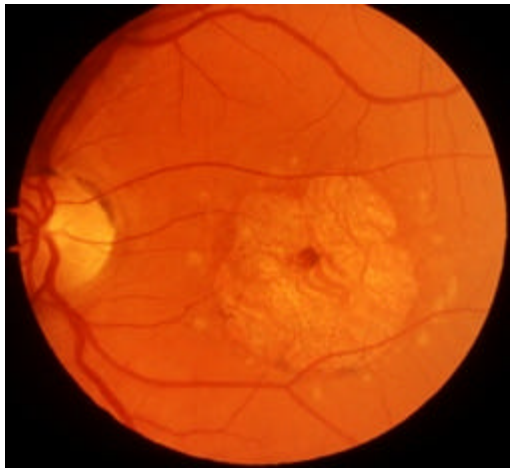
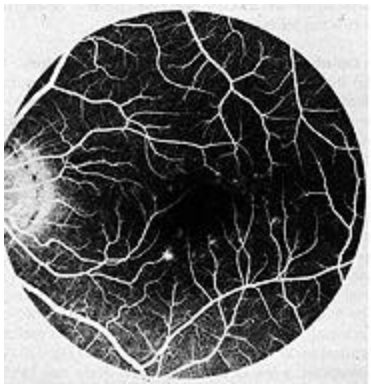
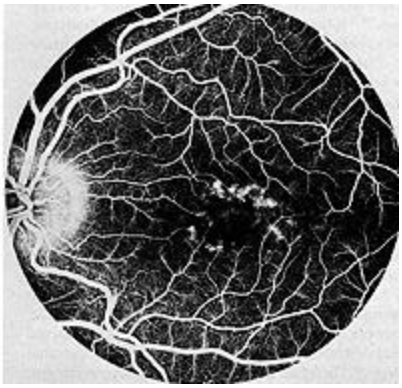
RETINA

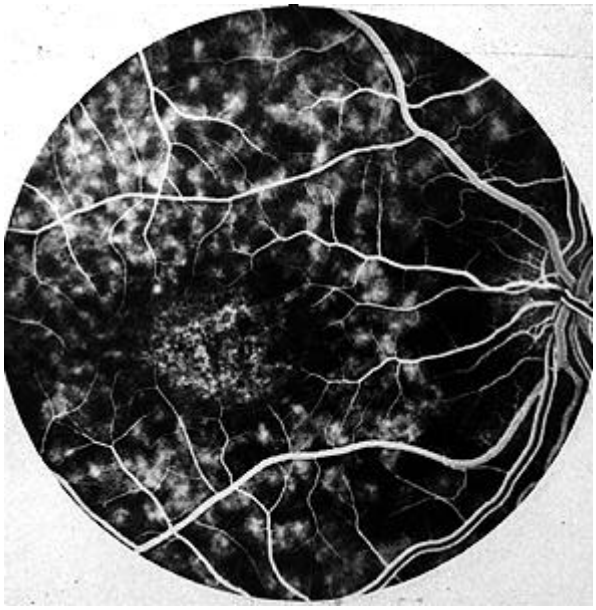
Q: BULLS EYE MACULOPATHY

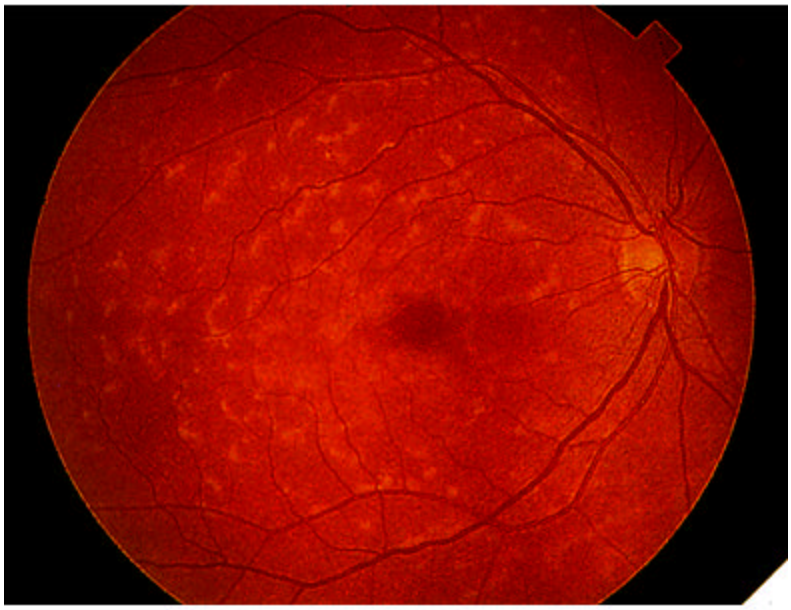
- Color picture and IVFA of Stargard's
- What is the Ddx?
- What is maximum dose of chloriquine?
- What is maximum dose of hydroxychloriquine?











