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Multifocal toxoplasmosis in an immunocompetent host

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Case presentation

- A 33 year old female patient presents with a history of recent onset blurring of vision and floaters of her left eye for 2 weeks.
- She is not known to be diabetic or hypertensive
- She is married with 2 children
- No history of similar attacks

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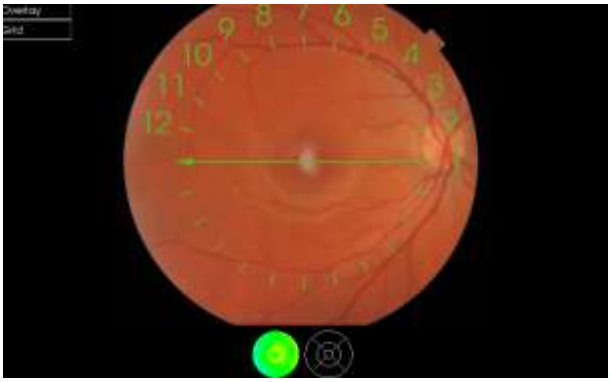
- Drug history : she is on oral prednisone prescribed by an ophthalmologist whom she sought his advice recently (he prescribed 60 mg/ day for 5 days, then 40 mg/ day for other 5 days then 20 mg/day for 5 days)
- She is also on oral contraceptive pills
- ROS: no other system complaint (No oral or genital ulcers, no cutaneous changes, no respiratory, GI, neurological, respiratory or musculoskeletal symptoms)

