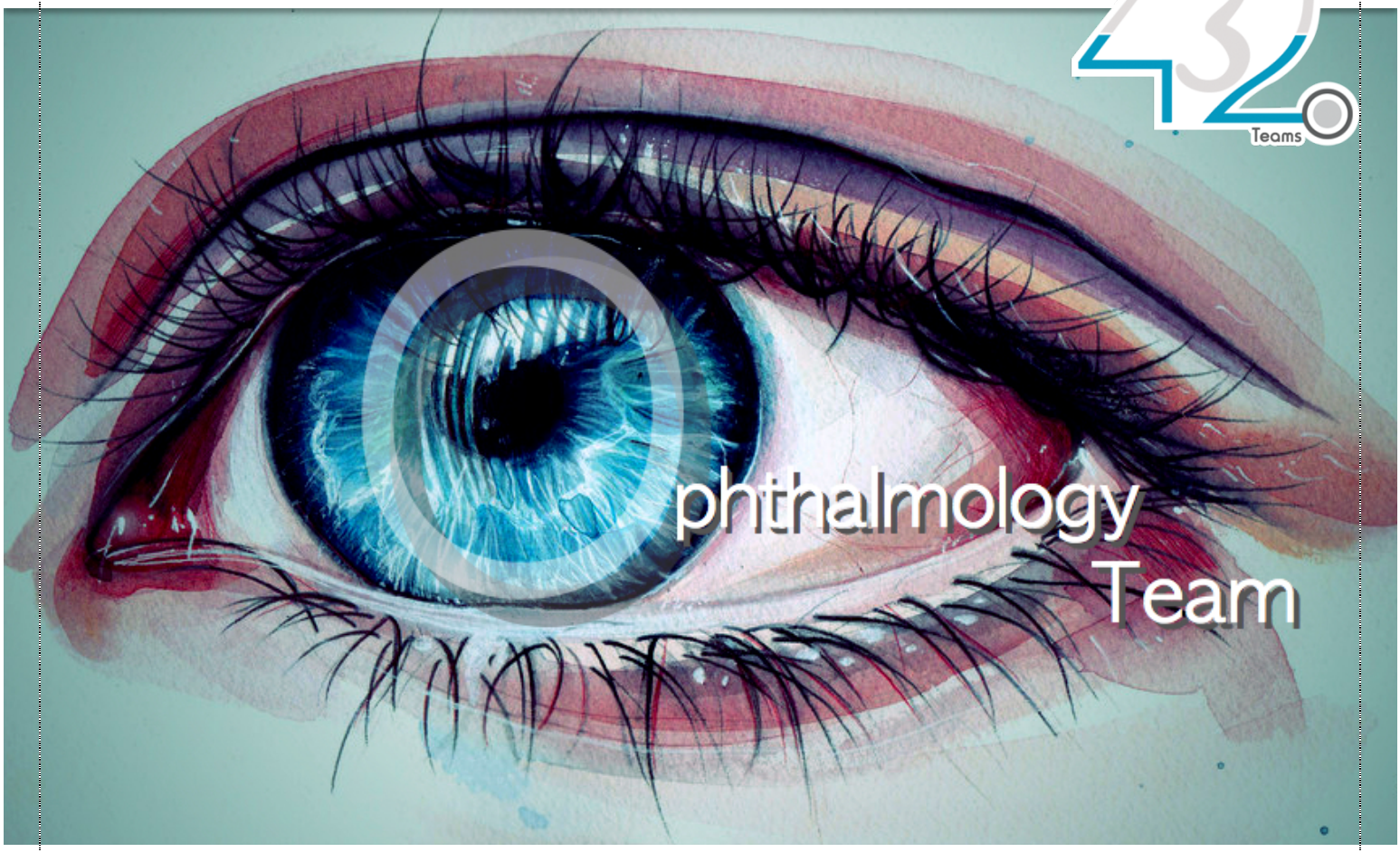


#11- Ocular Manifestation of Systemic Diseases

Done by: Tahani AlShaibani & Reem AlRakaf

Revised by: Sarah Al-Essa

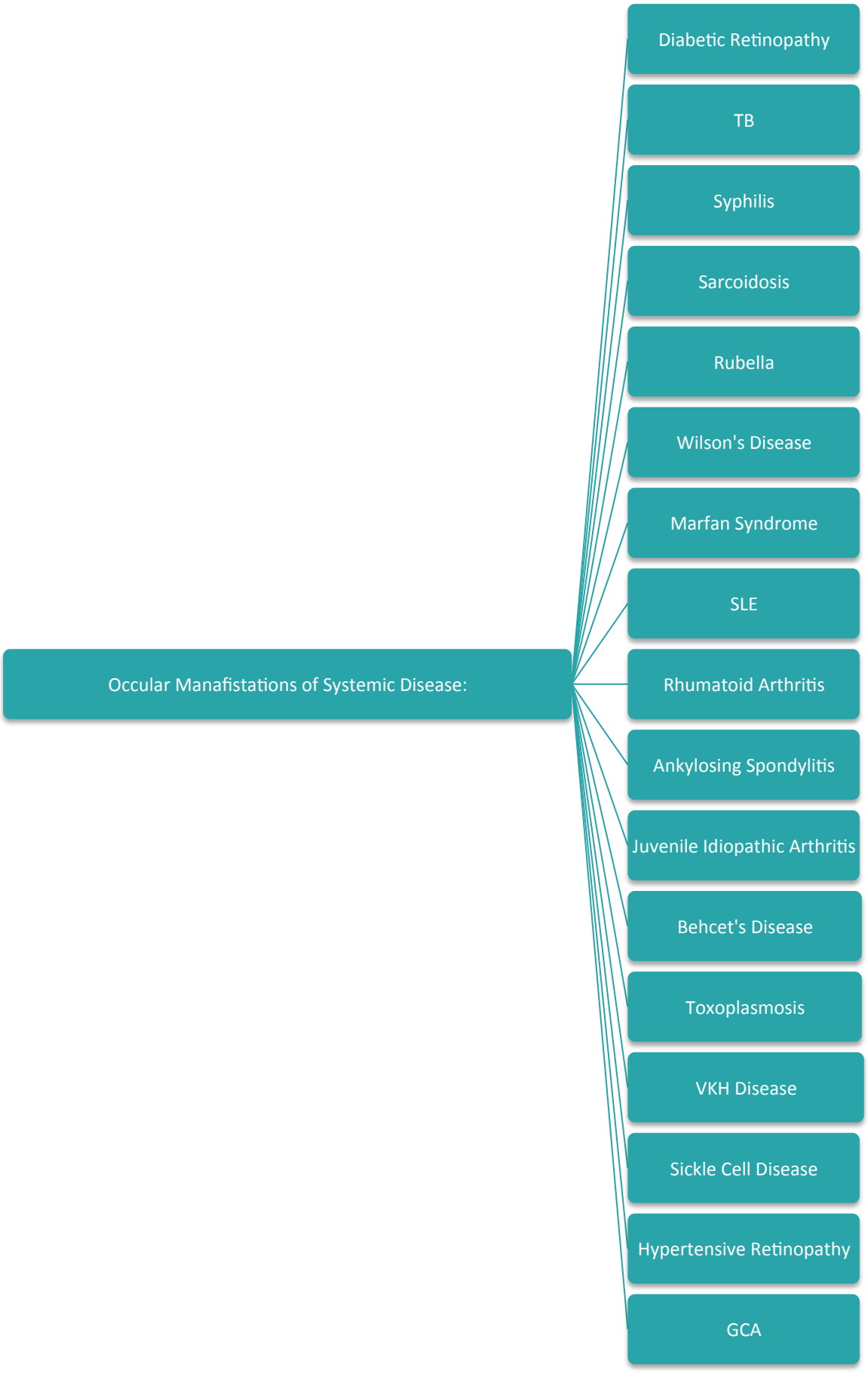
Team Leader: *Shaikha Aldossari*

Doctor's note **Team's note** **Not important**
Important **431 teamwork in a yellow box**

Objectives:

Not given ☹

The doctor did not provide the slides; we tried out best to write down everything mentioned during the lecture. The pictures in this document are photos taken from the lecture. Our main reference was Kanski Clinical Ophthalmology.
We advise reading the topics from Kanski and looking at the pictures there.


Occular Manafistations of Systemic Disease:
Diabetic Retinopathy
TB
Syphilis
Sarcoidosis
Rubella
Wilson's Disease
Marfan Syndrome
SLE
Rhumatoid Arthritis
Ankylosing Spondylitis
Juvenile Idiopathic Arthritis
Behcet's Disease
Toxoplasmosis
VKH Disease
Sickle Cell Disease
Hypertensive Retinopathy
GCA

Diabetic Retinopathy (DR):

Introduction:

- Systemic diseases involved in Retina can lead to blindness. This can be prevented by early treatment and control of the systemic diseases.
- The most common disease that involved the eye (particularly Retina) is DIABETES.
- The risk of related visual loss in people with diabetes is up to 25 times higher than the population not affected by diabetes.
- The most important/strongest risk for developing diabetic retinopathy is the duration of the disease.
- Diabetic eye disease comprises a group of eye conditions that affect people with diabetes. These conditions include diabetic retinopathy, diabetic macular edema (DME), cataract, and glaucoma.
- All forms of diabetic eye disease have the potential to cause severe vision loss and blindness.
- Diabetic retinopathy involves changes to retinal blood vessels that can cause them to bleed or leak fluid, distorting vision.
- Diabetic retinopathy is the most common cause of vision loss among people with diabetes and a leading cause of blindness among working-age adults (20-65 years).
- Diabetic macular edema is a consequence of diabetic retinopathy that causes swelling in the area of the retina called the macula.
- Controlling diabetes—by taking medications, staying physically active, and maintaining a healthy diet—can prevent or delay vision loss.
- Because diabetic retinopathy often goes unnoticed until vision loss occurs, people with diabetes should get a comprehensive dilated eye exam at least once a year.
- Early detection, timely treatment, and appropriate follow-up care of diabetic eye disease can protect against vision loss.
- Diabetic retinopathy can be treated with several therapies, used alone or in combination.
- Diabetic retinopathy is more common in type 1 diabetes than in type 2.

- Patients with diabetes can have ocular manifestation other than diabetic retinopathy, like: cataract, very sever type of glaucoma, retinopathy, optic nerve dysfunction, and 3rd and 4th and 6th nerve palsies.

Ophthalmic complications of diabetes:

• Common

- Retinopathy.
- Iridopathy (minor iris transillumination defects).
- Unstable refraction.

• Uncommon

- Recurrent styes.
- Xanthelasma.
- Accelerated senile cataract.
- Neovascular glaucoma (NVG).
- Ocular motor nerve palsies (3rd,4th,6th).
- Reduced corneal sensitivity.

• Rare

- Papillopathy, pupillary light-near dissociation.
- Wolfram syndrome (progressive optic atrophy and multiple.
- Neurological and systemic abnormalities, acute-onset.
- Cataract, rhino-orbital mucormycosis.

Risk Factors:

1- Duration of diabetes (non-modifiable risk factor): The longer the duration of diabetes, the more risk of DR (By 15 years of diabetes, almost all patients come with DR).
2- Poor control of diabetes (most important modifiable risk factor).
3- Pregnancy **(poor pre-pregnancy control, too rapid tightening of control during early stages).**
4- Hypertension.
5- Nephropathy (if sever, it is associated with worsening of retinopathy).

6- Others: Hyperlipidemia, smoking, cataract surgery, obesity and anemia.