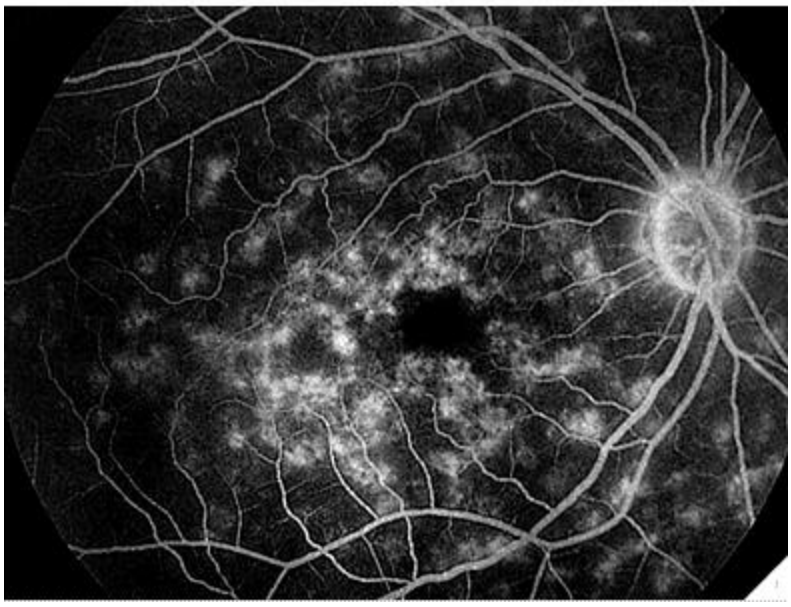
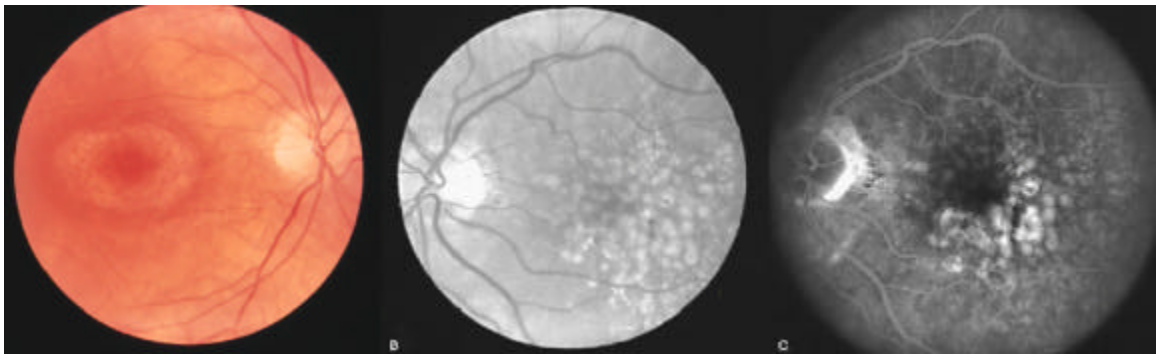


**Table 107–2. DIFFERENTIAL DIAGNOSIS OF BULL'S-EYE MACULOPATHY**

| |
|---|
| Cone degeneration |
| Chloroquine or hydroxychloroquine maculopathy |
| Cone-rod degeneration |
| Lipofuscinosis |
| Bull's-eye maculopathy associated with Stargardt's disease and fundus flavimaculatus |
| Fenestrated sheen macular dystrophy |
| Parafoveal atrophy of the retinal pigment epithelium secondary to drusen |
| Central areolar choroidal dystrophy |
| Juvenile Batten's disease |
| Fucosidosis |
| Clofazimine maculopathy |

- Chloroquine and hydroxychloroquine were first used for the prophylaxis and treatment of malaria and now are more commonly used in the treatment of the connective tissue diseases.
- Both produce identical retinopathies, which may progress from a mild macular pigmentary abnormality to the classic bull's-eye maculopathy which consists of a central, foveal area of hyperpigmentation surrounded by hypopigmentation.
- These findings may be better visualized on fluorescein angiography.
- Cornea verticillata may also be seen.
- Toxicosis from chloroquine or hydroxychloroquine usually does not occur with daily doses of 250 mg or less (cumulative dose 100 gm) and 400 mg per day, respectively.
- Follow-up examinations with testing of color vision (AOHRR), visual acuity, central visual field with a red Amsler grid, and EOG should be done approximately every 6 months.
- Once toxicosis is noted, progression may be seen even after discontinuation of the drug.



Bull's-eye macular lesion in a 28-year-old patient who had received a cumulative dose of almost 700 g chloroquine over 6 years. The pigmentary changes in the macular remain, even after discontinuation of the drug. Age-related macular degeneration in a 74-year-old patient. Multiple and confluent soft drusen are present in the macula (B). On fluorescein angiography (C), the soft drusen stain in the late frames without leakage of dye. This patient should be monitored closely since soft drusen are associated with formation of choroidal neovascular membranes.

