Ocular Toxoplasmosis – Updated Review of the Literature

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Summary

Ocular toxoplasmosis is the most common cause of posterior uveitis worldwide. It can be acquired congenitally or postnatally and ocular lesion usually present years after acute systemic infection. Current treatment options control ocular inflammation but have a limited role in preventing recurrences. We present a review and update on ocular toxoplasmosis and address misconceptions still found in the medical literature.

Introduction

Ocular toxoplasmosis is caused by the protozoa parasite *Toxoplasma gondii*, and can be acquired congenitally or by ingesting uncooked meat infected with cysts or vegetables and water contaminated by oocysts shed by cats [1].

T. gondii infects up to a third of the world's population and is the most frequent etiology of infectious intraocular inflammation (uveitis) [2]. In some countries, up to 50% of all cases of posterior uveitis in a given population can be attributed to toxoplasmosis [3, 4]. Up to 22% of the population of the United States is *T. gondii* serapositive, although it is unknown the percentage of patients that present with ocular disease it has been approximated at 2%. Brazil has a disproportionately high incidence and severity of ocular toxoplasmosis when compared to Europe and North America [5].

Population structure

Despite a sexual phase in the life cycle that occurs in feline enterocytes, it was accepted until recently, that the population structure of *T. gondii* was highly clonal, with low genetic variability. Parasite isolates have been classified into 3 genetic types (I, II, III) first on virulence in mice and later on the basis of restriction fragment length polymorphism [6]. However, data used to construct the lineages was based on European and North American isolates. Using *T. gondii* isolates from Brazil and newer markers for genetic characterization higher genetic variability has been detected than previously reported [7, 8]. Today classification is based on the three classical types and atypical genotypes [9].

The outcome of toxoplasmosis depends on the interaction of many factors, including the functions of immune system and parasite factors, such as inoculum, infective parasite stage, and genotype of *T. gondii* isolate. Type II strain is responsible

for more than 70 % of symptomatic human cases in France and the United States [10, 11]. Although there is no patient data characterizing the difference in strain expression in Brazil for systemic toxoplasmosis, various studies of wild and farm animals have been carried out demonstrating the high prevalence of type I, III atypical strains over type II [12-14].

The type I strain seems to be responsible for the majority of ocular infections in Brazil [3]. The population of Erechim, a southern Brazilian city, has a 17% prevalence of ocular toxoplasmosis with type I strain predominating [15]. Also in southern Brazil, parasites isolated from contaminated water were of the type I strain [16]. When the genotypes of the *T. gondii* isolated from patients with ocular toxoplasmosis from Erechim and Sao Paulo were analyzed they were found to be highly atypical compared to previously described cloning lineages [17]. It is these atypical strains that may be playing an increasingly important role in acquired infection.

In Erechim, samples from porcine tongue and diaphragm were obtained in both large and small abattoirs and tested for *T. gondii*. The results indicated a high prevalence of infection and suggested that unusual genotypes of *T. gondii* are found in Brazil also among domesticated pigs [18]. An epidemiological survey carried out in Erechim identified the risk factors for recently acquired toxoplasmosis included: eating undercooked meat; working in the garden or yard more than once per week; eating raw, cured, dried, or smoked meat and being male [15].

Ocular manifestations and diagnosis

Toxoplasmic retinochoroiditis can be seen in the setting of congenital or postnatally acquired disease as a result of acute infection or recurrence [19, 20]. This

disease typically affects the posterior pole of one eye, and the lesions can be solitary, multiple or satellite to a pigmented retinal scar (Figure 1).

Figure 1: Ocular toxoplasmosis with vitreous strand and vasculitis.

Active lesions present as grey-white focus of retinal necrosis with adjacent choroiditis, vasculitis, hemorrhage and vitreitis (Figure 2, 3 and 4). Cicatrization occurs from the periphery towards the center of the lesion, with variable pigmentary changes. Anterior uveitis is a common finding, with mutton-fat keratic precipitates, cells and flare, and posterior synechiae (iris-lens adhesion) [20].

Figure 2: Retinochoroiditis with vitreitis

Figure 3. Ocular toxoplasmosis with old pigmented scar and inferior recurrence to the macula.

The retina is the primary site of *T. gondii* infection in the eye but the choroid, vitreous and anterior chamber are also involved by inflammation. The choroid is secondarily affected, but choroidal lesions do not occur in the absence of retinal infection. An intense, secondary iridocyclitis may also be present [20, 21]. The optic nerve head can also be involved in ocular toxoplasmosis [22] (Figure 5).

Figure 4: Inferior area of retinochoroiditis and difuse vasculitis

Older or immunosuppressed patients may present with more aggressive, bilateral or multifocal disease (Figure 6). Older patients who are recently infected with *T. gondii* may have a higher prevalence of ocular involvement. Other atypical presentations include punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, rhegmatogenous and serous retinal detachments, unilateral pigmentary retinopathy mimicking retinitis pigmentosa, neuroretinitis and other forms of optic neuropathy, peripheral retinal necrosis and scleritis [23, 24].

Figure 5: Optic disk involved in a case of ocular toxoplasmosis

Ocular complications include choroidal neovascularization, cataract, glaucoma, optic nerve atrophy and retinal detachment, more frequently in children [25]. An association between ocular toxoplasmosis and Fuchs' heterochromic cyclitis has been described [26] and confirmed [27-29].

