Posterior Uveitis: A toolkit for the primary eye care provider

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I have no financial disclosures

Disclosures have been mitigated

Agenda

01 Uveitis review: from anterior to posterior segment

02 Etiologies of posterior uveitis

03 Further testing and referral

04 Infectious & Immune-related etiologies: Diagnosis, Treatment and Management

05 The future of treatment & main take-aways

01

Uveitis Review

Uveitis

“Inflammation of the uveal tract”

“Used to decribe a myriad of intraocular inflammation involving the uveal tract as well as the retina and its vessels”

FRCOphth, F. M. M. J. K. J. (2007). *Clinical Ophthalmology: A Systematic Approach* (6th ed.). Butterworth-Heinemann.

Uveitis – Classification

Anterior: Inflammation in the middle layer of the eye (iris & ciliary body)

Intermediate: Inflammation predominantly involving the vitreous

Posterior: Inflammation involving the fundus posterior to the vitreous base. Includes:

- Retinitis
- Choroiditis
- Vasculitis

Uveitis – Classification

Panuveitis: Inflammation throughout the uveal tract without a predominant nidus of inflammation (anterior chamber, vitreous, retina, choroid)

Endophthalmitis: inflammation involving all intraocular tissues except the sclera

Panophthalmitis: inflammation of the entire globe, often with orbital extension

Uveitis – Classification

Anterior: Inflammation in the middle layer of the eye (iris & ciliary body)

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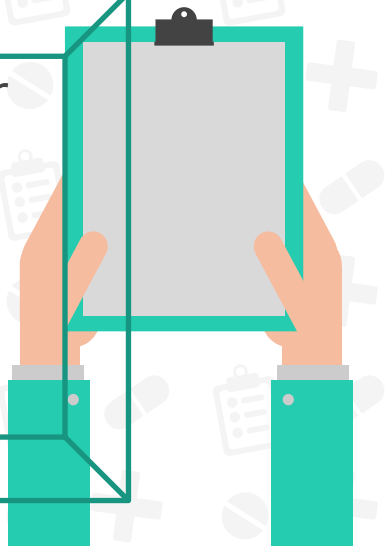


Uveitis – Definitions

Acute: sudden onset with limited duration

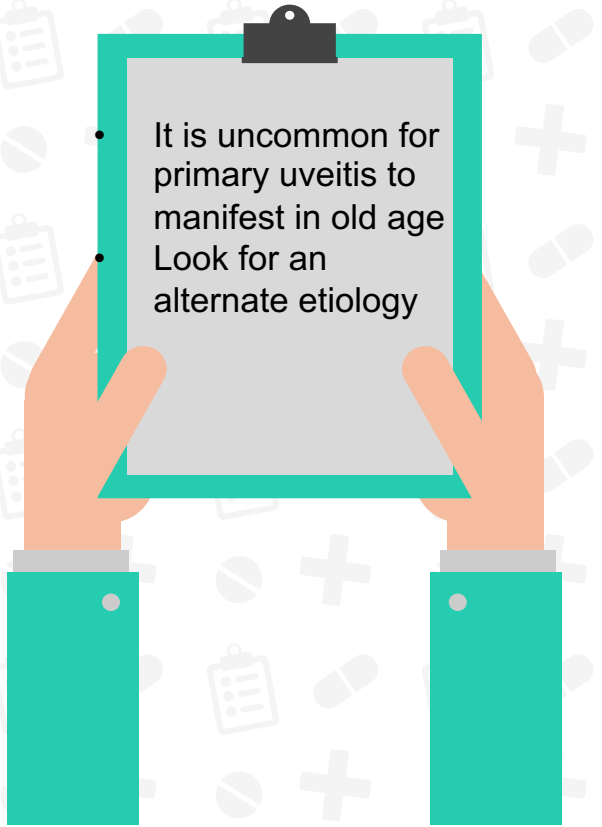
Recurrent: repeated episodes separated by at least 3 months of inactivity

Chronic: persistent inflammation identified by quick relapse (less than 3 months) after discontinuation of therapy

Remission: inactive disease for at least 3 months after treatment is stopped

Uveitis – Important elements of case history

- Age at presentation **
- Geographic origin
- Geographic location
- Ocular history
- Medical history
- Dietary habits
- Social history



Uveitis – When to do further testing

- Recurrent
- Granulomatous disease
- Bilateral presentation
- Posterior or intermedite involvement
- Systemic associations without a clear diagnosis
- When a diagnosis is suspected, and confirmation is needed

Uveitis – When NOT to do further testing

- Single occurrence of acute anterior uveitis
- Patient has known ocular disease entity that could be associated with the inflammation
- Patient has known systemic disease that could be compatible with uveitis diagnosis

Sève P, Cacoub P, Bodaghi B, Trad S, Sellam J, Bellocq D, Bielefeld P, Sène D, Kaplanski G, Monnet D, Brézin A, Weber M, Saadoun D, Chiquet C, Kodjikian L. Uveitis: Diagnostic work-up. A literature review and recommendations from an expert committee. Autoimmun Rev. 2017 Dec;16(12):1254-1264.

Noble J, Hollands H, Forooghian F, et al. Evaluating the cost-effectiveness of anterior uveitis investigation by Canadian ophthalmologists. *Can J Ophthalmol*. 2008;43(6):652–657

Standardization of Uveitis Nomenclature (SUN) for Disease Classification Criteria

EDITORIAL

Here Comes the SUN (Part 2): Standardization of Uveitis Nomenclature for Disease Classification Criteria

RUSSELL N. VAN GELDER, H. NIDA SEN, ADNAN TUFAIL, AND AARON Y. LEE

Nosology…is not a sport for the timid.
—Sherwin B. Nuland, MD[1]

AJO.com Supplemental Material available at AJO.com.

Nida Sen is currently employed by Jannsen Pharmaceuticals, Titusville, New Jersey.
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IN THIS ISSUE OF AJOPHT, THE STANDARDIZATION OF Uveitis Nomenclature (SUN) Working Group, under the leadership of Douglas A. Jabs, presents the results of a monumental, decade-long effort to define classification criteria for a wide range of uveitic conditions.[2-27] Such an endeavor has rarely been attempted in modern medicine and has not been undertaken previously in any major subspecialty of ophthalmology. The project consisted of collecting described cases (using specific descriptor terms) from a large group of uveitis specialists, determining expert consensus on features of canonical cases, and defining classification criteria based on these, followed by validation on a hold-out set of cases using machine learning techniques. The end results are criteria that can be used to define spe-

Uveitis: Clinical features

Anterior

- Visual acuity is usually good
- Circumlimbal injection
- Miosis
- Keratic precipitates/endothelial dusting
- Aqueous cells/flare

Uveitis – Grading cell

Grade	Cells in field
0	<1
1+	6-15
2+	16-25
3+	26-50
4+	>50

FRCOphth, F. M. M. J. K. J. (2007). *Clinical Ophthalmology: A Systematic Approach* (6th ed.). Butterworth-Heinemann.

Uveitis – Grading anterior chamber flare

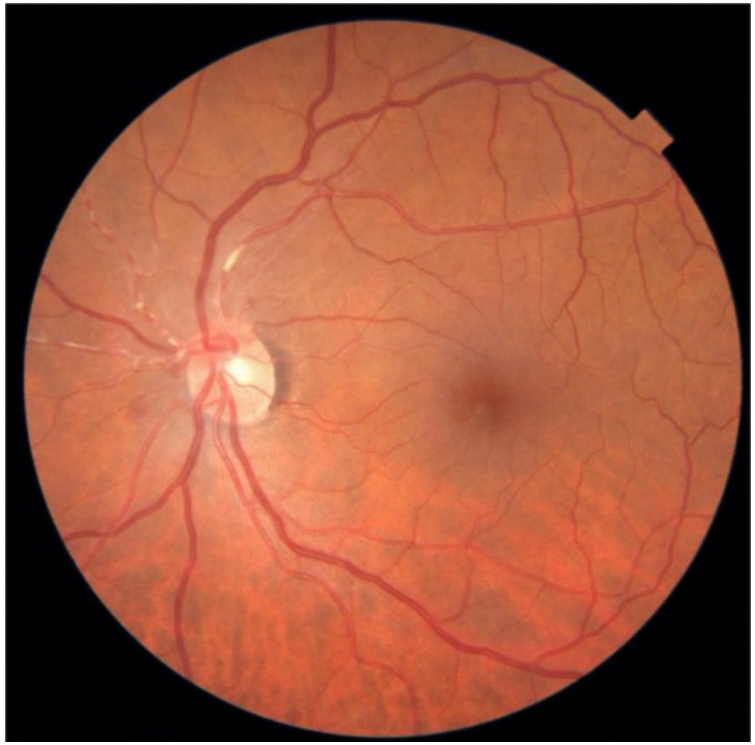
Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrous exudate present)

FRCOphth, F. M. M. J. K. J. (2007). *Clinical Ophthalmology: A Systematic Approach* (6th ed.). Butterworth-Heinemann.