Pathogenesis:

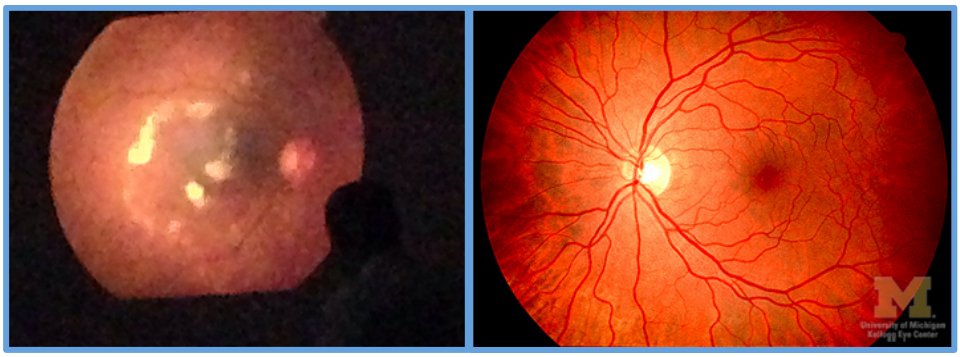
Development of progressive vasculopathy characterized by dysfunction of endothelial cells lining retinal capillaries and the loss of the inner Blood-Retina-barrier. The inner Blood-Retina-barrier contains tight-junctions that reduce the space between adjacent endothelial cells lining the fine capillaries of the retinal microvasculature to form a selective and regulatable barrier. So, if there is a breakdown of the blood-retinal barrier, which normally prevents water movement in the retina, fluid (lipoprotein) will accumulate in the retinal tissue leading to macular edema, thickening and swelling which distorts central vision.

This will also result in the occlusion of the capillaries causing to hypoxia and ischemia. The retina will react by producing angiogenesis factors like the Vascular Endothelial Growth factor (VEGF) and they will induce more breakdown of inner blood retinal-barrier (increasing the hyper permeability) and induce the formation of new vessels.

At this stage of new vessels, the disease called proliferative disease. These new vessels are not healthy; they can bleed causing loss the vision from hemorrhage in the eye (Vitreous hemorrhage) and can lead to the formation of fibrous tissue causing traction in the retina (Retinal detachment).

At the level of retinal microvasculature, the endothelial cells lining the capillaries become activated and they express adhesion of molecules (intercellular adhesion molecules (ICAMs) allowing the circulating leukocytes to come and adhere to the endothelial cells of the capillaries. This is known as leukostasis (inflammation in the diabetic retina).

In the case of sever ischemia; new vessels not only form in the retina, but in the iris as well (Rubeosis iridis). This results in neovascular glaucoma.



Diabetic retinopathy

Arteries and Veins of the Normal Optic Fundus

Normal image: The retinal arteries and veins emerge from the nasal side (left) of the optic disc. Vessels directed temporally have an arching course; those directed nasally have a radial course. Arteries are brighter red and narrower than veins; the veins are broader and darker than the arteries. The vessels supply and drain the inner retina, including the retinal ganglion cells and their axons and the bipolar cells. The choroidal circulation supplies the outer retina, including the rods and cones and retinal pigment epithelium.

In Diabetic retinopathy image: As a result of leakage, there is accumulation of hard exudate>> composed of lipoproteins>> the result of chronic leakage from the decompensated retinal vasculatures.

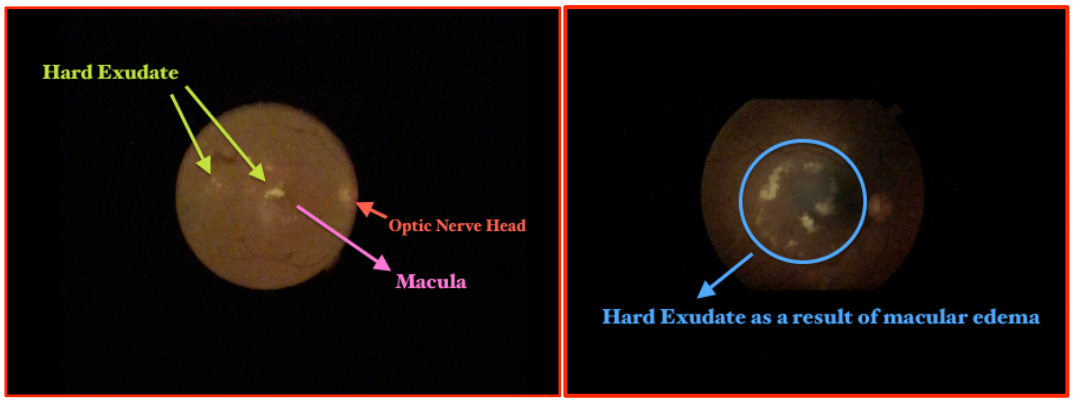
The red dots in the image are micro aneurysms (which will also contribute to the leakage). So, this patient has diabetic macular edema (DME). It's an important cause of visual loss.

Sever non-proliferative diabetic retinopathy: Does not cause hemorrhage (no new vessels); we see only sign of ischemia.

Proliferative diabetic retinopathy: there are new vessels.

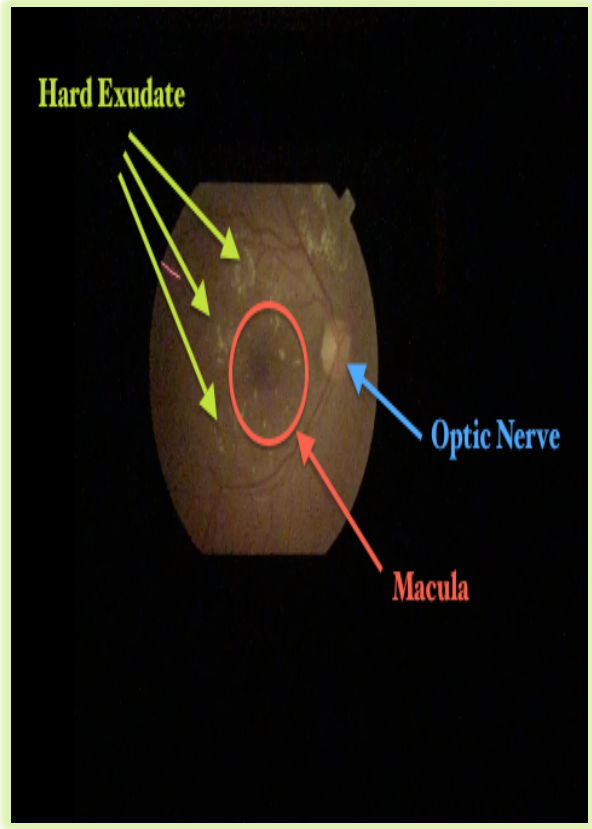
*The only means of preventing blindness due to diabetic retinopathy is through screening and early treatment.

The most common cause of blindness in non-proliferative disease is macular edema, while in



The hard exudate here is in the center of the macula (can cause a loss of central vision). It's a sign of macular edema.

*Nowadays, Optic coherence tomography (OCT) is used to diagnose early macular edema even in patients with very mild edema that you can't see it.



Tiny red dots: These are micro aneurysms that may leak plasma constituents into the retina as a result of breakdown in the blood-retinal barrier (The earliest sign of DR).

Hard Exudates: Waxy yellow/white lesions with relatively distinct margins arranged in clumps and/or rings at the posterior pole, often surrounding leaking microaneurysms. They are composed of lipoproteins that are the result of leakage (compensated capillaries that leak the lipoprotein). Sign of chronic leakage.

Treatment of diabetic macular edema (DMO):

1- **Focal laser photocoagulation:**

Treatment of micro aneurysms with laser (After 6 months there will be a scar from the laser treatment but no hard exudate). Very effective in controlling diabetic macular edema.

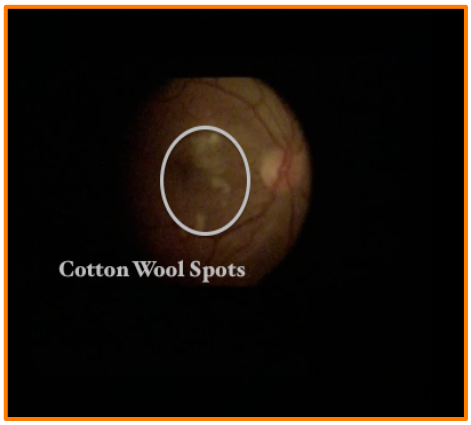
2- **Intravitreal injection of anti-VEGF agents (anti- vascular endothelial growth factor): (Ranibizumab or Bevacizumab)**
In addition to laser, we frequently inject Intravitreal injection of anti-VEGF agents to help control diabetic macular edema.

* Diabetic retinopathy patients have progressive macular vascular occlusion which will cause ischemia of retina (hypoxia).

Signs of Retinal Ischemia (Patient is at high risk to develop new vessels):

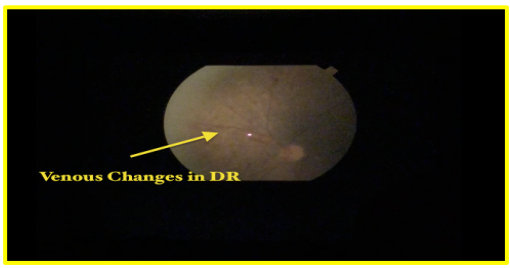
At this stage, sever non-proliferative diabetic retinopathy (Non-PDR). >>Patient should receive laser Panretinal photocoagulation.

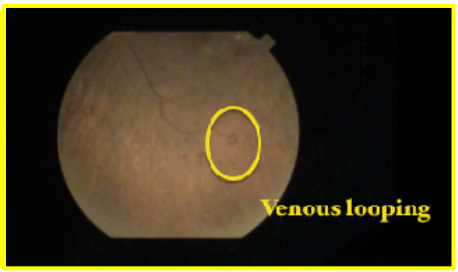
1. Cotton wool spots (less important sign and not used in the classification of non-PRD).
2. Venous changes (The most reliable signs of retinal ischemia in diabetic retinopathy).
3. Intraretinal microvascular abnormalities (IRMA): are arteriolar–venular shunts that run from retinal arterioles to venules, thus bypassing the capillary bed and are therefore often seen adjacent to areas of marked capillary hypoperfusion. * Dilated telangiectatic capillaries.
4. Intraretinal Hemorrhage: The extent of involvement is a significant marker of the likelihood of progression to proliferative diabetic retinopathy.



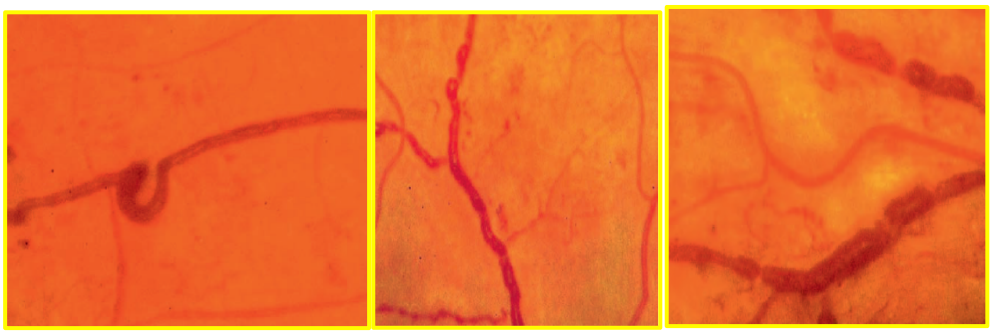
Cotton wool spots:

Small fluffy whitish superficial lesions that obscure underlying blood vessels. They are representing infarctions of the retina due to occlusion of precapillary arterioles. They result from ischaemic disruption of nerve axons of the retina. (Ischemia/infarction of the superficial retinal nerve fibers).

