Interpreting the Mantoux test in the context of uveitis can be complex, as uveitis itself is an inflammatory condition that may or may not be related to tuberculosis (TB) infection. The Mantoux test, also known as the tuberculin skin test (TST), helps identify individuals exposed to TB but does not confirm active disease. In cases of uveitis, the test may be used as part of a diagnostic workup to rule out TB-related uveitis.

Interpretation of the Mantoux Test in Uveitis:

1. Positive Mantoux Test:

- A positive Mantoux test indicates exposure to the TB bacterium (Mycobacterium tuberculosis) but does not necessarily confirm active TB disease.

- The test is considered positive if there is a significant induration (raised, red bump) at the injection site after 48-72 hours.

2. Size of Induration:

- The size of the induration is measured in millimetres.

- In general, for individuals without known risk factors for TB (such as uveitis), the following criteria are used to interpret the Mantoux test:

- ≥ 15 mm: Positive for individuals with no risk factors.

- ≥ 10 mm: Positive for individuals with risk factors (e.g., healthcare workers, immigrants from high-prevalence countries).

- ≥ 5 mm: Positive for individuals with immunosuppression (e.g., HIV-positive individuals, patients on immunosuppressive medications).

- However, in uveitis cases, the interpretation of the test may be more nuanced, especially if there is clinical suspicion of TB-related uveitis.

3. Clinical Correlation:

- The Mantoux test results should be interpreted in the context of the patient's clinical history, physical examination, and other diagnostic tests.

- A positive Mantoux test may not have relevance if patient has non-granulomatous acute anterior uveitis but has significance if it is granulomatous uveitis, retinal vasculitis or serpiginoid choroiditis

B. Human leukocyte antigen B27 (HLA-B27) is a genetic marker associated with several autoimmune diseases, including a subgroup of uveitis called HLA-B27-associated uveitis. Interpretation of HLA-B27 in uveitis involves understanding its significance, clinical relevance, and implications for diagnosis and management. Here is an interpretation of HLA-B27 in uveitis:

1. Association with Uveitis:

- HLA-B27 is a genetic marker found in a significant proportion of individuals with certain forms of uveitis, particularly anterior uveitis. Studies have shown a strong association between HLA-B27 and uveitis, particularly acute non-granulomatous anterior uveitis (AAU).

2. Clinical Significance:

- HLA-B27-associated uveitis often presents as a recurrent or acute episode of anterior uveitis. It may be unilateral or bilateral.

- Patients with HLA-B27-associated uveitis tend to have a more severe and recurrent course compared to non-HLA-B27 uveitis cases.

- The presence of HLA-B27 in uveitis patients may have implications for prognosis and the likelihood of developing systemic complications.

3. Diagnosis and Management:

- The presence of HLA-B27 can aid in the diagnosis of uveitis, especially when clinical features are suggestive of HLA-B27-associated uveitis.

- It is important to note that HLA-B27 is not a definitive diagnostic test for uveitis but rather a supportive factor when considering the diagnosis.

- A positive HLA-B27 test result can help guide treatment decisions. Patients with HLA-B27-associated uveitis may require more aggressive management and closer follow-up due to the risk of recurrent episodes.

4. Systemic Associations:

- HLA-B27 is strongly associated with several systemic conditions, including ankylosing spondylitis, reactive arthritis (formerly known as Reiter's syndrome), psoriatic arthritis, and inflammatory bowel disease.

- Uveitis in HLA-B27-positive individuals may be an extra-articular manifestation of these systemic diseases.

5. Monitoring and Follow-up:

- Patients with HLA-B27-associated uveitis should undergo regular examinations, even during asymptomatic periods, to monitor for recurrences or complications.

- Collaboration with rheumatologists or other specialists is required when systemic disease is suspected.

C. Serum angiotensin-converting enzyme (ACE) levels can be relevant in the evaluation of uveitis, especially in cases where the diagnosis may include conditions such as sarcoidosis. Serum ACE is an enzyme primarily produced by cells in the lung and endothelium, and elevated levels may indicate increased activity associated with certain systemic diseases. Here is an interpretation of serum ACE levels in uveitis:

1. Association with Sarcoidosis:

- Elevated serum ACE levels are commonly associated with sarcoidosis, a multisystem inflammatory disorder that can affect the eyes.

- Sarcoidosis-related uveitis can manifest as **granulomatous anterior uveitis, intermediate uveitis, or panuveitis.**

- Serum ACE levels are one of several markers used to support the diagnosis of sarcoidosis, especially when there is ocular involvement.

2. Diagnostic Utility:

- While elevated serum ACE levels can suggest the possibility of sarcoidosis, they are not specific to this condition and can be elevated in other disorders such as tuberculosis, fungal infections, liver disease and certain medications such as ACE inhibitors

- Therefore, serum ACE levels should be interpreted in conjunction with the patient's clinical presentation, imaging studies, and other diagnostic tests.

3. Monitoring Disease Activity:

- In patients with known sarcoidosis-associated uveitis, serial monitoring of serum ACE levels can help assess disease activity and response to treatment.

- A decrease in ACE levels over time may indicate improved control of the underlying systemic disease and uveitis.

4. Limitations:

- Normal serum ACE levels do not rule out sarcoidosis, as not all patients with sarcoidosis have elevated ACE levels, and ACE levels can fluctuate.

- Some individuals with elevated ACE levels may not have sarcoidosis, and further evaluation is necessary to determine the cause.

D. Treponema pallidum hemagglutination assay (TPHA) and Venereal Disease Research Laboratory (VDRL) interpretation in the context of uveitis primarily revolves around the possibility of syphilis-associated uveitis. Here are how these tests are interpreted and their significance in uveitis, along with references:

1. TPHA (Treponema Pallidum Hemagglutination Assay):

- TPHA is a specific serological test used to detect antibodies against Treponema pallidum, the bacterium that causes syphilis.

Interpretation:

- A positive TPHA result indicates exposure to the bacterium, regardless of the stage of syphilis (primary, secondary, latent, or tertiary).

- In the context of uveitis, a positive TPHA result suggests that syphilis may be associated with the uveitis.

- A negative TPHA rules out syphilis associated uveitis

2. VDRL (Venereal Disease Research Laboratory) Test:

- VDRL is another serological test for syphilis, specifically designed to detect antibodies against cardiolipin, a substance found in the cell membranes of the causative bacterium, Treponema pallidum.

Interpretation:

- A positive VDRL result indicates the presence of antibodies to syphilis. However, VDRL results can sometimes yield false positives or be reactive for reasons other than syphilis.

- In uveitis cases, a positive VDRL test, in conjunction with clinical findings, suggests the possibility of syphilis-associated uveitis.

Significance in Uveitis:

- Syphilis-associated uveitis can manifest as various uveitis subtypes, including anterior uveitis, posterior uveitis, or panuveitis.

- It is essential to consider syphilis as a potential cause of uveitis, as it is a treatable condition.

- In cases of uveitis with positive TPHA and VDRL results, further evaluation, including a detailed medical history, clinical examination, and cerebrospinal fluid analysis, may be necessary to determine the stage of syphilis and the appropriate treatment regimen.

Conclusion

The above-mentioned tests are not diagnostic on their own, and further evaluation, including clinical assessment and additional tests, is required to confirm the diagnosis and determine the appropriate treatment regimen.

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02. Anterior Uveitis

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Anterior i.e., front portion of the eye, the iris and ciliary body, are primarily affected in anterior uveitis. Inflammatory cells in anterior uveitis are seen in the anterior chamber (iritis), and sometimes the anterior vitreous (behind the lens, in iridocyclitis).

Diagnosis of anterior uveitis - at a glance - and appropriate targeted investigations

Clinical Presentation	Ocular Features	Systemic s/s	Diagnostic Concern	Laboratory Test
- Mild acute **non-granulomatous**; **- 1st attack**	- CCC, - cells, - flare, - KPs in Arlt's triangle	Nil	Nil	Nil
Above **with increased intraocular pressure**	- Sector Iris Atrophy - Moth eaten appearance	Nil	**Herpetic Uveitis**	- Clinical Diagnosis - AC tap with PCR if required
Above with **floaters**	**- Stellate KPs all over endothelium** - Vitritis +/-	Nil	**Fuch's Heterochromic Iridocyclitis (Fig. 1)**	Nil
- Granulomatous - Even if 1st attack	Mutton Fat KPs (Fig. 2)	- Cough, - Weight. loss, - Fever +/-	**- Tuberculosis** **- Sarcoidosis (Fig.3)**	- CBC, - Mantoux test, - Serum ACE - CT chest
Recurrent mild non granulomatous		Nil	- Syphilis	- CBC with ESR, - FTA-ABS - TPHA; VDRL
Child with recurrent or chronic iridocyclitis	- White eye +/- - Synechiae - Band keratopathy	- Arthritis +/-	**- Juvenile idiopathic arthritis** **- Juvenile Spondyloarthropathy**	- ANA, - HLA B27 - RA Factor
Sudden Onset Severe non-granulomatous with hypopyon &/ or fibrinous reaction.	Hypopyon (Fig. 4) &/ or fibrinous reaction	- Back stiffness - GI Symptoms - Abdominal pain - H/0 Injury/surgery - IV infusion; - Immunosuppression - Oral ulcer - Genital ulcer	**- Seronegative Spondyloarthropathies** **- TINU** **- Endophthalmitis** **- Behcet's Disease**	**- HLA B 27** (PCR method) - Urine Microglobulin - RFT - Vit tap/ AC tap

Clinical images of common finding in anterior uveitis:

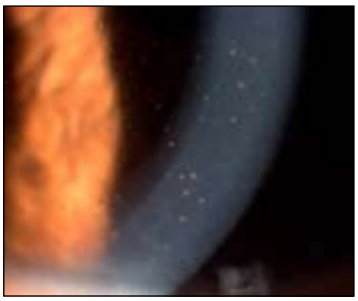

Fig. 1: Stellate Keratic Precipitates of Fuchs Heterochromic Iridocyclitis

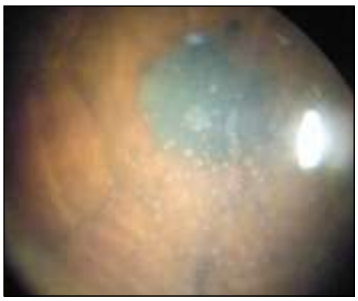

Fig. 2: Mutton Fat Keratic Precipitates of Granulomatous Uveitis

Fig. 3: Iris Nodules in Sarcoidosis

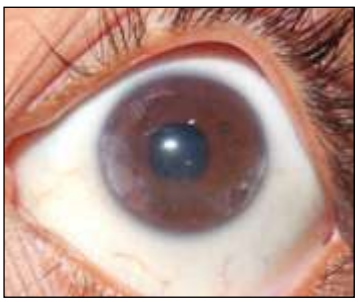

Fig. 4: Band Shaped Keratopathy

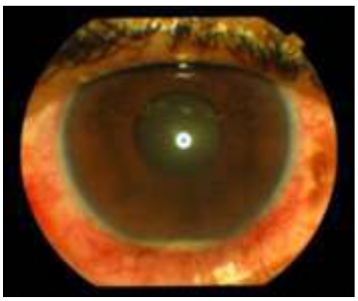

Fig. 5: Hypopyon in Anterior Uveitis

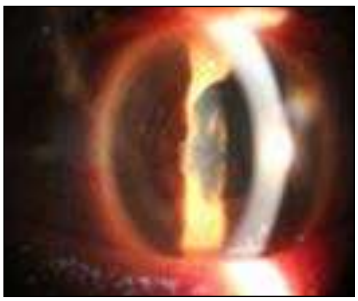

Fig. 6: Broad based synechiae

03. Cataract Surgery in Uveitis - The tips and tricks

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Introduction:

Management of Preoperative and Postoperative inflammation is most important in treating cataract patients with uveitis. Thorough preoperative check-up and control of inflammation, proper surgical technique and selection of proper implant, helps in achieving a good surgical outcome. Postoperative control of inflammation is of utmost importance. In patients with Behcet's disease and JRA associated uveitis, preoperative counselling is important. Patients of uveitis need to be explained about guarded visual prognosis prior to cataract surgery

Challenges in cataract surgery in patients with uveitis are due to:

1) Long-standing inflammation leading to cataract
2) Prolonged use of steroids leading to high risk of associated steroid-induced glaucoma
3) Surgical challenges due to: posterior synechiae,
atrophic iris,
small pupil,
pupillary membrane,
fibrotic anterior capsule,
mature cataract,
zonular weakness,
neovascularization of angle
4) Challenges in controlling post-operative inflammation, macular oedema and glaucoma
5) Anticipated postoperative complications:

- recurrence of inflammation
- Cystoid macular oedema
- Posterior capsular opacification

Preoperative control of inflammation:

Uveitis is most commonly associated with systemic diseases. Hence the multi-disciplinary approach is mandatory.