Uveitis: Clinical features

Posterior

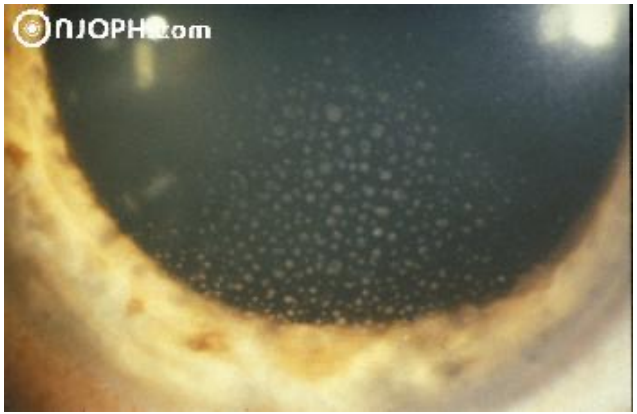
- Reduced visual acuity
- Floaters
- Retinitis
- Choroiditis
- Neuroretinitis
- Granulomas
- Vasculitis
    - Primary or secondary
    - Arteries (periarteritis) /veins (periphlebitis)



Uveitis: Clinical features - Chronic disease

Signs of chronicity

- Persistent aqueous cells and flare
- Keratic precipitates (KPs)
    - Granulomatous KPs have a greasy appearance (mutton fat) and may form in a triangle (Arlt's triangle)
    - Fine KPs (non-granulomatous) are smaller and finer deposits

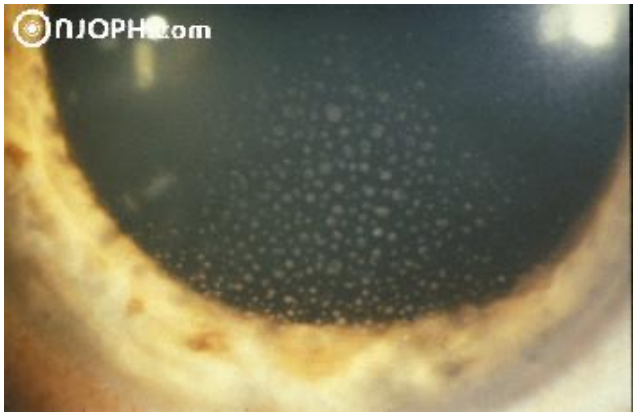


Atlas of Ophthalmology. (2001, September 19). Atlas of Ophthalmology. https://www.atlasophthalmology.net/photo.jsf?node=808&locale=en

Uveitis: Clinical features - Chronic disease

Signs of chronicity

- Posterior synechiae
- Iris nodules
- RPE hyperplasia or hypoplasia
- Fibrous bands

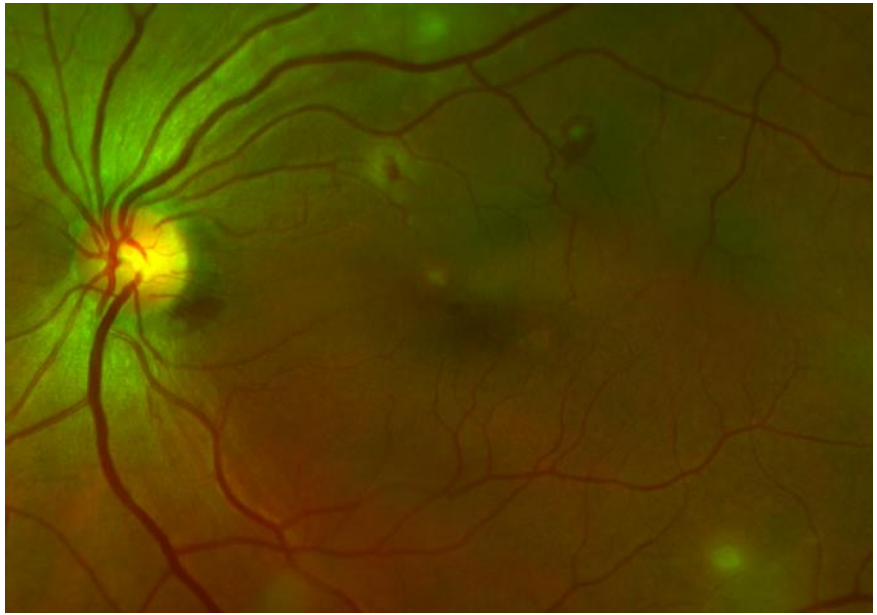


Atlas of Ophthalmology. (2001, September 19). Atlas of Ophthalmology. https://www.atlasophthalmology.net/photo.jsf?node=808&locale=en

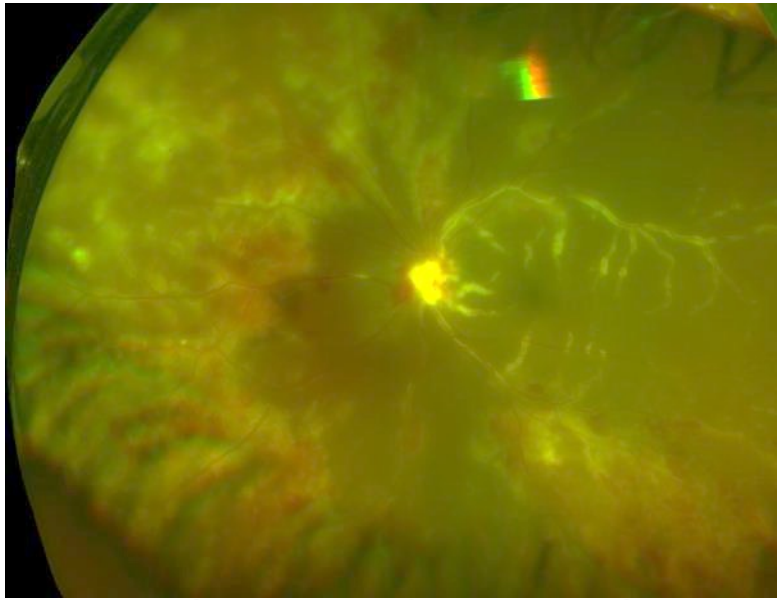
Uveitis: Vision-threatening complications

Adverse ocular sequelae

- Cataract
- Elevated intraocular pressure (IOP)
- Uveitic glaucoma
- Macular edema
- Retinal vascular occlusion
- Chorioretinal scarring
- Inflammatory optic neuropathy



Key facts: Posterior uveitis



- Posterior uveitis is the root cause of most uveitis related blindness
- Proportion of younger people affected by posterior uveitis is higher than the elderly
- Fourth leading cause of blindness of people of working age
- Early diagnosis, treatment and management is key to preservation of vision

02

Etiology

Key Categories

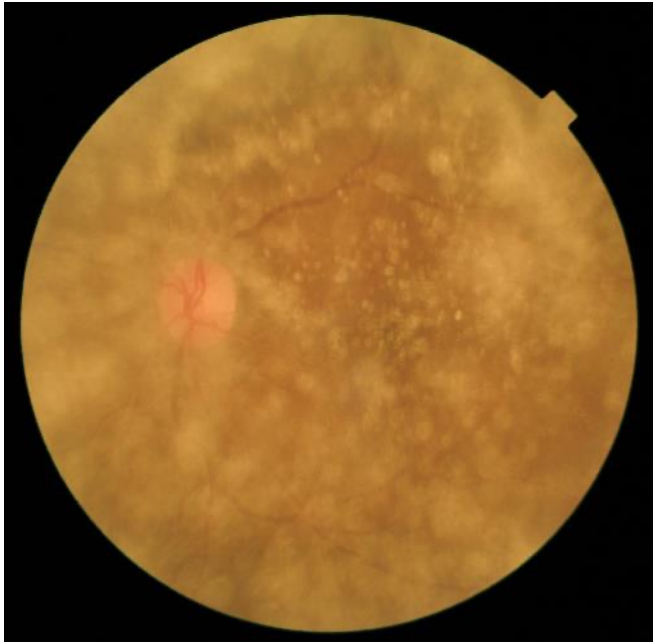
Infectious

Systemic immune mediated

Autoimmune (confined to the eye)

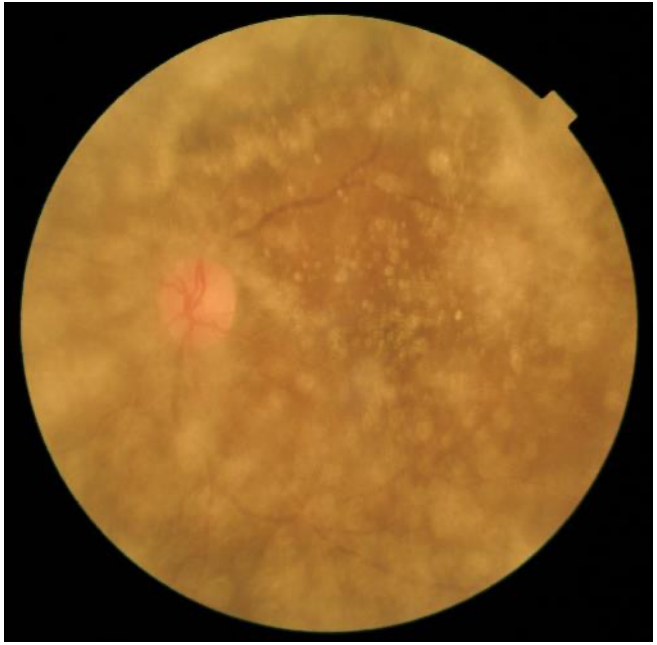
Systemic – Immune mediated

- Bechet's Disease
- Vogt-Koyanagi Harada Disease (VKH)
- Saracoidosis
- Inflammatory Bowel Disease(IBS)
- Undifferentiated spondyloarthropathies
- HLA-B27 associated diseases
  - Ankylosing spondylitis
  - Reactive arthritis**
  - Psoriatic arthritis



