REFERÊNCIAS BIBLIOGRÁFICAS

1. SMITH, R. E. & NOZIK, R. A. — Laboratory Testing. In: Uveitis. A clinical Approach to diagnosis and management. Williams & Wilkins 428 East Preston St. Baltimore MD 21202 USA. 1983, p. 33.
2. MAPSTONE, R. & WOODROW, J. C. — HLA-B27 and acute anterior uveitis. Brit. J. Ophthal. 59: 270, 1975.
3. ORÉFICE, F.; CARVALHO, M. A. P.; MOREIRA, C. & CRUZ F.º, A. — Uveítes reumáticas. Arq. Bras. Oftal. 44 (2): 10, 1981.
4. WEINREB, R. N. & KIMURA, S. J. — Uveitis associated with sarcoidosis and angiotensin converting enzyme. Am. J. Ophthal. 89: 180, 1980.
5. KARMA, A.; POUKKULA, A. & RUOKONEN, A. — Gallium 67 citrate scanning in patients with lacrimal gland and conjunctival sarcoidosis. Acta Ophthalmol. 62: 549, 1984.
6. WAKEFIELD, D. & PENNG, R. — Immunology of ocular toxoplasmosis. Austr. J. Ophthalmol. 10: 277, 1982.
7. KRILL, A. E.; CHISHTI, M.; KLIEN, B. A.; NEWEL, F. W. & POTTS, A. M. — Multifocal inner choroiditis. Trans. Am. Acad. Ophthalmol. Otolaryngol. 73: 222, 1969.
8. TAGAWA, Y.; SUGIURA, S. & YAKURA, H. et al. — The association between major histocompatibility antigens (HLA) and Vogt-Koyanagi-Harada syndrome. Acta Soc. Ophthalmol. Jpn, 80: 486, 1976.
9. SHIMIZU, T.; EHRLICH, G. E.; INABA, G. & HAYASHI, K. — Behçet disease (Behçet syndrome). Sem. in Arthr. and Rheum. vol. 8 n.º 4, 223, 1979.
10. BELFORT JR., R.; MOURA, N. C. & MENDES, N. F. — T and B lymphocytes in the aqueous humor of patients with uveitis. Arch. Ophthalmol., 100: 465, 1982.

Toxoplasmic Retinochoroiditis

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Ocurrence and Presentation:

Toxoplasma gondii is a protozoan parasite that is one of the most common causes of posterior uveitis in humans. Infection with toxoplasma is not rare. Up to 50% of the population in the United States has been infected. In less developed countries with poor sanitation, the infection rate may be even higher. Because of the ubiquitous nature of toxoplasmosis, the mere presence of a positive antibody titer against toxoplasmosis does not mean that the inflammatory disease seen is caused by **Toxoplasma gondii.** One must have a typical ocular lesion in order to make this diagnosis.

Ocular manifestations of toxoplasmosis consist primarily of posterior uveitis manifest as a focal retinitis. Histopathologically in the eye, toxoplasma have only been found in the retina. Inflammation that occurs in the choroid, iris and retinal blood vessels is believed to be immune in origin and not due to actual infection. The typical focal retinitic lesion can only be reproduced in experimental animals with live organisms. The inflammation that occurs in other structures including the blood vessels can be reproduced with dead organisms. Thus, when there is a typical focal retinitic lesion of **Toxoplasma gondii** present, it indicates that infection with actual living organisms is present.

Toxoplasma gondii can infect any portion of the retina. Most cases of ocular toxoplasmosis occur in the posterior pole. It is possible that the dense circulation in the posterior fundus brings more organisms to this site. It is also possible that posterior pole lesions are more likely to bring patients to the doctor than peripheral small lesions. Juxta-papillary and optic nerve head lesions may occur. (Figure 1)

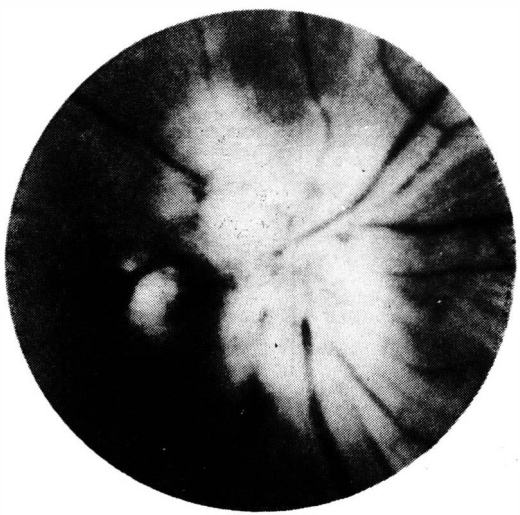

Fig. 1 — Juxtapapillary toxoplasmosis.