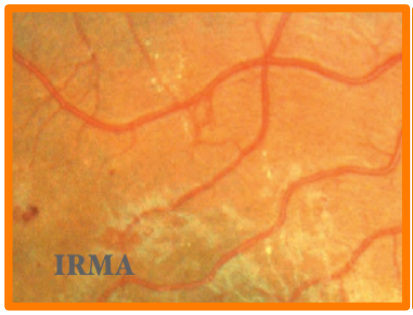


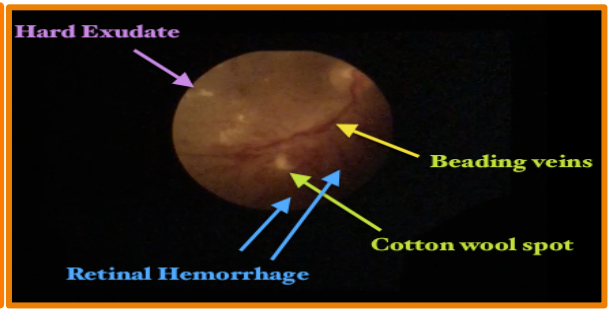


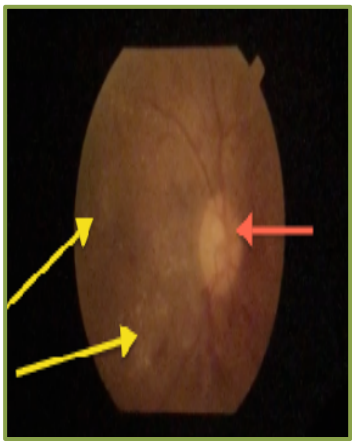
Venous changes: consist of generalized dilatation and tortuosity, looping, beading (focal narrowing and dilatation) and sausage-like segmentation. The extent of the retinal area exhibiting venous changes correlates well with the likelihood of developing proliferative disease.



Looping (Omega sign)	Beading	severe segmentation





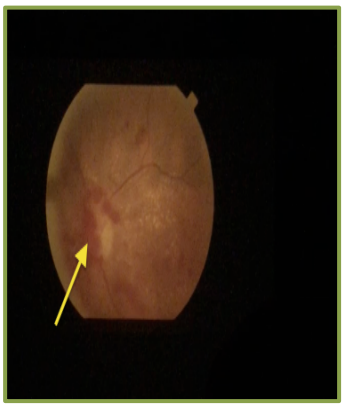


When Retina is ischemic:

Angiogenic factors are upregulated & new vessels developed.

*Vessels at optic nerve head (Red Arrow), causing early bleeding.

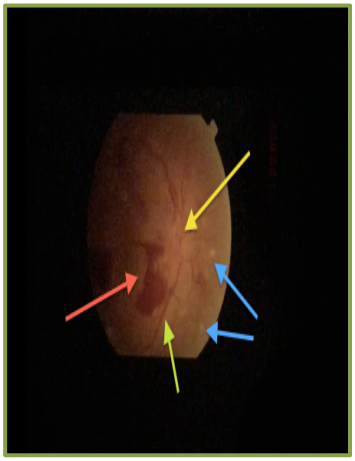
*Hard exudate (Yellow Arrow), Macular edema.



High-risk proliferative diabetic retinopathy:

- Presence of new vessels in the optic nerve head causing early bleeding + vitreous hemorrhage.

- Patient needs urgent panretinal photocoagulation laser. If no intervention within a few days, the hemorrhage becomes more dense and you can't do laser anymore.



High-risk proliferative diabetic retinopathy:

- New vessels at optic nerve head (Yellow Arrow).
- Cotton wool spots (Blue Arrow).
- Venous Changes (Green Arrow).
- Retinal hemorrhage (Red Arrow).

- Patient needs urgent panretinal photocoagulation laser. If no intervention then the hemorrhage become more dense and you can't do laser anymore.

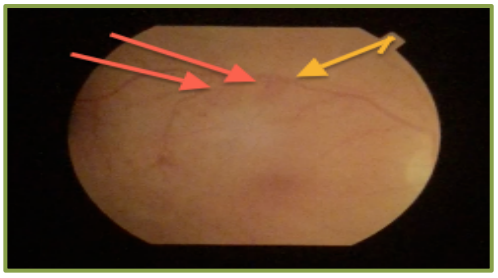
Proliferative Diabetic Retinopathy:

Fibrous tissue, initially fine, gradually develops in association as vessels increase in size. They are most commonly seen at the posterior pole:

- **New vessels at the disc (NVD):** describes neovascularization on or within one disc diameter of the optic nerve head.
- **New vessels elsewhere (NVE):** describes neovascularization further away from the disc; it may be associated with fibrosis if long-standing.
- **New vessels on the iris (NVI):** also known as rubeosis iridis, carry a high likelihood of progression to neovascular glaucoma.

New vessels elsewhere (Red Arrows):

- New vessels outside the optic nerve.
- All new vessels arise from the veins.



Treatment of Proliferative Diabetic Retinopathy:

1- Scatter laser treatment panretinal photocoagulation. (The mainstay of PDR treatment)

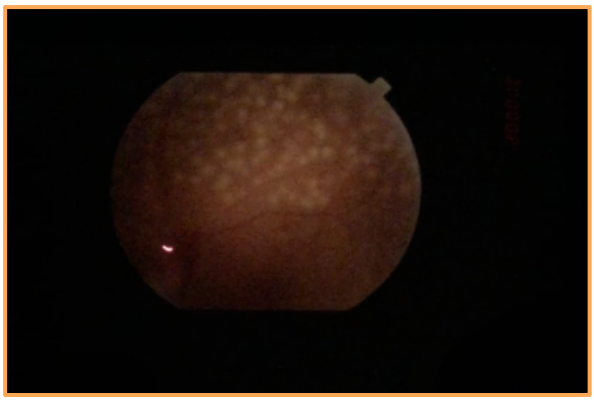
*Protect the patient from blindness.

*Apply scattered laser beams throughout the retina starting from the vascular arched, don't reach the macula and extend up to the periphery.

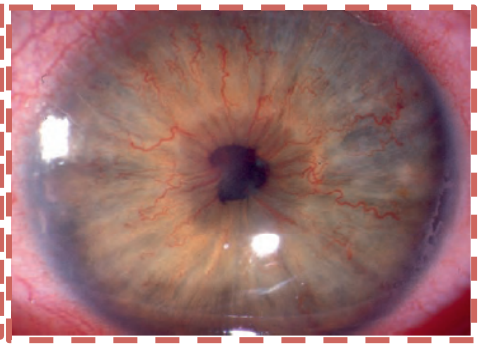
2- Intravitreal anti-VEGF injection.

Complications of Retinal photocoagulation:

1- Anterior segment complications such as corneal or lenticular opacification.
2- Transient visual loss.
3- Photocoagulation of the fovea.
4- Macular edema.
5- Hemorrhage.
6- Choroidal Effusion.
7- Color vision alterations.
8- Visual field defects and night vision problems.
9- Hemeralopia.



Laser scars everywhere except the macula and disc + Intraretinal Hemorrhage (It's a common feature in diabetic retinopathy)



New vessels on the iris (rubeosis iridis) can lead to neovascular glaucoma.

Two Types of Retinopathy:

Nonproliferative diabetic retinopathy (NPDR)	Proliferative Retinopathy
Most patients (95%).	With ongoing injury to the retinal vasculature, eventually the vessels occlude entirely lead to ischemic retina.
Progresses slowly.	Neovascularization (VEGF).
Seen on the fundus exam as vessel Micro aneurysms.	
Dot-and-blot hemorrhages.	
Cotton-wool spots (Sign of Ischemia).	

Tuberculosis (TB):

The three most common causes of intraocular inflammation in the kingdom:

1- Vogt–Koyanagi–Harada (VKH) syndrome

2- Tuberculosis

3 - Behçet disease

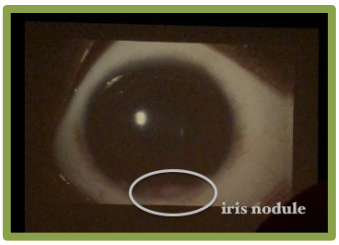
Introduction:

Tuberculosis (TB) is a chronic granulomatous infection usually caused in humans by Mycobacterium tuberculosis. TB is primarily a pulmonary disease but may spread by the bloodstream to other sites; ocular involvement commonly occurs without clinically overt systemic disease.

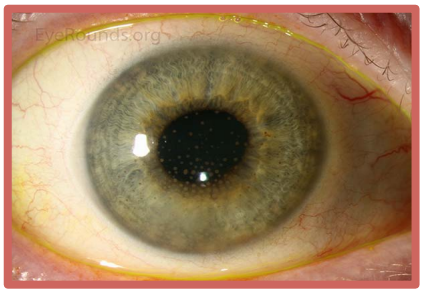
Ocular features:

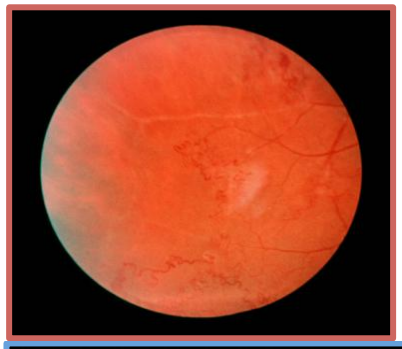
1- Anterior uveitis (it's a blinding disease if not treated): Granulation characterized by inflammatory deposed in the back of the cornea (anterior segment) ^The constituents of the uvea follow: iris labeled at top, ciliary body labeled at upper right, choroid labeled at center right.
2- Phlyctenular Keratoconjunctivitis: Is a nodular affliction characterized by formation of a small, circumscribed lesion at the corneal limbus.
3- Interstitial keratitis: Is any non-ulcerating inflammation of the corneal stroma without involvement of the epithelium or endothelium.
4- Vitritis (very common).
5- Choroidal granuloma.
6- Choroiditis independent.
7- Retinal vasculitis (Eales disease): Is an idiopathic obliterative vasculopathy that usually involves the peripheral retina of young adult. TB causes the most aggressive form of retinal vasculitis compared to other causes.
8- Mutton-fat keratic precipitation.
9- Iris or angle granulomas.

Iris nodule or angle granulomas: pinkish lesion in the angle and iris.

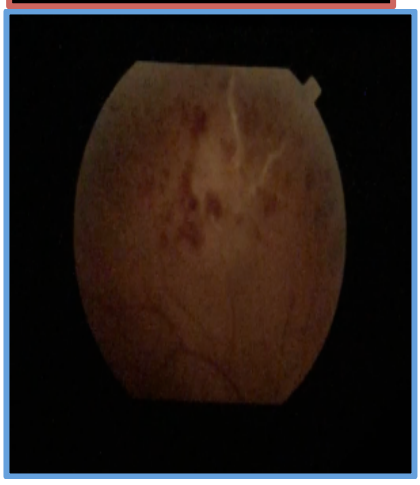


Mutton-fat keratic precipitation:
Collections of inflammatory cells on the corneal endothelium and become large with yellowish color.



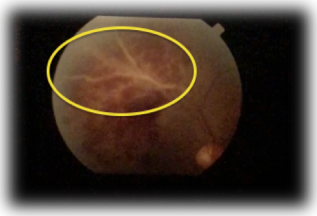


Eales disease: Fundus photo of the peripheral retina, revealing vascular tortuosity and peripheral retinal neovascularization.



* This patient has vasculitis. we can diagnose it without biopsy because we can see the fundus.

* The retinal blood vessels are inflamed; there is intraretinal hemorrhage around it because of the inflammation that will cause leakage of the blood into the retina.



Aggressive retinal vasculitis in a patient with Tuberculosis.

Treatment:

1- Prolonged multi-drug therapy (4 drugs in 2 months, then continue for 7 months with 2 drugs): isoniazid (with Vitamin B6 (pyridoxine) to prevent the development of peripheral neuropathy), rifampin, ethambutol, pyrazinamide.

2- Topical and systemic steroids may be used concomitantly to reduce inflammation-induced damage.

The most common infectious cause of intraocular inflammation is TB

Syphilis: Not common in our region

Congenital Syphilis:

Transplacental infection of the fetus occur, when the mother has become infected during or shortly before pregnancy. As a result of the syphilis, the patient may have saddle nose and Hutchinson teeth.