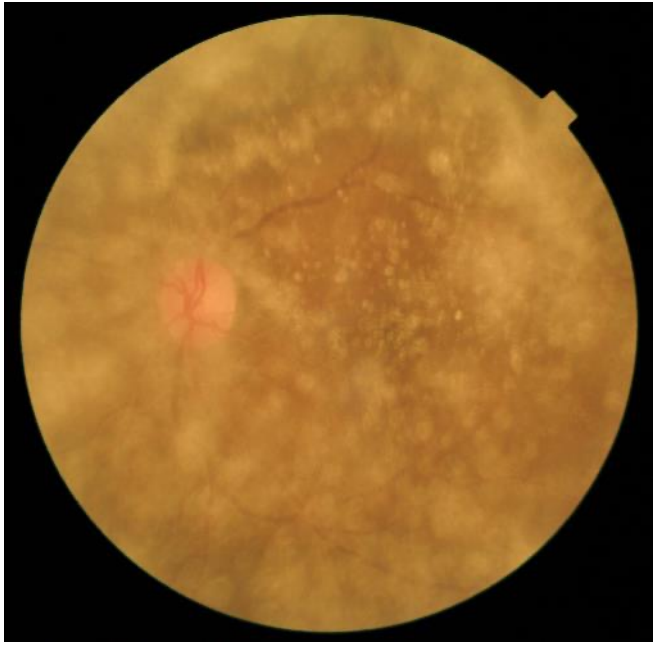
Autoimmune (confined to the eye)

- Sympathetic ophthalmia
- Birdshot chorioretinopathy
- Subretinal fibrosis and uveitis syndrome (SFU)



Autoimmune (confined to the eye)

- White dot syndromes (WDS)
  - Acute posterior multifocal placoid pigment epitheliopthy (**AMPPE**)
  - Multiple evanescent white dot syndrome (**MEWDS**)
  - Serpinginos choroiditis/Geographic helicoid peripapillary choroidopathy (**GHPC**)
  - Multifocal choroiditis (**MFC**)
  - Punctate inner choroidopathy (**PIC**)
  - Acute zonal occult outer retinopathy (**AZOOR**)



White dot syndromes:

Table 6: Comparative characteristics of clinical presentations of white dot syndrome[52]

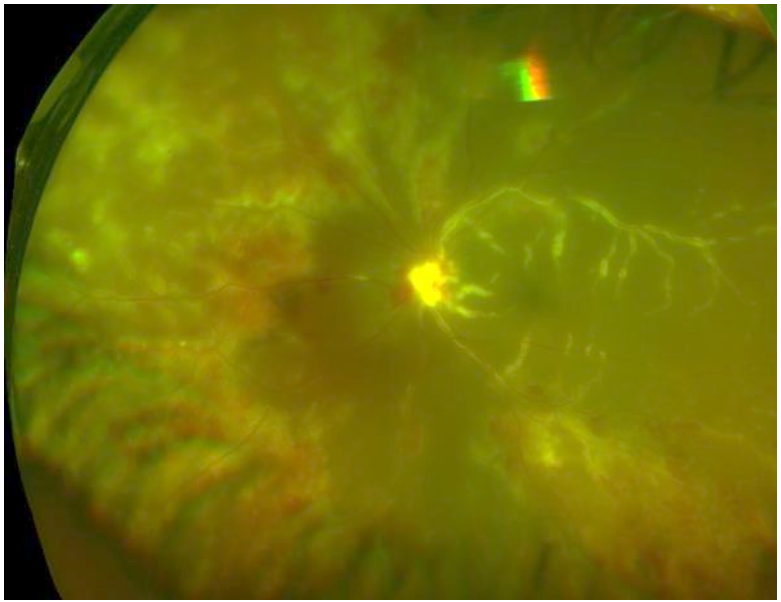
	APMPPE	Birdshot	PIC	MEWDS	MFC	GHPC	POHS
Age	Young (20–40) Rarely-children	Middle-aged (40–60)	Middle aged (myopes)	Young (20–40) myopes	Myopic (20–60)	Variable (30–60)	Middle aged
Sex	M=F	F>M	F>M	F>M	F>M	M>F	M=F
Laterality	Bilateral, asymmetric	Bilateral	Bilateral	Unilateral	Bilateral; asymmetric	Bilateral; asymmetric	Bilateral
Viral illness	+	-	+	+	+/-	-	+/-
Onset	Abrupt	Insidious	Abrupt	Abrupt	Insidious	Variable	Abrupt
Duration	Weeks–months	Chronic	Weeks–months	Weeks–months	Chronic	Chronic	Chronic
Recurrence	Rare	Recurrent	Recurrent	Rare	Recurrent	Recurrent	Rare
Vitritis	Mild	Moderate with disc edema, CME	Absent	Mild	Moderate and anterior uveitis	Mild	Absent/mild
ERG/EOG	Abnormal EOG	Abnormal ERG	Abnormal	Abnormal ERG	Abnormal ERG	Normal	Abnormal
HLA	B7, DR2	A29	-	-	-	B7	HLA-DR2 HLA-B7
Fundus - active	Multifocal, flat gray-white placoid lesions primarily-posterior pole at the level of RPE and chorio capillaries	Multiple depigmented yellow-white patches scattered throughout fundus in the post-equatorial region. These lesions radiate from optic nerve and follow larger choroidal vessels	Multiple, discrete, flat, yellow, round lesion (50–300 microns) at the level of RPE and inner choroid. Concentrated at posterior pole	Multiple small (100–200 µ), round, slightly indistinct, white/yellow-white spots distributed over posterior fundus, especially at perifoveal and peripapillary regions at the level of RPE	Multiple yellow or gray lesions at the level of choroid and RPE. Mid periphery (50–100 µ)	Macular, peripapillary or ampigenous -irregular, gray-white or cream-yellow subretinal infiltrates at the level of the chorio-capillaries and RPE -snake-like pattern	Peripapillary atrophy, atrophic chorioretinal lesions, CNV, punched out yellow lesions Linear streaks-midperiphery
Fundus-healed	RPE clumping and hyper-pigmentation	Lesions have a hyperpigmented edge but are frequently hypopigmented in the center		Heals rarely by scarring	Punched-out atrophic scars that develop pigmentation over time	Heals from center towards periphery	Scars
Pathogenesis	DTH	Auto immune	-	?Hormonal	-	Idiopathic/ ?infective	-

Wks–Weeks, DTH–Delayed type of hypersensitivity

Sudharshan, S1; Ganesh, Sudha K1; Biswas, Jyotrimay2, Current approach in the diagnosis and management of posterior uveitis, Indian Journal of Ophthalmology: Jan–Feb 2010 - Volume 58 - Issue 1 - p 29-43

Infectious

- Toxoplasmosis
- Toxocariasis
- Lyme disease
- Tuberclosis (TB)
- Syphilis
- Cat Scratch Disease (Bartonella henselae infection)
- Viral (Herpes Simplex, Varicella zoster, CMV, HIV-associated)
- Diffuse unilteral subacute neuroretinitis (DUSN)
- Presumed ocular histoplasmosis syndrome (POHS)



03

Further testing/referral

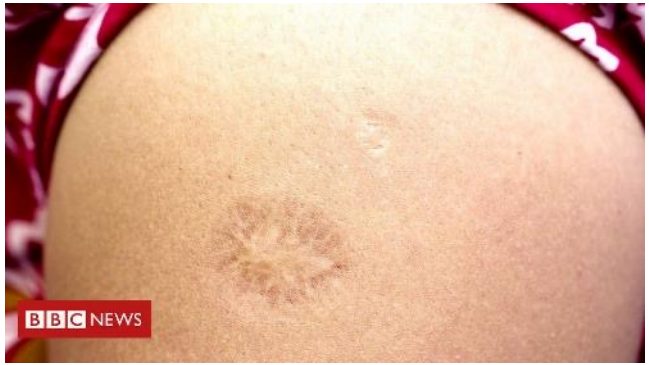
Bloodwork

- CBC with differential
- ESR (general inflammation)
- CRP (general inflammation)
- ANA (systemic immune -mediated disease)
- ANCA (systemic immune-mediated disease)
- ACE (sarcoidosis)
- Lysozyme (sarcoidosis)
- Lyme titers
- RPR, VDRL (syphilis – non-treponemal)
- FTA-abs, MHA-TP (treponemal)

Testing for tuberculosis

- Purified Protein Derivative (PPD)/Mantoux/Tuberculin skin test
- Quantiferon Gold

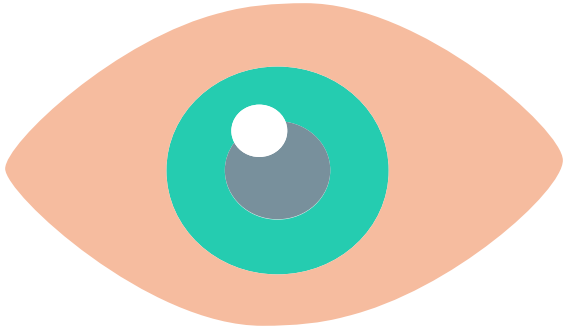
Should you perform PPD or QuantiFERON gold?