The focal necrotizing retinitis that is the hallmark of ocular toxoplasmosis is usually seen as a white or yellow-white lesion with fluffy or indistinct edges. The size varies

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from 1 to 5 or 6 disc diameters. The center of the retinitis is homogeneous in appearance. (Figure 2) Cells stream into the vitreous from this area of retinitis giving the picture of a smoking fire. The vitreous cellular reaction may be so dense at times that with a direct ophthalmoscope, it is difficult to appreciate the fundus lesion. Binocular indirect ophthalmoscopy may reveal the area of inflammation. Sometimes, even with the indirect scope, all one sees is a white lesion through dense haze.

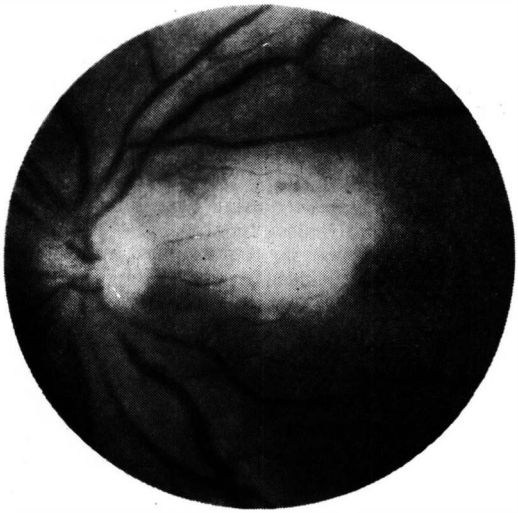

Fig. 2 — Typical focal retinitis of ocular toxoplasmosis.

The posterior vitreous phase often detaches from the retina. Precipitates occur on the posterior vitreous face resembling keratic precipitates on the corneal endothelium. In spite of the hazy vitreous, it is amazing how well some patients are able to see if the macula is not involved.

In most patients, ocular toxoplasmosis is believed to be a recurrent infection. Most ocular toxoplasmosis is believed to occur congenitally. Thus, recurrent toxoplasmic retinitis often "satellites" or occurs adjacent to an old pigmented scar. Hence, the appearance of a white fluffy active retinitis adjacent to a pigmented scar is highly suggestive of toxoplasmic retinitis. Inactive scars often show groupings of scars adjacent to each other so that one can trace the previous infection. (Figure 3)

Iritis commonly occurs as an immune reaction to the retinitis. The iritis can vary from mild nongranulomatous to severe granulomatous in form. There may be mutton fat KP. It is very important to remember that any patient with an anterior iritis may have an underlying retinitis. It is important

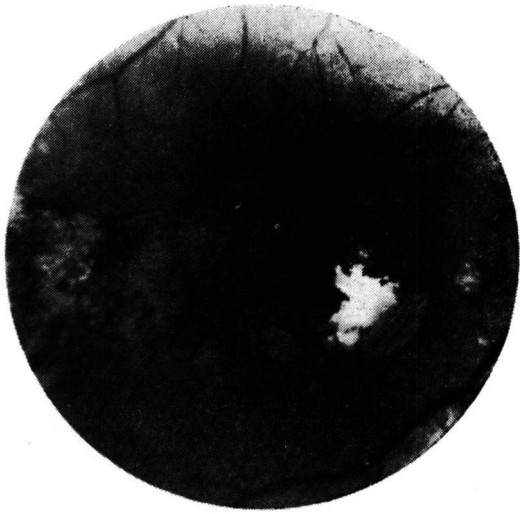

Fig. 3 — Satelliting. Multiple scars show previous episodes of retinitis.

to examine the fundus in all of these patients.

Retinal vasculitis is an immune phenomenon that commonly occurs with ocular toxoplasmosis. Segmental periarteritis and diffuse perivenular sheathing may occur. The sheathing usually occurs near the site of the inflammation. However, sometimes the sheathing may be diffuse and found in remote areas of the fundus. Arteriolar occlusions and branch vein occlusions also are reported.

An unusual manifestation of ocular toxoplasmosis is the so called "deep" retinal lesion. In these deep lesions, the affected area is yellow and homogeneous both in color and density. The area of retinitis has distinct orders that are not fluffy. Vitreous cells do not emanate from lesion. Thus, this type of retinitis appears quite diffrent than the typical toxoplasmic retinitis. (Figure 4) The overlying nerve fibre layer often appears healthy. Within one to two weeks, many of these deep lesions evolve into the more typical toxoplasmic lesion. If there are no scars in the fundus, the diagnosis of deep toxoplasmic retinitis is quite difficult.