Surgery should be done under steroid cover 1mg/kg/day of oral prednisolone or topical 1% drops eight times a day for ten days before surgery and I/V 500 mg

methylprednisolone in 100 ml of normal saline over 45 to 60 minutes on the day of surgery.

Additional use of topical NSAID one week before surgery is also useful

If inflammation is severe, systemic immunosuppressant drugs under the supervision of a rheumatologist can be used.

If you are planning IOL implant in patients with JIA associated uveitis, switching to biological agents may improve surgical outcome

Preoperative Retinal and Posterior segment evaluation:

A thorough check-up is a must to look for

1) Macular oedema
2) Optic atrophy
3) Macular scarring
4) CNVM
5) Epiretinal membrane

Ultrasound Bscan (USG) in mature cataracts t/r/o Vitritis, Exudative RD, Disc oedema and thickening of retino-choroidal complex

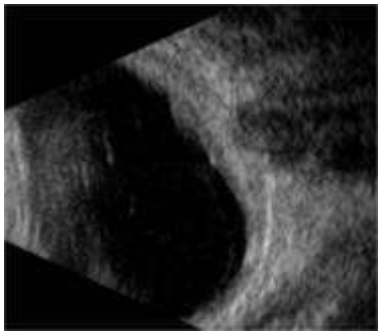

Fig. 1: Preoperative Bscan of a patient on treatment for panuveitis showing choroidal thickening and reduced axial length

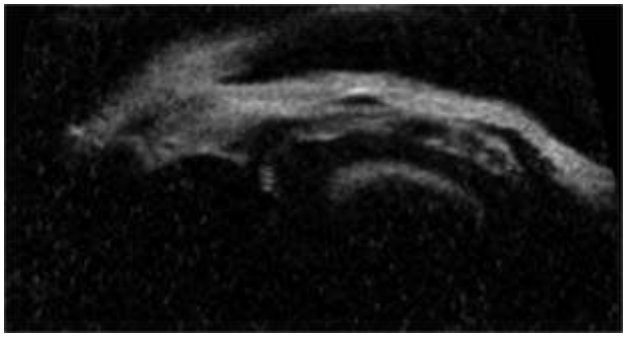

Fig. 2: Preoperative UBM of the same patient on treatment for panuveitis showing a disorganized anterior chamber with areas of ciliary body thickening and cyclitic membranes; prompting us to tackle the cataract

Ocular Coherence Tomography (OCT) for documenting and monitoring macular pathologies

Ultrasound Biomicroscopy (UBM)

to assess pars planitis, uveal effusion, cyclitic membrane and ciliary body atrophy in patients with hypotony

Potential Acuity Meter (PAM) to assess post-operative visual outcome

Surgery

Anaesthesia - Topical vs Blocks depending on the surgeon's choice, but a block (Peribulbar, Retrobulbar, Sub tenon) is preferred if we expect excessive handling of the iris and intraocular manipulations.

Type of Surgery - Manual SICS vs Phacoemulsification - Both surgeries are comparable regarding endothelial cell loss, complications and postoperative results

Incidence of CME is significantly more in SICS compared to Phacoemulsification. This is due to more surgical time in SICS

Management of Pupil

In patients with uveitis, the surgical challenge is due to small, non-dilating, rigid pupil and the presence of pupillary membrane and posterior synechiae.

Mechanical stretching with Kuglen's hooks or similar instruments

Use of **pupillary expansion devices** like iris hooks and rings

Dissection of the pupillary membrane with scissors and removal with forceps can help in achieving optimal intraoperative mydriasis

Gentle handling of the iris to avoid excessive pigment dispersion, hyphemia and postoperative inflammation

Capsulorhexis

Capsulorhexis is difficult due to small pupil, fibrotic anterior capsule in some patients and zonular weakness.

High molecular weight **Cohesive viscoelastic** substances are preferred

Large capsulorhex is is recommended as there is high chance of anterior capsular phimosis postoperatively

Large capsulorhexis also helps in easier implantation of IOL in the bag

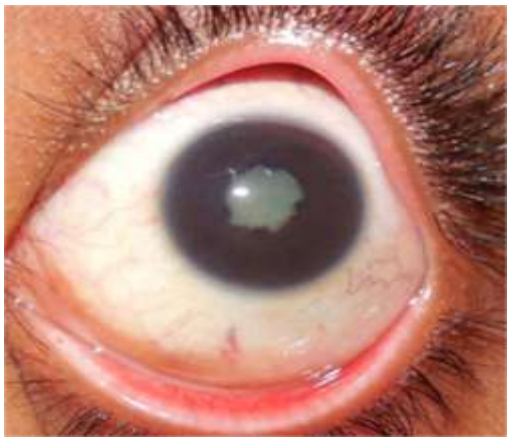

Fig. 3: Preoperative clinical picture of the same patient described above showing a mature cataract with an apparently controlled eye inflammation but USG Bscan and

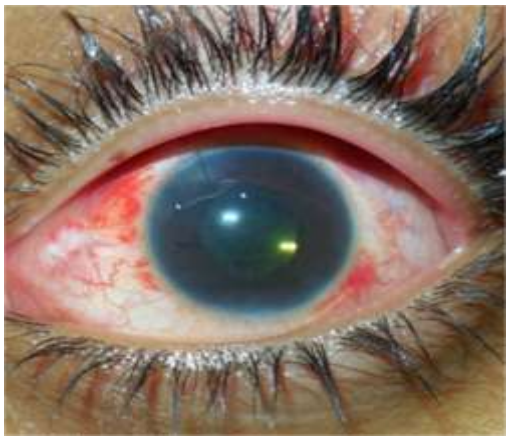

Fig. 4: 5th Day postoperative clinical picture of the same patient described above after cataract extraction with vitrectomy with silicon oil insertion and IOL implantation

Choice of IOL

Hydrophobic acrylic IOLs have less posterior synechiae

Heparin Surface Modified (HSM) IOLs are associated with less rate of postoperative uveitis

Angulated haptic design of IOLs reduces chances of inflammation by reducing contact of the optic of IOL with the iris

In the bag implantation is mandatory to decrease the chances of postoperative inflammation

Avoid implantation of IOL in severe inflammation like Behcet's and Juvenile idiopathic and rheumatoid arthritis-associated uveitis

Avoid implantation in sarcoidosis-associated pars planitis and in patients with pan uveitis

Control of IOP - Preoperative, Intraoperative and Postoperative

Avoid Prostaglandin analogues

Topical and systemic carbonic anhydrase inhibitors and beta blockers can be used

In uveitic glaucoma, combined surgery should be avoided

Postoperative Management

Control of inflammation should be done aggressively by 1hrly instillation of prednisolone drops in early postoperative period with tapering reduction subsequently

Cycloplegics for the first 2 weeks as these drugs reduce ciliary spasm, stabilize blood-aqueous barrier and reduce chances of posterior synechiae formation.

Monitor IOP

Topical NSAID

CME - posterior sub tenon's triamcinolone or intravitreal steroid injection

PCO - YAG Capsulotomy

Vitreous opacification, ERM - Refer to VR surgeon

Cause of uveitis	Cataract prevalence range (median)	Successful outcome BCVA ≥ 20/40 (Snellen)	Frequent complications
Fuchs uveitis	15–75% (50%)	83%	Intraoperative AC hemorrhage (3.6–76%) Hyphema Ocular hypertension (glaucoma) (3–35%) PCO (14.6%) Progressive vitreous opacification
Herpetic uveitis	15–75% (24%)	72.2%	Viral reactivation Iris posterior synechiae Secondary glaucoma
Juvenile idiopathic arthritis-associated uveitis	40–60% (50%)	60–70% (67%)	Exuberant postoperative inflammation Iris posterior synechiae Secondary glaucoma (25%) CME Cyclitic membrane Hypotony (Phthisis bulbi). Sometimes IOL explantation is necessary
HLA-B27 associated uveitis	9.2–20.1%	NA	Recurrent uveitis CME Iris synechiae
Pars planitis	36–42% (40%)	50–83%	Persistent vitritis (haze) CME (50%) Glaucoma (10%) PCO (10%) IOL Cocooning (29%) ERM Optic nerve atrophy
Adamantiades-Behcet disease	21–26% (38.5%)	72.5% (42.4%)	Exuberant inflammation (12.5%) Iris posterior synechiae (17.5%) CME (12.5%) ERM (7.5%) Papillitis (optic nerve atrophy) (5%) PCO (37.5% most common)
Vogt-Koyanagi-Harada disease	10–35%	68%	Exuberant inflammation Iris anterior and posterior synechiae Pupillary membrane PCO (76%) Macular scarring
Sympathetic ophthalmia	31.8%	67.79% (72.2%)	PCO (77.7%) Glaucoma
Sarcoidosis	21%	61%	PCO (57.1%) Recurrent uveitis CME Glaucoma

Table 1: Prevalence, visual outcome, and complications of cataract surgery in uveitis. 1 AC = anterior chamber; PCO = posterior capsule opacification; CME = cystoid macular edema; ERM = epiretinal membrane.

References:

Harapriya A, Anthony E. Managing cataract surgery in patients with uveitis. Community Eye Health. 2019;31(104):82-83. PMID: 31086436; PMCID: PMC6390518.

04. Intermediate Uveitis and Choroiditis

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Intermediate Uveitis

Clinical description:

▶ Intermediate uveitis describes the presence of inflammation primarily involving the vitreous humour. Associated inflammation of the anterior chamber, though minimal is also seen. IU is characterized by the presence of vitritis and cystoid macular edema. Often, a detailed examination of the peripheral retina can also depict sheathing of peripheral retinal vessels, suggesting their involvement in IU.

▶ Typically, there must be an absence of associated retinitis or choroiditis while we characterize a case as intermediate uveitis. IU may well consist up to 15% of all uveitis cases at tertiary care referral centers.

Demographics:

▶ IU is known to clinically present more often in the 3-4th decade of life, either unilaterally or bilaterally. It is reported to be slightly more common in females as compared to males (1:1.2)

Known Causes:

▶ In an endemic country like India, presumed tuberculosis is reported to be the most common case of intermediate uveitis (45%) while sarcoidosis is the next commonly known cause (20%). Multiple sclerosis or rarely infections like syphilis, Lyme's disease & masquerades such as primary vitreo-retinal lymphoma may also present as intermediate uveitis.

What is pars planitis:

▶ Despite extensive investigations in a case of IU, if a definitive cause fails to be established, then this type of “idiopathic” intermediate uveitis is termed as “pars planitis.” Pars planitis is thus a diagnosis of exclusion and contributes close to 25-30% of all cases of IU.

▶ Patients of pars planitis tend to have an accumulation of inflammatory aggregates over the inferior pars plana & peripheral retina. These aggregates are termed as “snowbanks” Similar inflammatory aggregates, when present in the mid-peripheral or the inferior vitreous are called “snowballs”

Symptoms and Signs:

▶ Patients may typically present with a recent onset but painless blurring of vision, associated with floaters.

▶ A detailed dilated fundus examination is essential to the clinical diagnosis of IU. All patients of IU will have varying degrees of vitritis or vitreous haze that should be graded according to SUN classification. Peripheral retinal changes such as snow banking, peripheral vascular sheathing & snowballs can be missed on routine slit lamp evaluation & are detected only on detailed indirect ophthalmoscopy.