Examination

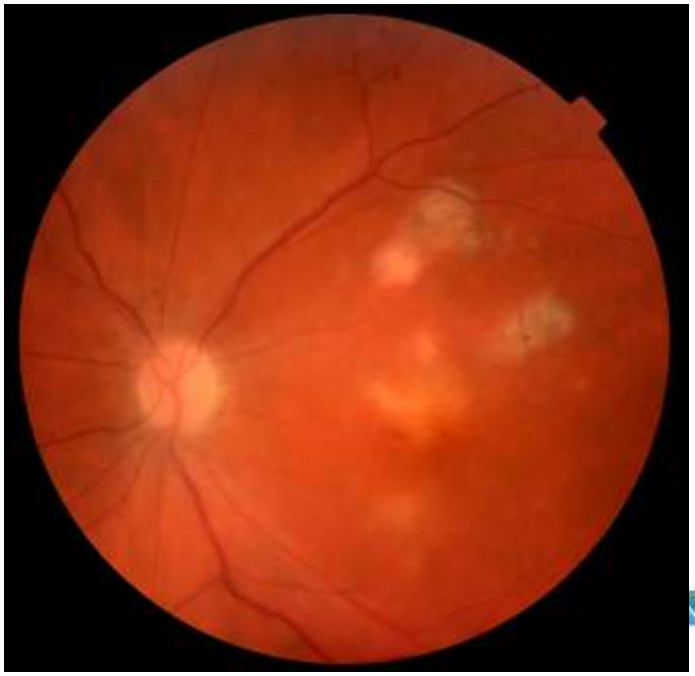
Right eye

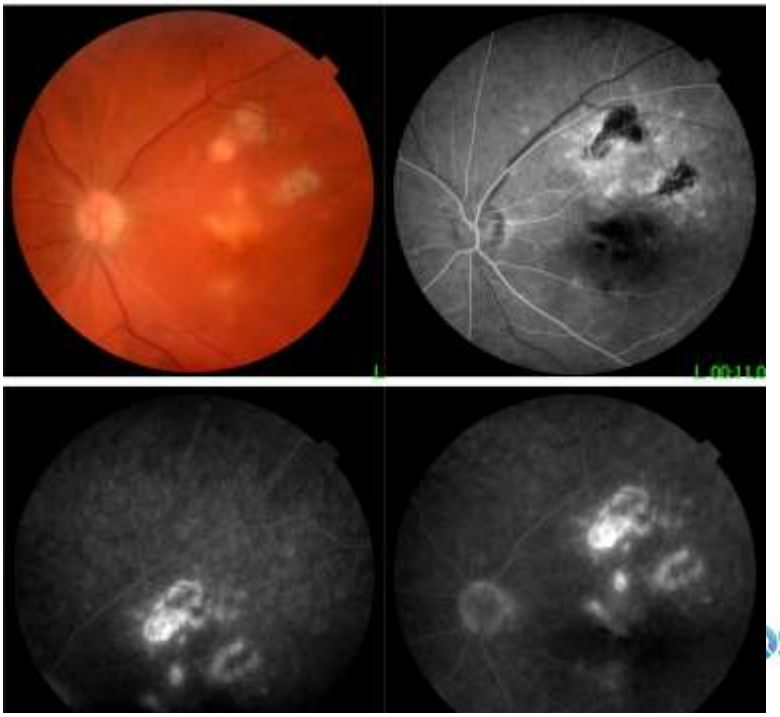
- Unremarkable ophthalmological examination (normal anterior segment, UCVA: 6/6, and normal posterior segment.
- Refraction: -0.25 sphere

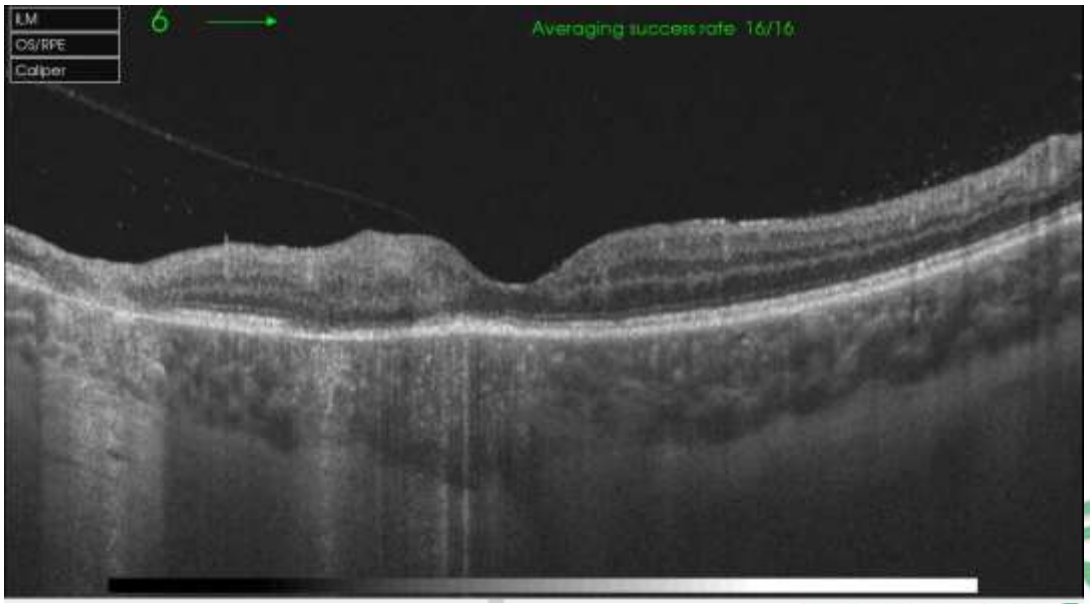


Left eye

- VA 3/60
- AC : 1+ AC cells, IOP: 28
- Vitreous cells and diffuse haze (1+ haze and cells)
- Fundus: multifocal yellowish well defined lesions involving the outer retina and choroid at the posterior pole, with healed edge of each lesion