- Clofazimine is used in the treatment of leprosy and Mycobacterium avium-intracellulare in patients with AIDS.
- Doses greater than 200 mg per day have been reported to cause bilateral bull's-eye maculopathies with normal central and color vision and reduction in the ERG b-wave amplitudes.

STARGARDT DISEASE (FUNDUS FLAVIMACULATUS)

- The terms "Stargardt disease" and "fundus flavimaculatus" are often used interchangeably to describe a degenerative retinopathy characterized by ill-defined yellowish spots.
- These occur within the posterior pole and in the pre-equatorial retina.
- Differentiation between these two categories can be made on the basis of the ophthalmoscopic findings.
- In fundus flavimaculatus there are ill-defined yellowish flecks throughout the fundus, including the macular region, but no associated macular atrophy.
- In Stargardt disease atrophic maculopathy may or may not be associated with yellow flecks throughout the fundus, associated with atrophic macular dystrophy.
- Both diseases, which may be variations of a single disorder, may be inherited in an autosomal recessive or autosomal dominant pattern.
- Fundus flavimaculatus typically occurs in adults and is not accompanied by macular dystrophy.
- Visual acuity is usually normal in these patients.
- The ophthalmoscopic features consist of bilaterally symmetric scattered, yellowish, ill-defined pisciform (fishtail-shaped) flecks which usually appear to be located deep to the retina
- Sometimes old flecks may disappear and new ones may arise.
- A delay in attaining the normal maximum b-wave amplitude is sometimes seen.
- The electro-oculogram's (EOG) light peak:dark trough ratio is subnormal in most patients, indicating widespread functional disturbance of the retinal pigment epithelium.
- This disorder is usually inherited in an autosomal recessive fashion.
- The term Stargardt disease refers to a maculopathy with various degrees of retinal pigment epithelial changes (atrophy, dispersion, granulation) throughout the macula
- Peripheral flecks may be associated.
- Children present between the ages of 6 and 20 years with a history of gradual bilateral deterioration of the central vision.
- The probability of maintaining 20/40 or better vision in at least one eye is estimated to be 52% by age 19, and 22% by age 39.
- Once acuity drops below 20/40, it tends to decrease rapidly to 20/200.
- Initial clinical macular changes in Stargardt disease include ill-defined yellowish perifoveal flecks; with progression, diffuse pigment epithelial abnormalities are recognized as a glistening area described as "beaten bronze"
- Foveal changes in early stages may not be clinically apparent at all.

- Fluorescein angiography may reveal subtle central pigment epithelial defects that were not clinically obvious.
- The macular retinal pigment epithelial atrophy occurs in a bull's-eye pattern which is more obvious angiographically than clinically.
- Choroidal "silence" or dark choroid is present in some cases of Stargardt disease, as well as in several other heritable retinal dystrophies, and may be due to the increased filtering action of abnormal lipofuscin-laden retinal pigment epithelium.
- In contrast to drusen, with which the fishtail flecks may be confused, the yellow flecks of fundus flavimaculatus typically appear nonfluorescent; if hyperfluorescence is present, it appears in an irregular pattern that does not correspond to the flecks.
- Hyperfluorescence associated with drusen usually corresponds precisely to drusen.
- The ERG is usually normal in Stargardt disease limited to the macula, while a delayed but otherwise normal b-wave pattern may be seen with peripheral fundus flavimaculatus or Stargardt disease with peripheral flecks.
- The EOG tends to be subnormal in some patients, indicating a widespread functional disturbance of the RPE.
- A subgroup of patients with Stargardt disease develops symptoms and signs of cone-rod type retinitis pigmentatosa, including nyctalopia, narrowing of retinal vessels, and ERG abnormalities.
- Histopathologic examination of patients with fundus flavimaculatus usually demonstrates that the retinal pigment epithelial cells are much larger and more densely packed with an intense PAS-positive substance, which is believed to be lipofuscin.
- The greatest concentration of lipofuscin pigment is within the posterior pole.
- The focal areas of hypertrophy of the cells are probably responsible for the nonfluorescent yellow flecks.
- The progression in this disorder occurs over several years and usually results in 20/200 vision or worse by the end of the second decade. No treatment is effective, although antioxidants have been suggested.

CONE DYSTROPHY

- Cone dystrophy is a rare, typically autosomal dominant disorder of progressive cone dysfunction heralded by diminished central vision and color vision in the first through third decades of life.
- Additional symptoms include photophobia, dark-to-light adaptation difficulty, and a history of better vision at night.
- Color vision may be affected out of proportion to the visual loss.
- Visual field examination may show central scotomas with preservation of the peripheral visual field.
- Ophthalmoscopy is characterized by central macular pigment epithelial atrophy, although early cases may appear normal.
- In some cases only a faint granular appearance may be present in the macula, while in others a bull's eye maculopathy or profound geographic atrophy is evident
- Additional findings include arteriolar attenuation, temporal pallor of the optic nerve head, and peripheral, sectoral granular or bone spicule pigmentary changes.

