

Toxoplasma Papillitis and Neuroretinitis

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Introduction:

Toxoplasma is a leading cause of posterior uveitis in immunocompetent patients manifesting as a focal posterior retinochoroiditis. It also causes systemic disease with potentially lethal complications. This obligate intracellular parasite has worldwide distribution with an estimated 1 billion people affected. 1

The typical Toxoplasma lesion consists of fluffy gray or white-yellow retinal infiltrates adjacent to an old pigmented scar with overlying exudation of the vitreous.2,3 Several unusual presentations in ocular toxoplasmosis have been reported, including: papillitis, neuroretinitis, retrobulbar neuritis, outer retinal toxoplasmosis,4 central serous retinopathy, retinal detachment, macular edema,5 scleritis,6 and multifocal diffuse necrotizing retinitis in the elderly.7 Complications of ocular toxoplasmosis include secondary glaucoma, CME,8 vascular occlusion,9,10,12 retinal neovascularization,10 choroidal neovascularization,11 subretinal neovascularization.12 We report a case of presumed ocular toxoplasmosis presenting initially as papillitis with minimal vitritis and severely diminished vision that evolved into neuroretinitis while under treatment. We also review several case reports of primary optic nerve involvement in toxoplasmosis.

Case: A 15-year-old male from South America, developed rapidly progressive blurring of vision, OS over a 1 week period and was referred on June 6, 1996. He felt mild pain exacerbated by eye movement. The patient was otherwise healthy. He had previously lived in Brazil, Argentina, Canada and was a current resident of Massachusetts. There was a past history of having been bitten by a dog, eating raw meat, drinking untreated water and suffering insect bites. The referring physician was suspicious for toxoplasmosis and had started prednisone 100 mg per orem daily. Visual acuity was 20/20 in the right eye and counting fingers in the left. Ocular motility and intraocular pressures were normal. The ocular findings in the right eye were unremarkable. A relative afferent pupillary defect of the left eye was present. The anterior chamber had a 1-2+ cell and 1-2+ flare reaction. The lens was clear and the iris normal. The vitreous contained 2+ cells and absent vitreous haze allowing a clear view of the fundus. Peripheral retinal findings were normal however disc margins were blurred especially on the temporal side. There was a fluffy inflammatory extension from the disc to the superior papillomacular bundle area. A few cells were seen tracking off the disc into the vitreous. There was serous elevation of the papillomacular bundle with choroidal granularity. (**Figure 1, 2**)

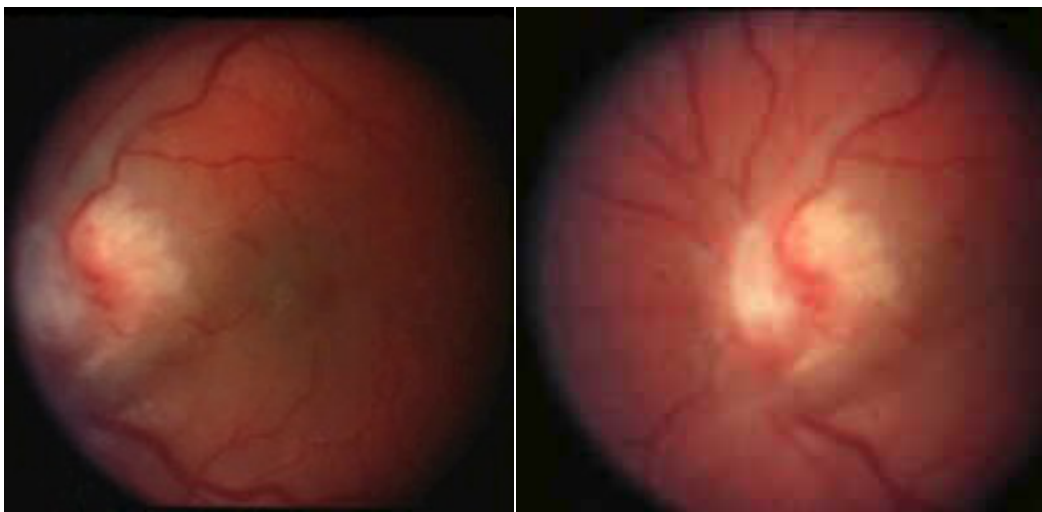


Fig 1 _____ Fig 2

The following lab studies were normal: complete blood count (CBC), sedimentation rate (ESR), FTA-ABS, RPR, ACE, catscratch panel, titers for Lyme disease and Toxocara. PPD testing was normal. Serology for Toxoplasma gondii IgG was positive at 300 IU/ml.