Radiology and other testing

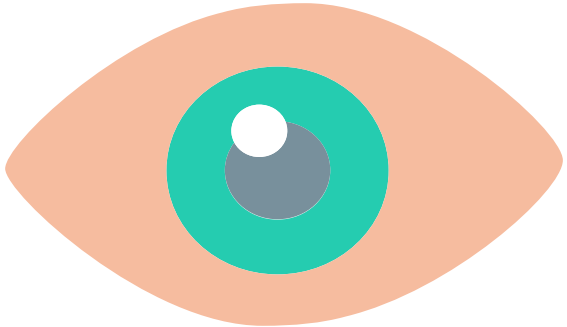
- Chest x-ray (TB, sarcoidosis)
- Spinal x-ray (spondyloarthropathy)
- CT brain
- MRI of the brain and/or optic nerve (syphilis, primary intraocular lymphoma, optic nerve involvement)

Auxillary eye testing



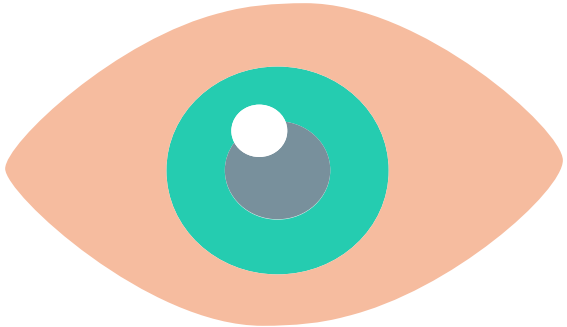
- Fundus photography
- Bscan
- Optical coherence tomography (OCT)
  - Vitritis
  - Retinal inflammatory lesions
  - Macular edema
  - Optic nerve disease
  - Choroidal pathology
  - En Face
  - OCTA

Auxillary eye testing



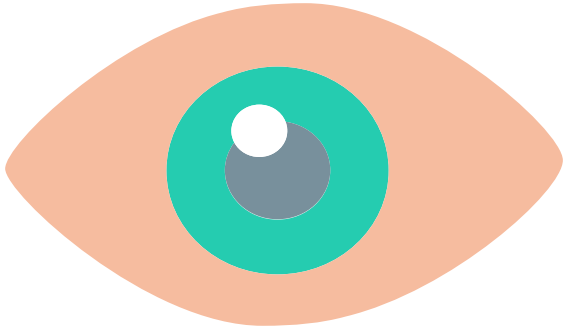
- Fluorescein angiography (FA)
    - Retinal vasculitis
    - Macular edema
    - Macular ischemia
    - Differentiation between inflammatory and ischemic disease
    - Detection of choroidal neovascular membrane (CNV)

Auxillary eye testing



- Indocyanine green angiography (ICG)
    - Choroidal disease (WDS)
- Intravitreal biopsy

Tips for Testing and Co-management



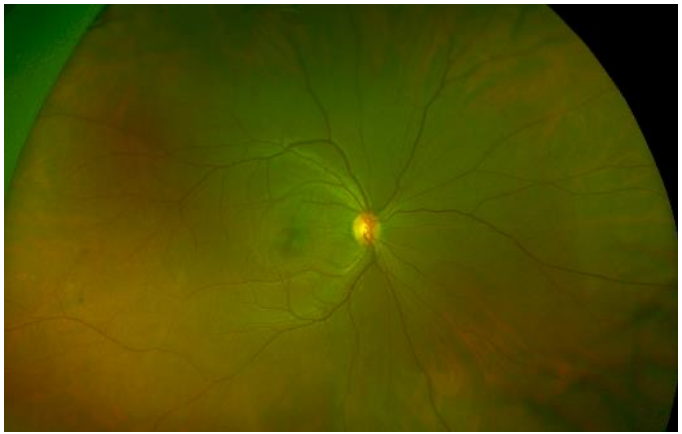
- Take detailed case history
- Dilate every patient with anterior uveitis
- Clearly document and take retinal images
- Order blood work
  - Consider testing to rule out TB early
- Proper referral (retina, rheumatology, etc)
- Consider referral to uveitis specialist the presentation is atypical or if the condition is non-resolving

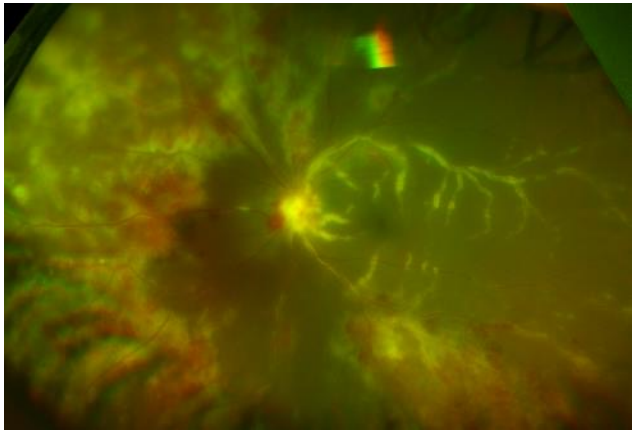
04

Cases

Patient #1

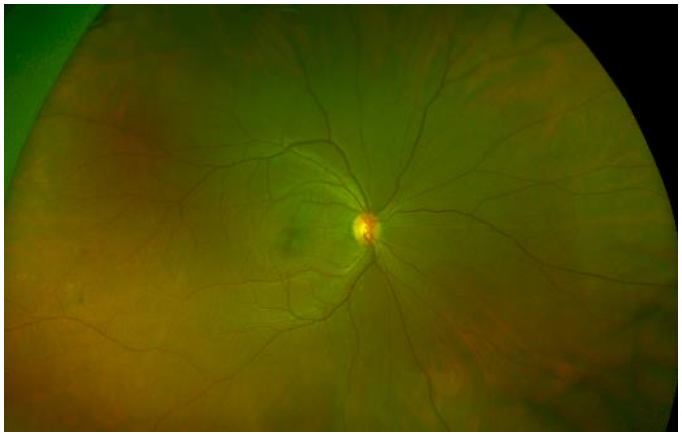
- 32 year old female patient

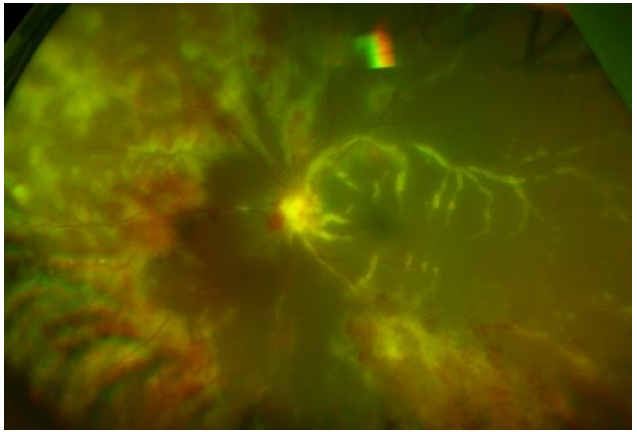




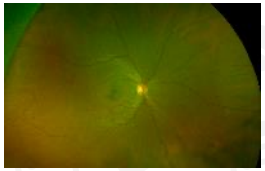
- Clue: Medical history – very low CD4 count

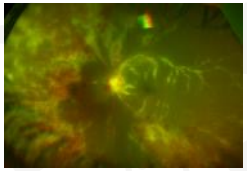
Cytomegalovirus (CMV) Retinitis





Cytomegalovirus (CMV) Retinitis





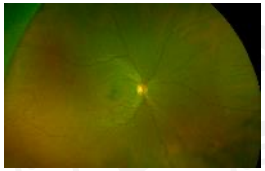
Cause: Cytomegalovirus
Risk factors:

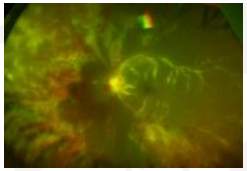
- Immunocompromised status (i.e., AIDs, post organ transplant patient)
- CD4 count <50 cells/ul

Clinical Presentation: hemorrhagic or granular appearance to the retina; wedged-shaped necrotizing retinitis with little to no vitritis

Diagnostic criteria: immune compromise, evidence of CMV retinal infection based on PCR assay or characteristic retinal appearance

Cytomegalovirus (CMV) Retinitis





Cause: Cytomegalovirus
Risk factors:

- Immunocompromised status (i.e., AIDs, post organ transplant patient)
- CD4 count <50 cells/ul

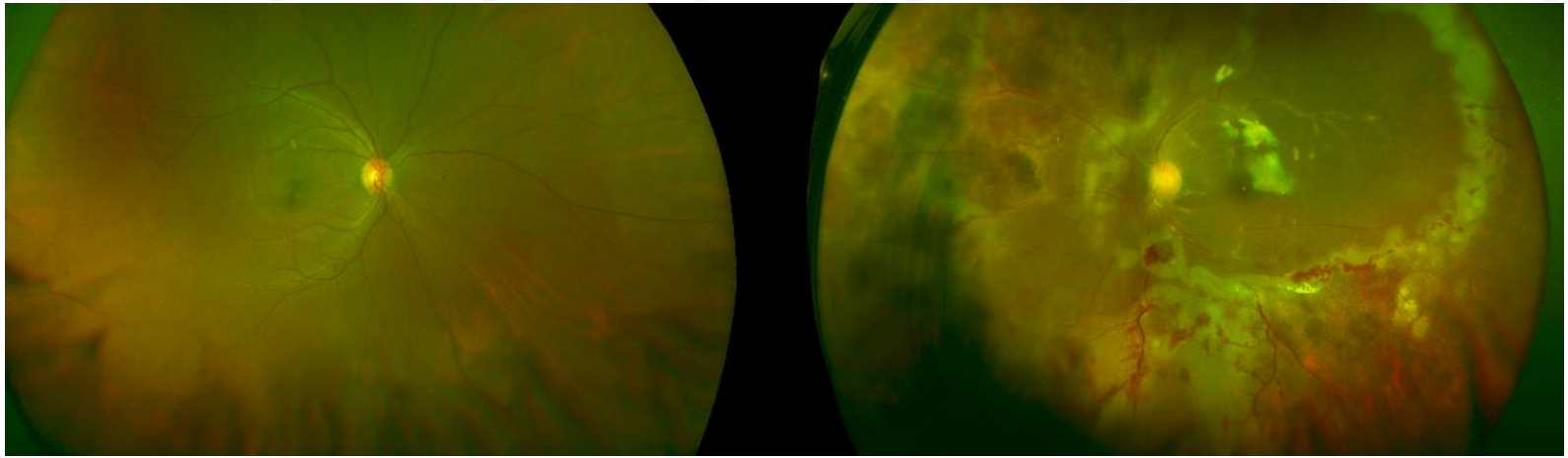
Treatment: Intravenous ganciclovir 5-7mg/kg/day – alternative intravenous foscarnet, intravenous cidoforvir