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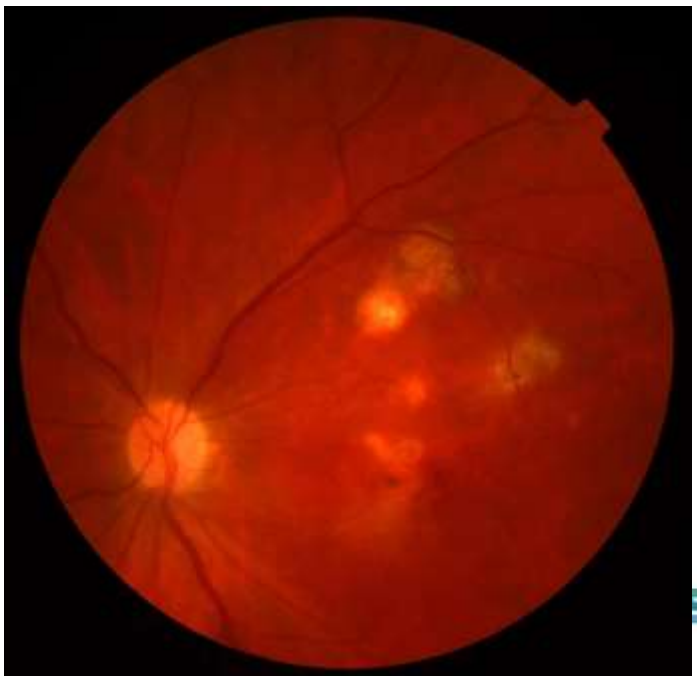
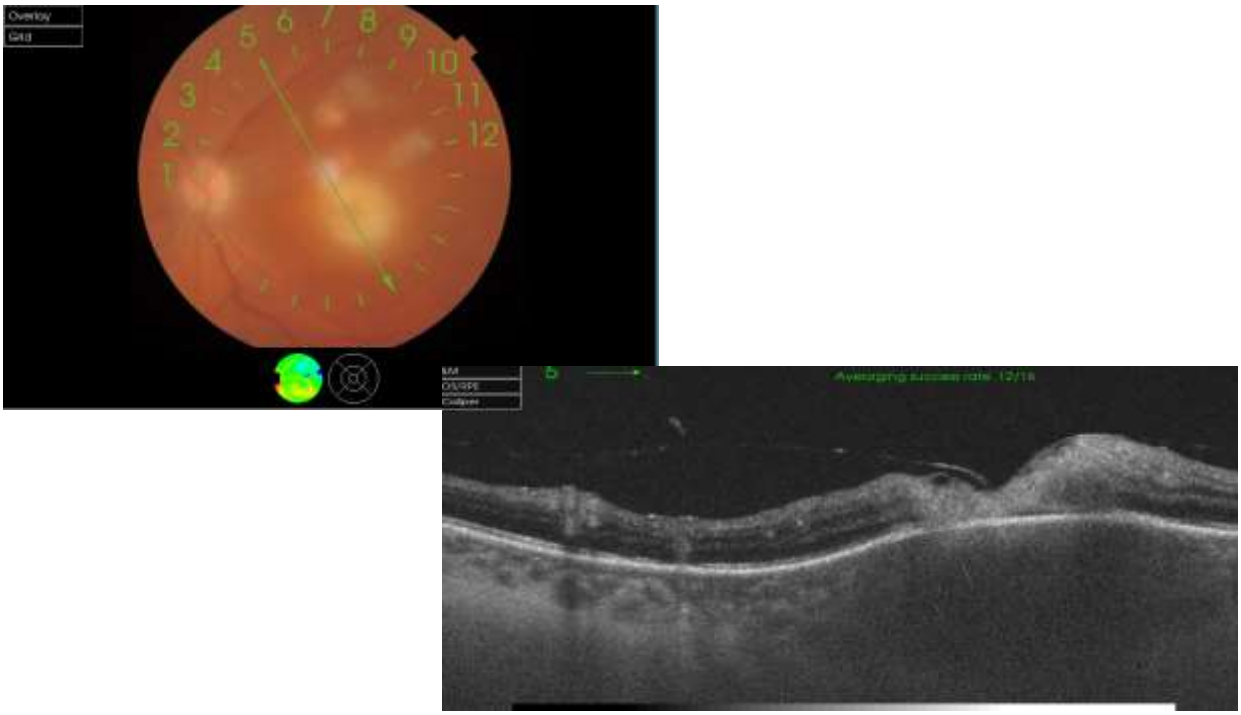
- Of those lesions include infectious and non infectious etiology.
- Work up was ordered to exclude some important infectious causes.
- Her labs showed within normal CBC, negative quantiferon Gold TB test, negative syphilis serology, within normal serum ACE levels.
- Toxoplasma serology was negative for both IgG and IgM.
- Because the clinical appearance of the lesions with scarred edges and OCT picture pointed to toxoplasmosis, we decided to repeat the test in another lab, but results came again negative !!!