- Interstitial Keratitis
- Chorioretinitis

Acquired Syphilis:

- Ocular chancre.
- Iridocyelitis.
- Interstitial Keratitis.
- Chorioretinitis.
- Neuro-ophthalmic (nerve palsies, optic neuritis…).

Sarcardosis:

Introduction:

It is a chronic disorder of unknown cause, manifesting with non-caseating granulomatous inflammatory foci. It more frequently affects Japanese people, it increases with good hygiene and it is one of the most common systemic associations of uveitis.

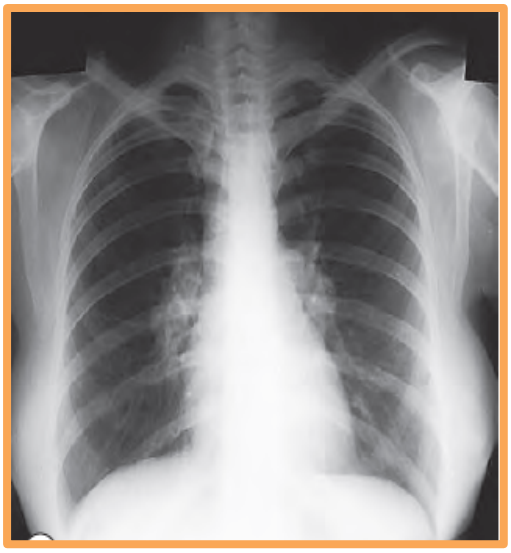
Eye Lesions:

- Lid margin and conjunctival granuloma.
- Acute iridocyclitis.
- Chronic granulomatous iridocyclitis.
- Peripheral retinal periphlebitis.
- Choroidal granulomas.
- Retinal granulomas.
- Optic N. granulomas.

Sarcoidosis and tuberculosis:

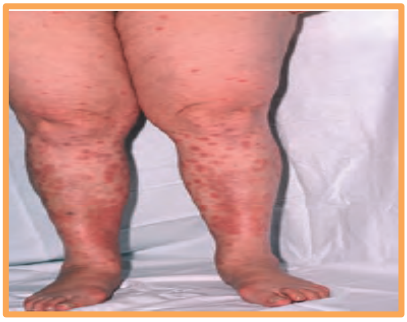
both can produce granuloma, which may be noncaseating.

Sarcoidosis can cause retinal vasculitis like TB, but less aggressive.

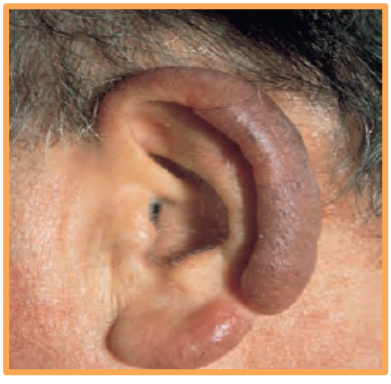


X-ray: Bilateral hilar lymphadenopathy in patient with granulomatous uveitis

* Sarcoidosis is confirmed by: chest x-ray, CT chest, ACE, serum lysozyme, Ca level and liver function.

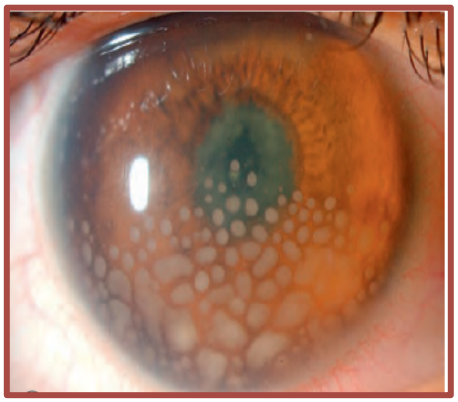


Erythema nodosum



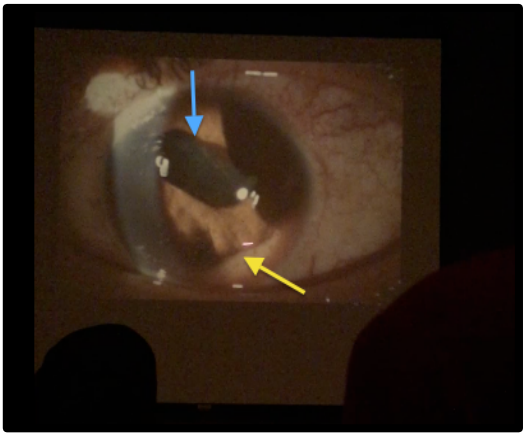
lupus pernio

Ocular features:



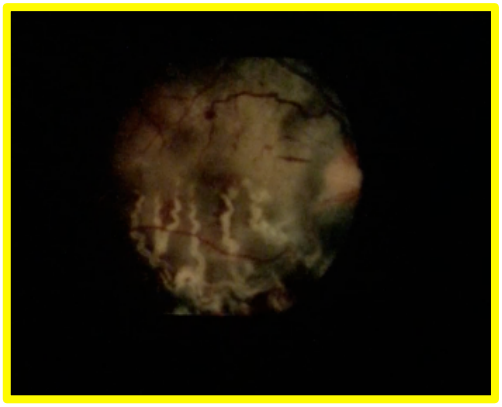
Mutton fat keratic precipitates: is an inflammatory cellular deposit seen on corneal endothelium.

This is a sign of granulomatous inflammation that is seen in:
TB, sarcardosis, viral infection like herpes, VKH syndrome and MS.



Yellow Arrow: Big granuloma in the iris>If you take biopsy from this mass it will show noncaseating granuloma.

Blue Arrow: Irregular pupil due to chronic inflammation there will be adhesions between the iris and the lens so when you dilate the pupil it won't dilate fully and will take irregular configuration



Case: 12 year old black boy, has aggressive vasculitis secondary to sarcoidosis and it respond very quickly to systemic corticosteroid therapy.

Rubella:

Transplacental transmission of virus to the fetus from an infected mother can lead to congenital abnormalities of multiple organ systems, with severity generally worse the earlier in gestation infection occurs. Latent rubella virus may cause chronic anterior uveitis relatively unresponsive to steroids, and has been implicated in the causation of Fuchs uveitis syndrome.

Ocular features of congenital rubella:

1- cataract
2- anterior uveitis
3- 'salt and pepper' pigmentary retinopathy
4- glaucoma and microphthalmos.

(Congenital Rubella):

Child in picture is born with congenital rubella with heart disease, he is wearing hearing aid and glasses because he had cataract surgery

Wilson's disease: (hepatolenticular degeneration)

A rare condition involving the widespread abnormal deposition of copper in tissues. It is caused by a deficiency of alpha 2 caeruloplasmin, the major copper-carrying blood protein.

Presentation:

1- liver disease.
2- basal ganglia dysfunction.
3- psychiatric disturbances.
4- Kayser-Fleischer ring (in 90% of patients with neurological signs): consists of a brownish-yellow zone of fine copper dusting in peripheral descemet membrane detected with gonioscopy (Important sign).
5- Anterior capsular 'sunflower' cataract (Not common): Copper deposition.

Marfan Syndrome:

It is an autosomal dominant disease; the most important feature in the eye in this patient is lens subluxation due to weakness of the lens zonulles. This patient can also have anomalies in the angle of the anterior chamber causing glaucoma. They are also at risk of developing retinal detachment.

SLE:

Case:

Patient has SLE which is characterized by positive ANA, positive dsDNA, decrase C4.

- If the patient has active disease, the retina is involved all the time. -
- The retina of this patient present with multiple retinal infarctions that manifesting as cotton wool spots due to occlusion of precapillary arteries (SLE retinopathy). -
- If the patient also has antiphospholipid antibodies >> the risk of SLE retinopathy is even higher. -
- SLE can cause keratitis. -

- If you see cotton wool spots in young woman>> you have to suspect SLE -
- Many cotton wool spots > suspect Systemic vasculitis -
- Infarction in macula, due to occlusion in central retinal artery (That cause large area of retinal infarction) (You have to suspect SLE) -

All these will lead to retinal dysfunction (Caused by microthrombosis) -

Rhumatoid Arthritis:

Not common here in our region, it's rare. The patient had positive Rheumatoid factor

- It manifest in the eye as keratoconjunctivitis sicca, dryness and keratitis

10-Ankylosing SpondylitisIMP

-Introduction:

Ankylosing spondylitis (AS) is characterized by inflammation, calcification and finally ossification of ligaments and capsules of joints with resultant bony ankylosis of the axial skeleton. It more commonly affects males, of whom 90% are HLA-B27-positive.

-Occular features:

Acute non-granulomatous anterior uveitis which is recurrent, alternating affecting one eye at a time. Infections such as Shigella, Salmonella and Campylobacter can also trigger the symptoms. Other ocular features include conjectivitis, scleritis, episcleritis, keratitis and mechanical ptosis.

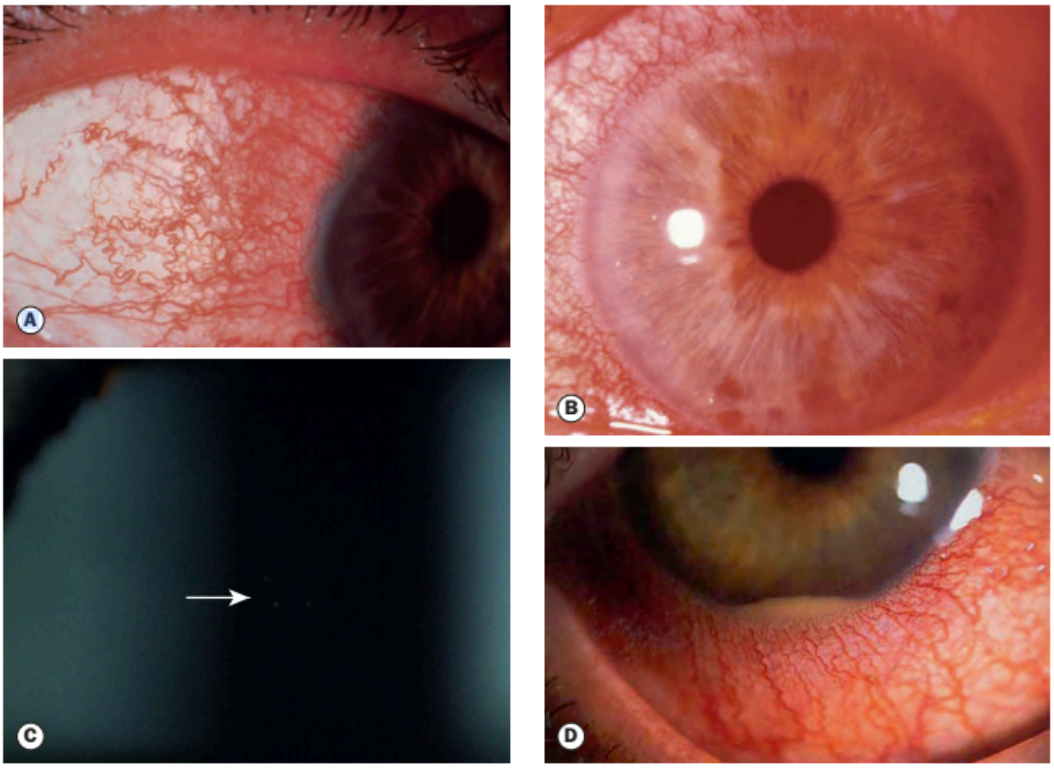
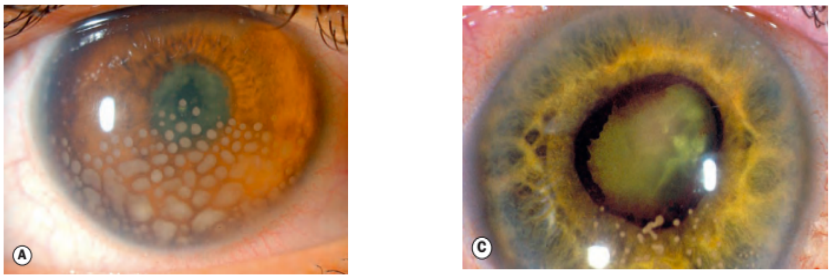


Fig. 11.2 Signs of acute anterior uveitis. **(A)** Ciliary injection; **(B)** miosis; **(C)** anterior chamber cells in mild anterior uveitis; **(D)** hypopyon



To know that it is non-granulomatous: There will be no mutton fat keratic precipitates.Mutton fat are shown in picture (A+C).