- Intravitreal injections of ganciclovir or foscarnet considered

** better control of immune disease**

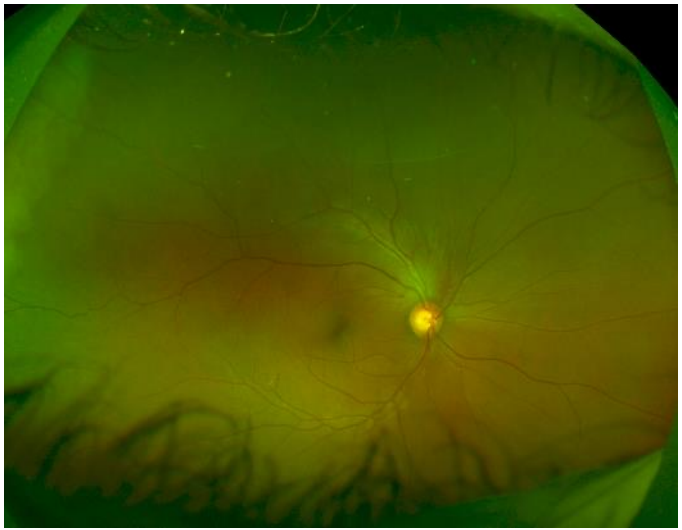
Cytomegalovirus (CMV) Retinitis

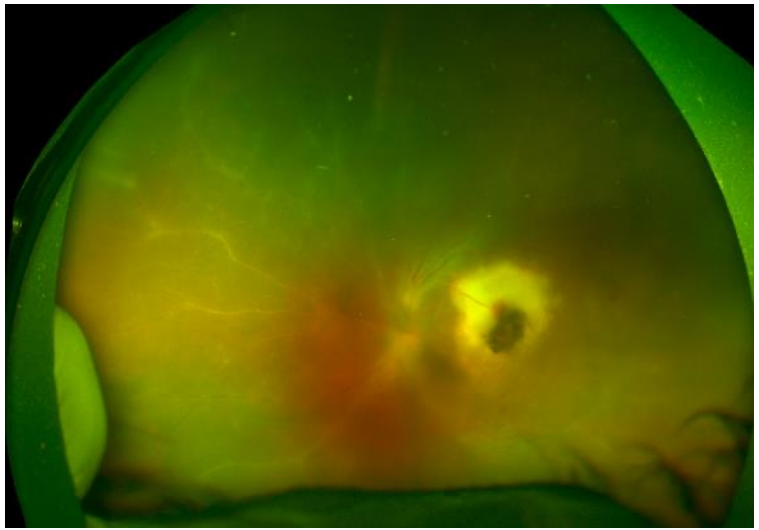
- One month after initial treatment (intravenous and intravitreal ganciclovir



Patient #2

- 26-year-old male patient

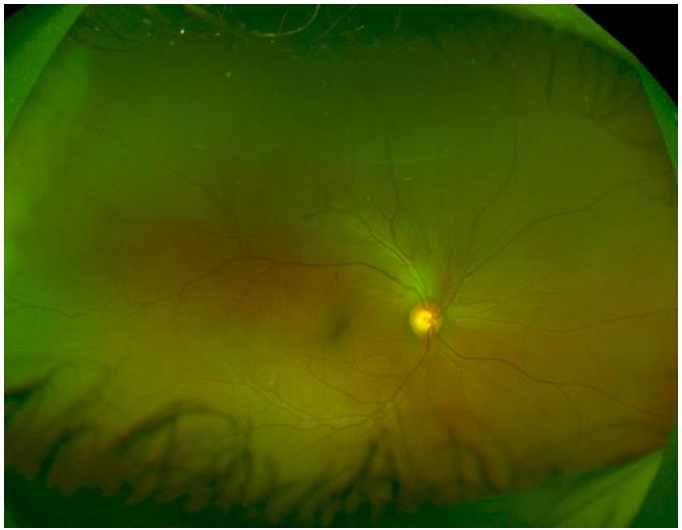


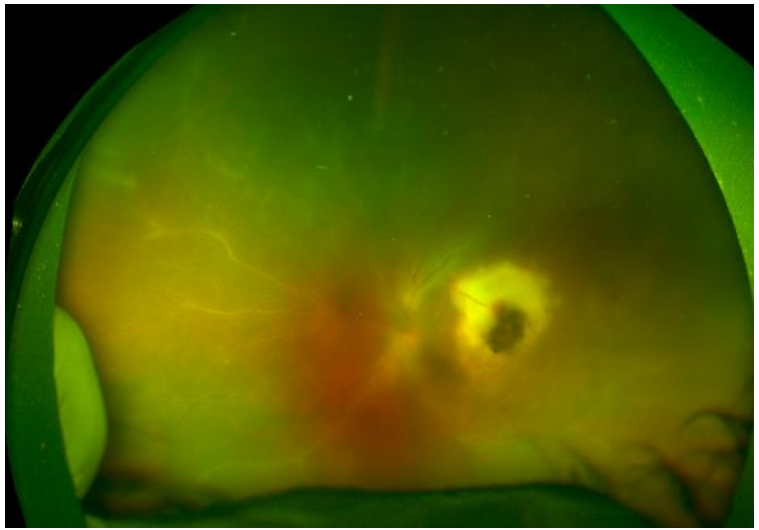


Patient had other peripheral scars in the retina

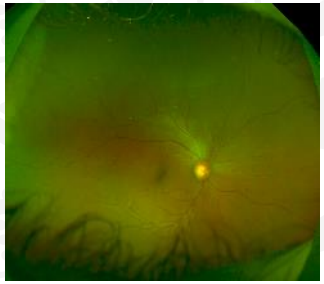
Ocular toxoplasmosis

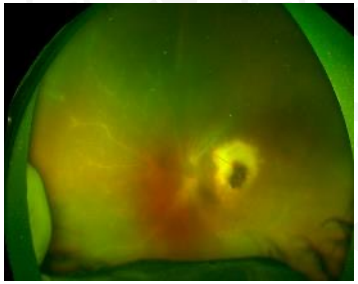
- 26 year old male patient





Ocular toxoplasmosis



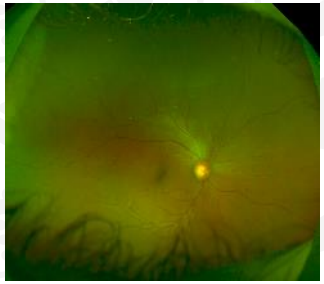


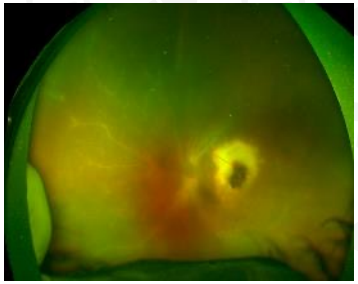
Cause: parasite *Toxoplasma gondii*
Risk factors:

- Positive history of contact with cats/dogs
- Ingestion of raw, undercooked meat or contaminated water
- Transplacental (congenital form)

Clinical Presentation: hyperpigmented and/or atrophic scar with rounded area of active retinitis or recurrent area of retinitis

Ocular toxoplasmosis





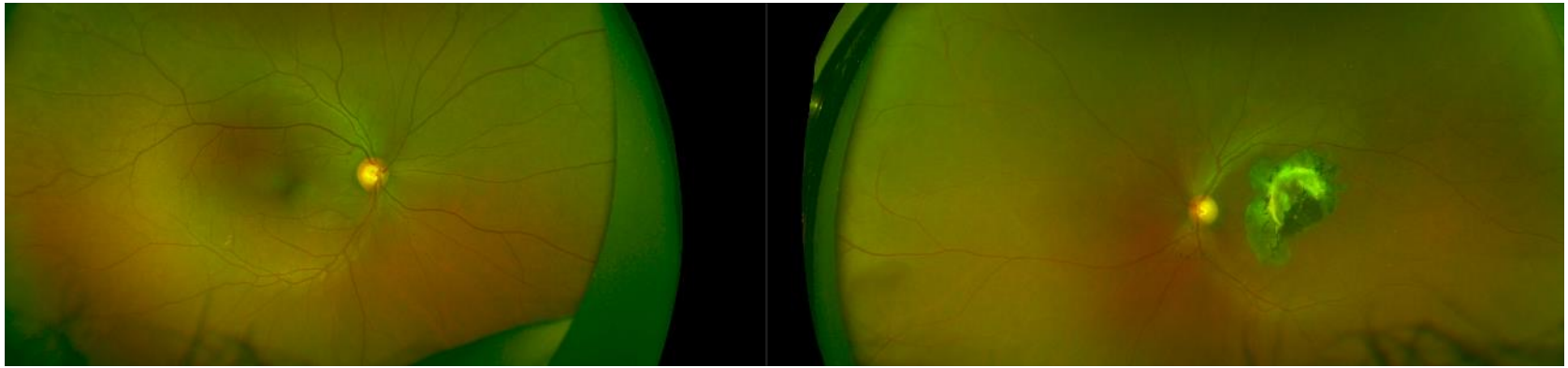
Diagnostic criteria: unifocal or panfocal active retinitis with either evidence of infection with T. gondii or the classic clinical picture