The appearance of toxoplasmic retinochoroiditis lesions vary. Their duration and intensity may be related to host, parasite, or environmental factors. Genotyping of the infecting parasite appears to be an important determinant of disease severity in immunocompetent patients [21].

Figure 6: Toxoplasmic scar in the macula and acute CMV in a patient with AIDS.

Retinal vasculitis and associated inflammatory reactions may be the only ophthalmic sign during the early stages of a newly acquired *T. gondii* infection. Later development of retinitis or scars consistent with toxoplasmic retinochoroiditis in the

same eye suggests that the initial, isolated inflammation may have been caused by the parasites [30].

Recurrent toxoplasmic retinochoroiditis is not associated with systemic symptoms and recurrence risk may be influenced by patient age. Ocular lesions may first develop many years after *T. gondii* infection and are often asymptomatic [20].

Transplacental transmission of *T. gondii* to the fetus during pregnancy is another important source of infection. The mother can transmit toxoplasmosis to the fetus if infected by *T. gondii* during pregnancy or a few months before conception [31]. The infection can result in visual and hearing loss, mental and psychomotor retardation, seizures, hematological abnormalities, hepatosplenomegaly, or death [32]. Retinochoroidal scars are the most characteristic eye manifestation of a congenital or prenatal infection [33] (Figure 7). Maternal infection in the first trimester of gestation has a lower chance of congenital transmission, but more severe consequences for the fetus when compared to the third [32]. Pediatricians, parents, and elder children with congenital infection should be aware that late-onset retinal lesions can occur many years after birth but that the overall ocular prognosis of congenital toxoplasmosis is satisfactory when infection is identified early and treated accordingly [34].

A British survey assessing the risk of visual impairment in 281 congenitally infected children with mean follow-up of 4.8 years demonstrated that 17% presented at least one retinal lesion. Out of 44 children with information on visual acuity 9% suffered from severe bilateral impairment. Also 52 % of the children with a posterior pole lesion and 17 % of those with only peripheral lesions were visually impaired in the affected eye [35]. Many children with congenital toxoplasmosis have substantial retinal damage at birth and consequent loss of vision. Nevertheless, vision may be remarkably

good in the presence of large macular scars. Active lesions become quiescent with treatment and may recur at any age [36].

Figure 7: Retinal scars linked by vitreous strand in congenital toxoplasmosis.

In one study evaluating 430 children treated for congenital toxoplasmosis, ocular involvement was present in 30% after a median follow-up of 12 years. The overall functional prognosis of these congenitally infected children was better than would be expected on the basis of literature findings, with only two of the 130 children suffering bilateral visual impairment [37].

Although it is classically known that only during primary infection the mother could transmit the infection to the fetus, there are few reports supporting the possibility of chronically infected women transmitting the disease congenitally [38].

The diagnosis of ocular toxoplasmosis is typically clinical. There are no new diagnostic tests to identify toxoplasmic uveitis. The presence of anti- *T. gondii* IgG antibodies cannot confirm a diagnosis of ocular infection but a negative IgG usually rules it out. Such antibodies can persist often at high titers for years after the acute infection, and there is a high prevalence of such antibodies in the general population [39].

Pathological diagnosis of ocular toxoplasmosis can be established by identifying the cysts in biopsies stained with hematoxylin and eosin (H&E), polyclonal or monoclonal antibodies by immunohistochemistry [40] or by polymerase chain reaction (PCR) [41]. Histologically, ocular toxoplasmosis usually presents extensive granulomatous inflammatory infiltration of the choroid and areas of necrosis of Bruch's membrane [42].

T. gondii DNA has been identified in ocular tissue sections of patients with presumed toxoplasmic retinochoroiditis by PCR techniques, even when typical tissue cysts are not identified on histopathologic examination [39, 41].

Examination of vitreous fluid by PCR in patients in which toxoplasmosis is considered in the differential diagnosis but where the presentation is atypical, is an useful diagnostic aid [43, 44]. To facilitate genotyping of *T. gondii* in vitreous fluid of patients with severe or atypical ocular toxoplasmosis, PCR restriction fragment length polymorphism (RFLP) assays were developed [45].

A study compared three biological methods, immunoblotting or Western blotting, the calculation of the Goldmann-Witmer coefficient and PCR for the diagnosis of ocular toxoplasmosis in aqueous humor and serum samples, showing that the combination of all three techniques improved the sensitivity to 97% [46].

On the other hand, nested-PCR is a reliable diagnostic technique for ocular toxoplasmosis, because of the amount of specimen required, speed, cost effectiveness, and high sensitivity and specificity to detect of *T. gondii* DNA in intraocular fluids [47, 48]. However, real-time PCR has replaced nested-PCR as a rapid and sensitive technique for quantitatively evaluating ocular samples for the presence of infectious pathogens [44, 49, 50].

Current laboratory diagnostics of ocular toxoplasmosis resulting from the reactivation of a latent infection by techniques such as the real-time PCR and Goldmann-Witmer Coefficent, on samples of vitreous humour, are inadequate because of the methods' low sensitivity [51]. Furthermore, the risks and complications associated with the biopsy retrieval must be considered. The respective contributions of aqueous humour analysis from both serological and PCR tests in confirming the diagnosis of ocular toxoplasmosis is still not clear [52].