Another unusual presentation of ocular toxoplasmosis is that of the massive granuloma. (Figure 5) These lesions are usually greater than 6 disc diameters in size. There are generally multiple inactive scars from previous episodes of infection. The massive granulomas have relatively sharp borders with a more amorphous center. Cellular exudation into the vitreous is usually very dense. These massive granulomas tend to respond poorly to therapy. This is probably accounted for by the size of the lesion and

the difficulty of antibiotics to penetrate into them.

Subretinal neovascularization is not commonly associated with ocular toxoplasmosis. However, it may occur. Chorioretinal anastomosis also occurs with ocular toxoplasmosis. In this condition, the retinal blood-flow connects to the chroidal circulation in the center of an inactive toxoplasmic scar.

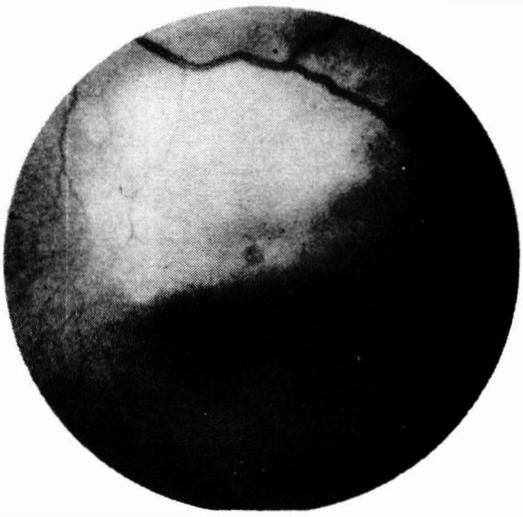

Fig. 4 — Deep toxoplasmic retinitis. Compare with more typical lesion in Fig. 2. Note distinctness of deep retinitis. After a week or two, these lesions often looks more like figure 2.

Fig. 5 — Massive granuloma. Note hazy media, relatively sharp borders and amorphous center.

An epiretinal membrane sometimes occurs after a bout of focal retinitis. The epiretinal membrane may occur in the macula even though the area of retinitis was away from the macula.

Retinal detachments also are reported with ocular toxoplasmosis. These do not occur commonly but are probably due to vitreous traction and retinal tears.

Diagnosis:

The diagnosis of ocular toxoplasmosis is made by having a typical retinitic lesion with a positive antibody titer. As stated previously, since occult infection occurs so commonly in the population, the mere presence of a positive antibody titer in the absence of a typical fundus lesion does not make the diagnosis of ocular toxoplasmosis.

The height of the antibody titer is usually not important in ocular toxoplasmosis. If the only active lesion in the body is in one eye, this may not be a sufficient source of antigen to significantly raise the systemic antibody level. Thus, any positive antibody titer, even at a 1:1 dilution is significant. Many laboratories do not test at dilutions below 1:8 or 1:16. The laboratories may report the absence of an antibody below these levels as negative. It is important for an ophthalmologist to ask for tests even at a 1:1 dilution if the higher dilutions are negative. There are occasional cases where the organism has been found histopathologically in the eye when the titer has only been positive 1:1 or 1:2.

Most laboratories use the indirect fluorescent antibody test. They usually measure IgG antibodies. IgM antibodies can also be measured when acquired infection is suspected. The Sabin-Feldman dye test is not used commonly these days because it requires live toxoplasmic organisms to be kept in the lab. Other available laboratory tests for toxoplasmosis include the indirect hemagglutination test, the enzyme-linked immunosorbent assay (ELISA) and a fluoroimmunoassay.

Differential Diagnosis:

The differential diagnosis of toxoplasma retinitis includes most posterior fundus lesions.

1. Tuberculosis may be mistaken for ocular toxoplasmosis. However, tuberculosis usually involves the choroid and tends to be multifocal rather than focal. Vitreous involvement is mild.

2. Syphilis more commonly involves retina as does toxoplasmosis. However, syphi-

lis is commonly a multifocal type of infection and vitreous involvement tends to be less severe than with toxoplasmosis.

3. Viral retinitis (cytomegalovirus, and herpes simplex) usually involves immunocompromised hosts. Retinal toxoplasmosis can occur in immunocompromised people since it is an opportunist organism but more commonly it is seen in patients with normal immunity. Viral retinitis usually involves diffusely the midperipheral retina with mild to moderate vitreous haze. The area of retinitis usually occurs in broad nonfocal areas of multiple coalescent yellow-like dots. There are frequent hemorrhages which give the lesion a bloodtinged appearance.