Treatment: retinal lesions are self-limited in immunocompetent patients

- Pyrimethamine + Sulfadiazine
- Systemic corticosteroid
- Folic acid supplement
- Topical cycloplegic or steroid for associated anterior uveitis

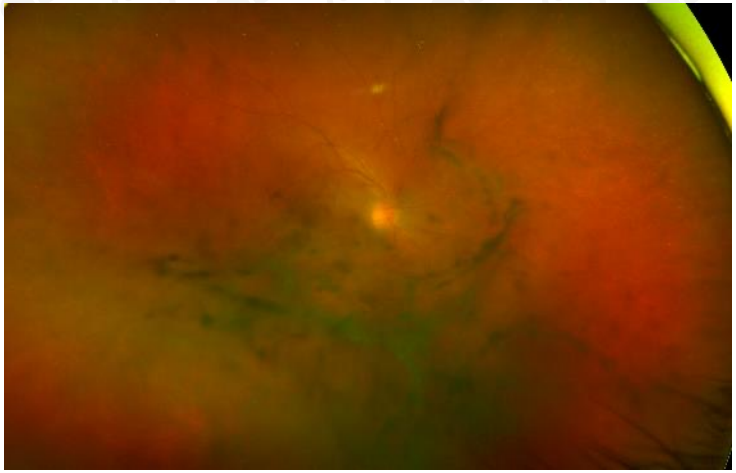
Ocular toxoplasmosis

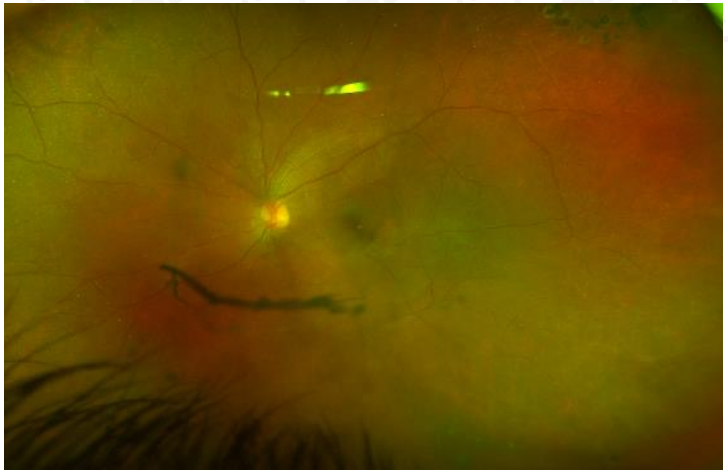
- One year after initial examination



Patient #3

43 year old male patient

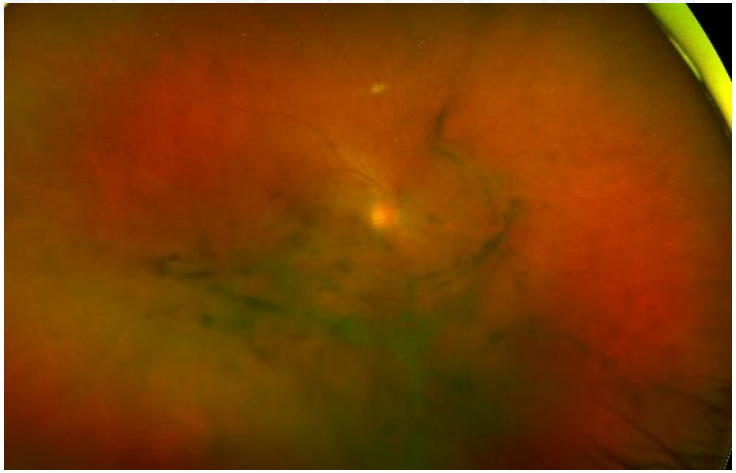


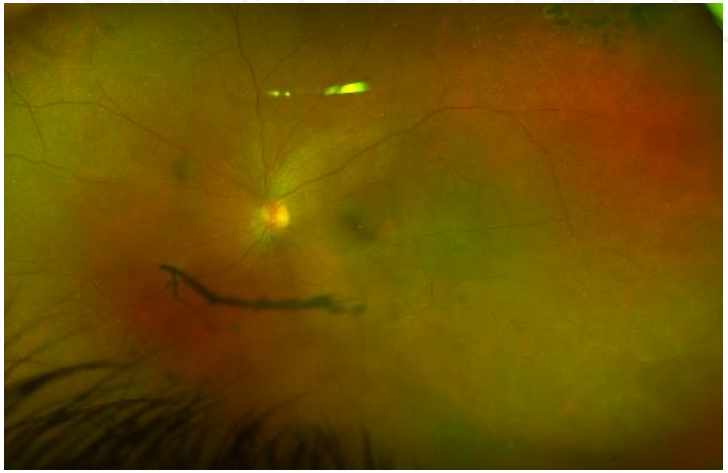


Had a history of contracting a sexually transmitted disease

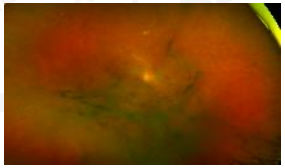
Syphilitic Posterior Uveitis

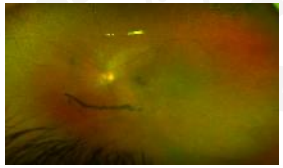
43 year old male patient





Syphilitic Posterior Uveitis





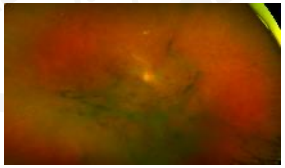
Cause: spirochete *Treponema pallidum*
Associated findings:

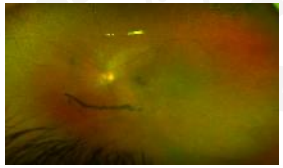
- Genital ulcers
- Disseminated rash
- Fever, fatigue, myalgia

Clinical Presentation:

- anterior uveitis
- placoid inflammation of the retinal pigment epithelium (RPE)
- necrotizing retinitis
- multifocal inflammation of the retina and or RPE, retinal vasculitis/retinal vascular sheathing and/or leakage

Syphilitic Posterior Uveitis





Diagnostic criteria: Uveitis with compatible uveitis presentation including:

- Anterior and/or intermediate and/or posterior uveitis with one of the aforementioned retinal presentations

AND

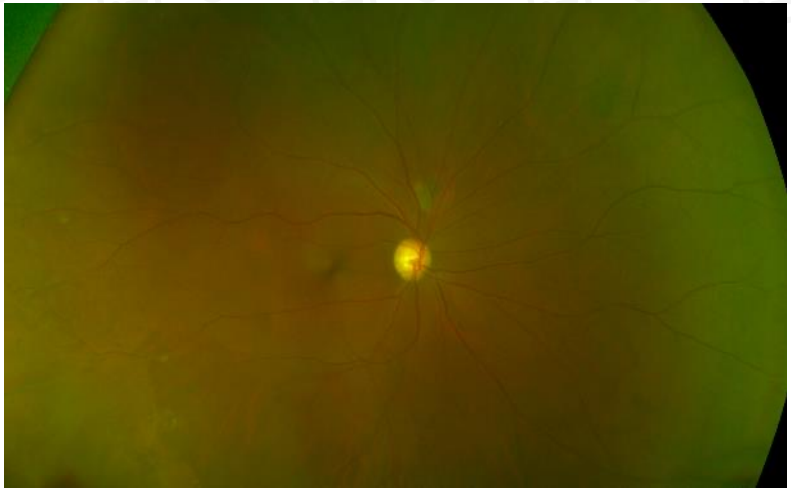
- Evidence of infection with Treponema pallidum by positive treponemal test (FTA-ABS, MHA-TP) and nontreponemal test (VDRL, RPR) or// positive treponemal test with two different non treponemal tests

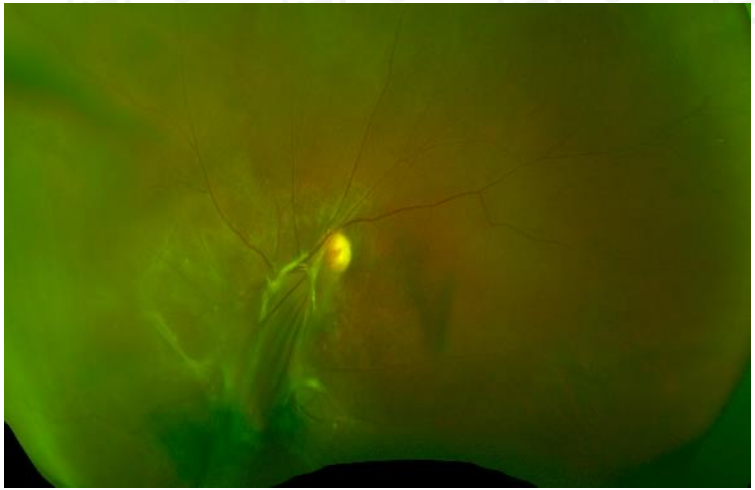
Treatment: long-acting intravenous penicillin