Systemic features: Pain and stiffness in the lower back with limitation of movement with calcification of spinal ligaments gives rise to a ‘bamboo spine’. Radiological changes often predate clinical symptoms.

Positive HLA-B27 diseases:

IBD, psoriasis, Reiter and Ankylosing spondylitis.

11- Juvenile idiopathic Arteritis

Most common cause of anterior uveitis in children but mainly in western countries.

It is defined as arthritis of unknown etiology that begins before the age of 16 years and persists for at least 6 weeks.
It can cause blindness so treat it early and aggressively.
Can have several forms:
1-Systemic onset Still's disease: Systemic, also known as Still (Still's) disease. Systemic features such as fever, episodic erythematous maculopapular rash, lymphadenopathy and hepatosplenomegaly may precede arthritis, and rare uveitis
2-Polyarticular onsent five or more joint are affected, uveitis is rare.
3-Oligoarticular is the most common form: Four or fewer joints are involved, the knees most commonly, followed by the ankles and wrists. Anterior uveitis is a key cause of morbidity in JIA "Patient doesn't complain". It is particularly common in oligoarticular JIA.

-**Screening:**

Antinuclear antibody (ANA) test ,Rheumatoid factor, HLA B-27.

-Other serious complications include: Glaucoma (common), amblyopia, maculopathy (cystoid macular edema, epiretinal membrane), cyclitic membrane and phthisis.

Risk factors of uveitis:
Oligoarticular onset
Being a girl
Young age < 4
Positive antinuclear antibody

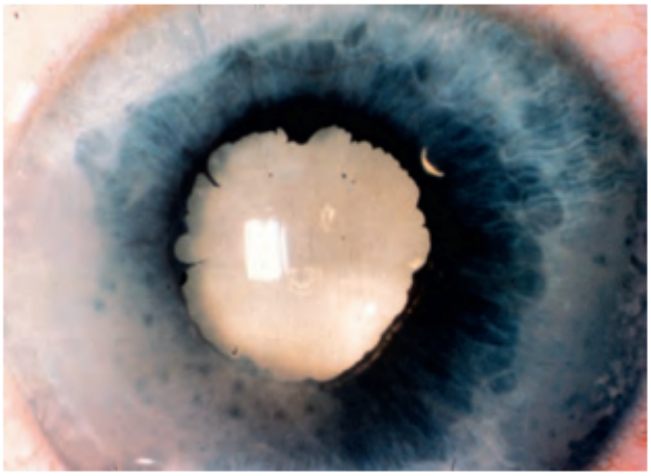


Fig. 11.14 Band keratopathy, posterior synechiae and mature cataract in chronic anterior uveitis associated with juvenile idiopathic arthritis

12- Behçet's disease

Behçet disease (BD) is an idiopathic, multisystem syndrome characterized by recurrent aphthous oral ulcers, genital ulceration and uveitis. It's not in whites but is common here.

Pathophysiology:

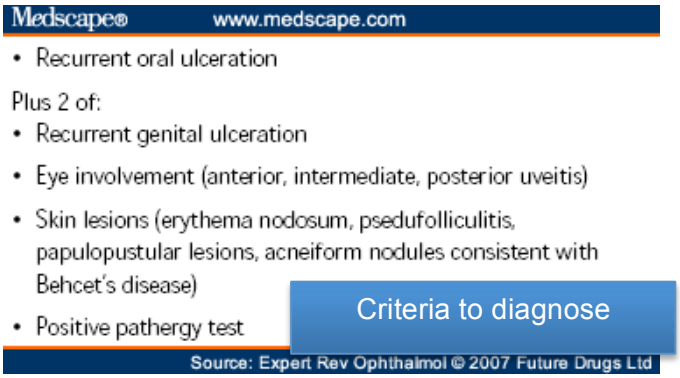
"Autoimmune vasculitis and hyperactivity of neutrophils". Hyper functioning neutrophil will recruit more cells, damaging the epithelial cells. 1/3 of Patients come with hypopyon in anterior chamber due to the neutrophils.

It is non-granulomatous with transient mobile hypopyon in a relatively white eye
Hypopyon in HLA-B27 is solid " doesn't move".
Retinitis can also occur.
It is an aggressive intraoccular inflammation, If not controlled properly it can lead to blindness.
It's major reason for blindness is recurrent attacks of explosive retinal vasculitis that will lead to retinal atrophy.

Diagnosis of bahcet disease?

Diagnosis is clinical! >>>>>>>>>>>>>>>

Patients with relapsing/remitting acute onset of bilateral panuveitis with retinal vasculitis and often spontaneous resolution even without treatment is the classical pattern of eye involvement; retinal vascular disease (vasculitis and occlusion) is the main cause of visual impairment.



Manegment: Steroid for a short time then Ciclosporin
Anti Alpha tumor necrosis agents"infliximab" if case is resistant.

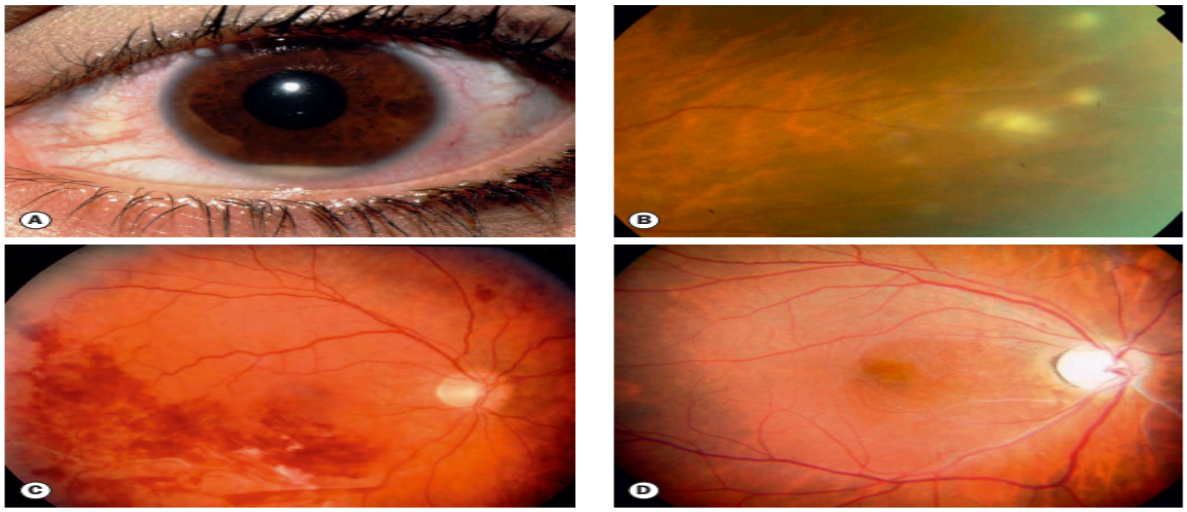


Fig. 11.32 Ocular lesions in Behçet disease. **(A)** Hypopyon in a white eye; **(B)** retinal infiltrates; **(C)** occlusive vasculitis; **(D)** end-stage disease
(Courtesy of A Dick – fig. C)

13- Toxoplasmosis

Most common cause of infectious uveitis in many countries. Common in France due to their habits." they eat raw meat"

Constitutes 20-60% of all posterior uveitis. It also comes with recurrent inflammation after a ruptured cyst that releases tachyzoits into a normal retina.

In our country it is secondary to Tuberculosis
Can be congenital: in the third trimester Showing ophthalmologic manifestation retinochoroiditis "fluffy white with pigmented scar", which has a predilection for the posterior pole. Bilateral in most cases.
Acquired: recurrent retinitis

-Symptoms: Unilateral floaters, blurring and photophobia.
-Ocular features:

Spill-over anterior uveitis, optic disc edema, posterior vitreous detachment and reactivation of live tissue cysts located at the border of the scars (recurrent ocular toxoplasmosis), the areas of newly active necrotizing retinitis are usually adjacent to old scars (so-called satellite lesions).

-Management:
Clindamycin and Co-trimoxazole, 48hr later add steroid to suppress inflammation.

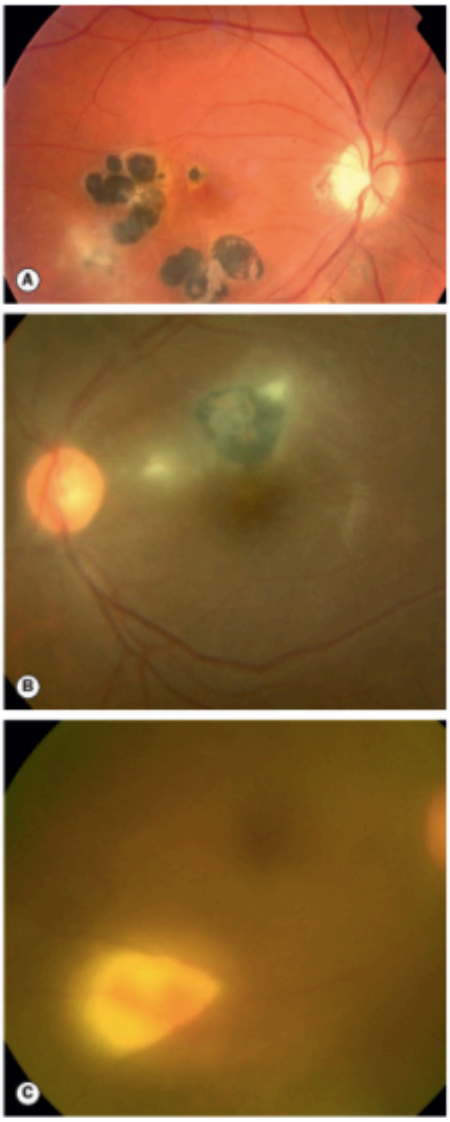


Fig. 11.36 Active *Toxoplasma* retinitis. **(A)** Typical 'satellite' lesion adjacent to an old scar; **(B)** two small foci; **(C)** severe vitreous haze and 'headlight in the fog' appearance of lesion
(Courtesy of S Chen – fig. A; C Pavesio – figs B and C)

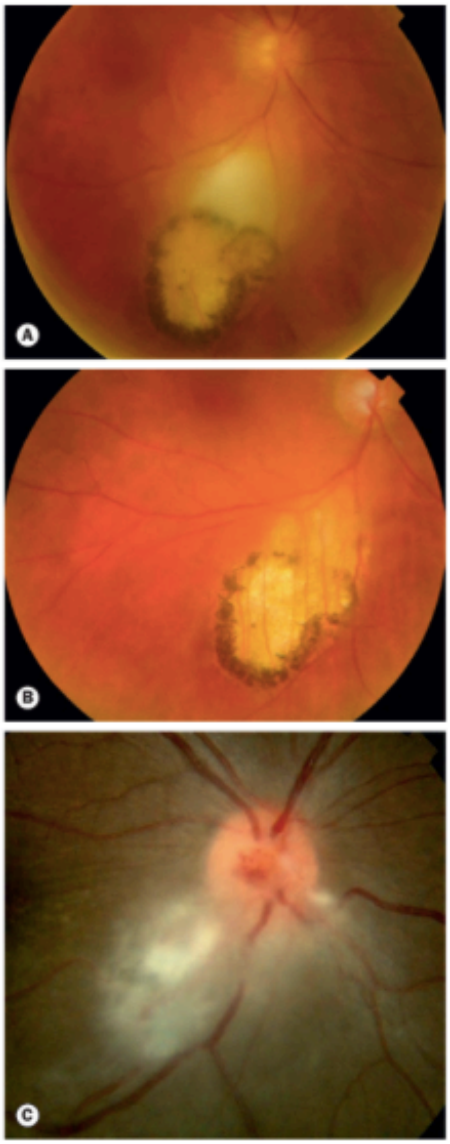


Fig. 11.37 Common complications of *Toxoplasma* retinitis. **(A)** Macular involvement, at presentation and **(B)** following treatment; **(C)** juxtapapillary lesion involving the optic nerve head

14- Vogt-Koyanagi-Harada (VKH) disease

Most common cause of uveitis in the kingdom, it also happens to children here 20%. Mean age is 28 years. Most common cause of intraocular inflammation.