- The differential diagnosis includes Stargardt's disease, retinitis pigmentosa, chloroquine toxicosis, North Carolina macular dystrophy, and central areolar choroidal dystrophy.
- The history can be helpful in distinguishing among these possibilities.
- Presence of the dark choroid effect on fluorescein angiography suggests Stargardt's disease.
- Early constriction of the peripheral visual field suggests retinitis pigmentosa.
- The course of disease is variable, even among members of the same family.
- Vision often declines to the 20/200 level by the end of the third decade.
- No treatment is known.
- Tinted glasses may help reduce photophobic symptoms.

Q: POHS

- Picture of histo spot
- Picture of CHNVM and IVFA
- What is it?
- How would you categorize it?
- Is it treatable?  What are the indications?

OCULAR HISTOPLASMOSIS SYNDROME (OHS)

- Histoplasma capsulatum is found in temperate climates throughout the world.
- It is endemic in the Ohio and Mississippi river valleys and some parts of the Mid-Atlantic states.
- Humans become infected by inhaling spores of the histoplasma organisms in windblown soils and aerosolized pigeon droppings.
- A mild influenza-like illness develops but is usually self-limited and resolves.
- Occasionally the organisms may disseminate into various organs during the initial illness, including the liver, spleen, and eyes, particularly the choroid.
- Signs of ocular histoplasmosis have been found in up to 13% of individuals in endemic areas.
- Approximately 1 in 1000 patients in such areas develop macular disease.
- Patients are usually between 20 and 50 years of age.
- OHS is uncommon in blacks.
- There appears to be an association of HLA-B7 in patients with disciform scarring and histo spots.
- Patients usually have no symptoms such as photophobia, redness, or pain, and there is an absence of anterior chamber or vitreous cellular reaction.
- The characteristic triad of findings of OHS consist of multiple punched-out atrophic choroidal scars, peripapillary atrophy and pigmentation, and macular scars with associated maculopathy.
- The maculopathy may consist of an active choroidal neovascular membrane (CNVM), atrophic scar, or disciform scar.
- Macular atrophic scars predispose to the development of subretinal neovascular membrane, which is the common cause of the visual loss.
- Patients usually complain of sudden decrease in central vision, metamorphopsia, or a central scotoma.
- There is often a serous and hemorrhagic retinal detachment, retinal pigment epithelial detachment, and an underlying CNVM.
- A disciform scar may eventually develop, and central vision can be permanently lost if the CNVM is untreated.
- Rarely has spontaneous improvement in visual acuity been reported.
- In a few patients, visual loss may be the result of reactivation of choroiditis near the macula, but this is rare, as well.
- Laboratory testing has little use in OHS because of the characteristic appearance of this syndrome.
- The incidence of histoplasma exposure in areas where this disease is endemic makes the skin test nondiagnostic; up to 90% of patients in these areas may be skin test positive.
- Furthermore, a skin test can reactivate macular lesions.
- Fluorescein angiography may be useful in detecting subretinal neovascular membranes so that laser photocoagulation can be done.
- Histoplasma capsulatum, although detected in histopathologic sections, has not been cultured from eyes with OHS.

- Histopathologically, choroidal lesions exhibit scarring, lymphocytic infiltration, and chorioretinal adhesions.
- In a few cases, necrotizing granulomas have been noted. It is in these necrotic areas that Histoplasma capsulatum has been found.
- Entities that look like presumed ocular histoplasmosis include :
  - scleral crescent associated with myopic chorioretinal atrophy in myopic degeneration.
  - Multifocal choroiditis
  - punctuate inner choroidopathy
  - subretinal fibrosis associated with multifocal choroiditis
- but all these entities have cells in the vitreous.
- Birdshot chorioretinopathy has less propensity for the development of choroidal neovascular membranes; the lesions are usually deeper, and they occur in older patients.
- Patients who have macular atrophic form of presumed ocular histoplasmosis should be monitored with an Amsler grid.
- Any new metamorphopsia or decreased visual acuity or scotomas should be followed up with examination and fluorescein angiography to determine if a CNVM exists.
- The Macular Photocoagulation Study (MPS) has clearly shown benefit in the treatment of:
  - extrafoveal subretinal neovascular membranes greater than 200 microns from the center of the foveal avascular zone with argon green laser,
  - juxtafoveal membranes between 1 and 199 microns from the center of the foveal avascular zone using krypton red.
- Using this approach, and with a 3-year follow-up, the MPS showed that:
  - only 7% of treated patients with extrafoveal CNVMs had greater than 6 lines of visual loss, compared with 19% of control subjects without treatment.
  - for juxtafoveal subretinal neovascularization treated with krypton laser photocoagulation, at 1 year 25% of control subjects, versus 7% of treated patients, had lost 6 lines of vision
- The recurrence of subretinal membranes within 5 years after laser has been shown by the MPS study to be approximately 26%.
- In cases of subfoveal subretinal neovascular membranes, there is no clear-cut evidence to support any single approach.
- It is thought that because reactivation of CNVMs may represent an immune response, subfoveal membranes can be treated with corticosteroids. But periocular and systemic corticosteroids have resulted in limited success.
- Recently, submacular surgery to remove CNVMs has been beneficial in several patients.
- In the absence of macular involvement, OHS is benign and self-limited.
- The main determinant of final visual acuity is the presence of macular subretinal neovascular membranes, particularly subfoveal neovascular membranes.
- Recurrence of subretinal membrane may be increased as much as 26% within 5 years of laser photocoagulation.