Tests:

Ancillary tests like fundus fluorescein angiography will help ascertain the degree of ocular inflammation in terms of cystoid macular edema and associated optic disc involvement. Wide-field fundus imaging (WF-FFA) is especially helpful in detecting subtle vascular leakages in the far retinal periphery. (Fig. 1)

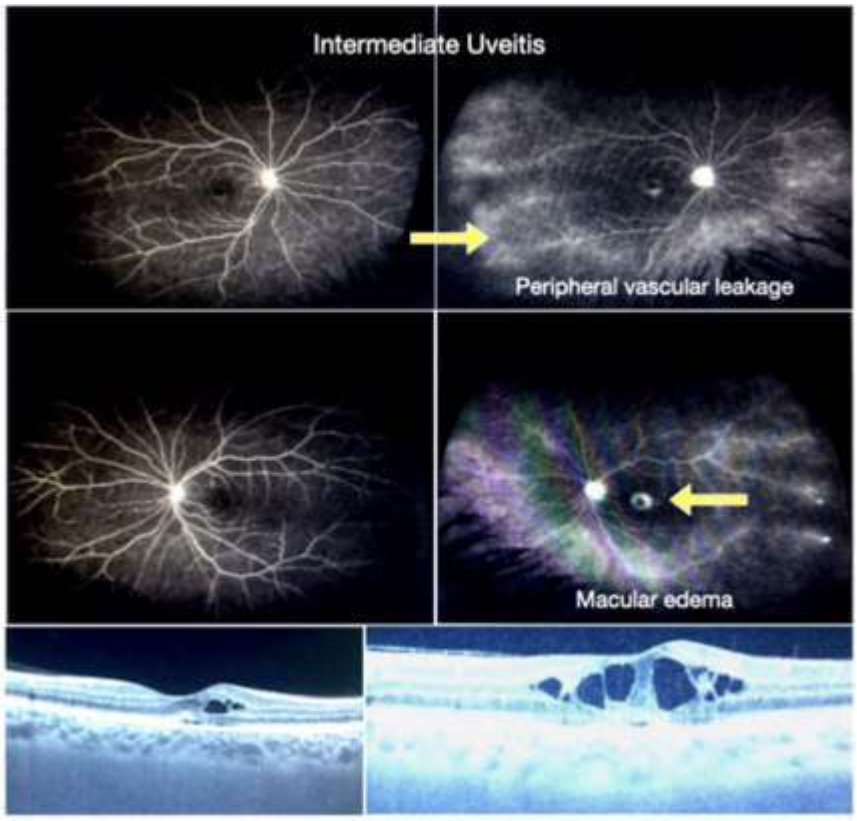

Fig. 1: Fundus fluorescein Angiography and Ocular Coherence Tomography in a patient of Intermediate Uveitis

▶ Ocular Coherence Tomography can detect & quantify macular edema, plus judge the response to treatment. (Fig. 1)

▶ Ultrasound Biomicroscopy is useful to determine pars plana exudates & tractional membranes extending anteriorly to the ciliary body.

▶ Targeted diagnostic tests mandate a detailed history should be sought that may hint towards a specific etiology & subsequent targeted investigation.

▶ Most tests are performed to rule out known causes of IU. These include CBC, ESR, tuberculin skin test, chest radiography (CT scan is preferred over X-Ray chest), TPHA (to rule out syphilis) & serum ACE levels. LDH levels, liver functions, MRI-brain & other tests can also be done on a case-to-case basis.

Treatment:

▶ Treating the primary cause of IU is important, especially if it involves the evidence of tuberculosis or syphilis. Cases presenting with bilateral inflammation and macular edema tend to benefit from systemic (oral) corticosteroids. Corticosteroids need to be stepped down or titrated based on the clinical response. Topical steroids & cycloplegics can be administered for concomitant anterior uveitis, though they are not an effective tool for controlling the primary vitreous inflammation.

▶ Considering the potential spectrum of complications, intravitreal depot steroids may be preferred over periocular steroids in unilateral non-infectious cases of IU.

▶ The subset of patients who respond well to steroids but recur on stopping or tapering off steroids, will eventually require steroid-sparing treatment. Immunomodulatory drugs & biologics should be used rationally, in a step-ladder approach and in consultation with a rheumatologist or an internist.

▶ Repeated attacks of IU, especially in extremes of age should be evaluated from the masquerade perspective and specific diagnostic steps should be taken in this regard.

Special concerns:

▶ Intermediate uveitis in children is a challenge to both diagnose and treat. IU consists 10-12% of all uveitis in children. Those associated with JIA and of the idiopathic variety are common causes.

▶ Detailed examination of the retinal periphery is also difficult in children. They often do not complain about eye symptoms, till the disease is picked up in advanced stages. Chronicity is common & pars planitis in children, is specifically known to have an aggressive course.

Complications:

▶ Chronicity of the disease contributes to most of its complications. Steroid responders have IOP spikes & glaucoma. Cataract development may be a contribution of the inflammation itself as well as by the steroids. Epiretinal membranes may develop over time in chronic cases.

▶ Fibro-inflammatory pars-plana aggregates may either contract over time causing tractional & rarely rhegmatogenous retinal detachment. Peripheral retinal phlebitis as well as vascularization of the pars-plana inflammatory aggregates can also cause repeated attacks of vitreous haemorrhage.

Monitoring:

▶ Close monitoring of inflammation, intra-ocular pressure, with dilated fundus examination, indirect ophthalmoscopy & OCT macula is a must. Monitoring of vision in children should be aimed at picking up complications and preventing amblyopia. A collaboration of allied specialties such as internal medicine, rheumatology & chest medicine may help in a holistic approach to treatment.

Choroiditis

Choroidal involvement in uveitis:

▶ The extent of choroidal inflammation can be differentiated into choroiditis & full thickness choroidal granulomas.

▶ Choriocapillaritis or simply choroiditis is used to define inflammation primarily involving the choriocapillaris. Inflammation may also involve the adjacent structures.

▶ Choroidal granuloma usually involves a large part of the choroidal stroma (defined as stromal choroiditis)

Spectrum of choroiditis:

▶ Serpiginous choroiditis, serpiginous-like choroiditis (SLC) or multifocal serpiginoid choroiditis (MSC), idiopathic multifocal choroiditis (MFC) acute posterior multifocal placoid pigment epitheliopathy (APMPPE), punctate inner choroidopathy (PIC), birdshot chorioretinopathy & other stromal choroiditis constitute the vast spectrum of choroidal inflammation.

Epidemiology & clinical profile:

▶ Considering the Asian-Indian population that we practice in, it is pertinent to understand the most common presentations of choroiditis in our population.

Clinical differentiation:

▶ Serpiginous choroiditis & serpiginous-like choroiditis (SLC) are similar sounding entities that are often used interchangeably, albeit by mistake.

▶ Classic serpiginous choroiditis (SC) is a rare, bilateral, chronic, recurrent and a relentlessly progressive condition affecting the inner choroid & retinal pigment epithelium. It starts in the peripapillary region as a confluent plaque & spreads in a centrifugal fashion with an active leading edge. More importantly, SC is an immune-mediated condition of hitherto unknown origin.

Serpiginous-like choroiditis (SLC), now preferably described as multifocal serpiginoid choroiditis (MSC) is different from SC in various aspects. Morphologically it presents as greyish-white, discrete multifocal choroiditis lesions that may eventually enlarge to coalesce together and acquire a leading "active edge" to spread in a similar fashion like classic serpiginous choroiditis. It is also associated with vitreous inflammation. MSC is commonly seen in TB endemic area & affects younger individuals of Asian-Indian origin. More importantly, MSC is a well-recognized manifestation of ocular tuberculosis (Fig. 2)

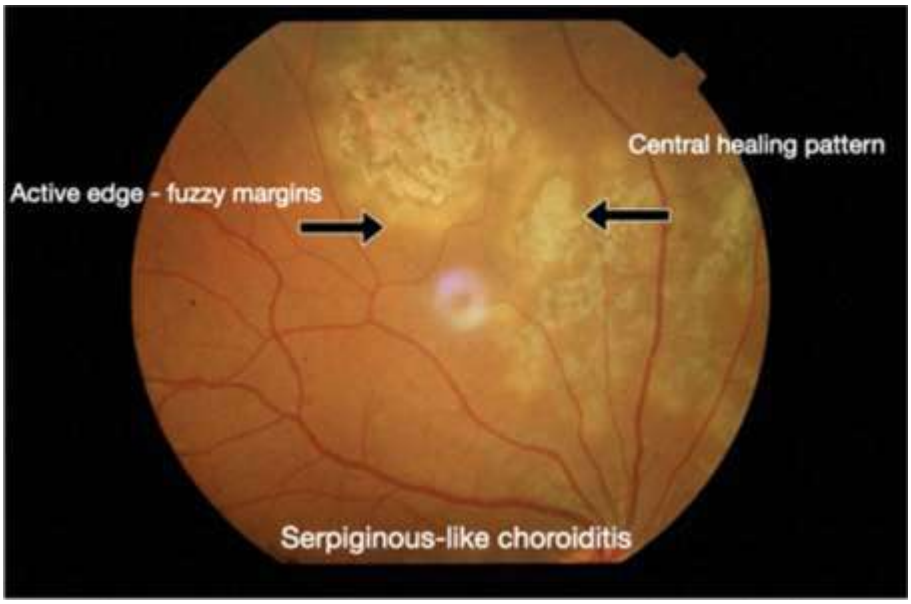

Fig. 2: Fundus picture of a patient with Serpiginous like Choroiditis

Symptoms:

▶ Painless, progressive blurring of vision with or without floaters. Symptoms can be unilateral or bilateral.

Ancillary testing:

▶ Active lesions tend to be multifocal or in a serpiginoid fashion and appear white-grey with fuzzy borders. As the lesions heal, they typically show atrophy of the outer retina and inner choroid with well-defined irregular hyperpigmented borders.

▶ FFA in active lesions shows irregular or patchy hypo-fluorescence in the early frames, progressing to hyper-fluorescent lesions. Ultra-widefield imaging can pick up choroiditis lesions in the periphery.

▶ Active lesions on ICGA shows hypocyanescence in early and late phases.

▶ Fundus auto-fluorescence (FAF) helps to monitor the activity of MSC lesions. Active lesions will show increased auto-fluorescence (hyper auto-fluorescence) which convert to varying degrees of reduced auto-fluorescence signal (hypo auto-fluorescence) as the lesions pass through the healing stages.

▶ SD-OCT (preferably EDI-OCT) shows hyper-reflectivity of RPE and associated outer retinal layers with minimal involvement of the inner retina in active stages. Progressive changes in the reflectivity of the involved layers are noted as they heal. Those changes noted on SD-OCT have shown to positively correspond with active-to-healed patterns observed on the FAF.

▶ Active stages on OCT-A show choriocapillaris flow-void pattern followed by resolution as the MSC lesions heal.

Diagnostic tests:

▶ Diagnosis of TB-choroiditis is usually presumptive, based on the local epidemiology & the above-described typical clinical picture.

These are then corroborated with immunological tests for TB and clinical or radiological signs of active or healed tuberculosis.

▶ Tuberculin skin test (TST) is a commonly available and preferred immunological test (positive if induration is 10mm or more). Interferon-gamma release assay or IGRA are the other immunological TB tests.

▶ Chest radiography such as X-Ray chest and CT-Chest (HRCT/CECT) to find evidence of active or healed tuberculosis.

▶ Other tests include CBC, ESR, blood sugar levels.

▶ Syphilis is a great masquerader in uveitis. TPHA/VDRL should also be done to exclude other known causes of infectious uveitis.

Diagnosis:

▶ Ocular biopsies for detection of mycobacterium tuberculosis by cultures are rarely performed. Sampling for PCR also poses a challenge; hence the clinician has to rely on the above clinico-epidemiological factors to make a diagnosis of TB-uveitis.

Treatment:

▶ Most cases of TB-MSC respond well to treatment, however recurrences are also reported. Oral corticosteroids are the mainstay in the treatment of TB-MSC. They should be slowly titrated according to evident clinical improvement. Treatment of presumed TB-choroiditis with ATT (antitubercular therapy) reduces the frequency of recurrences by 75%. Hence the decision to initiate ATT is primarily made by the treating ophthalmologist in collaboration with chest physicians or internists. ATT is ideally given for 9-12 months, similarly to the extra-pulmonary TB regimens.

Monitoring:

▶ Both ocular & systemic monitoring is required while patients are on systemic steroids. For example, intra-ocular pressures, development of cataract and blood sugar levels need regular evaluations. ATT may not be tolerated in some patients; hence the monitoring liver functions is also essential. Other systemic side effects of oral steroids also need to be closely monitored.