Treatment of ocular toxoplasmosis

Ocular toxoplasmosis therapy may include systemic antimicrobial drugs with or without corticosteroids. Some ophthalmologists treat all ocular toxoplasmosis cases while others only those with posterior pole lesions, intense vitreitis, lesions close to the optic disk or immunosuppressed patients [53]. Several drugs have been proposed including pyrimethamine, sulfadiazine, spiramycin, clindamycin, and trimethoprim-sulfamethoxazol [54, 55].

Results of a study comparing three drug combinations: association of pyrimethamine, sulphadiazine and corticosteroids; association of clindamycin, sulphadiazine and corticosteroids; and association of cotrimoxazole (trimethoprim and sulphamethoxazole) with corticosteroids showed no difference in the resolution of inflammatory processes [53]. The same group studied in 1993, showed a reduction in size of the retinal inflammatory lesion for 49% of the pyrimethamine-treated patients compared to 20% of the untreated patients [56]. The most frequent side effects were associated with pyrimethamine and included hematologic complications such as thrombocytopenia and leucopenia. In most cases folinic acid supplementation is believed to prevent side effects related to pyrimethamine treatment [53]. Folic acid does not prevent such complications and should not be used as a substitute for folinic acid [42].

The use of pyrimethamine, sulfadiazine, and corticosteroids is considered “the classical” specific therapy for ocular toxoplasmosis and is the most common drug combination used [31].

Patients with active toxoplasmosis may also be treated with trimethoprim-sulfamethoxazole with or without adjunctive clindamycin and prednisone for four to six

weeks. Trimethoprim-sulfamethoxazole appears to be a safe and effective substitute for sulfadiazine, pyrimethamine, and folinic acid in treating ocular toxoplasmosis [57, 58].

The therapeutic benefit from the use of pyrimethamine in combination with azithromycin was similar to the treatment with pyrimethamine and sulfadiazine. Multidrug therapy with the combination of pyrimethamine and azithromycin appears to be an acceptable alternative treatment for sight-threatening ocular toxoplasmosis [59].

The causes of recurrences in ocular toxoplasmosis remain unknown. They may be related to the rupture of dormant retinal cysts [60], or toxoplasma circulating in peripheral blood [61]. In some patients, recurrent toxoplasmic retinochoroiditis remains a major problem and can be associated with severe morbidity if disease extends to the macula and optic disk. Also, recurrent disease has the propensity to cause visual morbidity from inflammation or complications such as retinal detachment or choroidal neovascularization. In patients with frequent recurrences, long-term intermittent treatment with trimethoprim (160 mg)/sulfamethoxazole (800 mg), one tablet 3 times a week reduced the rate of recurrent toxoplasmic retinochoroiditis from 23.8% to 6.6% [62].

Traditional short-term treatment of active toxoplasmic retinochoroiditis lesions do not prevent subsequent recurrences. Various short-term therapeutic modalities had no effect on visual outcomes or future recurrence rates, with the exception of a poor visual outcome for patients who received corticosteroids without antiparasitic drugs [59]. It is still unclear if there exists a relationship between systemic corticosteroid use and reactivation of toxoplasmosis [63].

Intravitreal injection of clindamicyn and even steroids may be used in patients that have contraindication of systemic therapy specific for toxoplasmosis [64, 65]. Sobrin et al showed that intravitreal clindamycin injection was associated with

resolution of toxoplasmic retinochoroiditis [65]. On the other hand, intravitreal injections of clindamycin and dexamethasone [66] and subconjunctival injections of clindamycin [67] seem to be an interesting alternative to the use of the classical anti-toxoplasmic ocular therapy.

Ocular toxoplasmosis is a field wide-open for further clinical and experimental research. Regions with high burden of disease, like Brazil, may offer the most suitable conditions to better understand the disease. Specific areas where research is needed most include: diagnostics of atypical cases; more effective treatments and mechanisms of ocular recurrences.

