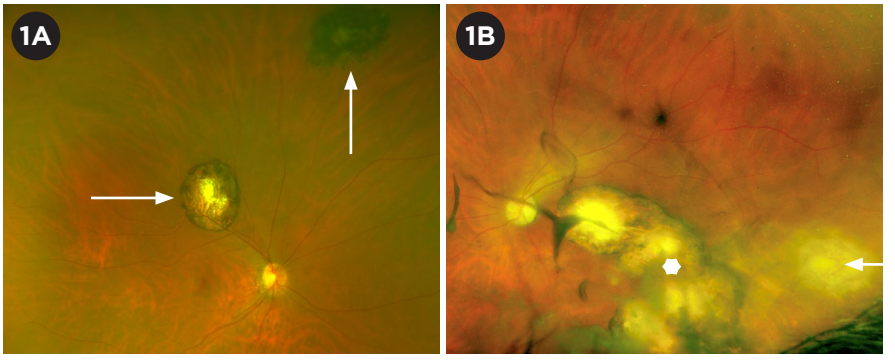
Ocular Toxoplasmosis: A Refresher



ACTIVE AND INACTIVE LESIONS. *(1A) Widefield color fundus photograph shows inactive ocular toxoplasmosis lesions (arrows). (1B) Widefield color fundus photograph demonstrates an active ocular toxoplasmosis lesion with an area of fluffy white, focal necrotizing retinitis (arrow) adjacent to a large chorioretinal scar (star). Fundus appearance is hazy secondary to vitritis.*

Ocular toxoplasmosis, an infection of the retina and choroid caused by the intracellular parasite *Toxoplasma gondii,* is the leading cause of posterior uveitis worldwide and a common cause of vision loss resulting from intraocular infection. About 25% to 30% of the world's population is systemically infected with *Toxoplasma,* the most common foodborne parasitic infection globally.[1] Despite the global burden of disease, many patients infected with *Toxoplasma* may be asymptomatic or may present with nonspecific symptoms such as fever and generalized fatigue.[2]

The prevalence of systemic toxoplasmosis varies greatly by region. North America, Southeast Asia, and Northern Europe have a low prevalence (10%-30%), while a moderate prevalence (30%-50%) has been found in Central and Southern Europe. The prevalence of *Toxoplasma* infection is more than 60% in Latin America and tropical countries, with Brazil identified as having one of the highest rates.[1] Factors that may contribute to the elevated prevalence of toxoplasmosis in Brazil and other Latin American countries include a higher infection rate of animal reservoirs, greater concentration of parasite load in the environment, poor sanitary conditions, and host genetic factors.[1,2] Because ocular toxoplasmosis is a preventable form of worldwide blindness, understanding the pathophysiology and manifestations of the disease may lead to significantly decreased rates of infection.

Pathophysiology

Cats are the definitive hosts of *T. gondii,* while humans and other mammals are intermediate hosts. There are two major routes of transmission for infection. An individual may be infected by ingesting *Toxoplasma* oocysts in food or water contaminated by cat feces or by eating raw or undercooked meat containing tissue cysts within skeletal muscle.[2] Women who are infected during pregnancy have a high risk of transmitting the infection to the fetus, leading to devastating fetal complications including retinal infection, congenital malformation, and even fetal death.[3]

Congenital versus acquired. Congenital infection with *T. gondii* was formerly thought to be the most frequent cause of ocular toxoplasmosis. However, increasing evidence suggests that postnatal infection is actually more common, as many patients are diagnosed with ocular toxoplasmosis in adolescence.[2,3] Approximately one-third of toxoplasma chorioretinitis cases are caused by congenital infection and two-thirds by infection acquired later in life.[4] There is increasing evidence that parasite-specific as well as host-specific factors lead to development of ocular manifestations in some but not all individuals diagnosed with systemic toxoplasmosis.[5] Postnatal ocular toxoplasmosis has been shown to occur in 2% of individuals who are seropositive for the disease.[5]

Pregnancy. Congenital systemic toxoplasmosis develops in about 30% to 50% of infants whose mothers were

BY **NIKHILA KHANDWALA, MS,** AND **CAGRI G. BESIRLI, MD, PHD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND BENNIE H. JENG, MD.

Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center

first infected during pregnancy, with 70%-90% of infected neonates developing ocular manifestations. The risk of congenital toxoplasmosis is highest when infection occurs in the third trimester, with an approximately 72% chance of developing the disease at 36 weeks' gestation compared with a 6% chance at 13 weeks. Systemic manifestations are more severe if the infection presents within the first trimester.[3]

Histopathologic findings. Ocular toxoplasmosis is characterized by focal coagulative retinal necrosis and granulomatous inflammation of the choroid near the site of infection in the retina. Leukocytic infiltration may be noted in areas adjacent to the affected retina, as well as disruption of the retinal pigment epithelium with accumulation of pigment in areas of necrosis. Other findings associated with ocular toxoplasmosis include retinal neovascularization, retinal detachment, and optic neuritis.[3]