Complications:

Vision can be severely impaired in a patient of choroiditis if the fovea is affected. Inflammatory choroidal neovascular membranes (CNVM) are a rare but amongst the known long-term complications of choroiditis. A high index of suspicion, imaging, prompt treatment & serial observations can help preserve vision in choroiditis patients.

05. Infectious retinitis and Panuveitis

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Retinitis is an inflammation of the retina, which can cause permanent vision loss. Numerous microbes can cause retinitis. These pathogens can affect patients differently depending on characteristics like age, location, and immune status.

Protozoa: Toxoplasma gondii

Viruses:

- Cytomegalovirus (CMV)
- Acute retinal necrosis (ARN) - varicella-zoster virus (VZV), other less common causes include Herpes simplex viruses (HSV-1 or HSV-2), Cytomegalovirus (CMV) or rarely Epstein-Barr virus (EBV)
- Progressive outer retinal necrosis (PORN) - varicella-zoster virus (VZV),
- Subacute sclerosing panencephalitis (SSPE) - genetically altered form of the measles virus
- Dengue
- Chikungunya

Bacteria

- Syphilis caused by the bacterium, Treponema pallidum,
- Cat scratch disease caused by Bartonella henselae
- Rocky Mountain Spotted fever by R. rickettsia
- Lyme disease (Borreliosis) -Borrelia burgdorferi
- Endogenous endophthalmitis

Fungus

- Candida and Aspergillus

Helminth

- Toxocariasis
- Diffuse unilateral subacute neuro retinitis (DUSN)

Post-fever retinitis

Retinal manifestations seen after a systemic febrile illness caused by either bacteria, viruses, or protozoa. It manifests approximately 2 to 4 weeks after onset of fever in the immunocompetent

Toxoplasma Retinochoroiditis (TRC)

Toxoplasma gondii is likely the most common cause of infectious retinochoroiditis (Fig. 1)

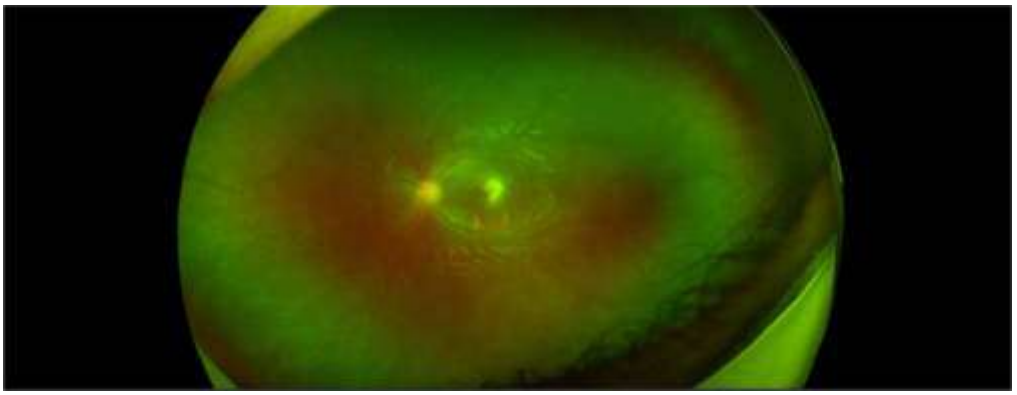

Fig. 1: Toxoplasma Retinochoroiditis

Patient presents as sudden onset of floaters, vision loss, hazy vision, pain, and/or photophobia. Small, active peripheral lesions, may be asymptomatic

Clinically appears as necrotizing chorioretinitis as a yellow-white chorioretinal lesion with indistinct margins combined with an overlying focal vitreous infiltrate (described as “a headlight in the fog”) adjacent to an old chorioretinal scar. A localized lobular perivasculitis may occur around arterioles in the area of the active lesion (called Kyrieleis plaques). Older pigmented lesions may be in clusters or strings. The congenital disease more often appears as a large, atrophic, chorioretinal scar. These scars are unfortunately often in the macula and have been described as a “macular coloboma.

TRC associated sequelae of intra-ocular inflammation are Epiretinal membrane, persistent vitreous opacities, vitreous bands connecting to the optic nerve, cystoid macular odema, cataract, as well as anterior segment findings that include posterior synechiae, and uveitic glaucoma.

In those patients with congenital TRC, microphthalmia, nystagmus, strabismus can be associated with ophthalmic findings.

Diagnosis - Largely clinical but following may be used:

Optical Coherence Tomography (OCT) Scanning

Active TRC displays a highly reflective signal that obscures the underlying choroid. The posterior hyaloid is usually thickened and detached over the lesion.

Fluorescein and Indocyanine Green Angiography

An active TRC lesion will be associated with early hyperfluorescence fluorescein angiography (FA) followed by progressive hyperfluorescence.

Indocyanine green (ICG) is associated with early hypofluorescence as well. ICG can provide additional information in that it can image hypofluorescent satellite lesions that are not visible with either FA or during clinical examination.

Ultrasonography

Ultrasonography is required when vitreous inflammation obscures a view of the fundus. Findings associated with TRC are punctiform echoes within the vitreous as well as thickening of the posterior hyaloid membrane. A partial or total posterior vitreous detachment and focal retinochoroidal thickening are commonly observed as well

Vitreous or Aqueous Sample

Anti-Toxoplasma immunoglobulin G or A (IgG or IgA) antibodies may be detected in these samples. A ratio of 8:1 of anti-Toxoplasma antibody in the eye versus serum is consistent with active ocular toxoplasmosis

In patients with TRC and AIDS, neuroimaging is indicated because central nervous system (CNS) toxoplasmosis lesions

Treatment

Treatment is usually initiated when a lesion is two-disc diameters from the centre of the fovea or one disk diameter away from the margins of the optic disc.

Treatment of the Immunocompetent Patient with Acute TRC with Oral medication

The “classic therapy” consists of 4 to 8 weeks of oral pyrimethamine, sulfadiazine, and folinic acid combined with oral steroids for concomitant ocular inflammation to be titrated on a case-to-case basis.

Pyrimethamine by mouth twice per day loading dose of 50 mg is followed by 25 mg twice per day.

Sulfadiazine is given as a 2 g orally 4 times a day loading dose, followed by 1 g 4 times a day. To avoid developing thrombocytopenia and leucopenia, 3 to 5 mg of oral folinic acid supplementation twice a week. Prednisone can be prescribed at 40-60 mg orally for several weeks to 1 month followed by a taper based on the severity of inflammation. Prednisone is usually started 3 days after the start of antibiotic therapy.

Other oral antibiotics including clindamycin (300 mg 4 times a day), spiramycin (1 to 4 g once daily), azithromycin (250 mg), trimethoprim-sulfamethoxazole (800/160 mg), and atovaquone (750 mg 4 times a day) have been tried in combination with a classic therapy or in other combinations.

Treatment of the Immunocompetent Patient with Acute TRC with intravitreal medications.

Treatment with intra-ocular steroids alone is contra-indicated as it typically causes extensive retinitis. Two clinical trials investigated intravitreous clindamycin (1mg) and dexamethasone (0.4 mg) one injection followed by additional injections every two weeks based on clinical course.

Treatments to Reduce the Rate of Recurrence of TRC.

Long-term use of trimethoprim-sulfamethoxazole (800/160 mg) every 3 days for 20 months in patients with a history of recurrent TRC in one trial, as well as a treatment every other day for one year after a 45-day treatment of active TRC was shown to reduce the rate of recurrence of TRC significantly

Viral retinitis

Cytomegalovirus (CMV) retinitis

CMV retinitis (Fig. 2) is primarily a disease of immunocompromised hosts, occurring in neonates, bone marrow and solid organ transplant recipients, and persons with acquired immunodeficiency syndrome (AIDS) from the human immunodeficiency virus (HIV). Rarely, CMV retinitis occurs in individuals immunocompromised from other causes, including malignancy, systemic immunosuppressive therapy, primary immunodeficiencies, and intravitreal corticosteroid injections. It is an AIDS defining illness, occurring primarily in infected individuals with CD4 T lymphocyte counts< 50cells/ microliters, CMV infection probably reaches the eye through hematogenous spread.

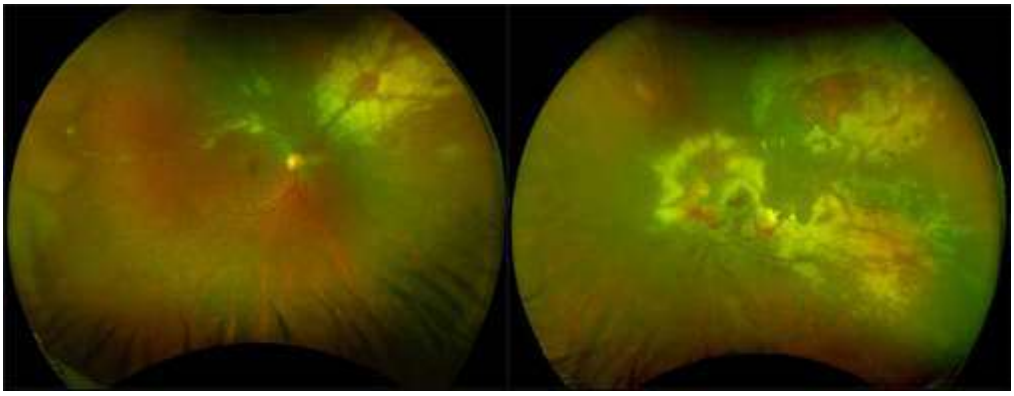

Fig. 2: CMV Retinitis

Three types of clinical appearance may be seen clinically in CMV retinitis:

- Wedge-shaped areas of a perivascular fluffy white lesion with many scattered haemorrhages (brush-fire)
- A more granular-appearing lesion that has few associated haemorrhages and often has a central area of clearing, with the atrophic retina and stippled retinal pigment epithelium (granular type)
- Rarely, retinal vasculitis with perivascular sheathing (an atypical manifestation with a clinical appearance like frosted branch angiitis)

The disease usually spreads centrifugally along the retinal vessels; the border of active retinitis is irregular, and small white satellite lesions are very characteristic.

Vitritis and anterior chamber are rare.

Diagnosis - Largely clinical but following may be used:

CMV PCR – on aqueous/vitreous samples or blood

Fundus autofluorescence and/or fluorescein angiography (FA) - hyperautofluorescence at the advancing border of retinitis, Areas of haemorrhage and active retinitis may exhibit hypoautofluorescence sometimes with stippled hyperautofluorescence, and areas of atrophy from healed retinitis exhibit hypoautofluorescence.

Treatment

Drug and Route	Induction	Maintenance
Ganciclovir (intravenous)	5 mg/kg twice daily for 14–21 days	5 mg/kg/day
Valganciclovir (oral)	900 mg twice daily	900 mg daily
Foscarnet (intravenous)	90 mg/kg twice daily for 14 days	120 mg/kg/day
Cidofovir (intravenous)	5 mg/kg weekly for 3 weeks	5 mg/kg every 2 weeks
Intravitreal Ganciclovir	2 mg 1–4 times as needed to halt retinitis	2 mg weekly
Foscarnet	1.2–2.4 mg 1–2 times weekly	1.2 mg weekly
Cidofovir	20 mg 1–8 times	20 mg every 5–6 weeks

Complications

Rhegmatogenous retinal detachment and Immune recovery uveitis (IRU)

Acute Retinal Necrosis

Acute retinal necrosis (ARN) is characterized by peripheral necrotizing retinitis usually due to infection with varicella-zoster virus (VZV), herpes simplex virus (HSV I or II). Typically occurs in immunocompetent individuals, however, it can occur in immunocompromised patients also.

The classical triad of ARN consists of (1) arteritis and phlebitis of the retinal and

choroidal vasculature (2) a confluent, necrotizing retinitis that preferentially affects the peripheral retina, and (3) a moderate to severe vitritis. American Uveitis Society criteria for the diagnosis of ARN requires the following clinical characteristics be seen: focal, well-demarcated areas of retinal necrosis located in the peripheral retina (outside of the major temporal vascular arcades); rapid, circumferential progression of necrosis (if antiviral therapy has not been administered); evidence of occlusive vasculopathy; and a prominent inflammatory reaction in the vitreous, and anterior chamber. Supporting clinical criteria include optic neuropathy or optic atrophy, scleritis, and pain.