REFERENCES

1. Silveira, C., et al., *Acquired toxoplasmic infection as the cause of toxoplasmic retinochoroiditis in families.* Am J Ophthalmol, 1988. **106**(3): p. 362-4.
2. Montoya, J.G. and O. Liesenfeld, *Toxoplasmosis.* Lancet, 2004. **363**(9425): p. 1965-76.
3. Vallochi AL, M.C., Martins MC, Silveira C, Belfort R Jr, Rizzo LV., *The genotype of Toxoplasma gondii strains causing ocular toxoplasmosis in humans in Brazil.* Am J Ophthalmol., 2005. **139**: p. 350-361.
4. Soheilian M, H.K., Yazdani S, Shahsavari M, Ahmadieh H, Dehghan M, *Patterns of uveitis in a tertiary eye care center in Iran.* Ocul Immunol Inflamm., 2004. **12**: p. 297-310.
5. Holland, G., *Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease.* American journal of ophthalmology, 2003. **136**(6): p. 973-988.
6. Howe DK, S.D., *Toxoplasma gondii comprises three clonal lineages: correlation of parasite genotype with human disease.* J Infect Dis., 1995. **172**: p. 1561-1566.
7. Lehmann, T., et al., *Variation in the structure of Toxoplasma gondii and the roles of selfing, drift, and epistatic selection in maintaining linkage disequilibria.* Infect Genet Evol, 2004. **4**(2): p. 107-14.
8. Ajzenberg, D., et al., *Genetic diversity, clonality and sexuality in Toxoplasma gondii.* Int J Parasitol, 2004. **34**(10): p. 1185-96.
9. Ajzenberg, D., et al., *Genotype of 86 Toxoplasma gondii isolates associated with human congenital toxoplasmosis, and correlation with clinical findings.* J Infect Dis, 2002. **186**(5): p. 684-9.
10. Nowakowska D, C.I., Remington JS, Grigg M, Golab E, Wilczynski J, Sibley LD., *Genotyping of Toxoplasma gondii by multiplex PCR and peptide-based serological testing of samples from infants in Poland diagnosed with congenital toxoplasmosis.* J Clin Microbiol, 2006. **44**: p. 1382-1389.
11. Howe DK, H.S., Derouin F, Sibley LD, *Determination of genotypes of Toxoplasma gondii strains isolated from patients with toxoplasmosis.* J Clin Microbiol., 1997. **35**: p. 1411-1414.
12. Dubey JP, G.S., Labruna MB, Camargo LM, Vianna MC, Marcet PL, Lehmann T, *Characterization of Toxoplasma gondii isolates in free-range chickens from Amazon, Brazil.* J Parasitol., 2006. **92**: p. 36-40.
13. Pena, H.F., et al., *Population structure and mouse-virulence of Toxoplasma gondii in Brazil.* Int J Parasitol, 2008. **38**(5): p. 561-9.
14. Yai, L.E., et al., *Genetic diversity among capybara (Hydrochaeris hydrochaeris) isolates of Toxoplasma gondii from Brazil.* Vet Parasitol, 2009.
15. Jones JL, M.C., Belfort R Jr, Holland GN, Roberts JM, Silveira C, *Recently Acquired Toxoplasma gondii Infection, Brazil.* Emerg Infect Dis., 2006. **12**: p. 582-587.
16. De Moura L, B.-O.L., Wada MY, Jones JL, Tuboi SH, Carmo EH, Ramalho WM, Camargo NJ, Trevisan R, Graça RM, da Silva AJ, Moura I, Dubey JP, Garrett DO., *Waterborne toxoplasmosis, Brazil, from field to gene.* Emerg Infect Dis., 2006. **12**: p. 326-329.

17. Khan A, J.C., Muccioli C, Vallochi AL, Rizzo LV, Belfort R Jr, Vitor RW, Silveira C, Sibley LD., *Genetic divergence of Toxoplasma gondii strains associated with ocular toxoplasmosis, Brazil.* Emerg Infect Dis., 2006. **12**: p. 942-949.
18. Belfort RN, et al., *Bilateral progressive necrotizing retinichoroiditis in a immunocompromised patient: histopathologic diagnosis.* Acta Ophthalmologica, 2008. **in press**.
19. Montoya, J. and J. Remington, *Toxoplasmic chorioretinitis in the setting of acute acquired toxoplasmosis.* Clin Infect Dis., 1996. **23**: p. 277-282.
20. Nussenblatt RB and Belfort Jr. R, *Ocular toxoplasmosis. An old disease revisited.* JAMA., 1994. **271**: p. 304-307.
21. Holland GN, *Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management.* Am J Ophthalmol., 2004. **137**: p. 1-17.
22. Eckert GU, Melamed J, and Menegaz B, *Optic nerve changes in ocular toxoplasmosis.* Eye., 2007. **21**: p. 746-751.
23. Smith JR and Cunningham Jr. ET, *Atypical presentations of ocular toxoplasmosis.* Curr Opin Ophthalmol., 2002. **13**: p. 387-392.
24. Bonfioli AA and Orefice F, *Toxoplasmosis.* Semin Ophthalmol., 2005. **20**: p. 129-141.
25. Bosch-Driessen LH, et al., *Retinal detachment in ocular toxoplasmosis.* Ophthalmology., 2000. **107**: p. 36-40.
26. Toledo de Abreu M, Belfort R Jr, and Hirata PS, *Fuchs' heterochromic cyclitis and ocular toxoplasmosis.* Am J Ophthalmol., 1982. **93**: p. 739-744.
27. Schwab IR, *The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis.* Am J Ophthalmol., 1991. **111**: p. 356-362.
28. La Hey E and Baarsma GS, *Contralateral active ocular toxoplasmosis in Fuchs' heterochromic cyclitis.* Br J Ophthalmol, 1993. **77**: p. 455-456.
29. Ganesh SK, et al., *Fuchs' heterochromic iridocyclitis following bilateral ocular toxoplasmosis.* Ocul Immunol Inflamm, 2004. **12**: p. 75-77.
30. Silveira C, B.R.J., Muccioli C, Abreu MT, Martins MC, Victora C, Nussenblatt RB, Holland GN., *A follow-up study of Toxoplasma gondii infection in southern Brazil.* Am J Ophthalmol., 2001. **131**: p. 351-354.
31. Montoya JG and Liesenfeld O, *Toxoplasmosis.* The Lancet., 2004. **363**: p. 1965-1976.
32. Montoya JG and Remington JS, *Management of Toxoplasma gondii infection during pregnancy.* Clin Infect Dis., 2008. **47**: p. 554-566.
33. Mets MB and Chhabra MS, *Eye manifestations of intrauterine infections and their impact on childhood blindness.* Surv Ophthalmol., 2008. **53**: p. 95-111.
34. Wallon M, et al., *Long-term ocular prognosis in 327 children with congenital toxoplasmosis.* Pediatrics, 2004. **113**: p. 1567-1572.
35. Tan HK, S.D., Stanford M, Teär-Fahnehjelm K, Ferret N, Salt A, Gilbert R;, *Risk of visual impairment in children with congenital toxoplasmic retinochoroiditis.* Am J Ophthalmol., 2007. **144**: p. 648-653.
36. Mets MB, H.E., Boyer KM, Swisher CN, Roizen N, Stein L, Stein M, Hopkins J, Withers S, Mack D, Luciano R, Patel D, Remington JS, Meier P, McLeod R., *Eye manifestations of congenital toxoplasmosis.* Am J Ophthalmol., 1997. **123**: p. 1-16.
37. Kodjikian L, W.M., Fleury J, Denis P, Binquet C, Peyron F, Garweg JG, *Ocular manifestations in congenital toxoplasmosis.* Graefes Arch Clin Exp Ophthalmol., 2006. **244**: p. 14-21.