- Patients with a disciform scar in one eye have a 25% chance of developing subretinal neovascular membrane in the fellow eye over a 3-year period if the fellow eye shows macular changes.
- Occasionally, subretinal neovascular membranes may develop de novo, without preexisting macular scars.

Q: TOXOPLASMOSIS

- Picture of active toxo along inf temp arcade
- What happens if we wait to treat?
- How would you treat?
- Is it transmittable to fetus if this is the eye of a pregnant women?

OCULAR TOXOPLASMOSIS

- Ocular toxoplasmosis is the most common cause of posterior uveitis, accounting for up to 50% of cases.
- It is caused by the intracellular protozoan, Toxoplasma gondii, for which the definitive host is the cat; humans are intermediate hosts.
- Toxoplasma infections in humans occur either after ingestion of sporozoites that are shed in cat feces and remain viable in the soil for many years, or by ingestion of encysted forms of the organism, the so-called bradyzoite, in undercooked meat.
- The latter is the most common source of infection in humans, and has a propensity to infect the cardiac muscle and neural tissues, including the retina.
- The encysted form can remain dormant in these particular tissues for years, and then reactivate because of changes in host factors.
- Changes in immunity of the host can result in rupture of the encysted forms; this releases the sporozoites, which transform into actively proliferating tachyzoites that may then cause reactivation of the infection.
- Ocular toxoplasmosis can be the result of congenital infection or acquired infection, although the majority of toxoplasma infections of the eye are congenital.
- In 40% of the cases, congenital infection is passed on by a previously asymptomatic female who becomes infected and subsequently infects the fetus via placental transmission.
- In most cases, infants born with toxoplasmosis are asymptomatic, however, congenital systemic disease (encephalomyelitis, hepatosplenomegaly, and retinochoroiditis), or isolated congenital ocular disease (retinochoroiditis) can occur rarely.
- The neural tissues are particularly susceptible to infection in the first trimester.
- Toxoplasmosis retinochoroiditis usually presents in older children or adults caused by a reactivation of congenital retinal lesions.

- Newly acquired toxoplasma infections in humans occur in six forms: the exanthematous, the influenzal, meningoencephalitic, ocular, visceral, and lymphadenopathic varieties.
- Typically, most immunocompetent patients who acquire the disease present with a mononucleosis-like illness accompanied by fever, lymphadenopathy, and malaise.
- The eyes are not commonly affected in this instance.
- In patients with AIDS, however, toxoplasma retinochoroiditis can be the presenting form of a newly acquired infection, and can have a devastating course that occasionally progresses to orbital cellulitis, despite treatment.
- Patients with toxoplasma infections caused by reactivation of congenital retinal lesions have symptoms of floaters or reduced vision, either from direct involvement of the optic disc or macula, or from dense vitritis.
- There is usually no pain or redness in the eye.
- In severe cases, there may be inflammation of the anterior segment, resulting in keratic precipitates, flare and cells in the anterior chamber, and formation of posterior synechiae.
- Characteristically, fundus examination reveals focal retinochoroiditis (whitening of the retina and choroid) with overlying inflammation in the vitreous.
- In most cases, only one eye is involved.
- There is usually evidence of old congenital toxoplasma scars (densely pigmented chorioretinal scars) in the same eye or in the fellow eye.
- The appearance of the white retinal lesions with overlying marked vitritis has been termed the "headlight in a fog" appearance when viewed by indirect ophthalmoscopy.
- An active retinochoroiditis is often seen as a whitish lesion at the edge of an old pigmented toxoplasmosis scar (i.e., satellite lesion).
- If there is no evidence of adjacent pigmented chorioretinal scar, the focus of retinochoroiditis in some patients may suggest a newly acquired infection.
- Adjacent retinal vessels, particularly the veins, may be sheathed.
- Typically, lesions of toxoplasma retinochoroiditis involve the inner retinal layers, although the outer retinal layers may be involved exclusively.
- For cases in which the outer retinal layers are involved, the overlying vitreous inflammation may be absent or minimal initially, but will increase as the infection progresses.
- Patients with AIDS often have devastating infections from toxoplasma, with a larger area of necrotizing retinochoriditis than in immunocompetent individuals.
- Intraocular inflammation is variable and correlates to the CD4 (T-helper lymphocyte) count.
- Patients with AIDS and ocular toxoplasmosis often have concurrent CNS involvement.
- Most patients have reactivation of past infections, but up to 25% of cases of toxoplasma retinochoriditis in AIDS patients are acquired.
- In the majority of patients the diagnosis of toxoplasma retinochoriditis is a clinical one.
- In uncertain cases, however, serologic testing is useful, including enzyme-linked immunosorbent assay (ELISA) of antibodies against toxoplasma.