Diagnosis - Largely clinical but following may be used:

- An anterior chamber paracentesis or vitreous tap for polymerase chain reaction (PCR) for herpesviruses (VZV, HSV, CMV, EBV)
- Viral titres (VZV, HSV, CMV)
- Fluorescein angiography demonstrates the occlusive nature of arthritis.
- Optical coherence tomography may show cystoid macular odema/ epiretinal membrane or disc odema.
- Ultrawide field fundus photography (Optos) may document and help in monitoring the progression of the disease.
- Ultrasonograms may be helpful to rule out retinal detachment in hazy media.

Treatment

Immediate treatment of the patient is required.

The goal is to decrease the incidence in the fellow eye.

Acyclovir should be started at 10-13 mg/kg every 8 hours or 1500 mg/m2/day intravenously (IV) for 5-10 days. This should be followed by acyclovir 800 mg five times daily orally for 6 weeks to 3 months.

Other options include:

- **Valacyclovir** can be given 1000-2000 mg orally every 8 hours. This has good bioavailability and avoids the need for intravenous access.
- **Famciclovir** should be given at 500 mg orally every 8 hours.
- **Valganciclovir** started at 900 mg twice daily orally for 3 weeks induction, followed by 900mg once daily orally for maintenance.

Prednisone 0.5-2.0 mg/kg/day orally for up to 6 to 8 weeks should be started 24-48 hours after the start of antiviral therapy or once regression of necrosis is demonstrated

Progressive Outer Retinal Necrosis (PORN)

PORN is characterized by a rapid progression of necrosis of the outer retina in immunocompromised patients. The most common etiologic agent is Varicella Zoster Virus, followed by Herpes Simplex Virus.

A hallmark feature of PORN is the lack of intraocular inflammation.

Large patches of discrete yellow-white retinal opacification consistent with necrosis of the deep retinal layers are seen either in the peripheral retina, posterior pole, or both. Multifocal lesions can progress rapidly to confluence without consistent direction of disease spread. These lesions can rapidly progress to full thickness. Retinal detachment can occur. Serous retinal detachments or rhegmatogenous.

Diagnosis - Largely clinical but following may be used:

- Fluorescein angiography (FFA) - Active areas of necrosis demonstrate late staining, while inactive, atrophic regions display window defects. Focal vascular occlusions may be evident on FA as well.
- Optical coherence tomography (OCT) - outer retinal disorganization, consistent with necrosis of the outer layers, hyper-reflectivity of the inner layers as well. Cystoid spaces and foveal thickening can also be observed.
- Fundus autofluorescence classically shows stippled areas of mixed hyper- and hypo- autofluorescence, indicative of adjacent "sick" RPE cells, accumulating lipofuscin (hyper-autofluorescent) and RPE and adjacent photoreceptor death (hypo-autofluorescent).
- Laboratory investigations - decreased CD-4 count or otherwise low white blood cell count, VZV-PCR, HSV-1, 2 PCR, CMV PCR.
- Vitreous / aqueous tap with viral PCR analysis is typically performed to isolate the pathogen.

Treatment

The current recommendations for PORN include antiviral intravitreal injections 3 times a week for 2 weeks **(ganciclovir or foscarnet)**, followed by injections once or twice a week until the retinitis is stabilized.

High doses of intravenous antiviral double therapy (ganciclovir or valganciclovir at induction doses for 3 weeks and foscarnet at induction doses for 2 weeks) are required to protect the other eye and the central nervous system, followed by maintenance antiviral therapy (oral valganciclovir and intravenous foscarnet) until complete healing.

Syphilitic retinitis

Syphilis has been always recognized as "the great mimicker" since it can have multiple clinical patterns of presentation. Treponema pallidum is capable to affect all the retinal layers.

Retinochoroiditis is the commonest

Acute syphilitic posterior placoid chorioretinitis (ASPPC)

It presents as a large, roundish, yellowish, placoid lesion occurring at level of the retinal pigment epithelium (RPE) at the macular/paramacular area. In the acute phase the uveitis is florid, it progresses rapidly, often associated with meningeal involvement.

Chorioretinitis, Neuroretinitis, retinochoroiditis, multifocal choroiditis, low-grade retinal vasculitis, pre-retinal precipitates, punctate retinitis as well as retinal necrosis represent other possible patterns of presentation. Vitreous involvement might be significant as well as papilledema

- Optical coherence tomography (OCT) - clinical hallmarks of ASPPC are very typical, showing an obvious choriocapillaris-RPE complex involvement.
- Fluorescein angiography (FFA) - progressive hyperfluorescence within the involved area with scattered focal hypofluorescence,
- Indocyanine Green Angiography - (ICGA) shows hypofluorescent areas
- Laboratory evaluation - RPR, VDRL- to quantify both IgG and IgM antibodies. FTA-ABS, TPHA - are specific treponemal antigen tests

Treatment - fractionated 18–24 MU /day of intravenous aqueous penicillin G administered every 4 h for 10–14 days or oral Doxyclicine 100 mg twice a day as loading dose followed by 100 mg daily for 2 weeks or injection ceftriaxone for 10-14 days.

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06. Non-infectious posterior uveitis & panuveitis

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Introduction

- Predominant inflammation of the posterior segment of the eye (primarily of the retina, choroid and/or the retinal pigment epithelium) is classified as posterior uveitis.
- If the anterior chamber, the vitreous, the retina & choroid are all equally inflamed (without any predominant involvement of any one site) then such inflammation is classified as panuveitis.
- Sarcoidosis, Behcet's disease & Vogt Koyanagi Harada disease are the commonly seen non-infectious entities that are enlisted herein.

Sarcoidosis

Basics

Description

- Sarcoidosis is a multisystemic idiopathic inflammatory disease predominantly involving lungs, lymph nodes, skin, liver, heart and the eyes. It is characterized by non-caseating granulomas.

Epidemiology

- Global disease, Ocular involvement occurs in 10-75% patients with systemic sarcoidosis. The ocular inflammation in sarcoidosis may be a presenting feature in 30-40% patients. Ocular involvement is commoner in females and is also seen in children. Majority of the cases present bilaterally.

Etiology

- Unknown

Pathophysiology

- Predominantly T cell/macrophage driven granulomatous inflammation that is triggered by an unknown antigen. Genetic susceptibility and certain environmental (e.g., mycobacteria, P. acnes) and occupational exposures (e.g. bioaerosols, beryllium) are suspected to play a role in development of sarcoidosis

Diagnosis

Common Systemic features

▶ Constitutional symptoms (e.g. fever, anorexia), pulmonary (e.g. dyspnea, cough etc.) or dermatological (e.g. erythema nodosum) symptoms can be seen at presentation. The diagnosis is essentially established on chest imaging and confirmed by endobronchial biopsy. About 5% of patients may be asymptomatic (incidental detection on chest imaging).

Common Ocular features 1

1. Other causes of granulomatous uveitis must be ruled out.
2. Intraocular clinical signs that are suggestive of ocular sarcoidosis:
   a. Mutton-fat keratic precipitates and/or iris nodules
   b. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae.
   c. Snowballs/string of pearls vitreous opacities.
   d. Multiple chorioretinal peripheral lesions.
   e. Nodular and/or segmental periphlebitis (candle wax drippings) and/or macroaneurysm in an inflamed eye.
   f. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule.
   g. Bilaterality (based on ocular examination and imaging (for subclinical inflammation)); can present unilaterally.
3. Ocular surface manifestations
   a. Conjunctival nodule/ chronic conjunctivitis
   b. Scleritis
   c. Keratoconjunctivitis sicca
4. Adnexal/orbital/neuro-ophthalmic manifestations
   a. Lacrimal gland inflammation
   b. Diffuse orbital inflammation/ pseudo tumor
   c. Cranial neuropathy (facial/optic)- infiltrative+/- compressive

Ocular complications

1. Complicated cataract
2. Secondary glaucoma (open/closed angle)
3. Cystoid macular oedema (CME)
4. Sequelae of retinal vasculitis: neovascularization, vitreous haemorrhage and

tractional retinal detachment

5. Inflammatory choroidal neovascular membrane (CNVM)

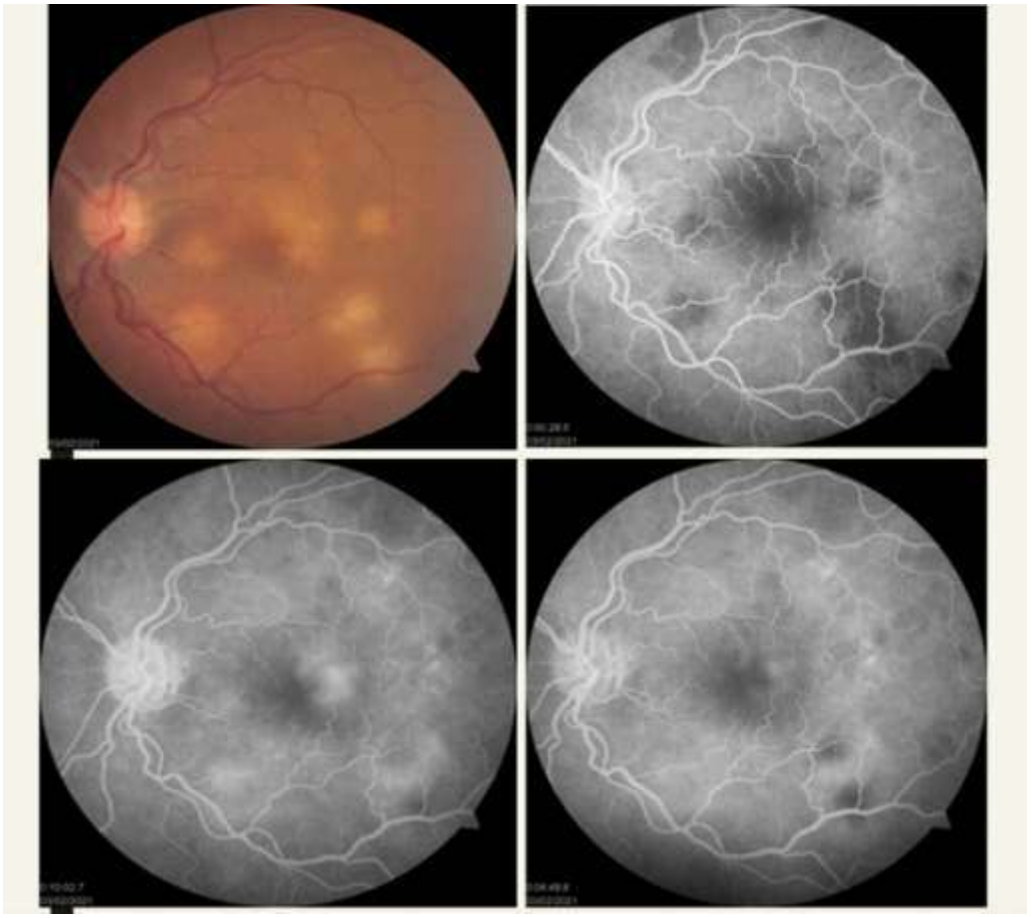

Fig. 1: Sarcoidosis: Choroidal granuloma. Clockwise from top left: 1. Fundus photo showing multiple, yellow elevated granulomas at the level of Choroidal stroma. Fundus fluorescein angiography images, early (2), mid (3) and late (4) phases, showing early hypofluorescence, with progressive late leakage.

Diagnostic tests and interpretation

1. Systemic investigations 1

a. Bilateral hilar lymphadenopathy (BHL) by chest X-ray and/or chest computed CT scan.

b. Negative tuberculin test or interferon-gamma releasing assays. (IGRA)

c. Elevated serum angiotensin-converting enzyme (ACE).

d. Elevated serum lysozyme.

e. Elevated CD4/CD8 ratio (>3.5) in bronchoalveolar lavage fluid.

f. Abnormal accumulation of gallium-67 scintigraphy or 18F-fluorodeoxyglucose positron emission tomography imaging.

g. Lymphopenia.

h. Parenchymal lung changes consistent with sarcoidosis, as determined by pulmonologists or radiologists.