- Oral steroids given to the patient resulted in improvement of vitreous cells and haze initially, but once we started tapering below 20 mg/day, recurrence of haze and floaters occurred.
- Decision was made to start her on spiramycin 4.5 mIU/ day in addition to trimethoprim/sulfamethoxazole 160/800 mg twice daily.
- Two weeks later, resolution of inflammatory reaction was noted. In addition, lesions at the posterior pole became well defined, darker yellowish i.e. started to become inactive
- VA improved to 6/36

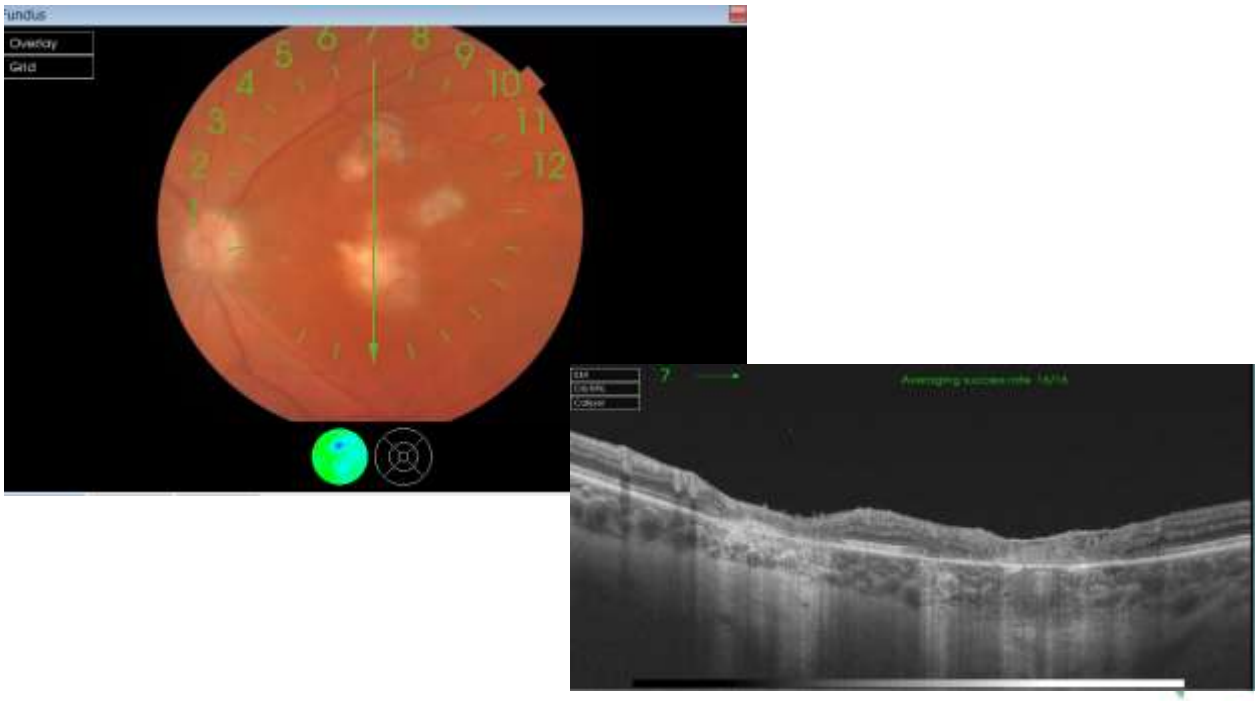


- This therapeutic response confirmed the clinical diagnosis of toxoplasmosis.
- The patient denied any history of contact with cats.
- HIV serology was ordered and came back negative.
- Treatment was continued for 1 month and stopped.

- Few months later, she came again with another attack.
- Examination showed recurrence of inflammation, with recuurence of the perifoveal lesion and enlargement to involve the foveal center this time.