The patient was started on per orem therapy of: pyrimethamine (Daraprim) 75 mg loading then 25 mg/day; sulfadiazine 1600 mg loading then 800 mg qid, clindamycin 300 mg/day; folinic acid 5 mg qod and prednisone 40 mg/day.

After 1 week of therapy, visual acuity improved to 20/80; patient noted an inferior blind spot; anterior chamber reaction quieted down and vitreous cells decreased to 1+. After 2 weeks, vision was 20/60. There was a 60% reduction in disc and peripapillary swelling; a patch of nerve fiber layer hemorrhage in the temporal disc; and an incipient stellate pattern of lipid exudates in the macula giving the appearance of neuroretinitis. (**Figure 3**)

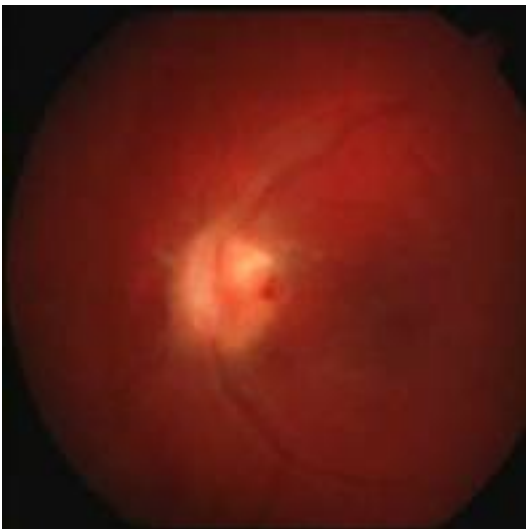


Fig 4
After 6 weeks of treatment, visual acuity improved to 20/25, anterior chamber and vitreous inflammatory reaction were absent, the hemorrhage was resolving and the disc had returned to near normal appearance. There was a strip of vitreous exudation from the disc into the posterior hyaloid (**Figure 4**). Steroids were tapered. After 7 weeks, vision was 20/20-3 and the only residual sign was that of minimal inactive vitreous exudation.

Discussion:

T. gondii was discovered in 1908 inside the brain of a North African rodent, the *gondii*. It was first recognized to cause ocular disease in 1923. The life cycle of *T. gondii* is complex. Cats are the definitive hosts. The organism matures and reproduces in the intestines and oocysts are released in the feces. These sporulate and become infected in room temperatures. When ingested, these oocysts change into extracellular forms, the trophozoites which are responsible for acute disease. *T. gondii* may also be transmitted transplacentally, through mucous membranes, after blood transfusion and organ transplantation¹³.

Congenital transmission occurs with primary maternal infection. The frequency of transmission is related to the stage of pregnancy: 11% transmission in the first trimester, when the placental blood flow is relatively small and up to 90% in the third trimester when the placenta is large. Early transmission is associated with severe effects and may result in stillbirth or abortion; later infection has milder manifestations. The trophozoites use specialized organelles to actively invade phagocytic cells and avoid the lethal metabolites of the respiratory burst generated during phagocytosis. Additionally, inside the cell, the trophozoite forms a parasitophorous vacuole which consists of host cell membrane and *T. gondii* proteins. These proteins alter the host membrane and prevent lysosomal fusion. Thus protected, the parasites grow, multiply and spread to different body organs. The organism has a predilection for muscular and nervous tissue including the retina. After injection of *Toxoplasma* into the suprachoroidal space, it is later recovered in the nerve fiber layer. The mechanism for this tropism is not well understood¹³.