- Patients should also have a lumbar puncture to rule out neurosyphilis

Patient #4

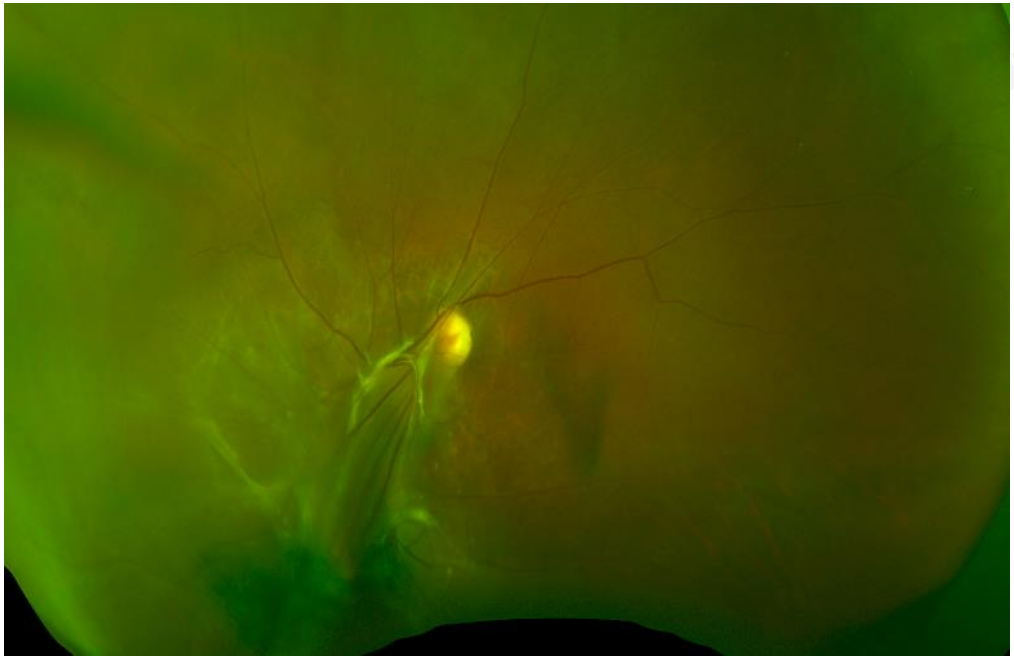
21 year old female patient



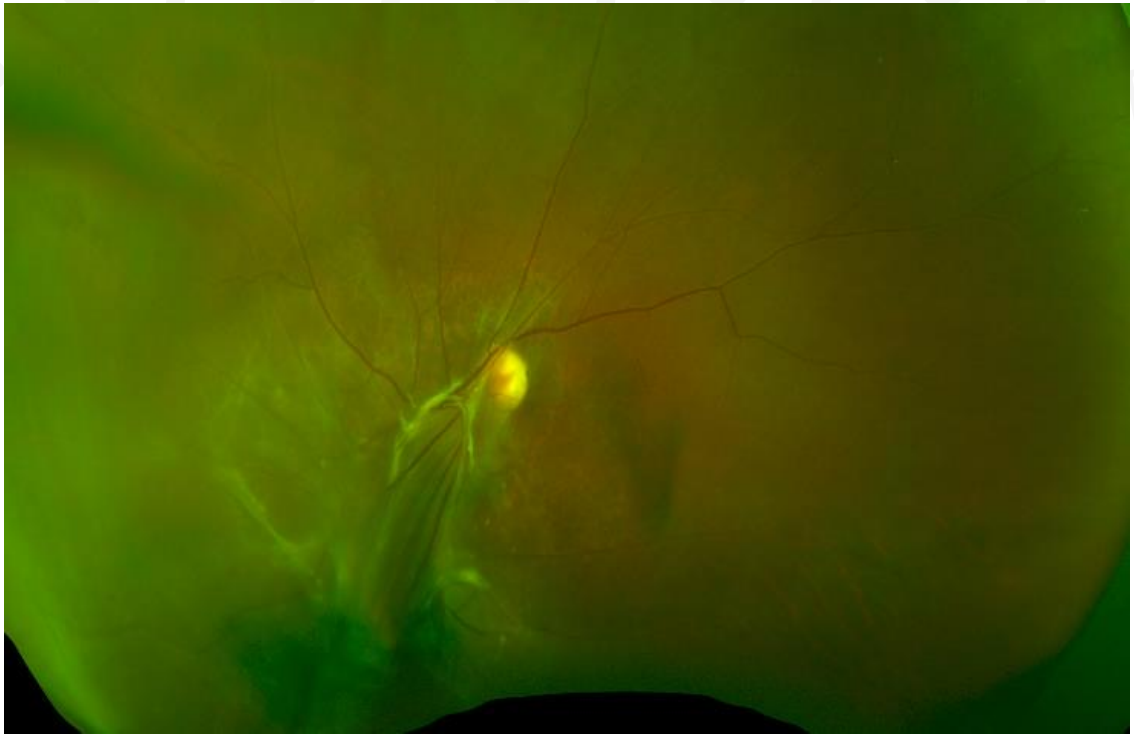


Patient suffered from pica

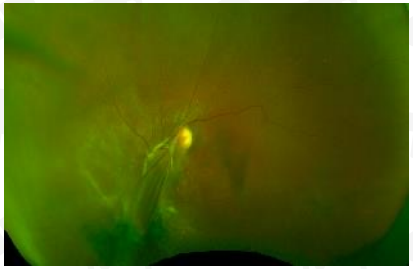
Patient #4



Ocular toxocariasis



Ocular toxocariasis



Cause: parasite *Toxocara canis*
Risk factors:

- Positive history of contact with feces of infected animas
- Ingestion of undercooked meat

Clinical Presentation: unilateral posterior pole granuloma with whitish inflammatory mass without pigmentation, vitritis, peripheral granuloma, localized traction

Diagnostic criteria: classic clinical picture , presence of serum antibody to Toxocara larvae

Treatment: topical and systemic corticosteroids

- Use of anthelmintic drugs are controversial (Albendazole)

05

New Treatments & Take-aways

New Treatments for non-infectious uveitis

Current therapy

Corticosteroids

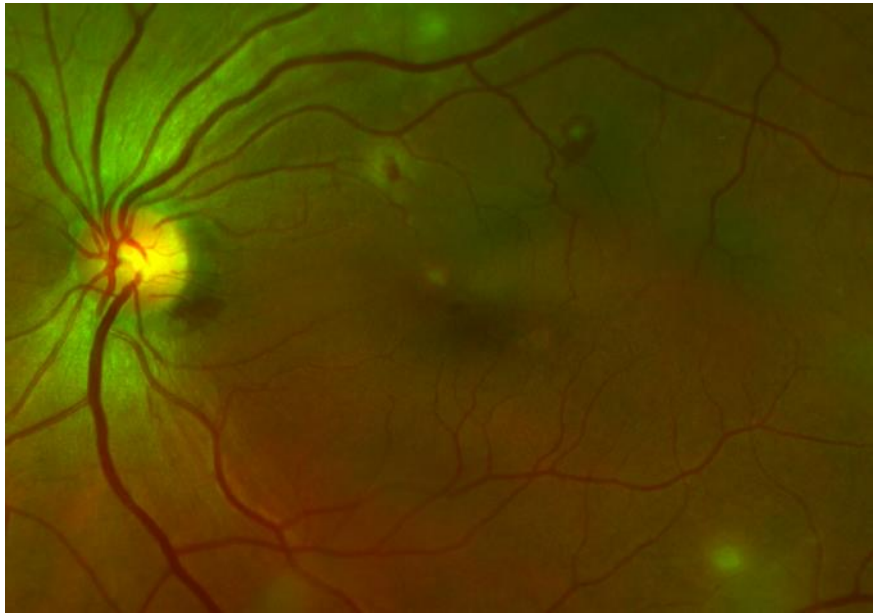
Newer directions

- Intravitreal therapies
- Systemic bDMARDs
- Future anti-inflammatory treatments

Newer directions

Intravitreal implants

- Retisert (fluocinolone acetonide)
- Vitrasert (ganciclovir)
- Ozurdex (dexamethasone)
- Iluvien (fluocinolone acetonide)
- Serolimus (submitted for approval)