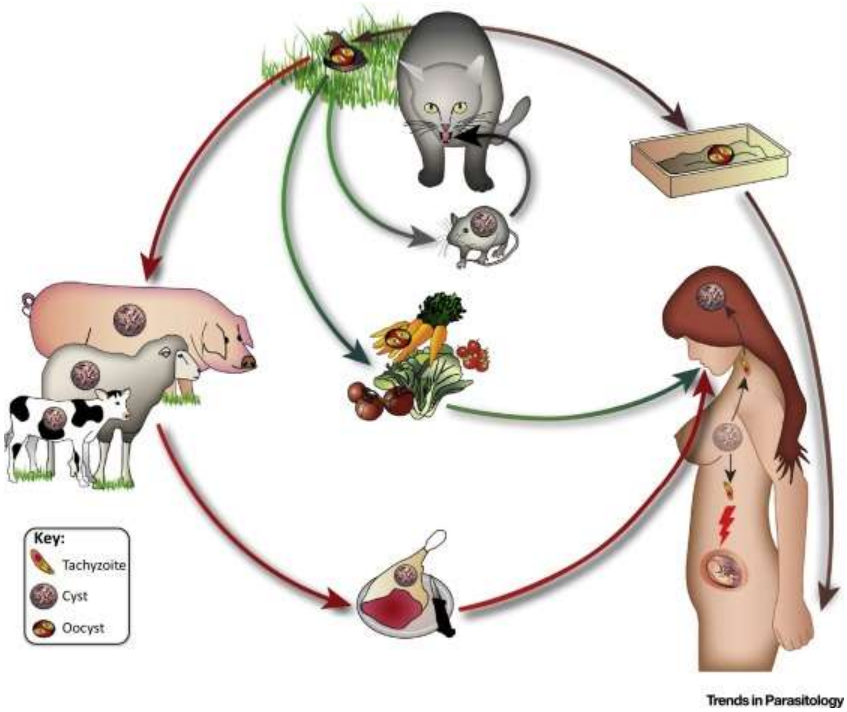


- Treatment with spiramycin and septrin was repeated in addition to low dose oral prednisone 20 mg/day but we decided to maintain septrin for a longer duration

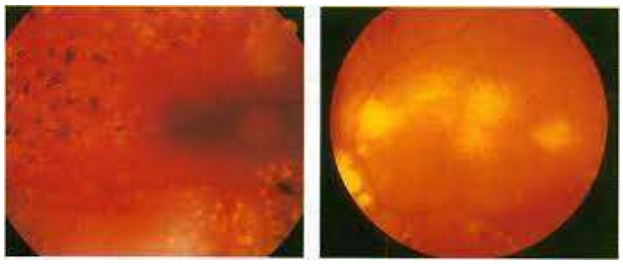


Discussion

- Toxoplasma retinitis is the most common cause of posterior uveitis and infectious retinochoroiditis in adults and children, with a lifetime occurrence of approximately 2% of the population.
- In the non-immunosuppressed host, toxoplasma retinitis typically presents as a unifocal lesion with rapid-onset vision loss.



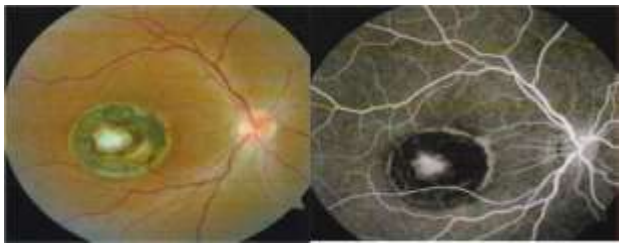
- On the other hand, in immunosuppressed patients, toxoplasma retinitis can be multifocal or even may involve confluent areas mimicking viral retinitis.