38. Silveira C, F.R., Muccioli C, Nussenblatt R, Belfort R Jr., *Toxoplasmosis transmitted to a newborn from the mother infected 20 years earlier.* Am J Ophthalmol., 2003. **136**: p. 370-381.
39. Ongkosuwito JV, B.-D.E., Kijlstra A, Rothova A., *Serologic evaluation of patients with primary and recurrent ocular toxoplasmosis for evidence of recent infection.* Am J Ophthalmol., 1999. **128**: p. 407-412.
40. Rao, N.A. and R.L. Font, *Toxoplasmic retinochoroiditis: electron-microscopic and immunofluorescence studies of formalin-fixed tissue.* Arch Ophthalmol, 1977. **95**(2): p. 273-7.
41. Brézin AP, E.C., Burnier M Jr, Silveira C, Mahdi RM, Gazzinelli RT, Belfort R Jr, Nussenblatt RB, *Identification of Toxoplasma gondii in paraffin-embedded sections by the polymerase chain reaction.* Am J Ophthalmol., 1990. **110**: p. 599-604.
42. Belfort, R.N., et al., *Bilateral macular hemorrhage as a complication of drug-induced anemia: a case report.* J Med Case Reports, 2009. **3**: p. 16.
43. Montoya, J.G., et al., *Use of the polymerase chain reaction for diagnosis of ocular toxoplasmosis.* Ophthalmology, 1999. **106**(8): p. 1554-63.
44. Rothova A, et al., *Usefulness of aqueous humor analysis for the diagnosis of posterior uveitis.* Ophthalmology., 2008. **115**: p. 306-311.
45. Grigg ME, G.J., Boothroyd JC, Margolis TP, *Unusual abundance of atypical strains associated with human ocular toxoplasmosis.* J Infect Dis., 2001. **184**: p. 633-639.
46. Fekkar A, B.B., Touafek F, Le Hoang P, Mazier D, Paris L, *Comparison of immunoblotting, calculation of the Goldmann-Witmer coefficient, and real-time PCR using aqueous humor samples for diagnosis of ocular toxoplasmosis.* J Clin Microbiol, 2008. **46**: p. 1965-1967.
47. Mahalakshmi B, T.K., Madhavan HN, Biswas J, *Diagnostic value of specific local antibody production and nucleic acid amplification technique-nested polymerase chain reaction (nPCR) in clinically suspected ocular toxoplasmosis.* Ocul Immunol Inflamm., 2006. **14**: p. 105-112.
48. Calderaro A, P.G., Gorrini C, Peruzzi S, Zerbini L, Bommezzadri S, Dettori G, Chezzi C., *Comparison between two real-time PCR assays and a nested-PCR for the detection of Toxoplasma gondii.* Acta Biomed., 2006. **77**: p. 75-80.
49. Lin MH, C.T., Kuo TT, Tseng CC, Tseng CP, *Real-time PCR for quantitative detection of Toxoplasma gondii.* J Clin Microbiol., 2000. **38**: p. 4121-4125.
50. Dworkin LL, G.T., Van Gelder RN, *Real-time quantitative polymerase chain reaction diagnosis of infectious posterior uveitis.* Arch Ophthalmol., 2002. **120**: p. 1534-1539.
51. Fekkar, A., et al., *Comparison of immunoblotting, calculation of the Goldmann-Witmer coefficient, and real-time PCR using aqueous humor samples for diagnosis of ocular toxoplasmosis.* J Clin Microbiol, 2008. **46**(6): p. 1965-7.
52. Fardeau, C., et al., *Diagnosis of toxoplasmic retinochoroiditis with atypical clinical features.* American journal of ophthalmology, 2002. **134**(2): p. 196-203.
53. Rothova A, B.H., Meenken C, Baarsma GS, Boen-Tan TN, de Jong PT, Schweitzer CM, Timmerman Z, de Vries J, Zaal MJ, et al., *Therapy of ocular toxoplasmosis.* Int Ophthalmol, 1989. **12**: p. 415-419.
54. Pleyer U, T.N., Liesenfeld O, *Ocular toxoplasmosis.* Ophthalmologe, 2007. **104**: p. 603-615.
55. Antoniazzi E, et al., *Ocular impaiment of toxoplasmosis.* Parasitologia, 2008. **50**: p. 35-36.