-Introduction: Idiopathic Multisystem, autoimmune disease directed against melanocyte-containing tissues such as the uvea, ear and meninges.

-Systemic features:

Skin: localized alopecia, poliosis" decrease or absence of melanin (or color) in head hair, eyebrows, or eyelashes" and vitiligo. **Inner ear**: tinnitus, vertigo and deafness. **Meninges**: Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back) CSF will be full of pleocytosis " inflammatory cells".

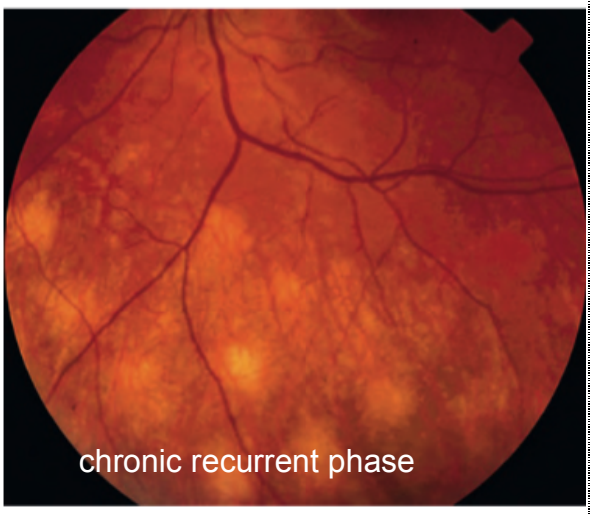


Fig. 11.20 'Sunset glow' fundus

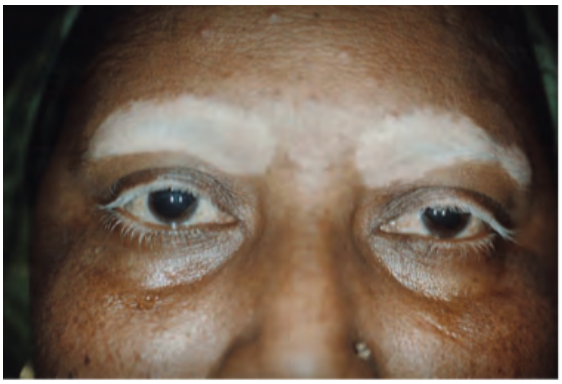


Fig. 11.19 Vitiligo and poliosis in Vogt–Koyanagi–Harada syndrome

Ocular features: Depigmented fundus appearance ('sunset glow' fundus)

Complication:
Glaucoma, cataract, choroidal neovascularization, subretinal fibrosis, retinal atrophy.

Early stage of the disease: Causes bilateral exudative retinal detachment best stage to treat with combined steroid.

Chronic recurrent phase:
Characterized by smoldering anterior uveitis with exacerbations with mutton fat keratic precipitate, iris nodule losing all the pigments.

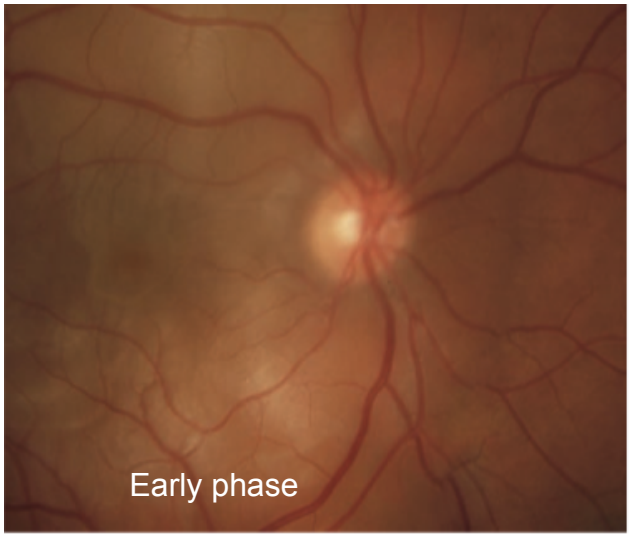


Fig. 11.18 Multifocal exudative retinal detachments in the acute uveitic phase of Vogt–Koyanagi–Harada syndrome

Table 11.8 Modified diagnostic criteria for Vogt–Koyanagi–Harada syndrome

1. Absence of a history of penetrating ocular trauma
2. Absence of other ocular disease entities
3. Bilateral uveitis
4. Neurological and auditory manifestations
5. Integumentary findings, not preceding onset of central nervous system or ocular disease, such as alopecia, poliosis and vitiligo

15-Sickle cell Disease

Retinopathy due to sickling of RBC causing peripheral vascular occlusion of the circulation and neovasculization in the periphary. Looks like "Sea fans"

Sickle cell C disease (SC – is the most likely type to develop severe retinopathy). Carbonic anhydrase inhibitors (CAI) should be avoided in sickling disorders as they can precipitate sickling and vascular occlusion.

Ocular features:

Anterior segment: Conjunctiva: Dark red corkscrew- or comma-shaped vessels that are typically transient.Iris: Patches of ischaemic atrophy.

Retina:

Nonproliferative retinal changes: Nonproliferative or background sickle retinopathy includes the following manifestations:

- Venous tortuosity: Due to arteriovenous shunting from the retinal periphery. It can occur in many patients with hemoglobin SS and hemoglobin SC disease.
- Salmon-patch hemorrhage: Superficial intraretinal hemorrhages. They are usually seen in the mid periphery of the retina adjacent to a retinal arteriole
- Schisis cavity: Caused by the disappearance of the intraretinal hemorrhage. Nonproliferative sickle retinopathy features iridescent spots and glistening refractive bodies in the schisis cavity
- The black sunburst: Round chorioretinal scars usually located in the equatorial fundus. These lesions result from pigment accumulated around the vessels. They do not cause any visual symptoms.

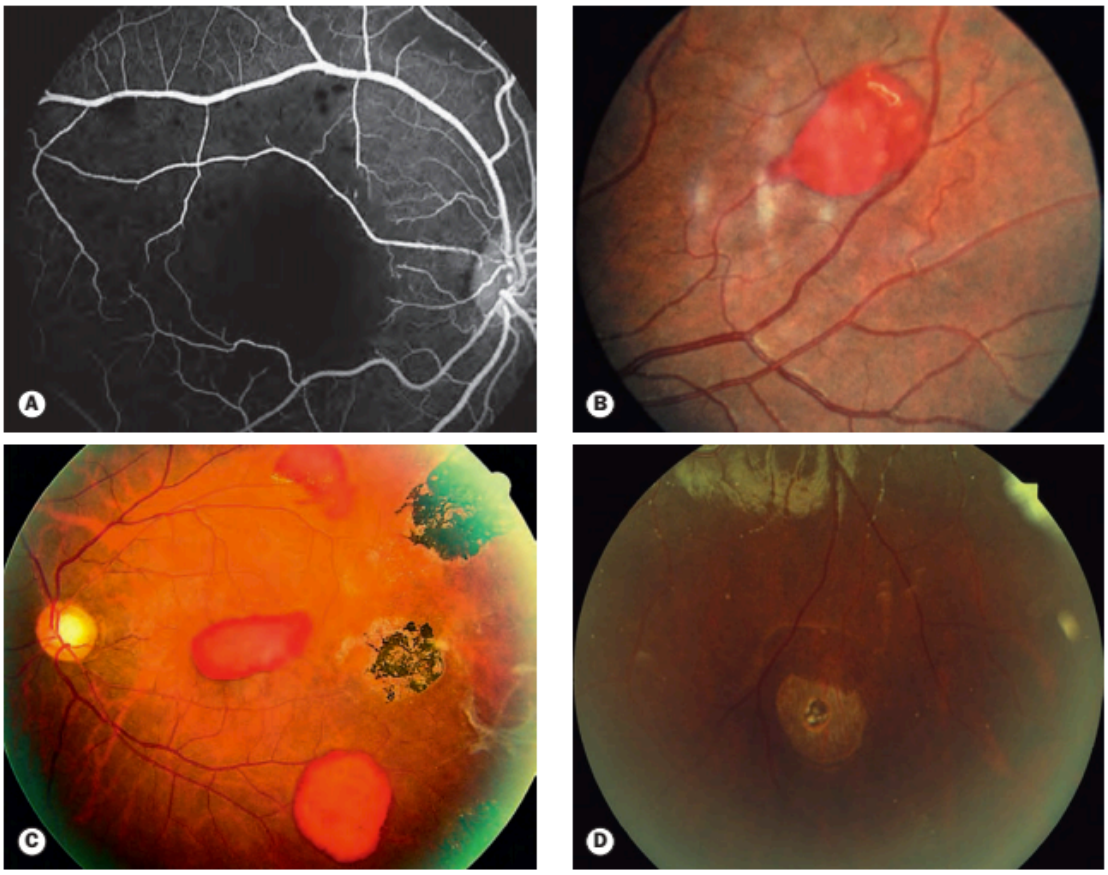


Fig. 13.47 Non-proliferative sickle-cell retinopathy. **(A)** FA shows macular ischaemia; **(B)** preretinal haemorrhage ('salmon patch'); **(C)** RPE hyperplasia ('black sunburst') and preretinal haemorrhages; **(D)** retinal hole and an area of whitening superiorly

Proliferative sickle retinopathy:

Proliferative sickle retinopathy (PSR) is the most severe ocular change in SCD. This is a peripheral retinal change most frequent in patients with hemoglobin SC. PSR is progressive. A desirable objective is to treat the neovascular tissue before a vitreous hemorrhage occurs.

Goldberg classified PSR into the following 5 stages:

1. Peripheral arteriolar occlusions
   In stage I, the peripheral arteriolar vessels occlude, with anteriorly located avascular vessels evident. Early in the process, the occluded arterioles are dark-red lines, but eventually they turn into silver-wire–appearing vessels.
2. Arteriolar-venular anastomosis
   In stage II, peripheral arteriolar-venular anastomosis occurs as the eye adjusts to peripheral arteriolar occlusion, and blood is diverted from the occluded arterioles into the adjacent venules. Peripheral to these anastomoses, no perfusion is present.

3. Neovascular proliferation
   In stage III, new vessel formation occurs at the junction of the vascular and avascular retina. These neovascular tufts resemble sea fans.

Initially, the sea fans can be fed by a single arteriole and draining vessel.