Chronic disease is characterized by intracellular tissue cyst formation of the brain, skeletal muscles, heart and eyes. Cysts contain bradyzoites that have slow metabolic activity. It is unclear why cyst formation occurs but rupture of tissue cysts is associated with recurrences of infection. Injection of dead organisms in the eye does not produce retinal necrosis implying that live and multiplying organisms cause retinal disease. However, the difficulty of recovering organisms or even DNA from the anterior chamber and vitreous cavity implies that hypersensitivity to released antigens may be chiefly responsible for anterior chamber and vitreous reaction. ¹³

The most common symptom is blurred vision. Floaters, photophobia, eye redness, pain and systemic signs (fever, malaise) are less frequent complaints. Children may initially manifest with strabismus, nystagmus, low vision on entering school or hydrocephalus. The common signs of active toxoplasmosis are: active retinochoroiditis and vitreous cells, inactive scars are present in almost all patients. About half of patients may have anterior chamber inflammation and about a fourth have keratic precipitates. The classic description of active retinochoroiditis is a fluffy, fresh, white elevated focus of necrotising retinitis near a pigmented scar (satellite lesion). This may be oval to circular and be of varying sizes. They are frequently posterior to the equator and there may be associated dense vitreous exudation giving a "headlight-in-fog" appearance.^{2,3}

Among the different systems, ocular toxoplasmosis is most commonly with CNS disease.³ (Table 1)

Table 1. Ocular toxoplasmosis and systemic involvement

Associated systemic involvement	% of ocular toxoplasmosis patients
CNS	30.9
Pulmonary	13.3
CVS	8.0
Adenopathy	0.8

Toxoplasma papillitis and *neuroretinitis* are rare presenting findings in ocular toxoplasmosis. We reviewed fifteen case reports^{14,15,16} of patients who presented with either of these two findings. Their ages ranged from 9 – 45 years old with a median age of 20. No sexual predilection was observed. Initial visual acuities ranged from hand movement to 20/20. Seven of fifteen (47%) had initial visual acuities worse than 20/50.

All patients had unilateral activity with the other eye being normal or having inactive scars. Eye findings (Table 2)

Table 2. Eye findings in 15 eyes with acute Toxoplasma optic disc involvement

Finding	Frequency (%)
Optic disc edema	15 (100)
Vitreous inflammation	15 (100)
Relative afferent pupillary defect	10 (67)
Visual field defect	8 (53)
Macular edema	8 (53)
Extra-papillary inflammation	7 (47)
Anterior chamber inflammation	7 (47)
Peripheral scars	6 (40)
Macular star	5 (33)
Vascular sheathing/occlusion	2 (13)
Active macular lesion	1 (7)
Disc neovascularization	1 (7)

Eight of 15 (53%) received anti-Toxoplasma medications; 6/15 (40%) did not receive medication. All except one patient who was HIV positive experienced improvement in vision. Final visual outcomes were 20/40 or better in 11/15 (73%); 7/15 (47%) developed optic atrophy. The small number of patients precludes meaningful statistical analysis of the data. However, a poorer prognosis is associated: HIV infection, active macular lesion and vascular occlusion/sheathing. Grossniklaus et al reported an AIDS patient who developed optic neuritis and retinochoroiditis who progressed to no light perception.¹⁷

Time-sequence analysis of our patient showed an initial picture of optic disc edema with minimal vitreous inflammation and extrapapillary extension which only partially involved the papillomacular bundle. After treatment was started, he developed further macular swelling and incipient macular star formation. This describes a progression from papillitis to neuroretinitis. These two presentations may be part of the same spectrum of disc involvement in ocular toxoplasmosis. Vitreous inflammation of any degree is the most suggestive finding and should prompt a suspicion of toxoplasmosis. Visual prognosis is generally good and a visual field defect is a common sequelae.

Diagnosis of ocular toxoplasmosis is mainly based on clinical grounds. Differential diagnosis include entities resulting in retinitis and secondary vitritis including ARN from herpes simplex and zoster, cytomegalovirus, candidiasis, syphilis, TB, Lyme disease and sarcoid. Retinal detachment and hemorrhages are rare in toxoplasma but common in ARN.. Toxoplasma may be differentiated from CMV retinitis by the presence of more prominent anterior and vitreous reactions, lack of retinal hemorrhage and fluffy thick borders. CMV has relative quiet chambers, prominent hemorrhages and dry, granular borders. ¹⁸

Attempts at parasite identification in tissue and body fluid specimens are often unproductive. Parasites may be cultured by inoculation of patient tissues into mice peritoneum or tissue culture cells.¹⁹ Alternatively, polymerase chain reaction analysis (PCR) can be used to detect the toxoplasma DNA in tissues.^{20,21,22}

Detection of toxoplasma DNA in intraocular fluids by PCR has also been demonstrated; however, low yields have been reported thus necessitating simultaneous serological testing.