- A positive IgM titer suggests recently acquired infection, while a positive IgG titer alone indicates reactivation of old infection.
- It is important to realize that many individuals who have no evidence of ocular toxoplasmosis may have positive IgG titers. Thus, a positive IgG titer does not necessarily confirm the diagnosis.
- However, in a patient with clinical features suggestive of toxoplasma retinochoroiditis, any positive titer may be significant.
- These tests must be done on undiluted serum, since many laboratories report titers of less than 1:16 or 1:32 as negative.
- The Sabin-Feldman dye test used in the past is not used today, since it needs live toxoplasma organisms.
- Patients with congenital toxoplasmosis may show intracranial calcification on CT scans.
- Toxoplasma infection of the eye primarily involves the retina, usually with secondary choroiditis.
- Tachyzoites and bradyzoites within cysts may be found within the retina, which often undergoes necrotic change.
- In the chronic stage, RPE hyperplasia is noted at the margin of the necrotic retina.
- The differential diagnosis of toxoplasma retino-choroiditis is limited in most instances, and in immunocompetent individuals the appearance is characteristic.
- In immunocompromised individuals, differential diagnosis should include other forms of necrotizing retinitis, including CMV retinitis, progressive outer retinal necrosis, and syphilis.
- Toxoplasma retinochoroiditis is a self-limiting intraocular inflammation in most immunocompetent individuals.
- Peripheral lesions of the retina are usually not sight threatening, and because of the self-limited course, do not need to be treated.
- However, when lesions occur within the temporal arcades, or are close to the disc or macula, treatment is indicated.
- A combination of sulfadiazine and pyrimethamine is the treatment of choice; folinic acid is given concurrently to counteract the myelosuppressive effects of pyrimethamine.
- Clindamycin may be used in place of pyrimethamine in patients who are allergic to sulfa medications. This regimen also avoids the bone marrow toxicosis of pyrimethamine. Since clindamycin can cause pseudomembranous colitis, the drug should be discontinued in patients who develop diarrhea.
- Prednisone (1 to 1.5 mg/kg/day) can also be given to patients who have lesions that threaten the optic nerve or the macula.
- Generally, antitoxoplasma medication should be continued for 4 to 6 weeks.
- Steroids should be tapered quickly after the first 2 weeks, and deposteroids injections into the sub-Tenon's space should be avoided.
- Systemic corticosteroids are not indicated in patients who are immunocompromised.

TABLE 34–1 Treatment for Ocular Toxoplasmosis

| Drug | Mechanism of Action | Dosage | Side Effects |
|---|---|---|---|
| Pyrimethamine | Inhibits DHF Reductase (DHF = dihydrofolate) | 25 mg po BID | Myelosuppression—Base line CBC and QD wk |
| Sulfadiazine | Inhibits folate metabolism | 2 g loading dose 1 g po QID | Rash, Stevens-Johnsons syndrome |
| Clindamycin | Kills toxoplasma organisms | 300 mg po QID | Pseudomembranous colitis/GI distress |
| Prednisone | Decreases inflammation Lesions threatening macula or optic nerve | 1–1.5 mg/kg/d | See side effects of corticosteroids |

Note: 1.Folinic acid—5 mg po QD to BID should be given with pyrimethamine as citrovorum rescue