- While ocular toxoplasmosis usually presents in the classic form, it may as well present in variable clinical spectrum.
- Transmission of infection can be verical (congenital form) or acquired by ingestion of contaminated food or water

Congenital toxoplasmosis

- Typical presentation in the retina is an atrophic hyperpigmented scarred macular lesion that is described as ‘wagon-wheel’ lesion caused by congenital toxoplasmosis. It shows a central area composed of glial and pigmented material connected by pigmented strands to a peripheral ring of pigment at the edge of the lesion

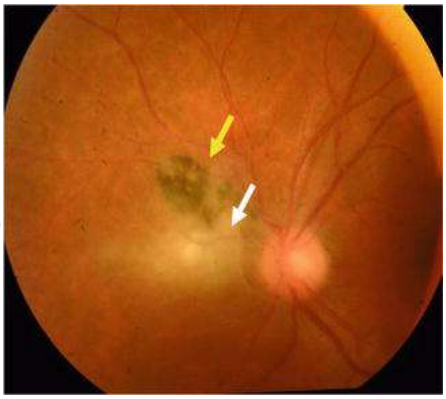


- Acquired ocular toxoplasmosis commonly manifests in the second through fourth decades . Approximately 10% of otherwise healthy individuals who contract the infection report nonspecific symptoms, such as fatigue, fever and myalgias and cervical lymphadenopathy.

- Though floaters with altered vision may be the most common symptom of toxoplasma retinitis, however, clinical presentation ranges a wide spectrum.
- Anterior uveitis is a common finding, with mutton-fat keratic precipitates, fibrin, cells and flare, iris nodules and posterior synechiae . Raised intraocular pressure has been reported in (30%–38%) of the cases

Typical toxoplasma retinitis

- This usually manifests as active focal necrotizing retinitis, at the edge of an old, pigmented scar with overlying vitritis .
- Bosch-Driessen et al. reported 72% of the patients had pre-existing retinochoroidal scars, indicating prior subclinical disease. The pigmented scar has been described to harbor the cysts that remain dormant until the cyst ruptures with release of organisms into the surrounding retina inducing adjacent retinitis



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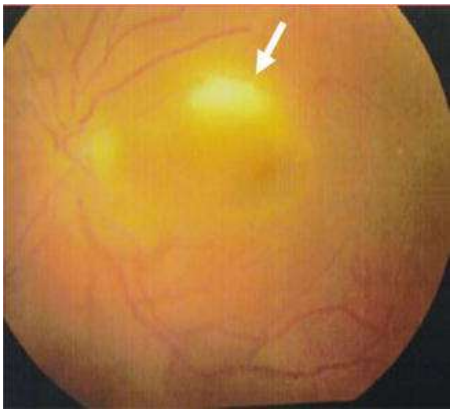
- Toxoplasma retinitis may occasionally manifest without an adjacent scar . It is known that tissue cysts can exist in normal-appearing retina. The retina may be infected at the time of an initial systemic infection, but without clinically apparent lesions at the time



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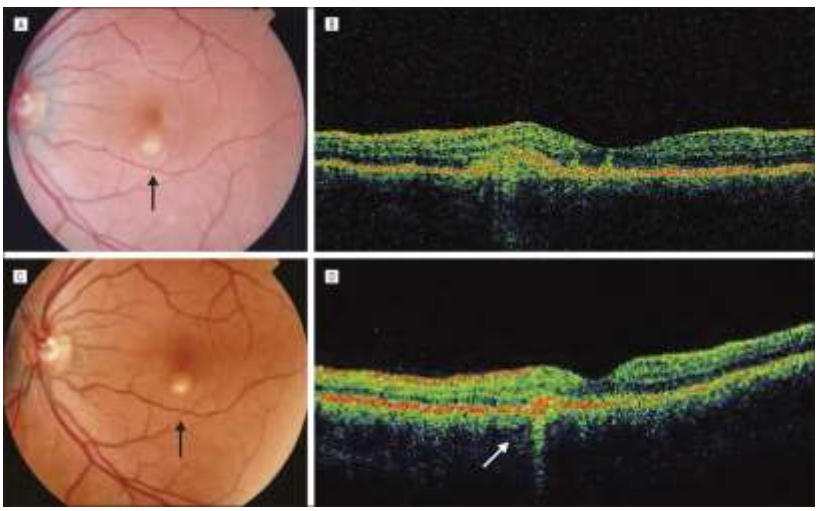
Pathology