4 Acute retinal necrosis (ARN) resembles viral retinitis. In fact there is evidence that ARN is caused by a virus. Large broad areas in the mid-peripheral fundus become white to yellow-white. Hemorrhage is not as commonly seen as with viral retinitis. These patients are immunologically normal. Retinal detachment occurs frequently in these patients as the necrotized areas of retina heal with pigment stippling.

5. Candida endophthalmitis may initially present as a superficial granuloma that mimics toxoplasmic retinitis. The candida granuloma rapidly enlarges and looks like a puff-ball. It quickly breaks out into the vitreous. Toxoplasmic lesions remain at the retina. Patients at risk for candida endophthalmitis include those with a history of intravenous drug abuse or long term intravenous drug therapy.

6. Ocular histoplasmosis occurs in the choroid rather than the retina. Inactive scars of ocular histoplasmosis may resemble those of toxoplasma retinitis. The lesions of histoplasmosis tend to be smaller and there is often a ring of peripapillary atrophy. Moreover, in ocular histoplasmosis, the vitreous is clear and there is really no sign of inflammation.

7. Behcet's disease with retinal infarction may cause large white cotton wool spots. These may resemble toxoplasmic retinitis. These white lesions are usually at the level of the nerve fiber layer and they do not exude cells in the manner of toxoplasmosis. There is also an occlusive vasculitis with hemorrhage in Behcet's disease.

8. A sarcoid granuloma may resemble a toxoplasmic retinal lesion. Sarcoidosis does not have necrosis and so the lesion is not as white and fluffy as in toxoplasmosis. The lesion has more distinctness to its surface and edges.

9. A toxocara granuloma might be mistaken for toxoplasmic retinitis. In toxocara, the lesions are usually white and elevated. Vitreous strands adhere to the granuloma distorting the retina. Toxoplasmic granulomas are usually flat and vitreous bands are usually not adherent.

Therapy:

Not all ocular toxoplasmosis requires therapy. **Toxoplasma gondii** is an opportunist. That is, patients with normal immunity generally can overcome the infection without medication. The purpose of treatment is to prevent damage to vital ocular structures. Moreover, therapy for ocular toxoplasmosis frequently risks undesireable side-effects. Patients should be told of these side effects and also told that they may heal without therapy. If there is a peripheral nonvision threatening lesion, often just reassurance is all that is required. A useful guide of when to treat is:

1. A threatened optic nerve.
2. A threatened macula (such as when the active retinitis is within the posterior vascular arcade)
3. When the vitreous is so hazy that visual acuity is below 20/70.

There is no universally accepted regimen of treatment for ocular toxoplasmosis. There are no long term controlled clinical trials.

Most physicians, who specialize in uveitis, do not use corticosteroids alone to treat ocular toxoplasmosis. Since all evidence points to the fact that active replicating organisms are present in the ratina, there is a risk in the suppression of the body's immune response when corticosteroids are used. There are reports in the literature of patients who became worse when corticosteroids alone were used to treat their ocular toxoplasmosis. There is no evidence, however, of patients who became worse when corticosteroids were used with appropriate antibiotic coverage. Thus, if the clinician makes a decision to use corticosteroids in an attempt to eliminate inflammatory induced damage, appropriate antibiotic coverage should be used. Repository corticosteroids are risky in ocular toxoplasmosis. These repository steroids are released over a long period of time and it may be difficult for the ophtalmologist to determine how long they are effective. Oral corticosteroids, even used for short periods, are alsc risky. Patients should be warned of the risks of induced diabetes mellitus, hypertension, psychic changes, ulcers, weight gain and bone fracture. If taken every other day at breakfast, the recommended dose for oral corticosteroids is often sufficient to temper immunologic damage and reduce side effects of the drug.

Trisulfapyrimidine (triple sulfa) combines the action of the sulfadiazine with that of sulfa merazine and sulfamethazine. It is my prefered sulfa preparation. The combination of different sulfa salts lessens the risk of renal stones without reducing antibiotic activity. Alternatively, sulfadazine alone may be used. Side effects of sulfonamide drugs include renal stones and allergic reactions. Although uncommon, the Stevens'-Johnson syndrome (erythema multiforme) may be triggered by sulfonamides.