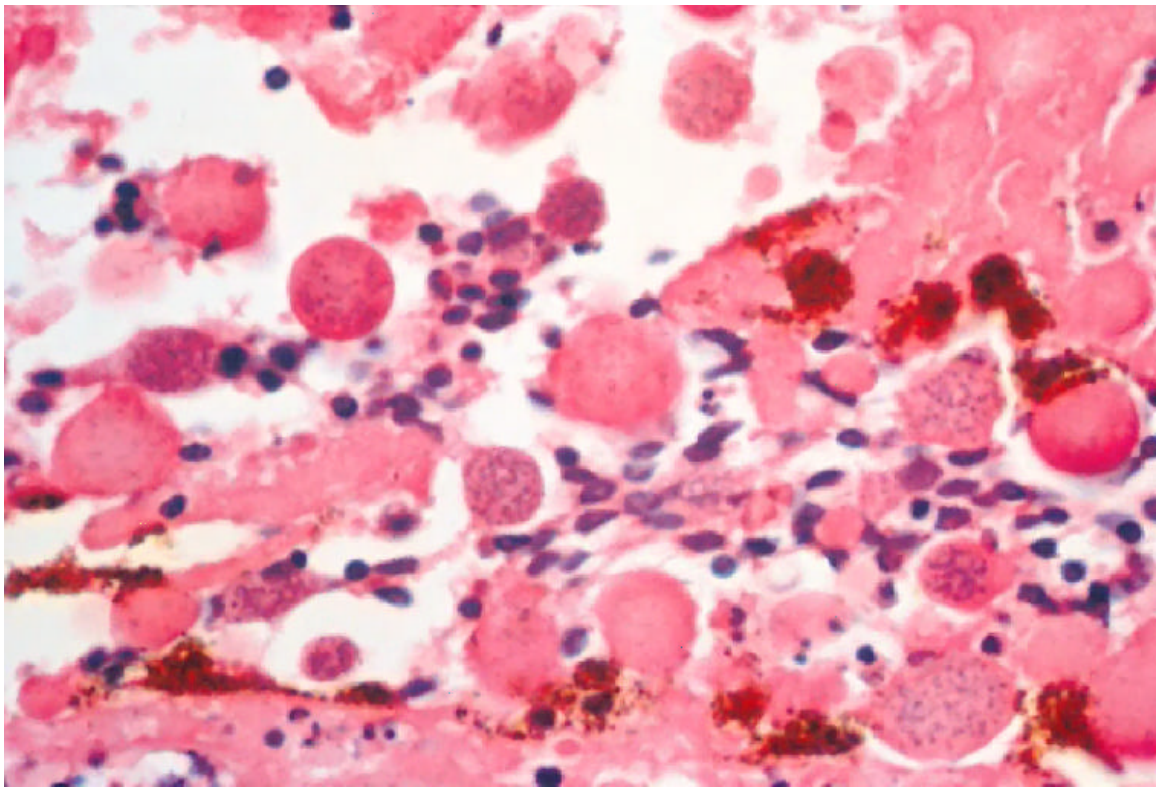
2.Patients with AIDS—Avoid corticosteroids, may need three antibiotics, indefinite maintenance on two or three drugs at one-half of usual doses.

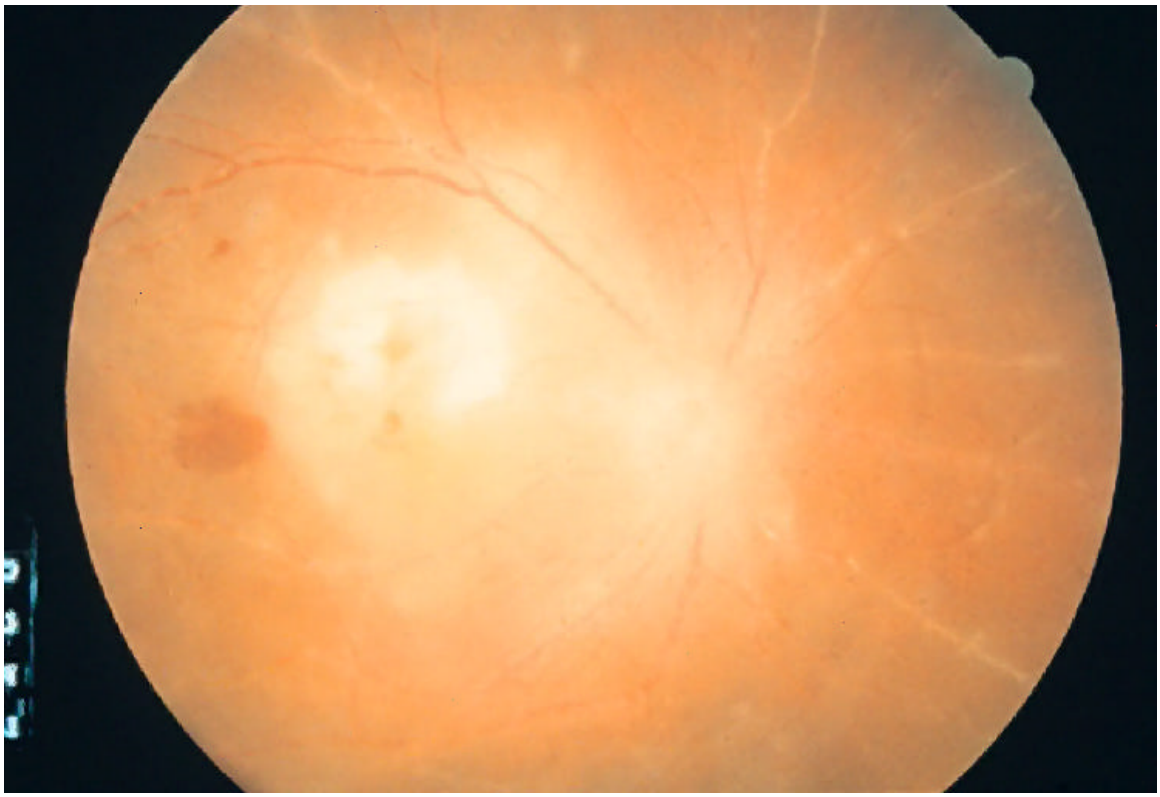
3.Congenital toxoplasmosis—pyrimethamine 1 mg/kg/QD 3 days and sulfadiazine 50–100 mg/kg/d po × 3 weeks

—use corticosteroids if sight-threatening lesions

4.Begin antibiotics and steroids together and taper steroids before antibiotics. Continue antibiotics for 2 weeks longer. Thus, total course of treatment lasts 4–6 weeks.