4. Vitreous hemorrhage.
5. Rhegmatogenous or tractional Retinal detachment.

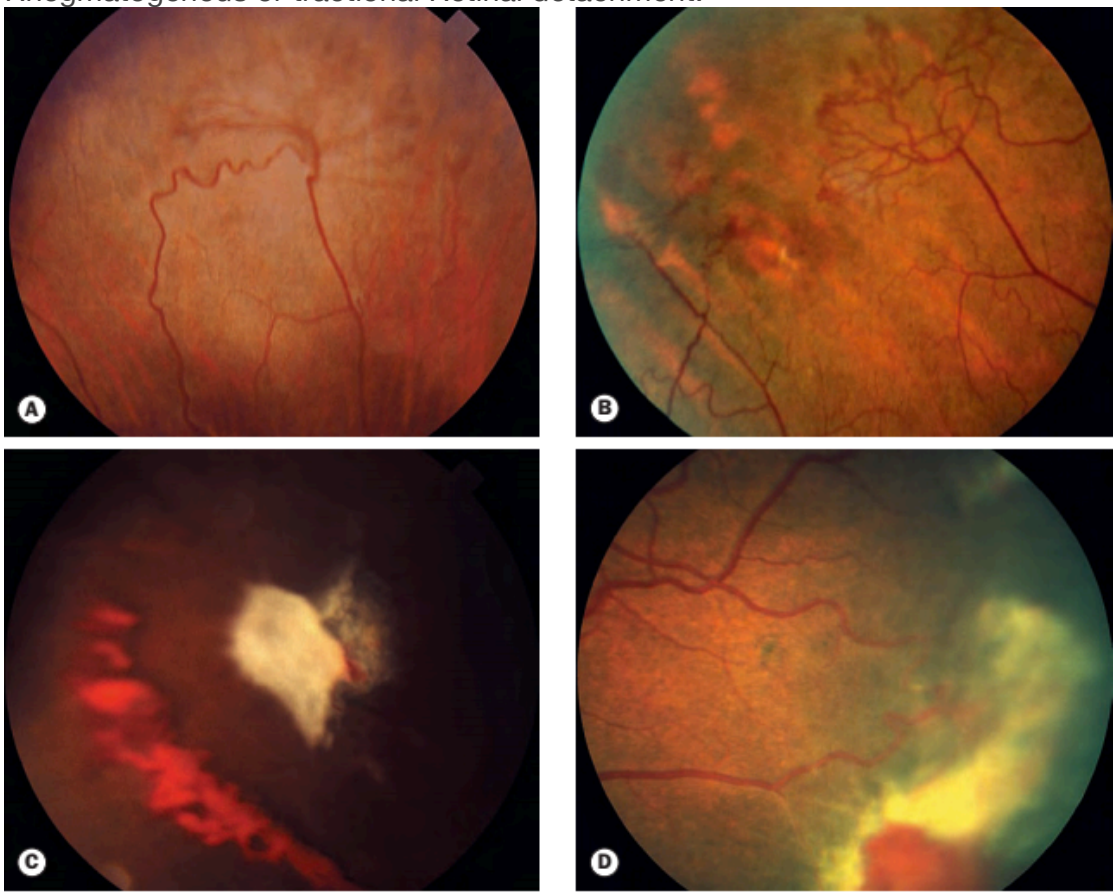


Fig. 13.48 Proliferative sickle cell retinopathy. **(A)** Peripheral arteriovenous anastomosis (mild neovascularization is also present); **(B)** 'sea fan' neovascularization; **(C)** haemorrhage from the new vessels; **(D)** extensive fibrovascular proliferation;

Later, as the sea fan grows in size, it is difficult to distinguish the major feeding and draining vessels. The sea fans may acquire a glial and fibrotic tissue envelope. This envelope may pull on the vitreous. A full-thickness retinal break, which may lead to total rhegmatogenous retinal detachment, may occur.
Treatment: Laser or cryotherapy ablation of peripheral non-perfused retina is probably the optimal approach,

16- Hypertensive Retinopathy

The primary response of the retinal arterioles to systemic hypertension is vasoconstriction; this is less marked in older individuals due to involutional sclerosis conferring increased rigidity. Arteriolosclerosis refers to hardening and loss of elasticity of small vessel walls, manifested most obviously by arteriovenous (AV) Nipping(nicking) at crossing points; its presence makes it probable that hypertension has been present for many years, even if the BP is currently controlled. Nipping: Thinning of the vein after the artery and it's changing direction, to avoid pressure by the artery.

Signs of hypertensive retinopathy:
Attenuation of the arterioles, increase light reflex as a result of chronic hypertension there will be thickening of arterioles giving the appearance of **silver**

wire and **copper wire** in the artery. **Cotton wool spots**, **hard exudate** (chronic retinal edema may result in the deposition of hard exudates around the fovea as a 'macular star'" typical in this case"), **retinal hemorrhage** and **edema**. In sustained hypertension the inner blood–retinal barrier is disrupted, increased vascular permeability leading to flame-shaped retinal hemorrhages and edema.

Last stage "Stage 4": bilateral edema of the optic nerve head. A marker of malignant hypertension.

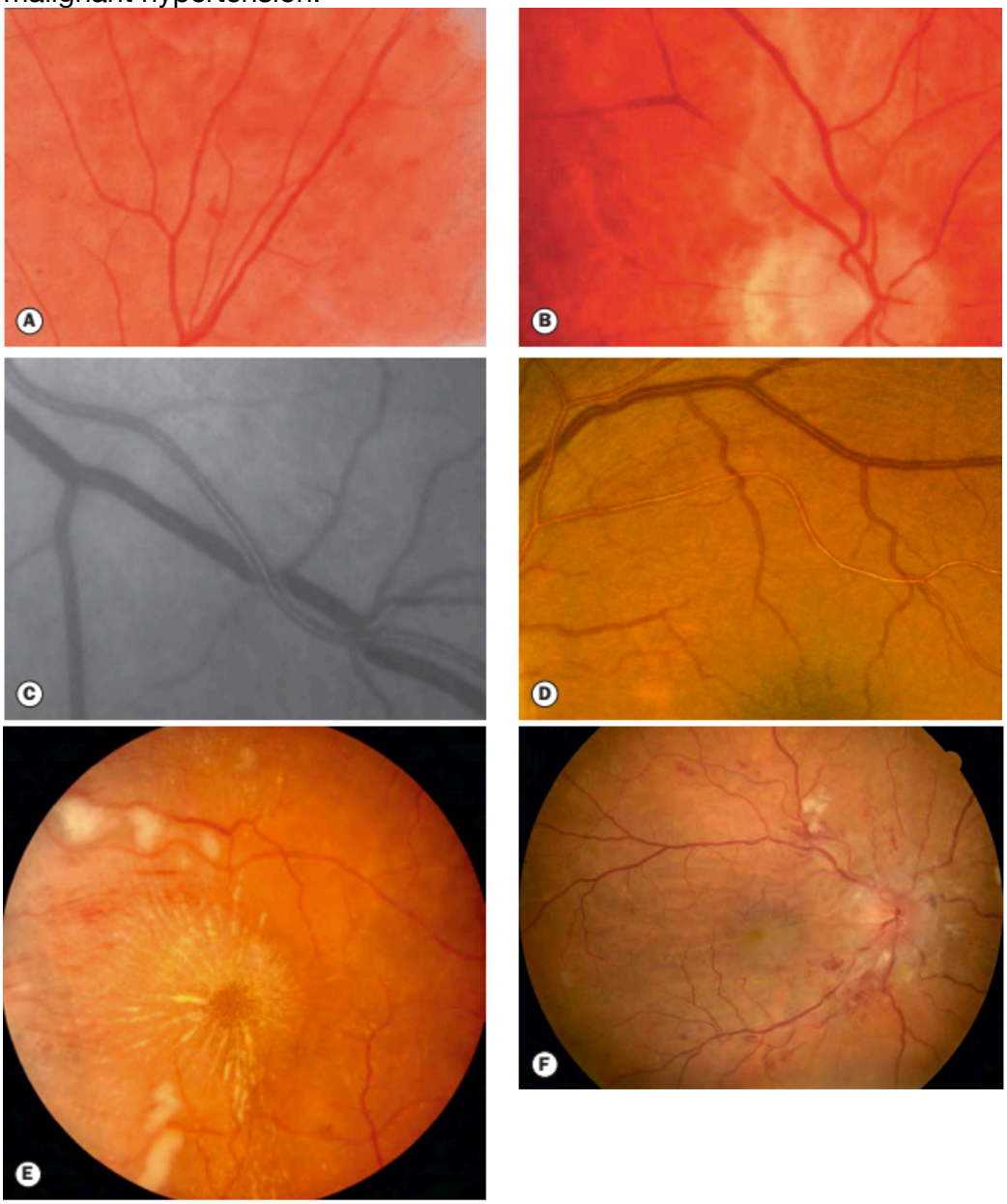


Fig. 13.43 Hypertensive retinopathy. **(A)** Generalized arteriolar attenuation; **(B)** focal arteriolar attenuation; **(C)** red-free photograph showing arteriovenous nipping; **(D)** 'copper wiring'; **(E)** grade 3 retinopathy with macular star; **(F)** grade 4 hypertensive retinopathy

17- Giant Cell Arteritis (GCA)

Affect medium and large vessels. Anterior ischemic optic neuropathy is divided into two types: Arteritic , Non-Arteritic.

Non-arteritic anterior ischaemic optic neuropathy (NAION): more common, caused by occlusion of the short posterior ciliary arteries resulting in partial or total infarction of the optic nerve head. More common, comes with people with diabetes, hypertension, hyperlipidaemia, collagen vascular disease, antiphospholipid antibody syndrome, hyperhomocysteinaemia, sudden hypotensive events, cataract surgery, sleep apnoea syndrome and erectile dysfunction." Patient complains of: Sudden painless monocular visual loss; this is frequently discovered on awakening, suggesting a causative role for nocturnal hypotension.

Arteritic anterior ischaemic optic neuropathy (AAION): Caused by giant cell arteritis (GCA). About 50% of patients with GCA have polymyalgia rheumatica (PMR)" pain and stiffness in proximal muscle groups, typically the shoulders and biceps, that is worse on waking".

Risk factors: Old age, Females, smoking, low body mass index and early menopause.

Systemic features: Scalp tenderness noticed when combing the hair. Headache localized to the frontal, occipital or temporal areas or is more generalized. Jaw claudication.

Ocular features: Ocular motor palsies, including a pupil-involving third nerve palsy, Sudden, profound unilateral visual loss not uncommonly preceded by transient visual obscurations (amaurosis fugax) (Latin *fugax* meaning *fleeting*, Greek *amaurosis* meaning *darkening*, *dark*, or *obscure*) which is a painless transient monocular visual loss. And sometimes by double vision. Periocular pain is also common**. Signs**: strikingly pale 'chalky white' edematous disc is particularly suggestive of GCA.
Investigation: Erythrocyte Sedimentation Rate (ESR): Often very high, with a level of >60 mm/hr

Full blood count: elevated platelets and normocytic normochromic anemia are commonly present, and Temporal artery biopsy (TAB).
Treatment: Large dose of steroids to save and protect the other eye.
Simultaneous bilateral involvement is rare but rapid involvement of the second eye, with resultant total blindness, should always be regarded as a substantial risk.