Pyrimethamine (daraprim) is synergistic with sulfonamides in the treatment of toxoplasmosis. Pyrimethamine is a strong folic acid antagonist and the white blood cell count and platelet count of patients taking this drug must be monitored weekly. Folinic acid (leucovorin) can be given with the pyrimethamine to counteract the side effects. Folinic acid is available now in oral from.

Clindamycin has also been used to treat ocular toxoplasmosis. Combined administration of clindamycin with sulfonamide has given more consistent improvement than the use of clindamycin alone. Pseudomembranous colitis is the major side effect and risk with clindamycin. Oral vancomycin 600 mg every 6 hours for ten days will usually correct pseudomembranous colitis caused by overgrowth of **Clostridium difficile.** The combined used of sulfonamides with clindamycin may inhibit clostridial overgrowth. However, pseudomembranous colitis has occured on rare occasions with sulfonamides alone.

Because toxoplasmosis is such a difficult disease to treat in eye, it is to be noted that combinations of antibiotics tend to be more effective than single antibiotics. I prefer a quadruple therapy using prednisone, triple sulfa, clindamycin and pyrimethamine. I have had rapid responses to this therapy without significant side effects. Most patients, except those with massive granulomas have responded to treatment in 1 to 2 weeks and in most cases therapy is discontinued after 3 weeks. If prednisone cannot be used (because of diabetes mellitus, or because one in uncertain of the diagnosis), the patient improves but less rapidly than when prednisone is used. Allergies occur in some patients (usually to the sulfonamide). If allergy occurs, the other drugs should be continued and the sulfonamide eliminated. Platelet and white blood counts are usually unnecessary because the pyrimethamine is given for only one week.

In all patients, if there is no response or only minimal response after 3 weeks of antibiotic therapy, it is probably not worth risking the toxic effects of the drug by keeping the patient on long term treatment. None of the currently available drugs prevents the recurrence of toxoplasmic retinitis. Thus all patients are at risk for disease in the future. Laser photocoagulation and retinocryopexy can destroy the cysts of the organism in the eye. However, it is difficult to know where the organisms are and these therapies have not been of great benefit in prventing recurrences. If laser or cryocoagulation are used during acute episodes of toxoplasmic retinitis, there is a risk of stirring up additional inflammation.

Pars plana vitrectomy may be beneficial in those patients who have dense vitreous opacities that persist for more than 6 months or to prevent retinal detachment. Patients with the acquired immune deficiency syndrome (AIDS) are also at risk for developing retinal as well as systemic toxoplasmosis.

TABLE
Therapy of Ocular Toxoplasmosis

Drug	Loading Dose	Maintenace
Trisulfapyrimidine or Sulfadiazine	2-6 gm	1-4 gm daily (100-200mg/kg/day)
Pyrimethamine	75-150mg	25-50 mg/day 1 mg/kg/day
Clindamycin		300 mgm QID
Prednisone		60-80 mg every other day (reduce by 20 mg weekly)

REFERENCES

1. TESSLER, H. H. — Diagnosis and Treatment of Ocular Toxoplasmosis. Vol. III. Module 2 in Clinical Modules for Ophthalmologists. American Academy of Ophthalmology, 1985.
2. O'CONNOR, G. R. — Ocular Toxoplasmosis, in Symposium on Medical and Surgical Diseases of the Retina and Vitreous: Transactions of New Orleans Academy of Ophthalmology. St. Louis, CV Mosby, 1983 p. 108-121.
3. SCHLAEGEL, T. F. Jr. — Toxoplasmosis, in Duane, T. D., Jaeger, E. A. (eds): Clinical Ophthalmology, Vol. 4., Philadelphia, Harper and Row, 1978, chap. 51, pp 1-16.
4. SMITH, R. E. & NOZIK, R. M. — Uveitis: A Clinical Approach to Diagnosis and Management. Baltimore Williams and Wilkins, 1983 pp 120-128.
5. FRIEDMAN, C. T. & KNOX, D. L. — Variations in recurrent active toxoplasmic Retinochoroiditis. Arch Ophthalmol. 81: 481-493, 1969.
6. NOZIK, R. A. — Results of treatment of ocular toxoplasmosis with injectable corticosteroids. Trans Am Acad Ophthalmol Otolaryngol 83: 811-818, 1977.
7. TABBARA, K. F. & O'CONNOR, G. R. — Treatment of ocular toxoplasmosis with clindamycin and sulfadiazine Ophthalmology 87: 129-134, 1980.
8. TESSLER, H. H. — Ocular Toxoplasmosis. Int. Ophthalmol Clin 21 (3): 185-199, 1981.