- Most cases of toxoplasma retinochoroiditis in immunocompetent individuals resolve spontaneously once the host immune system controls the infection.
- Macular lesions or optic nerve lesions, however, may result in irreversible visual loss.
- When posterior segment inflammation spills into the anterior segment, complications of anterior uveitis, glaucoma, and cataract may develop.
- Exudative, tractional, and rhegmatogenous retinal detachments can occur when the inflammation of the posterior segment is severe.
- In addition, subretinal neovascularization may also occur since Bruch's membrane and the RPE are often disrupted adjacent to the toxoplasma chorioretinal scar.
- These retinal complications are rare, however.





Q: RETINAL DETACHMENT/PVR (*2)

- Picture of RD with macula off and PVR stage C1 or C2
- What are the stages of PVR?

Q: BEST'S DISEASE

- Picture of Best's pseudohypopyon stage
- What is the Dx?
- What stage is it?
- What are the various stages?
- What are the genetics?
- If you had one test to help make the Dx what test would you do? (EOG)
- Picture of CHNVM under burned out Best's

Q: RETINITIS PIGMENTOSA

- Picture of RP
- What is the Dx?
- What is the DDx/causes of RP?
- What are the genetics of RP?

- Which is the most common?

Q: OPTIC NERVE COLOBOMA
- Picture of 1 year old with disc coloboma
- How would you assess and treat?
- You cannot do field, but what VF defect would you expect?

Q: CHOROIDAL MELANOMA (*4)
- Picture of choroidal mass lesion
- What is DDx?
- What ancillary tests would you do to help make Dx?
- What are the prognostic factors?
- How would you classify them?
- What is the management?
- Another question has a picture of nevus which grows over time?
- What is the management of a choroidal nevus?

Q: SICKLE CELL RETINOPATHY
- Picture of peripheral NV
- Dx?
- How would you manage?

Q: FOCAL RETINITIS
- Picture of white focal retinitis
- What is Ddx?

Q: ANGIOD STREAKS
- Picture of angiod streaks
- What are the associations?
- How would you manage?

Q: CRAO
- Picture of Macular edema
- What is Ddx?
- Picture of CRAO with cilioretinal artery sparing
- How many patients have cilioretinal arteries?
- How would you manage an cute CRAO?

Q: TUBEROUS SCLEROSIS
- Picture of astryocytic hamartoma of ON and adenoma sebaceum on face
- What is Dx? DDx?
- What are the associated findings? Any life threatening? (cardiac rhabdomyoma)

Q: SCLERAL BUCKLE COMPLICATIONS

- Flat chamber post SB
- What might the problem be?
- How would you manage choroidals? Would it be any different if they were kissing?

Q: CHRNVM (*3)
- Extrafoveal net picture
- How would you manage this
- DDx of CHRNVM

Q: PERIPHERAL TRACTION
- Picture of peripheral traction without RD
- How would you manage?
- What parameters of laser would you use?

Q: DM WITH CSME
- CSME picture
- How would you manage?
- When would you treat?

Q: MACULAR HOLE (*2)
- Picture of macular hole
- Classify?
- When do you treat?

Q: CRVO
- Picture of CRVO
- Ischemic vs. non ischemic how do you differentiate?
- How do you manage each?
- When is the vascularization of the retina complete?

Q: NEOVASCULARIZATION
- What are the 3 requirements for neovascularization to occur?

Q: DM
- Picture of proliferative DM
- How would you manage?
- Why does PRP cause regression?

Q: ARMD
- Classic CNVM
- Why is this classic?
- Subdoveal CRNVM
- How would you manage?

Q: CMV
- Picture of CMV
- DDx?
- HIV and CWS spots?

Q: PVD
- What happens in a PVD?
- How do you Dx?
- What is the incidence of tears?

Q: TEARS
- What conditions predispose to retinal tears?
- How would you do focal laser and cryo?
- What is the pathology of lattice degeneration?
- What is the incidence and prevalence of tears?

Q: IVFA
- What are the various stages of IVFA

Q: ANATOMY
- Draw the histology of the macula
- Draw RPE, Bruch's and the choriocapillaris
- Describe problems in Bruch's membrane
- What are the different layers of Bruch's membrane and their pathology
- Where are the attachments of the vitreous
- What is the embryology of the vitreous?

NOTE – LIFE THREATENING OCULAR EVENTS/SIGNS
- Must know all of these for orals
- $3^{rd}$ n – PCA Aneurysm
- bear tracks – gardner's polyposis
- astrocytic hamartoma – TS – cardiac rhabdomyoma
- corneal nerves – MEN IIb – thyoid ca
- aniridia – wilm's