Serology may be a useful adjunct but interpretation may be difficult. High prevalence of toxoplasmosis in some areas lead to false positive results. Furthermore, some immunocompromised patients may not produce significant levels of antibodies.

The methylene blue dye test (Sabin Feldman) is the gold standard IgG assay but requires use of live organisms thus is not widely available. Indirect fluorescent antibody test (IFA) is more readily available. ELISA testing is the most widely available test and is very sensitive. Elevated IgG indicates exposure and is confirmatory in the presence of typical clinical findings of Toxoplasmosis.

Double-sandwich ELISA or capture-ELISA detects IgM. It is more sensitive than IFA-IgM and is positive in up to 73% of congenital infections. IgM immunosorbent agglutination test (ISAGA) is the most sensitive test but is not widely available. IgM antibodies have been shown to persist for at least 9 months up to 18 months after infection. 20, 23, 24

Acquired toxoplasmosis may be diagnosed on the basis of seroconversion, presence of IgM antibodies, rapidly rising IgG antibodies, and high anti-Toxoplasma titers. IgA or IgE antibodies are also helpful in the diagnosis of acute infections.²⁵

Fluorescein angiography is a useful adjunct in the diagnosis and management of ocular Toxoplasmosis. Active lesions show hyperfluorescence; early leakage and late staining is observed in areas of vasculitis. Inactive lesions manifest as dye blockage and late staining. Other FA findings include window defects, later scleral staining and presence of choroidal neovascularization.²⁶

Cell mediated immunity is believed to be the primary mechanism of defense against Toxoplasmosis. Toxoplasma antigens have been isolated (p30 and p22 surface protein antigens) and lymphocyte proliferation has been demonstrated with the p22 membrane antigen. These antigens may be responsible for inducing the inflammatory response.²⁷ Interferon gamma is important in macrophage activation and parasite killing. INF-gamma is essential for protection against Toxoplasma.²⁸ Cytokines such as IL-4, IL-12, macrophage chemotactic and activating factors (MCAF) have protective effects against Toxoplasmosis.²⁹⁻³²

A recent survey of members of the American Uveitis Society revealed a wide variation in treatment strategies. Most consider the following indications for treatment: reduction in vision, lesions within 1 disc diameter of the fovea, lesions greater than 1 disc diameter in size, presence of moderate to severe vitritis, persistent or multifocal infections, acquired infections and immunocompromised state.³³

Various agents are available and effective in the treatment of most cases of ocular toxoplasmosis. Pyrimethamine (Daraprim) is a folic acid antagonist which inhibits dihydrofolic acid reductase and deprives the trophozoite of DNA precursors. Treatment begins with a loading dose of 75-100 mg followed by 25 – 75 mg/ day for 4-6 weeks. Bone marrow suppression can result from pyrimethamine treatment thus complete blood counts should be obtained on a weekly basis. Folinic acid may prevent complications of pyrimethamine therapy.

Sulfonamides are competitive inhibitors of p-aminobenzoic acid. A synergistic effect is obtained with pyrimethamine as they block sequential steps in folic acid metabolism of trophozoites. Sulfadiazine is started with a loading dose of 2-4 grams then maintained at 1 g 4 times per day for 4-6 weeks. Adverse effects include allergic reactions, and nephrolithiasis. ³⁴

Cotrimoxazole (Bactrim) is an alternative regimen given twice daily. This drug is more readily available than Daraprim/ sulfadiazine.³⁵

Corticosteroids are given to counter the inflammatory response to toxoplasma. They should never be given without concomitant antibiotics and should not be given by depot steroid injections which may lead to uncontrolled infection. Sometimes steroids treatment may be delayed to allow systemic antibiotic levels to rise.³³

Clindamycin (Cleocin) is a semisynthetic antibiotic with protozoacidal activity. It acts by a different mechanism from the folic acid antagonists and may be synergistic with them. Clindamycin has high ocular tissue concentration, has been shown to have activity against the cyst form. The usual dosage is 150-300 mg four times a day. Clindamycin does not carry the same risk of toxicity as the folic acid antagonists however, its use is associated with pseudomembranous colitis in a small number of patients. This is readily reversible with vancomycin. One way of avoiding systemic administration is by giving clindamycin subconjunctival injections of 50 mg on alternate days for a month.³⁶