56. Rothova A, M.C., Buitenhuis HJ, Brinkman CJ, Baarsma GS, Boen-Tan TN, de Jong PT, Klaassen-Broekema N, Schweitzer CM, Timmerman Z, et al., *Therapy for ocular toxoplasmosis.* Am J Ophthalmol., 1993. **115**: p. 517-523.
57. Opremcak EM, S.D., Sharpe MR, *Trimethoprim-sulfamethoxazole therapy for ocular toxoplasmosis.* Ophthalmology., 1992. **99**: p. 920-925.
58. Soheilian M, S.M., Ghajarnia M, Dehghan MH, Yazdani S, Behboudi H, Anisian A, Peyman GA., *Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis.* Ophthalmology., 2005. **112**: p. 1876-1882.
59. Bosch-Driessen LH, B.T., Ongkosuwito JV, Rothova A, *Ocular toxoplasmosis: clinical features and prognosis of 154 patients.* Ophthalmology., 2002. **109**: p. 869-878.
60. Abreu MT, Belfort Jr R, and Oréfice F, *Toxoplasmose Ocular*, in *Uveites*, Oréfice F and Belfort Jr. R, Editors. 1987, Roca: São Paulo. p. 211-230.
61. Silveira C, et al., *Toxoplasma gondii in the peripheral blood of patients with acute and chronic toxoplasmosis.* Br J Ophthalmol, Manuscript submitted.
62. Silveira C, B.R.J., Muccioli C, Holland GN, Victora CG, Horta BL, Yu F, Nussenblatt RB., *The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis.* Am J Ophthalmol., 2002. **134**: p. 41-46.
63. Morhun PJ, et al., *Recurrent ocular toxoplasmosis in patients treated with systemic corticosteroids.* Retina, 1996. **16**: p. 383-387.
64. Aggio FB, Muccioli C, and Belfort Jr. R, *Intravitreal triamcinolone acetonide as an adjunct in the treatment of severe ocular toxoplasmosis.* Eye., 2006. **20**: p. 1080-2.
65. Sobrin L, Kump LI, and Foster CS, *Intravitreal clindamycin for toxoplasmic retinochoroiditis.* Retina, 2007. **27**: p. 952-957.
66. Kishore K, C.M., Peyman GA, *Intravitreal clindamycin and dexamethasone for toxoplasmic retinochoroiditis.* Ophthalmic Surg Lasers, 2001. **32**: p. 183-192.
67. Colin J and Harie JC, *Presumed toxoplasmic chorioretinitis: comparative study of treatment with pyrimethamine and sulfadiazine or clindamycin.* J Fr Ophtalmol., 1989. **12**: p. 161-165.

Figures

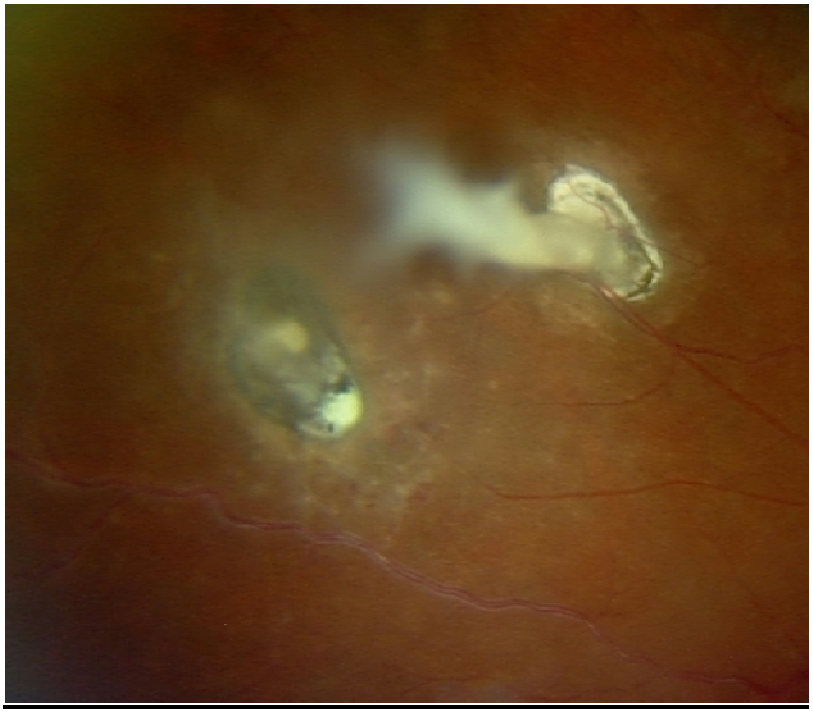

Figure 1: Ocular toxoplasmosis with vitreous strand and vasculitis.