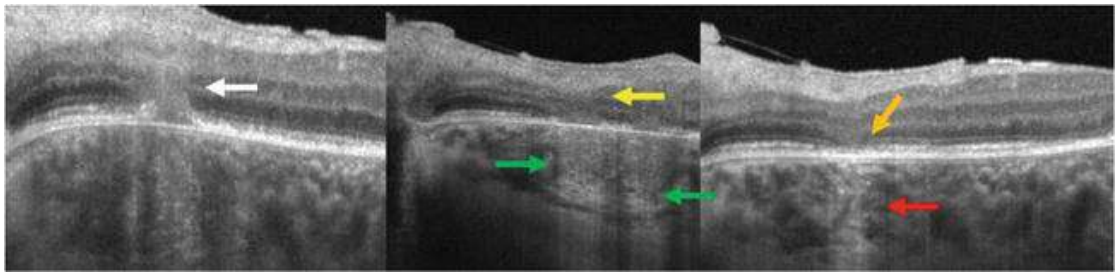
- The focus of retinitis is of necrotizing nature and usually involves the full thickness of the retina, although occasional limited involvement of either inner or outer retina occurs, as described by Friedmann and Knox. Depending upon the thickness of involved retina, the overlying vitreous and underlying choroid are variably involved.
- On regression of the retinitis, a pigmented scar that is smaller than the actual size of the retinitis forms.

Other forms of ocular toxoplasmosis

Punctate outer retinal toxoplasmosis (PORT)

- Punctate outer retinal toxoplasma (PORT) was first described in 1985 by Doft and Gass .
- They elucidated the outer variation of punctate toxoplasmosis that primarily affects the outer retinal layers of the macular area.
- This entity usually presents in younger, immunocompetent patients.





- **White arrow**: active lesion showing inflammatory nodular infiltrate breaking through the RPE and extending to the inner plexiform layer . The underlying choroid shows loss of architecture
- As the lesion heals the infiltrate decreases in height (yellow arrow) and the choroid appears less thickened with incomplete recovery of the normal choroidal vasculature (green arrow)
- Complete recovery of the lesion with complete disappearance of the nodular infiltrate, leaving thinned depressed inner retinal layers (orange arrow) with partial recovery of the RPE and increased choroidal transmission with recovered choroidal vasculature (red arrow)

- These can be either a single or several deep retinal infiltrates that may extend as far as the inner plexiform layer (IPL). The underlying retinal pigment epithelium is interrupted with variable involvements of the Bruch's membrane and choroid. These lesions have been detected in the same eye with typical retinal toxoplasma lesions or in eyes with no previous toxoplasma lesions
- PORT lesions resolve slowly, leaving an atrophic chorioretinal scar and frequently recur in adjacent areas of the macula.

Retinal vascular involvement of ocular toxoplasmosis

- Inflammatory vascular involvement in acute toxoplasma retinochoroiditis constitutes an invariable clinical sign of the disease and was reported in (100%) of cases in a previous study.
- Inflammation of the retinal vessels can occur in close proximity to the area of retinitis. The intensity of the vascular involvement was reported to be more prominent were the vessel traverses the active lesion. Vasculitis may also present away from the actual focus of inflammation and involve vessels in all four quadrants.

Optic nerve involvement in ocular toxoplasma

- Optic nerve involvement may be due to parasitic invasion or reactive inflammation .
- Eckert et al., reported optic nerve changes in 5% of the cases. In 35% of the cases, retinitis was juxtapapillary .
- In pure papillitis, the parasite affects the optic disc directly, causing a swollen ONH with sheathing of the peripapillary veins and there may be no concurrent active retinochoroiditis lesion.

- Optic nerve involvement may induce severe visual field defects as well as loss of color vision .
- Neuroretinitis has also been described as a unique presentation of ocular toxoplasmosis

Diagnosis

- In most cases depends on characteristic clinical appearance.
- In atypical cases, laboratory confirmation is required.
- Serum levels of antibodies against T. gondii is the most frequently used test. However, it is not confirmatory for diagnosis.