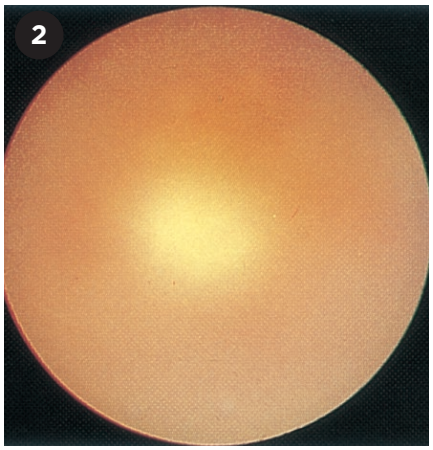
Clinical Features

Symptomatic ocular toxoplasmosis usually presents within the first two to four decades of life.[2]

Classic presentation. The typical finding of ocular toxoplasmosis is an area of fluffy white, focal necrotizing retinitis adjacent to a pigmented chorioretinal scar (Fig. 1). Vitreous inflammation may obscure the active lesion on dilated fundus examination, resulting in the headlight-in-fog sign (Fig. 2).

Other common signs of ocular toxoplasmosis include a satellite lesion (a new lesion adjacent to an inactive retinochoroidal scar), focal or widespread vasculitis, and inflammatory ocular hypertension. Patients often present with blurry vision secondary to vitritis, although some may be asymptomatic. Children with congenitally acquired ocular toxoplasmosis may present with cataract associated with retinochoroiditis. Up to 24% of patients have 20/200 vision or worse on presentation.[1]

Atypical presentation. Immunocompromised patients often present with a more aggressive form of the disease than those who are immunocompetent. Although immunocompromised patients may have some of the classic features of ocular toxoplasmosis, they may demonstrate atypical findings including multifocal retinochoroiditis, lack of vitritis, an active lesion larger than 2 disc diameters, absence of a retinochoroidal scar, bilateral ocular involvement, optic disc involvement, and retinal neovascularization.[1] Furthermore, immunocompromised individuals have a higher incidence of potentially fatal toxoplasmic encephalitis.[3]



A CLASSIC SIGN. *Vitreous inflammation may result in the headlight-in-fog sign.*

Recurrence. In most immunocompetent individuals, *Toxoplasma* cysts remain inactive within or near the retinal scar for a long period. Reactivation of retinitis usually occurs at the border of old scars, with the rupture of tissue cysts releasing organisms into the surrounding retina. The five-year recurrence rate was found to be 79%, and some patients have a propensity for multiple recurrences.[2] Patients who have undergone treatment for ocular toxoplasmosis have demonstrated a significant decrease in recurrence rate compared to those who did not receive treatment (6.6% vs. 23.8%, respectively).[1]

Diagnosis

Because most patients present with the classic features of a chorioretinal scar with a satellite lesion and areas of active retinochoroiditis, the diagnosis of ocular toxoplasmosis is often made on clinical presentation alone. However, if the clinical diagnosis is not definitive, laboratory tests and imaging may be helpful.

Laboratory tests. Serologic tests such as serum anti-*Toxoplasma* IgM and IgG are often obtained to confirm the diagnosis. Serum IgM and IgG antibodies are produced within one to two weeks after infection, with IgM levels rising in the first week and becoming undetectable within six to nine months. Nonreactive IgG rules out a diagnosis of toxoplasmosis in most immunocompetent individuals.

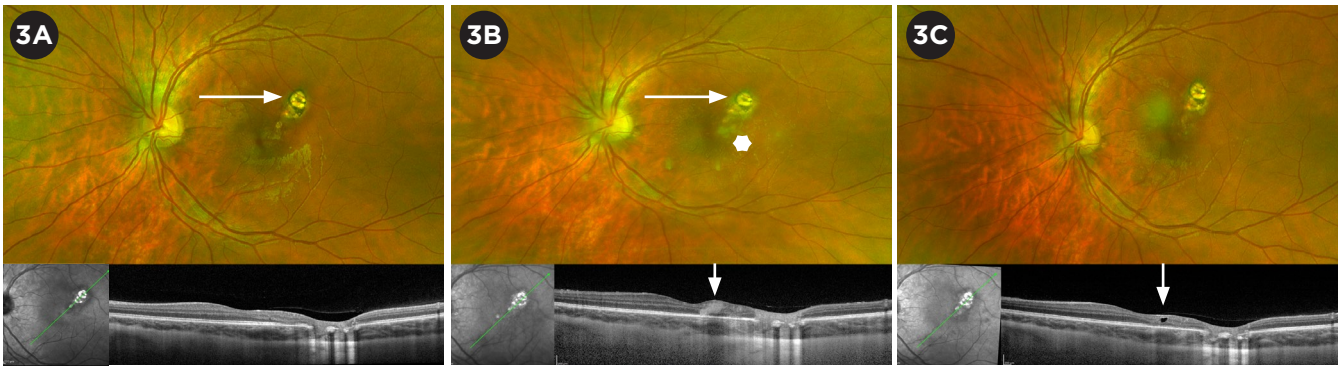
However, IgG and IgM levels should not be relied on for immunocompromised patients when there is high clinical suspicion for ocular toxoplasmosis; diagnosis should be based on clinical presentation along with other diagnostic tests, including ocular *T. gondii* antibody titers and polymerase chain reaction (PCR). Recently, PCR analysis of aqueous and vitreous samples has become available for diagnosis of ocular toxoplasmosis and may characterize various types of *T. gondii*.