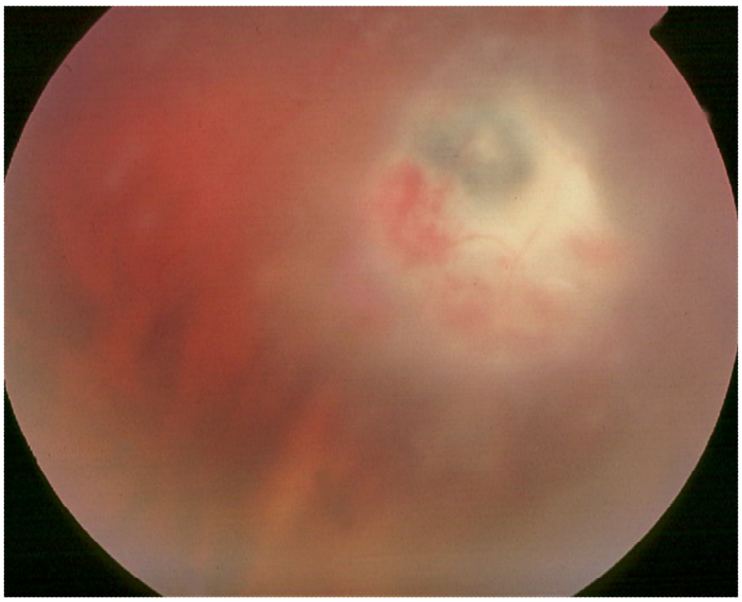

Figure 2: Retinochoroiditis with vitreitis

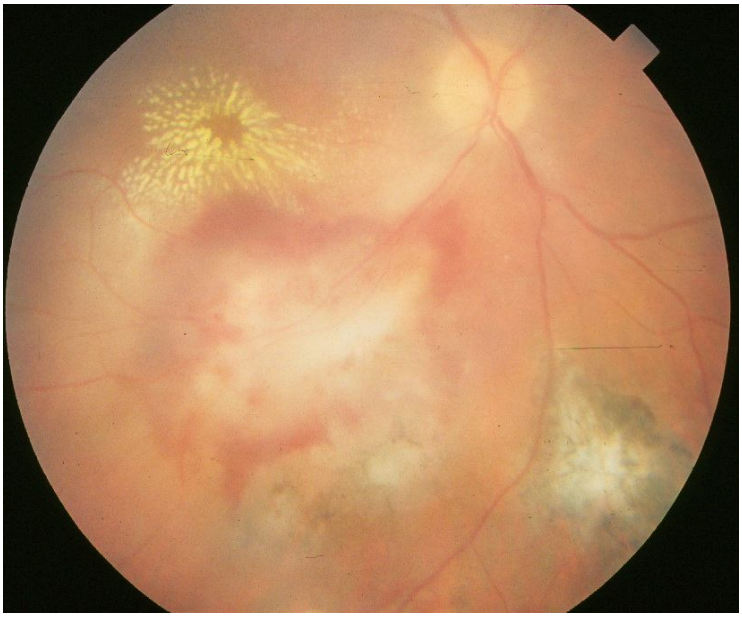

Figure 3. Ocular toxoplasmosis with old pigmented scar and inferior recurrence to the macula.