Spiramycin is a macrolide antibiotic with proven antiprotozoal activity. It has minimal side effects is used in pregnancy because it has been shown to reduce the incidence of congenital infection. However, it has been reported to have a relatively higher rate of reinfection. Tetracyclines have

also been used by some ophthalmologists.³³

New drugs are being tested for use against toxoplasmosis. One promising agent is atovaquone (Mepron) which is a hydroxynaphthoquinone used in the treatment of malaria. It acts by interfering with the parasite mitochondrial electron transport system. The recommended dosage is 150 mg qid for 4 weeks. Trials are currently being conducted with this agent.³⁸

Also under investigation are sulfanilamides,³⁹ arprinocid-N-oxide (HM) and rifabutin.⁴⁰

Azithromycin is a macrolide which acts by inhibiting protein synthesis. It has activity against cysts in vitro; ⁴⁰ however, its clinical effectivity is still in question.^{41,42} Combination with pyrimethamine may lead to a more rapid response.^{43,44}

Combination treatment may be more effective in obtaining a more rapid resolution. For peripheral lesions with mild-moderate vitritis, clindamycin 300 mg qid combined with sulfadiazine 2 gm loading then 1 gm qid may be given. With moderate-severe vitritis, triple therapy with prednisone 1 mg/kg/day may be added and tapered according to response to treatment. For juxtamacular lesions, pyrimethamine 75 mg loading dose followed by maintenance of 25 mg per day is suggested.³⁴

Though no particular combination has been definitely shown to be superior to others, the use of pyrimethamine may result in smaller scars and may be of benefit to those with macular, juxtamacular, papillary, and peripapillary lesions.⁴⁵ Our patient responded rapidly to quadruple therapy and had not developed scars by the end of therapy.

Laser photocoagulation is an adjunctive therapy which may be of benefit in patients with sight threatening lesions, lack of response with or intolerance to medications or who are pregnant.

Cryotherapy may be used for patients with peripheral lesions. Vitrectomy may be employed in the treatment of active infections or for removal of vitreous debris to improve vision.^{46,47}

Toxoplasmosis affects 1-3% of AIDS patients and is the second most frequent cause of retinitis next to cytomegalovirus. Ocular toxoplasmosis may be the initial manifestation of AIDS. It is associated with CD4+ counts of less than 200/uL. Toxoplasma retinitis in immunocompromised patients differs greatly from immunocompetent patients; the lesions tend to be larger, thicker, more opaque, multiple, sometimes confluent and occur in the absence of old scars.^{48,49} There are also case reports of patient with atypical presentations such as ocular toxoplasmosis progressing to panophthalmitis and orbital cellulitis (Moorthy), miliary retinitis (Berger), diffuse retinochoroiditis and retinochoroiditis with optic neuritis (Grossnicklaus). CNS involvement is also more frequent.

The approach to AIDS patients with ocular toxoplasmosis is also different. Several issues should be kept in mind. Use of steroid therapy in immunocompromised patients is dangerous and should be avoided. AIDS patients have high relapse rates when treatment is discontinued (40-80%). Lifetime maintenance therapy should be given to AIDS patients with previous episodes of toxoplasmosis. To compound the problem, higher drug toxicity rates with anti-protozoal medications have been reported in AIDS patients. Dose-related cytopenias and rash may develop with pyrimethamine therapy; rashes, nausea, cytopenia and nephrotoxicity occur more frequently with sulfonamide use⁴⁹; increased incidence of gastrointestinal disturbances, rash, neutropenia and pseudomembranous colitis may be seen with clindamycin. Combination of clindamycin and pyrimethamine may produce fewer adverse reactions versus sulfadiazine and pyrimethamine (23% versus 33%).⁴² Also, the half life of pyrimethamine in serum has been reported to be much shorter than in those who without AIDS; however, a subsequent study showed no pharmacokinetic interaction between pyrimethamine and zidovudine.⁵⁰

It is hoped that the new agents currently under study such as new antibiotics and cytokine treatment will prove to have fewer adverse reactions and to be more effective against the cyst form thus decreasing the risk of relapse.

In summary, this case illustrates that toxoplasma papillitis and neuroretinitis are part of the same spectrum of ocular nerve involvement in toxoplasmosis. The prognosis for treated patients is generally good with poorer visual outcomes associated with immunocompromised state and those who develop active macular lesions and vascular occlusion. We also reviewed the different manifestations of ocular toxoplasmosis as well as the recent developments in diagnosis and therapy.

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