2. Ancillary ophthalmic investigations

a. OCT to detect CME. OCT-A to detect inflammatory CNVM.

b. Fundus fluorescein angiography showing the extent of inflammation in retinal periphlebitis and capillary non-perfusion areas. It also helps in detecting CME & inflammatory CNVM

c. Visual fields, colour vision for optic neuropathy

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Vogt Koyanagi Harada (VKH) disease

Basics

Description

▶ Presents as bilateral granulomatous panuveitis. VKH is a multisystemic (involving the eyes, ears, meninges). An essential feature to the diagnosis of VKH is the absence of penetrating ocular trauma or surgery that is needed for its distinction from sympathetic ophthalmitis (SO).

▶ Sympathetic ophthalmitis closely resembles VKH in almost all clinical features, with the exception of, the history of trauma in the fellow eye preceding the onset of ocular inflammation.

Epidemiology

▶ Global disease, predominantly involves pigmented populations, young adults

(onset 20-40yrs). Slight female preponderance in certain populations.

Etiology

- Unknown
- Pathophysiology
- T-cell mediated autoimmune reaction directed against antigens associated with melanin, melanocytes and retinal pigment epithelium (RPE). (tyrosinase or tyrosinase related proteins).

Diagnosis

- The diagnosis of VKH disease is essentially a clinical diagnosis by recognizing the pattern of ocular features detailed below.

Clinical features

Ocular signs

Four stages have been defined.

1. Prodromal stage: headache, photophobia, neck stiffness: "meningismus" (resembles viral infections/meningitis)

2. Uveitic stage: blurred vision, hyperemic optic disc oedema with peripapillary retino-choroidal thickening (best appreciated on ultrasound B-scan), multiple pockets of serous retinal detachments (can be possibly bullous at times), anterior uveitis (however is a predominant posterior uveitis)

3. Chronic/convalescent stage: Vitiligo/poliosis/depigmented choroid. Pale disc with bright orange-red choroid (characteristic "sunset glow fundus").

4. Recurrent stage: Recurrent panuveitis with ophthalmic complications stemming out of uncontrolled disease of prolonged duration (see below).

Systemic associations

1. Sensorineural hearing loss, tinnitus, vertigo
2. Vitiligo involving face, hands, shoulders, lower back
3. Poliosis, alopecia

Ocular complications

1. Complicated cataract
2. Secondary glaucoma (open/closed angle)

3. Cystoid macular oedema (CME)

4. Inflammatory choroidal neovascular membrane (CNVM)

Diagnostic tests and interpretation

a. Fundus fluorescein angiography: Early patchy hypo-fluorescence that leads to later hyper-fluorescence. Multiple pin-point leaks at the level of RPE, pooling of the dye in serous detachments, "hot" discs are all known patterns on the FFA

b. Optical Coherence tomography (OCT) Cystoid macular oedema, choroidal thickening (OCT-EDI imaging), neurosensory detachments.

c. Optical Coherence tomography angiography (OCT-A) for detecting inflammatory CNVM

d. Ultrasound B-scan: Choroidal thickening (pronounced in peripapillary region), serous retinal detachments

Differential diagnosis

1. Sympathetic ophthalmia

2. Posterior scleritis

3. Uveal effusion syndrome

4. Other entities associated with bilateral serous retinal detachments e.g., accelerated hypertension

5. Intraocular lymphoma

Behcet's disease

Basics

Description

▶ Multi-system vascular disease, typically manifesting as a triad of oral aphthous ulcers (> 90%), genital ulcers and ocular inflammation (70%). If left untreated, close to a fourth of patients (25%) can end up with irreversible & severe visual loss. Behcet's is clinically characterized by non-granulomatous necrotizing occlusive vasculitis.

Epidemiology

▶ More commonly seen in the Far east and in Middle eastern nations along the "silk-route". Ocular involvement is more common and more severe in males.

Etiology

- Unknown. Associated with HLA B51.

Diagnosis

Common Systemic features 1

1. Oral aphthous ulcers (recurrent but heal without scarring)

2. Skin: erythema nodosum (painful, purple nodules over shins/upper torso), Pseudo folliculitis

3. Genital ulcers: these are usually long-standing and cause scarring.

4. Systemic vasculitis: involves both arteries and veins. Vascular occlusions, varices, aneurysms are known complications.

5. Neurological: Venous sinus thrombosis, strokes, psychiatric symptoms

6. Joint involvement - Polyarthritis, involving the large joints, non-deforming arthritis

Common Ocular features 1

1. Non-granulomatous anterior uveitis. The presence of a "mobile hypopyon" is a distinctive feature.

2. Retinal inflammation: multiple patches of "retinitis" with associated vitritis.

3. Retinal vasculitis

- involves both arteries and veins
- can cause both retinal venous & arterial occlusions. Multiple retinal hemorrhages, cystoid macular oedema
- untreated, can lead to retinal atrophy with pigment clumping at macula.

4. Ischemic optic neuropathy

Ocular complications

1. Complicated cataract

2. Secondary glaucoma (open/closed angle), neovascular glaucoma

3. Cystoid macular oedema (CME)

4. Sequelae of retinal vasculitis: neovascularization, vitreous haemorrhage & subsequent complications

5. Inflammatory choroidal neovascular membrane (CNVM)

Diagnostic tests and interpretation

The diagnosis of Behcet's disease is essentially a clinical diagnosis by recognizing the constellation of ocular signs and is then corroborated by the systemic features.

1. Systemic investigations

▶ No single pathology test is available for diagnosis. Positive testing for HLA B51. ESR & CRP helps to determine systemic inflammatory activity

2. Pathergy test: Papule equal or greater than 2 mm in size that develops 24-48 hours (reaction to a needle insertion 5mm deep into the forearm skin) However this test is less sensitive in Indian patients.

Ancillary ophthalmic investigations

▶ Ocular Coherence Tomography to detect CME. OCT-A in chronic cases to detect inflammatory CNVM.

▶ Fundus fluorescein angiography showing the extent of inflammation in retinal vasculitis. At times, all branches of the retinal vascular tree may be involved suggesting the "ferning pattern" on angiography. The extent of vascular occlusions can also be clearly made out on angiography. It also helps in detecting CME & inflammatory CNVM

▶ Visual fields, colour vision for optic neuropathy

Differential diagnosis

HLA B-27 associated anterior uveitis, other vasculitidis (e.g. SLE). Acute retinal necrosis in early or evolving stages & in the burnt-out stages (herpetic/non-herpetic) may also mimic features of Behcet's disease

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Treatment of non-infectious posterior uveitis:

▶ Systemic treatment: Since the disease may manifest with recurrent inflammations requiring long term systemic immune-suppression, it is preferred to have an internist or rheumatologist on board.

Systemic steroids:

a. Intravenous methylprednisolone (1gm IV for 3-5 days): for acute uveitic phase.

After excluding systemic infections and other contraindications. Requires hospitalization.

b. Oral steroids: oral Prednisolone is preferred drug in the dose of 1-1.5mg/kg to begin with. This is then followed by slow tapering that is proportional to the desired clinical response. Common adverse effects like hypertension, elevated blood sugars, gastritis needs monitoring & treatment.

Immunosuppressive medicines:

▶ Ocular inflammation in VKH responds very well to systemic steroids. However, recurrences of inflammation occur after steroids are tapered off. Hence, it is pertinent to consider initiating steroid-sparing treatment early in the disease. Methotrexate, azathioprine, mycophenolate mofetil or cyclosporine can be chosen in patients requiring repeated doses of oral steroids to control inflammation. Regular tests such as CBC, ESR, liver & renal functions are needed to monitor side-effects of systemic immunosuppressive drugs. Biologics such as TNF-alpha inhibitors (adalimumab) can be considered in case of inadequate response to steroids and immunosuppressives.

Ocular treatment

a. Topical steroids (for anterior inflammation)

b. Intravitreal steroid injections are preferred over peri-ocular steroids in view of their predictable response.

c. Treatment of complications: Injection anti-VEGF for inflammatory CNVM, anti-glaucoma medications.

d. Surgical management of complications e.g., cataract surgery (after 3 months of quiescence). Vitrectomy for retinal complications such as epiretinal membranes,

07. Infectious & non-infectious scleritis

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Clinical description:

▶ Inflammation of the episcleral and scleral tissues is termed as episcleritis & scleritis respectively

Classification:

▶ Based on the affected site, scleritis is classified as anterior or posterior scleritis but rarely, can present as a mixture of both subtypes.

▶ Anterior scleritis can further be classified as nodular, diffuse, necrotizing or Scleromalacia Perforans.

Terminology:

▶ The nodule represents a localized, rounded but tender area of scleral elevation (fixed to the underlying tissue) with adjacent scleral congestion. (Fig. 1)

▶ Necrotizing scleritis represents an area of scleral inflammation with a whitish appearing avascular area. This avascular area can eventually lead to necrosis, thinning and sometimes perforation of the sclera. Thus, scleritis is a painful, ocular inflammatory disorder with a wide spectrum of presentation & severity.

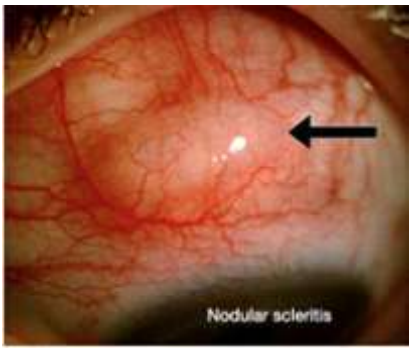

Fig.1: Nodular Scleritis

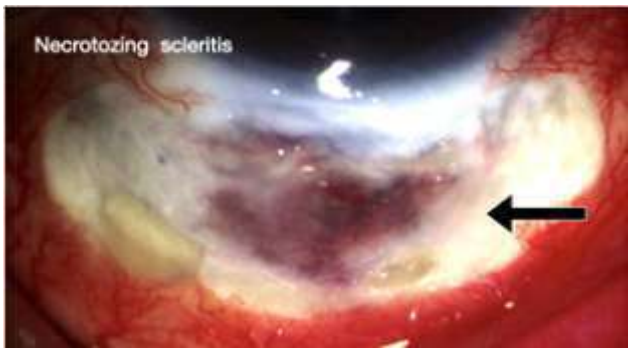

Fig. 2: Necrotizing Scleritis

Diagnosis:

▶ Scleritis is essentially a clinical diagnosis. Patients of scleritis present a with dull boring pain that may typically disturb their sleep or daily activities.

▶ They involved area shows a violaceous hue of scleral congestion (diffuse or sectoral & with or without a scleral nodule) This “scleral congestion” primarily

involves the deep episcleral vascular plexus along with its adjacent plexuses, which typically persists after administration of 10% phenylephrine eye drops.

▶ Involvement of the adjacent cornea is also known to occur in severe inflammation.

▶ The symptomatology of scleritis & the failure to blanch the congested vessels with 10% phenylephrine eye drops differentiates it from episcleritis & conjunctivitis.

▶ A case of healed scleritis will show as thinned out sclera with a blue-grey discoloration (suggesting visibility of underlying uveal tissue)

Infectious scleritis:

▶ Scleritis secondary to local ocular or systemic infections is termed as infectious scleritis. It may occur after a known ocular trauma and can be a rare complication of a prior ocular surgery, called as surgically induced necrotizing scleritis (SINS)

▶ At times, the trauma may be so trivial that the history of ocular trauma may not be forthcoming.

Investigations:

▶ Scleritis is known to be associated with an underlying systemic disease in about 30-35% of all known cases. Detailed evaluation must be performed with an aim to exclude an underlying inflammatory disease.

▶ History of trauma, prior surgery, underlying infectious diseases such as tuberculosis, conjunctivitis, fungal infections, herpes infections, malignancies & uveitis other than scleritis must be excluded.

▶ CBC, ESR, CRP, RA, ANA, anti-CCP, ACE, p-ANCA, c-ANCA, urine (R/M), Chest X-Ray, HLA-B27, tuberculin skin test (TST) is amongst some of the tests.

▶ More such tests can be ordered & the list may be exhaustive, but they must be tailored to individual cases.

Treatment:

▶ Since non-infectious scleritis may manifest as a spectrum of other systemic diseases, presenting initially or later during treatment, it is preferred that treatment be done in liaison with a rheumatologist.

▶ Oral NSAIDs can be used in milder cases to tide over the symptoms till the underlying cause is detected.

▶ Oral steroids (prednisolone 1mg/kg/day) are the mainstay of treatment to combat inflammation & have to be tapered off as inflammation improves.