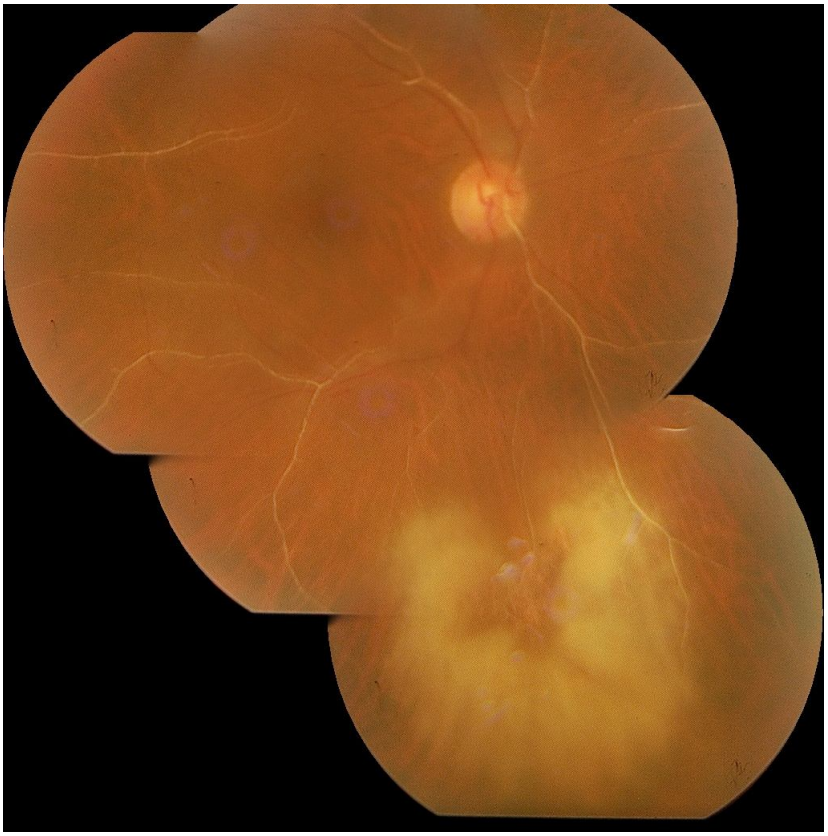

Figure 4: Inferior area of retinochoroiditis and difuse vasculitis

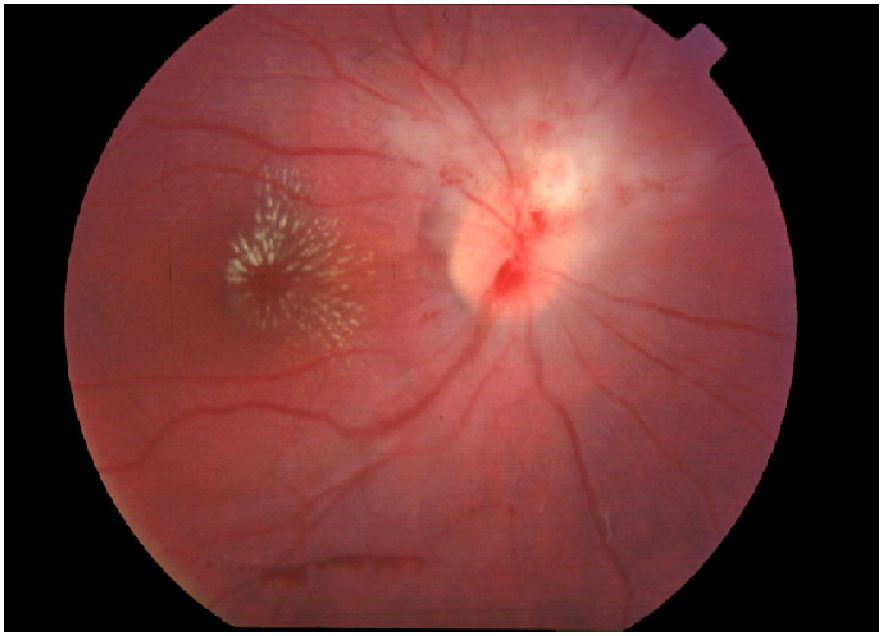

Figure 5: Optic disk involved in a case of ocular toxoplasmosis

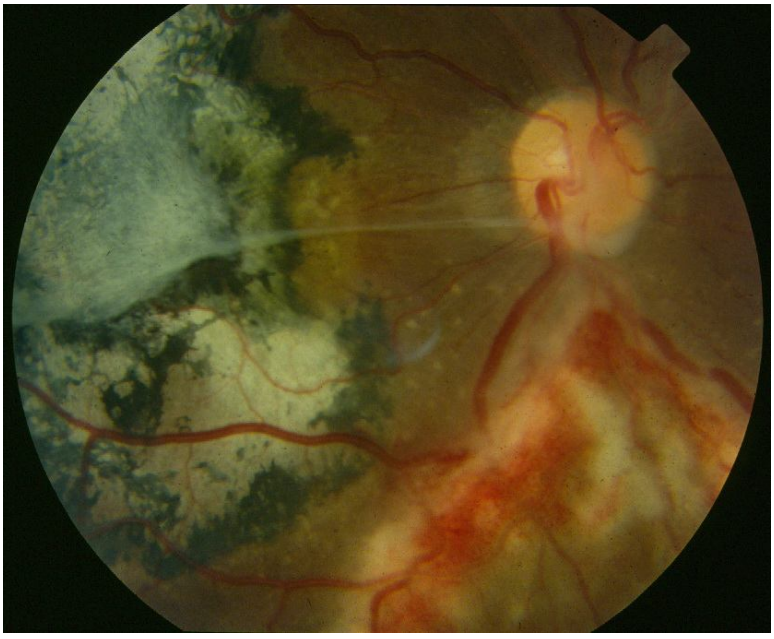

Figure 6: Toxoplasmic scar in the macula and acute CMV in a patient with AIDS.

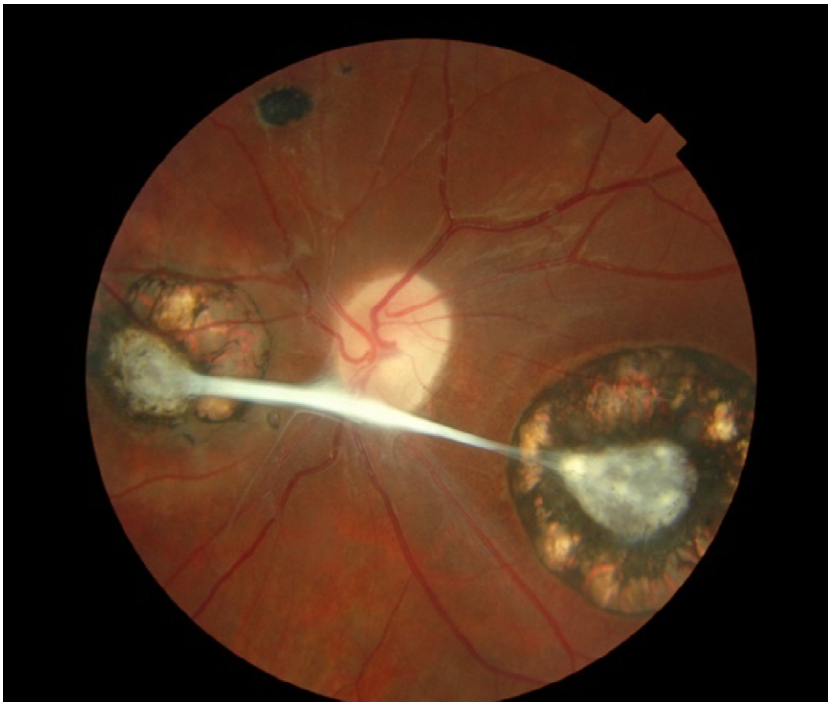

Figure 7: Retinal scars linked by vitreous strand in congenital toxoplasmosis.