Table 19.2 American College of Rheumatology 1990 classification criteria for giant cell arteritis

1. Age at disease onset 50 years or older 2. New headache 3. Temporal artery tenderness to palpation or decreased pulsation 4. Erythrocyte sedimentation rate of 50 mm/hr or greater 5. Abnormal artery biopsy: biopsy specimen showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells
For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least three of these five criteria are present

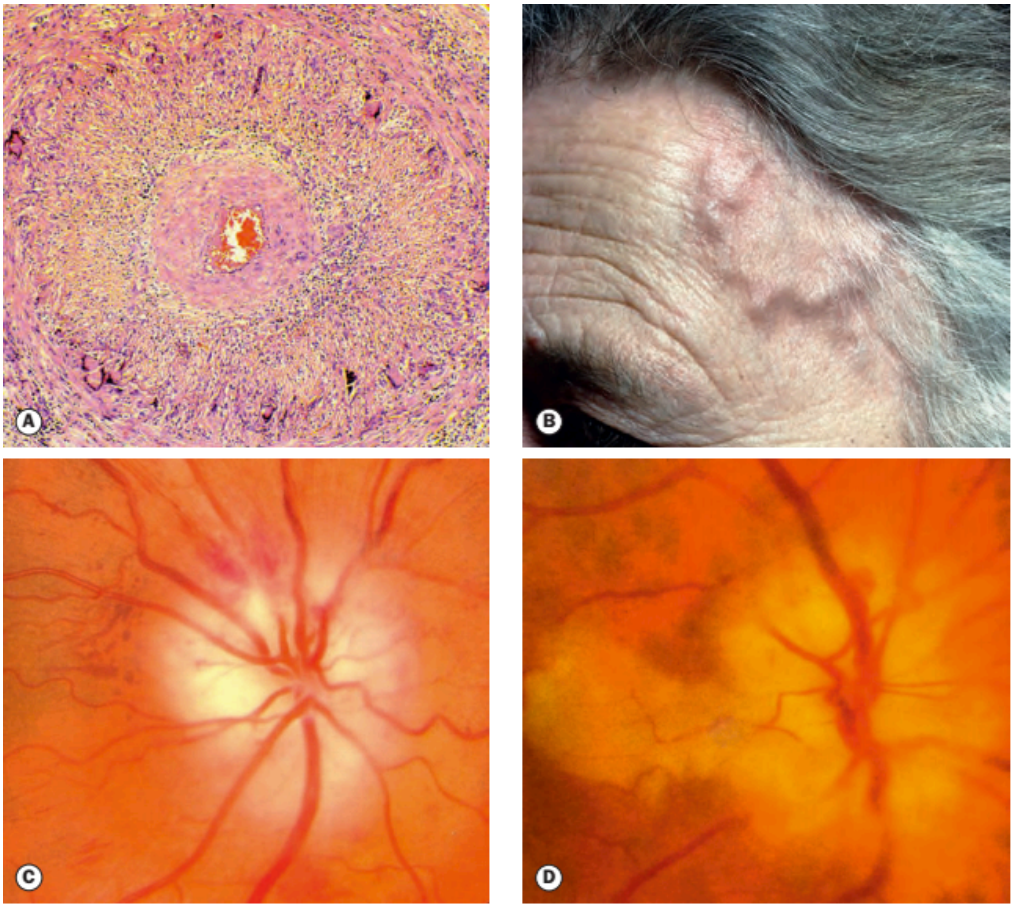


Fig. 19.14 Giant cell arteritis. **(A)** Histology shows transmural granulomatous inflammation, disruption of the internal elastic lamina, proliferation of the intima and gross narrowing of the lumen; **(B)** the superficial temporal artery is often pulseless, nodular and thickened; **(C)** pale swollen disc in arteritic ischaemic optic neuropathy; **(D)** ischaemic optic neuropathy and cilioretinal artery occlusion

Summary

Diabetic retinopathy:

- The strongest risk for developing diabetic retinopathy is the duration of the disease.
- Patients with diabetes can have ocular manifestation other than diabetic retinopathy, like: cataract, very sever type of glaucoma, retinopathy, optic nerve dysfunction, and 3rd and 4th and 6th nerve palsies.
- There is accumulation of hard exudate>> composed of lipoproteins>> the result of chronic leakage from the decompensated retinal vasculatures.
- Diabetic macular edema is treated by focal laser coagulation and Intraretinal injection of anti-VEGF agents.

1- Sever non-proliferative diabetic retinopathy:

- Does not cause hemorrhage (no new vessels); we see only sign of ischemia.
- The most reliable sign is venous changes.
- The most common cause of blindness in non-proliferative disease is macular edema.

2- Proliferative diabetic retinopathy: there are new vessels.at the disc, iris or elsewhere.

- New vessels on the iris (rubeosis iridis) can lead to neovascular glaucoma.
- Management: pan retinal photocoagulation.
- Patients with new vessels at optic nerve head, cotton wool spots, venous changes and retinal hemorrhage are considered high risk proliferative retinopathy and need urgent panretinal photocoagulation.
- The most common cause of blindness in proliferative disease is tractional retinal detachment.

TB:

- Caused by Mycobacterium tuberculosis.
- The most common infectious cause of intraocular inflammation is TB.
- TB causes the most aggressive form of retinal vasculitis compared to other causes.
- Anterior uveitis is seen in TB (it's a blinding disease if not treated).
- Treatment:
  1- Isoniazid (with pyridoxine), rifampin, ethambutol, pyrazinamide.
  2- Topical and systemic steroids may be used to reduce inflammation-induced damage.

Syphilis:

- Congenital:
  Interstitial keratitis, chorioretinitis.
- Acquired:
  Ocular chancre, iridocyelitis, interstitial keratitis, chorioretinitis, neuro-ophthalmic (nerve palsies, optic neuritis…).

Sarcoidosis:

- Increases with good hygiene and it is one of the most common systemic associations of uveitis. It responds very well to systemic corticosteroid therapy.
- Can cause retinal vasculitis like TB, but less aggressive.
- Sarcoidosis is confirmed by: chest x-ray, CT chest, ACE, serum lysozyme, Ca level and liver function.

Rubella:

- Severity generally worse the earlier in gestation infection occurs.
- Child born with cataract, anterior uveitis, 'salt and pepper' pigmentary retinopathy, glaucoma and microphthalmos

Wilson's disease: (hepatolenticular degeneration):

- Widespread abnormal deposition of copper in tissues. It is caused by a deficiency of alpha 2 caeruloplasmin.
- Kayser-Fleischer ring (in 90% of patients with neurological signs) is an important sign, a brownish-yellow zone of fine copper dusting in peripheral descemet membrane detected with gonioscopy.

Marfan syndrome:

- Autosomal dominant disease.
- Lens subluxation due to weakness of the lens zonulles (most important), glaucoma may also be present. There is a risk of developing retinal detachment.

SLE:

- If the patient has active disease, the retina is involved all the time, keratitis may be present.
- SLE retinopathy: multiple retinal infarctions that manifesting as cotton wool spots due to occlusion of precapillary arteries.
- If the patient also has antiphospholipid antibodies >> the risk of SLE retinopathy is even higher.

Rheumatoid arthritis:

- Keratoconjunctivitis sicca, dryness and keratitis may be present.

Ankylosing spondylitis:

- HLA-B27-positive.
- Acute non-granulomatous anterior uveitis which is recurrent, alternating affecting one eye at a time. Other ocular features include conjectivitis, scleritis, episcleritis, keratitis and mechanical ptosis.

Juvenile idiopathic arthritis:

- Most common cause of anterior uveitis in children, especially in females aged 4 years and less, positive antinuclear antibody and oligoarticular onset.
- Glaucoma is another serious complication.

Behcet's disease:

- Agressive intraoccular inflammation, if not controlled properly it can lead to blindness.
- Major reason for blindness is recurrent attacks of explosive retinal vasculitis which leads to retinal atrophy and blindness.
- Retinal vascular disease (vasculitis and occlusion) is the main cause of visual impairment.
- 1/3 of Patients come with hypopyon in anterior chamber due to the neutrophils.
- Retinitis can also occur.
- Treatment: Steroid for a short time then infliximab if case is resistant.

Toxoplasmosis:

- Common in France, secondary to TB in our country.
- Congenital infection: retinochoroiditis ”fluffy white with pigmented scar”.
- Acquired infection: recurrent retinitis.
- Symptoms: Unilateral floaters, blurring and photophobia.
- Management: Clindamycin and Co-trimoxazole, add steroid to suppress inflammation.

Vogt-Koyanagi-Harada disease:

- Most common cause of uveitis in the kingdom.
- Most common cause of intraocular inflammation.
- Autoimmune disease directed against melanocyte-containing tissue.
- Ocular features: Depigmented fundus appearance (‘sunset glow’ fundus).
- Early stage of the disease: Causes bilateral exudative retinal detachment best stage to treat with combined steroid.
- Chronic recurrent phase: Characterized by smoldering anterior uveitis with exacerbations with mutton fat keratic precipitate, iris nodule losing all pigments.
- Complication: Glaucoma, cataract, choroidal neovascularization, subretinal fibrosis, retinal atrophy.

Sickle cell disease:

- Retinopathy due to sickling of RBC causing peripheral vascular occlusion of the circulation and neovasculization in the periphery. Looks like “Sea fans”

Hypertensive retinopathy: ocular manifestation:

- Attenuation of the arterioles, increase light reflex as a result of chronic hypertension there will be thickening of arterioles giving the appearance of silver wire and copper wire in the artery. Cotton wool spots, hard exudate (chronic retinal edema may result in the deposition of hard exudates around the fovea as a ‘macular star’" typical in this case"), retinal hemorrhage and edema.
- Nipping: Thinning of the vein after the artery and it's changing direction, to avoid pressure by the artery.
- Edema of the optic nerve head in last stage.

Giant cell arteritis:

- Arteritic anterior ischaemic optic neuropathy or Non-arteritic anterior ischaemic optic neuropathy “more common".
- Ocular features: Ocular motor palsies, including a pupil-involving third nerve palsy, sudden, profound unilateral visual loss not uncommonly preceded by transient visual obscurations.
- Sign: strikingly pale ‘chalky white’ edematous disc.
- Investigation: Erythrocyte Sedimentation Rate and Temporal artery biopsy (TAB).
- Treatment: Large dose of steroids to save and protect the other eye.

The three most common causes of intraocular inflammation in the kingdom are in this order:

1- Vogt–Koyanagi–Harada (VKH) syndrome.

2- Tuberculosis “most common infectious cause”.

3 - Behçet disease.

Note: When you see a patient with intraocular inflammation distinguish if it is infectious or not, if infectious, treat with anti-infectious agents. If you treat only with steroids, this will cause fulminating infection.

Note:

- Diabetic retinopathy: neovascularization at the posterior retina.
- Sickle cell disease retinopathy: neovascularization at the periphery.

Note:

- Arteries are brighter red and narrower than veins; the veins are broader and darker than the arteries. This is helpful when looking at the images.

Non-granulomatous uveitis	Granulomatous uveitis
Sero-negative arthropathy and uveitis	Tuberculosis
Traumatic	Sarcoidosis
Behcets syndrome	Syphilis
Leptospirosis	Leprosy
EarlySarcoidosis	Herpetic
Early tuberculosis	VKH
Early Syphilis	Sympathetic ophthalmia
	Lens induced uveitis
	Parasitic
	Viral
Non-granulomatous unilateral uveitis	**Non-granulomatous bilateral uveitis**
HLA B27 uveitis	Leptospirosis
Traumatic uveitis	Behcet's, syndrome
Behcet's, syndrome	TINU
Fuch heterochromic uveitis	
Leptospirosis	
Drug induced uveitis	
Unilateral granulomatous uveitis	**Bilateral granulomatous uveitis**
Viral anterior uveitis	Vogt Koyanagi Haradas syndrome
Lens induced uveitis	Sympathetic ophthalmia
Sarcoid	Sarcoid
Syphilis	Syphilis
Tuberculosis	Tuberculosis
Parasitic	Phaco anaphylaxis

VKH: Vogt Koyanagi Harada's, TINU: Tubulo Interstitial Nephritis Uveitis syndrome, HLA: Human Leukocyte Antigen

MCQs:

1. A 65-year-old female with history of jaw claudication presented to ER with sudden loss of vision in one eye. Erythrocyte sedimentation rate 100 mm/hour.

What is the best test to confirm the diagnosis?

A. Visual field.

B. Temporal artery biopsy.

C. Serum ANA and P-ANCA.

D. MRI brain.

2. **Ankylosing Spondylitis is associated with:**

A. Anterior uveitis.

B. Episcleritis.

C. Kerato conjunctivitis.

3. **Which of the following indicates ischemic retina in diabetic retinopathy:**

A. Venous beading/looping.

B. Macular edema.

C. Retinal detachment.

4. A patient presented to the uveitis clinic, on examination there was fine keratic precipitate over the posterior cornea and irregular pupil.

What is your diagnosis?

A.sarcoidosis

B.rubella

C.toxoplasmosis

D.Behchet's Disease

If you have any questions/suggestions regarding Ophthalmology teamwork please via:

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