Imaging. The use of spectral-domain optical coherence tomography has been shown to aid in the identification of the various stages of ocular toxoplasmosis. The active phase of the disease is characterized by disruption, thickening, and hyperreflectivity of the retina. With improvement of the disease, the hyperreflectivity resolves, leaving scarred lesions and retinal atrophy (Fig. 3).

Differential diagnosis. Several other diseases may feature focal necrotizing lesions similar to those of ocular toxoplasmosis, including viral retinitis, fungal infections, tuberculosis, and syphilis. Therefore, when the clinical presentation is not specifically diagnostic for ocular toxoplasmosis or when signs are seen in immunocompromised patients at high risk for opportunistic infections, serologic testing may be obtained to rule out other causes of infectious retinochoroiditis.

Management

There is no consensus on a treatment regimen for ocular toxoplasmosis. Most immunocompetent patients do not require medical treatment, as ocular toxoplasmosis is a self-limited disease that resolves spontaneously within four to eight weeks.[3] However, patients who



BEFORE AND AFTER. *(3A) Color fundus photograph shows an inactive ocular toxoplasmosis lesion in the macula (arrow). The optical coherence tomography (OCT) image below demonstrates a focal area of chorioretinal scarring and atrophy. (3B) Color fundus photograph taken two months later reveals an active ocular toxoplasmosis lesion (arrow) with adjacent fluffy white, focal necrotizing retinitis (star). Fundus view is slightly hazy because of mild vitritis. OCT showed corresponding full-thickness hyperreflectivity of the retina within previous area of infection as well as a new satellite lesion (arrow). (3C) Resolution of ocular toxoplasmosis following antiparasitic treatment. OCT below shows inner retinal cavitation and outer retinal collapse (arrow).*

present with reduced vision, those with lesions in vision-threatening anatomic areas, and immunocompromised patients are more likely to require treatment.

Classic treatment. The classic therapy for ocular toxoplasmosis consists of antiparasitic and anti-inflammatory medications, most commonly oral pyrimethamine and sulfadiazine, along with a systemic corticosteroid. However, the adverse effects associated with this regimen, notably leukopenia and thrombocytopenia, have led physicians to seek alternate effective therapies.[3]

Other approaches. A prospective multicenter study divided patients into three treatment groups: one receiving pyrimethamine, sulfadiazine, and corticosteroid; the second receiving clindamycin, sulfadiazine, and corticosteroid; and the third receiving trimethoprim-sulfamethoxazole and corticosteroid. It was reported that the most important determinant of the duration of ocular inflammation was the size of the retinal lesion itself, independent of treatment. The mean recurrence rate after three years was 49% for all patients, with no difference noted among treatment groups. The pyrimethamine group experienced the highest rate of side effects, which included thrombocytopenia and leukopenia.[6]

Patients with active ocular toxoplasmosis are often treated for a period of four to six weeks with either the classic triple-drug therapy of pyrimethamine, sulfadiazine, and corticosteroid or with trimethoprim-sulfamethoxazole monotherapy. If systemic treatment is contraindicated, intravitreal injection of clindamycin may be an alternative local treatment option.[7] Corticosteroids may be used in select cases to suppress inflammation and minimize chorioretinal damage associated with the host immune response against infection. The timing and dose of corticosteroids must balance suppression of the immune system with severity of the disease.[1]

Preventing recurrence. Individuals who have a history of frequent recurrence of ocular toxoplasmosis may benefit from long-term therapy to prevent subsequent recurrences. A study that randomized patients to long-term trimethoprim-sulfamethoxazole therapy versus placebo for a period of 20 months found a decreased recurrence rate in treated patients (6%) compared with untreated patients (23.8%).[8]

Conclusion

Ocular toxoplasmosis is the most common cause of infectious posterior uveitis and one of the leading causes of panuveitis worldwide. The prevalence of ocular toxoplasmosis varies based on geographic location. Diagnosis of ocular toxoplasmosis relies primarily upon clinical presentation, although laboratory testing and imaging may play a key role in atypical cases. Immunocompetent individuals may not need treatment because the disease typically regresses spontaneously within two months; however, patients who have vision-threatening lesions or are immunocompromised may require a combination of antiparasitic and anti-inflammatory treatment. Prompt recognition of atypical presentations and development of more efficacious therapies may prevent vision loss secondary to ocular toxoplasmosis.

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Ms. Khandwala is a fourth-year medical student at the University of Michigan. **Dr. Besirli** is an assistant professor in the Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center. *Relevant financial disclosures: None.*

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Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center