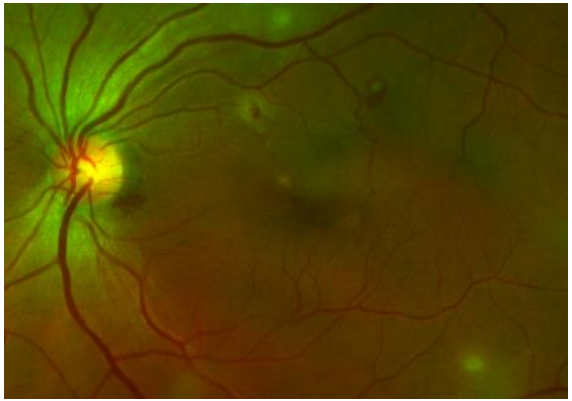
Newer directions

Disease modifying antirheumatic Drugs - nonbiologic

Antimetabolites
- Methotrexte, azathioprine, mycophenolate

Calcineurin inhibitor
- Ciclosporine A, tacrolius

Alkylating
- Cyclophosphamide
- Chlorambucil

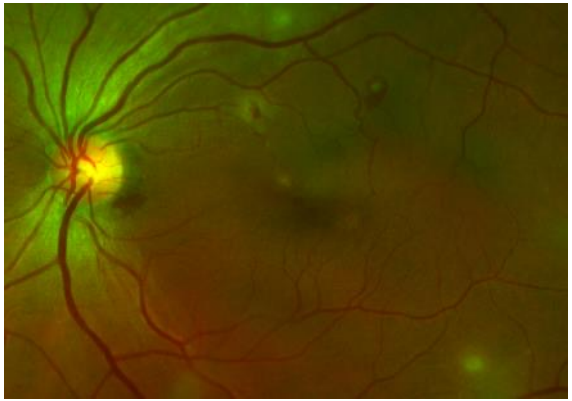


Newer directions

Disease modifying antirheumatic Drugs - biologic

Anti Tumor Necrosis Factor (TNF)-alpha

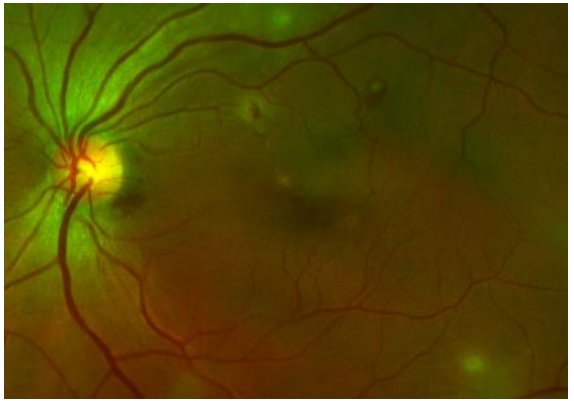
- Etanercept
- Infliximab
- Adalimumab
- Rituximab
- Golimumb
- certolizumab



Newer directions

Future therapies

- Gene therapy
- Mesenchymal stem cells



UVEITIS: ETIOLOGY

Systemic immune mediated

- Ankylosing Spondylitis
- Reactive Arthritis (Reiter's disease)
- Psoriatic Arthritis
- Spondylitis associated with Inflammatory Bowel Disease (IBS)
- Isolated acute anterior uveitis
- Undifferentiated spondyloarthropathies
- Bechet's Disease
- Vogt-Koyanagi Harada Disease (VKH)

Autoimmune confined to the eye

- Sympathetic Ophthalmia
- Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)
- Birdshot Chorioretinopathy
- Multifocal Choroiditis and Panuveitis
- Multiple Evanescent White Dot Syndrome (MEWDS)
- Punctate Inner Choroiditis (PIC)
- Serpiginous Choroiditis
- Acute Zonal Occult Outer Retinopathy (AZOOR)

Infectious

- Lyme disease
- Presumed Ocular Histoplasmosis Syndrome (POHS)
- Syphilis
- Toxocariasis
- Toxoplasmic chorioretinitis
- Tuberculosis (TB)

White dot syndromes:

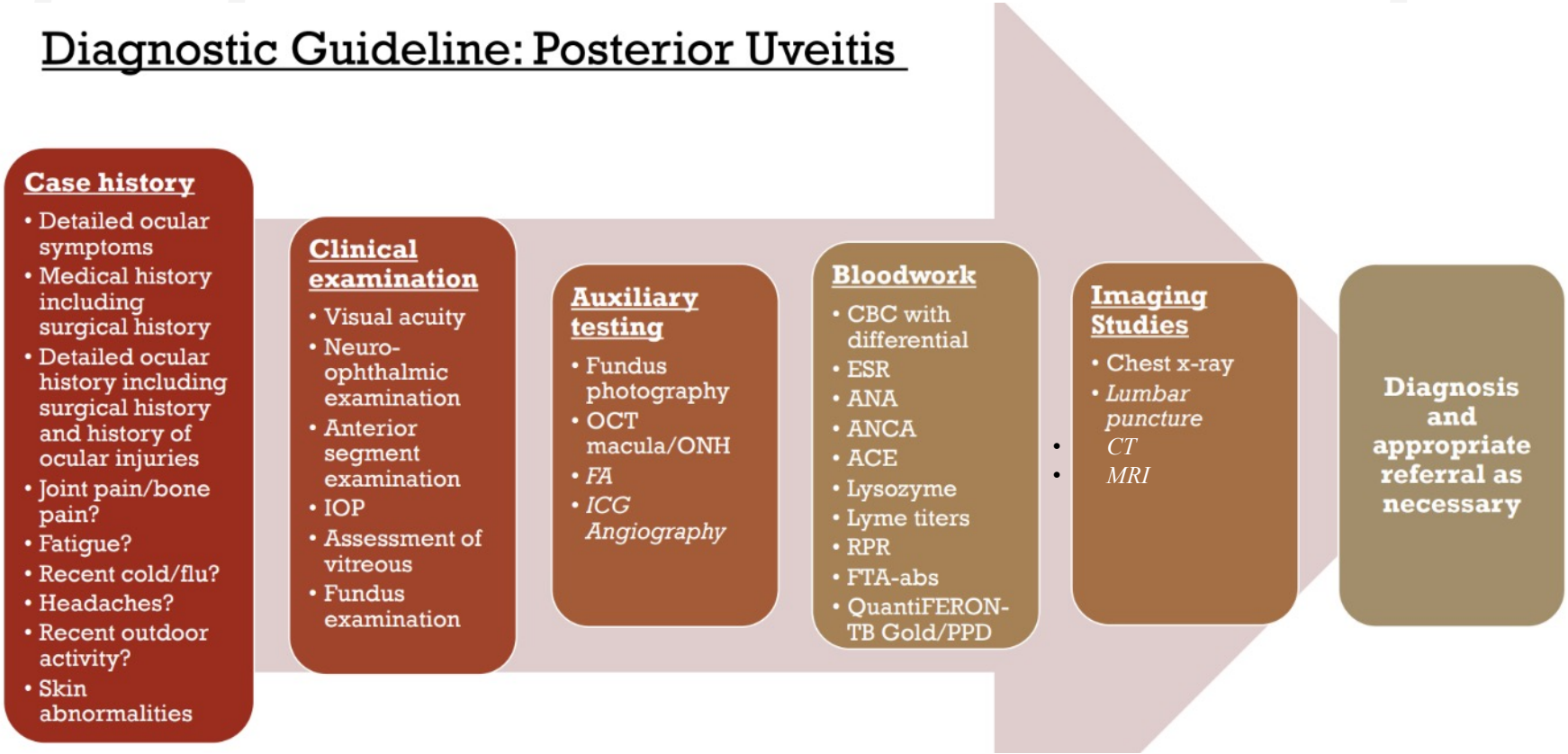
Table 6: Comparative characteristics of clinical presentations of white dot syndrome[52]

	APMPPE	Birdshot	PIC	MEWDS	MFC	GHPC	POHS
Age	Young (20–40) Rarely-children	Middle-aged (40–60)	Middle aged (myopes)	Young (20–40) myopes	Myopic (20–60)	Variable (30–60)	Middle aged
Sex	M=F	F>M	F>M	F>M	F>M	M>F	M=F
Laterality	Bilateral, asymmetric	Bilateral	Bilateral	Unilateral	Bilateral; asymmetric	Bilateral; asymmetric	Bilateral
Viral illness	+	-	+	+	+/-	-	+/-
Onset	Abrupt	Insidious	Abrupt	Abrupt	Insidious	Variable	Abrupt
Duration	Weeks–months	Chronic	Weeks–months	Weeks–months	Chronic	Chronic	Chronic
Recurrence	Rare	Recurrent	Recurrent	Rare	Recurrent	Recurrent	Rare
Vitritis	Mild	Moderate with disc edema, CME	Absent	Mild	Moderate and anterior uveitis	Mild	Absent/mild
ERG/EOG	Abnormal EOG	Abnormal ERG	Abnormal	Abnormal ERG	Abnormal ERG	Normal	Abnormal
HLA	B7, DR2	A29	-	-	-	B7	HLA-DR2 HLA-B7
Fundus - active	Multifocal, flat gray-white placoid lesions primarily-posterior pole at the level of RPE and chorio capillaries	Multiple depigmented yellow-white patches scattered throughout fundus in the post-equatorial region. These lesions radiate from optic nerve and follow larger choroidal vessels	Multiple, discrete, flat, yellow, round lesion (50–300 microns) at the level of RPE and inner choroid. Concentrated at posterior pole	Multiple small (100–200 μ), round, slightly indistinct, white/yellow-white spots distributed over posterior fundus, especially at perifoveal and peripapillary regions at the level of RPE	Multiple yellow or gray lesions at the level of choroid and RPE. Mid periphery (50–100 μ)	Macular, peripapillary or ampigenous -irregular, gray-white or cream-yellow subretinal infiltrates at the level of the chorio-capillaries and RPE -snake-like pattern	Peripapillary atrophy, atrophic chorioretinal lesions, CNV, punched out yellow lesions Linear streaks-midperiphery
Fundus-healed	RPE clumping and hyper-pigmentation	Lesions have a hyperpigmented edge but are frequently hypopigmented in the center		Heals rarely by scarring	Punched-out atrophic scars that develop pigmentation over time	Heals from center towards periphery	Scars
Pathogenesis	DTH	Auto immune	-	?Hormonal	-	Idiopathic/ ?infective	-

Wks–Weeks, DTH–Delayed type of hypersensitivity

Sudharshan, S1; Ganesh, Sudha K1; Biswas, Jyotrimay2, Current approach in the diagnosis and management of posterior uveitis, Indian Journal of Ophthalmology: Jan–Feb 2010 - Volume 58 - Issue 1 - p 29-43

Diagnostic Guideline: Posterior Uveitis



Thanks!

Do you have any questions?
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