▶ Intravenous steroids can also be administered for extremely severe

inflammation; however, infections must be first ruled out.

- Since scleritis is a severe sight threatening inflammation and is known to recur as the oral steroids are tapered, systemic immunosuppressives need to be considered simultaneously.
- Non-infective sight threatening necrotizing scleritis, not adequately responding to intravenous steroids & oral immunosuppression need to be treated with systemic biologic agents such as TNF-alpha inhibitors (e.g., infliximab, adalimumab) in a bid to save the eye.
- Topical steroids can be used supportively for anterior chamber inflammation; however, their use is limited to counter the severity of inflammation.
- Surgical debridement along with an antibiotic wash may be needed to remove debris or infected foreign body in infectious scleritis. This additionally helps in sampling for microbiology & histopathology evaluation.
- Oral or systemic antibiotics, anti-fungals or anti-virals and their respective topical fortified preparations need to be administered according to culture-sensitivity patterns in infectious scleritis.
- A liaison with the infectious disease expert should be strongly considered in infectious scleritis associated with resistant organisms, multiple infections & systemic involvement.
- Scleral patch grafting may be required in a bid to restore the tectonic integrity of the sclera in cases of extreme scleral necrosis & prolapse of the uveal tissue and eventually preserve vision.
- All patients of scleritis need long term treatment & follow up. Additionally, they need monitoring to check for side effects of steroids and systemic immunosuppressives.

08. The Role of Immunomodulation in Management of Uveitis

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Introduction:

We now know the various etiologies and basic science pathways that cause intraocular inflammation and now have new therapeutic approaches, including immunomodulatory agents (corticosteroid sparing therapies), which have expanded treatment options for uveitis. These agents provide individualized, patient-tailored treatment approaches with the goal of durable, corticosteroid-free remission. 1

The aim of treatment in uveitis:

The preferred practice pattern in the care of patients with non-infectious uveitis should be aimed at "cure" and this should be in stages.

The first stage in the successful pursuit of cure would be the induction of durable, corticosteroid-free remission - and doing whatever it takes to accomplish that goal - while at the same time doing no harm, not producing quality of life-altering side effects or complications from the strategies employed in that quest for durable remission. In order to achieve durable corticosteroid-free remission or cure of the disease, a long-term stepladder approach is utilized (Fig. 1), involving initiation of the lowest appropriately aggressive therapy for the specific disease process and severity, and advancement up the ladder to other modalities as needed. 1

Fig 1: The New Step Ladder Approach for treatment of uveitis with an aim to achieve "cure" of uveitis. 1

How to achieve durable, corticosteroid-free remission in Uveitis?

Many forms of uveitis can be placed into corticosteroid-free durable remission, with eventual withdrawal of all immunomodulatory medication and no relapse of ocular inflammation for 5 or more years. This occurs, as in some other autoimmune diseases, because of a "resetting or re-education" of the immune system, such that it is

no longer inclined to mount an immune response against tissue of self. 1

What about long-term side effects of Immunomodulation?

The multicenter SITE study (Systemic Immunosuppressive Therapy for Eye diseases) 2 looked for side effects that increased mortality and malignancy associated with immunomodulators. 2 The study concluded that immunomodulatory agents for the care of patients with chronic or recurrent uveitis under close monitoring can be both effective and safe and did not (except for TNF-alpha inhibitors), place the patient at increased risk for mortality or malignancy. Especially for bilateral disease, systemic therapy may be a better first choice given its efficacy and systemic and ocular safety. 3 Recently reported seven-year extended follow-up showed an average 7.2-letter visual acuity advantage of systemic therapy immunomodulatory therapy vs. local therapy with fluocinolone implant. 3 In the current era, it is obvious that disease quiescence with a goal of remission or cure can be accomplished with a therapeutic strategy combining corticosteroids with the early introduction of corticosteroid-sparing immunomodulatory therapy if the disease is perceived to be recurrent or chronic. 2

Uveitis requires Tailored Investigations to Tailored Care…

Thus, the need in management of Uveitis is executing a proper therapeutic strategy over a time frame measured in years. The aim should be to provide individualized tailored care to our patients, and, enhancing their overall quality of life should be the goal.

A word of caution with immunomodulation:

“ Primum non nocere” is a Latin phrase that means "first, to do no harm". Non-maleficence is one of the principal precepts of bioethics which states that, "given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good." It reminds physicians to consider the possible harm that any intervention might do. It is invoked when debating the use of an intervention that carries an obvious risk of harm. This is the essential precept that any ophthalmologist attempting to treat a patient with uveitis must always remember especially so because while undertreatment can be sight threatening in uveitis; overtreatment or inappropriate treatment can be sight and life threatening as well.

Case Scenario:

A 47-year-old lady - Practicing Homeopath, presented to us in March 2019 with a right eye decrease of vision 2 years back. She had a Granulomatous Panuveitis treated only with steroids. She had now developed a Complicated Cataract and referred for

opinion on Cataract Surgery. She was investigated and started on Oral Methotrexate in March 2019. She underwent Cataract Surgery in September 2019 and achieved a vision of 20/120, N12 with a sunset glow fundus (Vogt Koyanagi Harada Disease).

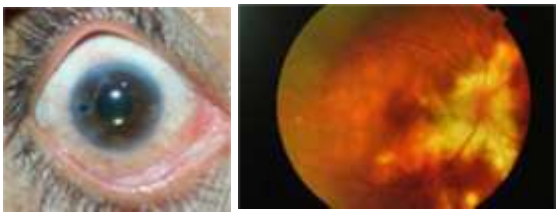

Fig 2: Clinical Picture of a 47-year-old lady who had a cataract surgery after achieving quiescence; 6 months on oral Methotrexate with a Sunset Glow Fundus limiting vision

Take Home Message from the case scenario: Immunomodulators introduced into the treatment; 2 years after onset of disease were able to achieve quiescence; but outcome not completely satisfactory because of an irreversible chorioretinal sequelae.

General Guidelines:

Ensure the below before suggesting immunomodulation:

- Absence of infections.
- Absence of masquerades.
- Absence of haematological disorders.
- Absence of pregnancy.
- Patient commitment to meticulous follow up with ophthalmologist and physician.

Understand and explain to patient the below before suggesting immunomodulation:

- These drugs take several weeks to have an effect.
- Immunosuppressive drug regimens for initial therapy of ocular inflammation typically should include high-dose oral corticosteroids as well.
- Once the disease is quiet, the corticosteroids are tapered either to a low level or, if possible, discontinued.

Drugs and dosages for common immunomodulation drugs: 4

Drug	Does	Common Uses	Adverse effects
Azathioprine	2-3 mg/kg/day	VKH, Sympathetic ophthalmia	Gastrointestinal upset Cytopenia Hepatitis
Methotrexate	15 mg/kg/day	JIA Behcer's disease Sarcoidosis	Hepatitis Cytopenia
Mycophenolate mofetil	1 gm BID	JIA, Intermediate uveitis	Diamhea Cytopenia
Cyclophosphamide	2 mg/kg/day	VKH, Wegener's granulornatosis	Cytopenia Bladder loxicity
Chlorambucil	0.1 mg/kg/day	Adamantiades-Behcet's disease Sympathetic Ophthalmia	Cytopenia
Cyclosporine	2-5 mg/kg/day	Behcer's disease	Hypertension Nephrotoxicity Hirsutism
Tacrolimus	2-3 mg BID	Behcer's disease	Nephrotoxicity Neurotoxicity

Common indications of immunomodulation: 4

Power of Association	Diseases
Strong	Behcet disease Sympathetic ophthalmia Vogt-Koyanagi-Harada syndrome Rheumatoid necrotizing scleritis Wegener granulomatosis Relapsing polychondritis with scleritis Juvenile idiopathic arthritis

Average monthly cost of treatment with various immunomodulation drugs: 4

Drug	Does	Cost Rs/tab	Total monthly cost Rs
Azathioprine	50 mg/BD	Rs 10/50 mg tab	600
Methotrexate	15 mg/weekly	Rs 35/15 mg tab	140
MMF	1000 mg/BD	Rs 50/500 mg tab	6000
Cyclosporine	50 mg/BD	Rs 50/50 mg tab	3000
Tacrolimus	2-3 mg/BD	Rs 40/1 mg tab	2400
Cyclophosphamide	50 mg/BD	Rs 4/50 mg tab	240
Chlorambucil	5 mg/BD	Rs 200/5 mg tab	6000
Adalimumab	40 mg biweekly	Rs 25000/40 mg	50000
Etanercept	25 mg twice a week	Rs 6500/25 mg	68000
Infliximab	250 mg/8 weekly maintenance dose	Rs 42000/100 mg	52000

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09. Managing uveitis and scleritis- The rheumatologist's perspective

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Virtually all the systemic inflammatory diseases that require rheumatologic care tend to affect the eye or its surrounding structures.

Key Points

- Symptoms of uveitis vary widely based on the location of the inflammation within the eye and the suddenness of onset.
- Ankylosing spondylitis is the systemic rheumatic disease most often associated with uveitis. During a lifetime, acute anterior uveitis develops in about 40% of patients with ankylosing spondylitis.
- The uveitis associated with HLA-B27 tends to be unilateral, recurrent, and sudden in onset. Recurrences sometimes affect the opposite eye.
- Sarcoidosis frequently manifests as uveitis, however can affect any portion of the eye. Testing for serum ACE level, Mantoux test, Chest X ray and sometimes Chest CT scan should be considered in all patients.
- Most patients with retinal vasculitis do not have systemic vasculitis.
- Many patients with scleritis have a systemic disease, such as rheumatoid arthritis and systemic vasculitis. Anti-neutrophilic cytoplasmic antibody, Rheumatoid Factor and anti- CCP serology testing helps identify a subset of patients with severe scleritis.
- Behçet's syndrome can cause vision threatening uveitis. It is a clinical diagnosis and a history of recurrent oro-genital ulceration should be elicited in all patients with uveitis, especially posterior uveitis.
- All paediatric patients with uveitis should be screened for anti-nuclear antibody by immunofluorescence method

Ocular Immune Response

The eye generally is regarded as an immune privileged site. 1 From a teleological perspective, many scientists believe that the eye has developed mechanisms to avoid becoming inflamed because of the consequences that inflammation has for visual acuity. Like the brain, the internal portion of the eye has no lymphatics, although the conjunctiva on the ocular surface has lymphatic drainage. Portions of the eye—the cornea and the lens—are avascular. The aqueous humor contains several factors that

are known to be immunosuppressive, including transforming growth factor-β and α-melanocyte–stimulating hormone. Several tissues within the eye express ligands that promote apoptosis, including tumour necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) and Fas ligand. If a soluble antigen is injected into the anterior chamber, a cellular immune response is suppressed. This phenomenon is known **as anterior chamber–associated immune deviation (ACAID).** These factors are important to consider in the effort to understand why the eye sometimes is targeted as part of an immune or inflammatory disease

Ocular Anatomy and Physiology

The term uvea derives from the Latin word for "grape." The anterior chamber is filled with aqueous humor, which has homology to cerebrospinal fluid. When the blood- aqueous barrier is intact, the aqueous humor contains no leukocytes and very little protein. The blood-aqueous barrier, which resembles the blood-synovial barrier, is disrupted in anterior uveitis. In this case, a routine, non-invasive biomicroscopic or slit lamp examination would reveal leukocytes and increased protein in the anterior chamber. **An ophthalmologist has the opportunity to observe two universal hallmarks of inflammation noninvasively.**

Anatomic subsets of uveitis include anterior uveitis, which consists of iritis or iridocyclitis (ciliary body inflammation); intermediate uveitis, in which leukocytes are present within the vitreous humor; and posterior uveitis, in which the choroid and the retina are inflamed. Panuveitis occurs when all portions of the uveal tract are inflamed. An attempt has been made to standardize the nomenclature used to describe uveitis by the Standardization of Uveitis Nomenclature Working Group 2 and all ophthalmologists may be advised to follow the same while classifying uveitis.

Uveitis

Rheumatologists may be consulted to identify a systemic disease in a patient with uveitis, and a rheumatologist often is asked to assist in the management of immunosuppression in select patients with uveitis. In some referral practices for patients with uveitis, 40% of patients might have an associated systemic illness.