- Since seropositivity is very common in most communities, the positive predictive value of IgG is low, and a positive IgG cannot be interpreted as indicative of active toxoplasmic infection. However, a rise in titer of specific IgG antibodies over a 3-week period has been used as an indicator of recent infection

- In immunosuppressed subjects, positive serological tests indicate infection, however, negative tests do not exclude previous or concurrent infections.
- Levels of antibodies in aqueous humor and their relationship to serum antibodies may help in establishing the diagnosis of ocular toxoplasmosis.

GWC (Goldmann Witmer coefficient) is

- Anti-Toxoplasma IgG in aqueous humor/total IgG in aqueous humor)/(anti-Toxoplasma IgG in serum/total IgG in serum)

PCR

- PCR testing of ocular sample (Aqueous tap) can be useful in presumed toxoplasmosis in patients older than 50, in cases with inflammation (Tyndall ≥1/2+, panuveitis), area of retinochoroiditis>3 DA, and when ocular sampling performed within 1 week of presentation after onset of symptoms and up to 4 months

Treatment

Classic therapy is a combination of

- Pyrimethamine 25 mg–50 mg daily orally
- Folinic acid 5 mg every other day
- and sulfadiazine 1 g four times daily
- systemic corticosteroid.

- Oral corticosteroids are used during the active phase to reduce the retinal inflammation and thus further collateral tissue damage and also to prevent blood-retinal barrier breakdown. Hence, it can also reduce toxoplasma scarring.
- Steroids are usually started from 1 to 3 days after starting antiparasitic agent and continued for approximately 1 month.
- They are not used if the patient is immunocompromised.

- Pyrimethamine side effects include gastrointestinal and dermatological manifestations as well as hematological adverse events, including leukopenia and thrombocytopenia, that mandate monitoring of the blood picture regularly throughout the treatment course.

Alternative therapy

- Trimethoprim-sulfamethoxazole 160 mg–800 mg twice daily orally with systemic corticosteroid, which is a well-tolerated combination although sulfonamide-related reactions may occur.
- The common side effects include mild gastrointestinal symptoms and mild maculopapular rash. However, this regimen is relatively well tolerated with side effects requiring discontinuation in 4% of patients in contrast to 26% with the classic therapy.

In severe /resistant cases, we may add any of the following

- Clindamycin 300 mg four times daily
- Atovaquone 750 mg three/four times daily orally
- or azithromycin 250 mg daily orally

Intravitreal injections

- Intravitreal clindamycin (1 mg) and dexamethasone (400 µg) have been used, injections can be repeated at 2-week intervals, based on a 5.6-day half-life of intravitreal clindamycin.
- This is indicated in severe sight threatening conditions or in pregnant ladies

Prophylactic treatment

- Trimethoprim and sulfamethoxazole may be used in the prevention of recurrent attacks of ocular toxoplasmosis.
- Silveira et al. found that trimethoprim-sulfamethoxazole (160 mg–800 mg), taken orally every 3 days for 20 months, significantly reduced the risk of recurrent toxoplasmic retinochoroiditis from 23.8% in untreated control subjects to 6.6%

Take home messages

- Some uveitis cases are NOT treated with steroids
- Infectious uveitis
- Toxoplasmosis is the most common cause of posterior uveitis
- There are many pictures of toxoplasmosis other than the classic head light in the fog lesion with an adjacent retinal scar.
- Awareness by the physician of those different pictures can raise suspicion in order to initiate appropriate treatment

- OCT is a valuable tool in diagnosis of the etiology of posterior uveitis by recognizing different signs that constitute special patterns depending on etiology, and also for follow up.

- Serology is not 100% accurate tool. Sometimes, false positive and false negative results can occur.
- The only sure diagnosis of infectious cases is by isolation of the organism itself (smears and cultures) or its DNA/RNA (by PCR) from involved tissues

- Different drugs are available for treatment of toxoplasma retinochoroiditis. Among those, septrin is recommended for long term prophylaxis in patients who show frequent recurrences

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Thank you