The primary parameters that can be used to characterize subsets of uveitis are:

1. Anatomic location of inflammation: anterior, intermediate, posterior, or panuveitis.

2. Laterality: unilateral (can be asynchronous) or bilateral (occurring in both eyes simultaneously)

3. Onset: sudden or insidious.

4. Duration: limited (≤3 months) or persistent (>3 months).

5. Course: acute (sudden onset and limited duration), recurrent (repeat episodes separated by ≥ 3 months), chronic (persistent disease with relapse within 3 months of discontinuation of therapy).

Anterior uveitis

From an epidemiologic perspective, anterior uveitis is more common than posterior or intermediate uveitis. 5 Anterior uveitis accounts for 50% to 92% of all cases of uveitis. The most common associations are idiopathic and **HLA-B27-associated with or without an associated spondyloarthropathy**

About 50% of persons with anterior uveitis are positive for human leukocyte antigen (HLA)-B27. The uveitis associated with HLA-B27 is almost always unilateral, recurrent, of relatively short duration (<3 months per attack), resolves completely between attacks, and is associated with reduced intraocular pressure (in contrast to herpes simplex, which can cause recurrent anterior uveitis associated with increased intraocular pressure). 3 Hypopyon or pus in the anterior chamber sometimes is present in patients with HLA-B27–associated uveitis. Recurrent episodes can affect the contralateral eye, but simultaneous bilateral involvement is rare

Uveitis develops in approximately 5% of persons with **inflammatory bowel disease** and 7% of persons with **psoriatic arthritis.**

Sarcoidosis is the second most common systemic disease associated with uveitis. Sarcoidosis is promiscuous within the eye, meaning that it can affect a wide range of structures, including the orbit, lacrimal gland, anterior uvea, vitreous humor, choroid, retina, or optic nerve. Sarcoidosis frequently involves the conjunctiva, which is an accessible tissue for biopsy confirmation of the diagnosis. Ocular inflammation with sarcoidosis frequently is termed granulomatous because large collections of cells deposit on the back of the cornea. A retinal vasculitis can be a prominent feature of sarcoidosis, even though systemic vasculitis is not a typical feature of the disease; this phenomenon results in part from the manner in which vasculitis is diagnosed in the retina.

Most rheumatologists find the term retinal vasculitis misleading because the classic systemic vasculitides, such as polyarteritis nodosa and granulomatosis with polyangiitis, are rarely associated with retinal vasculitis 4

Initially, sarcoidosis frequently manifests as an ocular problem. An ocular symptom is the initial manifestation almost as frequently as a pulmonary symptom. In most series of patients with uveitis, about 30% of patients have uveitis that defies placement within a diagnostic category. Many of these patients may have sarcoidosis that is difficult to find outside the eye. The sensitivity and specificity of studies such as a serum angiotensin-converting enzyme level or gallium scan for sarcoid that is primarily ocular are unknown. One can consider obtaining a chest computed

tomography (CT) scan to look for symmetric hilar adenopathy in any patient who has uveitis of unknown origin5.

Juvenile Idiopathic Arthritis comprises several different diseases6. Patients with juvenile ankylosing spondylitis resemble their adult counterparts in that a sudden-onset, unilateral anterior uveitis can develop. The subset of JIA that is most classically associated with uveitis tends to be female, with onset of arthritis between the ages of 2 and 8 years. The joint disease is pauciarticular, and most patients are positive for anti-nuclear antibodies. The uveitis tends to have an insidious onset, such that pain and redness are almost always absent. Joint disease can be minimal as well, and some patients are not diagnosed until a visual screening examination is performed when starting school. The eye disease usually is bilateral and very persistent, although remissions have been well described. Band keratopathy, which is the deposition of calcium superficially in the cornea, is a well-known and frequent complication of this form of uveitis. Patients also may experience glaucoma and posterior synechiae

Other forms of uveitis associated with joint disease include Behçet's disease, relapsing polychondritis, and vasculitis such as Cogan's syndrome and Kawasaki's disease. In Behçet's disease, uveitis is often the symptom that "drives" the therapy—that is, it is often the manifestation that most often requires systemic immunotherapy. Eye inflammation usually is bilateral and recurrent. In contrast to the recurrences typical of ankylosing spondylitis, recurrences of uveitis with **Behçet's disease,** usually do not have complete resolution between attacks. A hallmark of Behçet's disease– associated uveitis is a retinal vasculitis. Retinal arteries are especially prone to be affected. The visual prognosis with Behçet's disease can be grim, and blindness is a frequent concomitant of untreated ocular disease.

Juvenile idiopathic arthritis (JIA), **tubulointerstitial nephritis and uveitis** (TINU), **and Kawasaki disease** are the most common associations in the paediatric population. Fuchs' Heterochromic iridocyclitis is a common cause of chronic, unilateral anterior uveitis characterized by iris heterochromia.

Scleritis and Corneal Melt

Scleritis often is divided into five categories: diffuse anterior, nodular, necrotizing, Scleromalacia Perforans, and posterior. Each of the first three categories' results in a red, painful eye. Pain is more variable in Scleromalacia Perforans, in which a nodule pathologically like a rheumatoid nodule forms in the sclera. Pain also varies with posterior scleritis, and because the sclera extends back to the optic nerve, posterior scleritis can occur in a localized fashion that does not lead to a red eye. Because of the risk of perforation, the sclera is not normally biopsied, but biopsy studies have shown that scleritis is often a granulomatous inflammation of scleral tissue.

Patients with scleritis can experience complications within the eye, including uveitis, glaucoma, optic nerve odema, and retinal or choroidal distortion. A corneal melt or peripheral thinning of the cornea sometimes develops in persons with severe scleritis and represents a potentially blinding complication of the disease.

About 50% of patients with scleritis have an associated systemic illness. 7 The most common of such illnesses are limited granulomatosis with polyangiitis and rheumatoid arthritis. Generally, the associated rheumatoid arthritis is long standing and seropositive. Patients may have associated nodules, vasculitis, or pleuropericarditis. They have a shortened life expectancy compared with other patients with rheumatoid arthritis. 8 It is unusual for scleritis to be an initial manifestation of rheumatoid arthritis.

Granulomatosis with polyangiitis is commonly associated with scleritis. In contrast to rheumatoid arthritis, scleritis can be the initial manifestation of granulomatosis with polyangiitis. Obtaining anti- neutrophilic cytoplasmic antibody, Rheumatoid factor and anti- CCP serology for any patient who presents with scleritis without an obvious systemic disease association is appropriate. Other systemic associations with scleritis include inflammatory bowel disease, relapsing polychondritis, other vasculitides such as giant cell arteritis, and ankylosing spondylitis.

Scleritis tends to be a painful and persistent disease that often lasts for years. In contrast, episcleritis involves more superficial tissue and is usually transient. Episcleritis may be a feature of rheumatoid arthritis, although many patients with episcleritis may not have any associated systemic illness. Complications within the eye, such as glaucoma or uveitis, are absent. Mild discomfort, rather than frank pain, is the usual presenting symptom. In contrast to scleritis, patients with episcleritis have vessels that constrict completely after 2.5% phenylephrine is placed on the surface of the eye.

Some patients with scleritis, especially those who do not have an associated systemic illness, are treated adequately with an oral nonsteroidal anti-inflammatory drug. Some experts treat scleritis with locally injected corticosteroids, but this approach should be avoided if the sclera is thin (a sign of necrotizing disease). In addition, corticosteroids have the theoretical risk of promoting thinning. The usual option for patients who do not respond to nonsteroidal anti-inflammatory drugs is oral prednisone. Some patients can be effectively treated with low doses of prednisone, but many patients require the addition of an antimetabolite like Methotrexate9 as a steroid-sparing drug. Scleritis usually responds to treatment of the underlying disease if an associated disease is present. Thus, control of rheumatoid arthritis or inflammatory bowel disease usually results in control of associated scleritis. Rituximab is reportedly effective for most patients with scleritis who fail to respond to antimetabolite therapy.10

Medication related Ocular Toxicity

A variety of medications have the potential to cause uveitis. These medications include rifabutin, intravenously administered bisphosphonates, moxifloxacin, TNF inhibitors, and ipilumumab.

Conclusion

In some ways, from a rheumatologist's perspective, the eye is a microcosm of the body. Its complex structures frequently reflect inflammation elsewhere. Treatment of many forms of ocular inflammation requires collaboration between a rheumatologist and an ophthalmologist.

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10. Frequently asked Questions (FAQs) for the general ophthalmologist in Uveitis Practice

▸ What are the basic laboratory investigations for a patient with Anterior Uveitis ?

The first episode of non-granulomatous anterior uveitis need not be investigated. Recurrent Non-granulomatous anterior uveitis especially if unilateral and associated with early morning lower back stiffness should prompt the clinician to request for HLA B27 testing.

Basic investigations in a case of Granulomatous Anterior Uveitis should be directed to look for Tuberculosis / Sarcoidosis and should include a Mantoux Test, Serum ACE and radiological imaging (X Ray Chest / CT Scan Chest).

▸ What are the basic investigations in a patient with Intermediate Uveitis ?

The basic investigations for a patient with Intermediate Uveitis should include tests to look for Tuberculosis / Sarcoidosis / Syphilis and should include Mantoux Test, Serum ACE and radiological imaging (X Ray Chest / CT Scan Chest) and VDRL / TPHA

▸ How long should one wait before advising cataract surgery in uveitis and which lens material should be preferred ?

One should have a quiescent period of at least 3 months (with or without treatment) before advising cataract surgery in a patient with uveitis. This period may be increased to upto 6 months in a paediatric cataract. The preferred lens material should be hydrophobic acrylic material.

▸ Are all uveitis cases treated with steroids ?

The essence of clinical evaluation in uveitis is to differentiate “infective patterns” of uveitis entities from “non-infections patterns”

Indiscriminate use of steroids (either through oral, intravenous, peri-orbital or intravitreal routes) without a diagnostic judgment can cause irreversible damage to the vision. Steroids are hence a double-edged sword. They should only be used appropriately after a detailed clinical pattern recognition and understanding the potential risks and benefits.

▸ How long should Anti-Koch's Treatment be given in a patient with Ocular Tuberculosis ?

For a patient with Ocular Tuberculosis; as per ICMR Guidelines; the treatment regimen should be 9 to 12 months.

▸ What is classic therapy for Ocular Toxoplasmosis ?

The "classic therapy" consists of 4 to 8 weeks of oral pyrimethamine, sulfadiazine, and folinic acid with combined oral steroids for concomitant ocular inflammation to be titrated on a case-to-case basis.

▸ What is the treatment for Ocular Syphilis ?

Fractionated 18–24 MU /day of intravenous aqueous penicillin G administered every 4 h for 1014 days or oral Doxyclicine 100 mg twice a day as loading dose followed by 100 mg daily for 2 weeks or injection ceftriaxone for 10-14 days.

▸ Which are the diseases associated with Non-infectious Scleritis and what basic investigations are requested for the same ?

Many patients with scleritis have a systemic disease, such as rheumatoid arthritis and systemic vasculitis. Anti-neutrophilic cytoplasmic antibody, Rheumatoid Factor and anti- CCP serology testing helps identify a subset of patients with severe scleritis.

▸ When to consider Immunomodulation in uveitis and which basic drugs to be used ?

In a patient with Non-infectious uveitis; if inflammation relapses on tapering steroids (at doses of oral Prednisolone 5 mg/day with 3 drops of 1% Prednisolone Acetate eye drops or above); Immunomodulation may be considered. The basic drugs used include anti-metabolites i.e Methotrexate, Azathioprine and Mycophenolate.

▸ What are the characteristics of the subset of patients of JIA that are most commonly associated with uveitis ?

The subset of JIA that is most classically associated with uveitis tends to be female, with onset of arthritis between the ages of 2 and 8 years. The joint disease is pauciarticular, and most patients are positive for antinuclear antibodies. The uveitis tends to have an insidious onset, such that pain and redness are almost always absent. Joint disease can be minimal as well, and some patients are not diagnosed until a visual screening examination is performed when starting school.

▸ What are the most important emergencies in uveitis ?

All vascular occlusions, especially the arterial occlusions should also be considered as emergencies. The Clinical pattern recognised as "retinitis" and lesions involving or threatening the optic disc, macula/fovea must always be weighed as a priority.

Necrotising scleritis and giant cell arteritis also fall in the emergency category of uveitis

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