

# Ocular toxoplasmosis – case report and literature review

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## ABSTRACT

Ocular toxoplasmosis is a retinochoroiditis caused by *Toxoplasma gondii* infection, the most common<sup>3</sup> cause of posterior infectious uveitis worldwide. Main features: it is a unilateral recurrent focal retinochoroiditis infection, with early manifestation after primary systemic infection, or with late manifestation after reactivation of intraretinal infectious cysts. The diagnosis is mainly clinical, being supported paraclinically by laboratory tests. Associated features: the most common is a unilateral focal ocular pathology, with multiple and bilateral active lesions occurring in a recently acquired infection or in immunocompromised patients. Ocular toxoplasmosis is characterized by posterior, intermediate, and anterior ocular damage; is a retinochoroiditis infection with significant involvement of the vitreous, with increased inflammation, retinal vasculitis, optic disc edema and anterior uveitis. Therapeutic management includes antiparasitic medication and corticosteroid therapy. Regarding pregnancy, it is essential to screen and capture the moment of maternal acute infection during pregnancy in patients with negative IgGs in order to treat the infection, to minimize or even prevent transplacental passage.

**Keywords:** ocular toxoplasmosis, posterior infectious uveitis, retinochoroiditis, *Toxoplasma gondii*

## INTRODUCTION

Toxoplasmosis is caused by infection with *Toxoplasma gondii*, an apicomplexan parasite that affects a third of the human population, and is a common cause of intraocular inflammation and scarring, the world’s leading cause of posterior infectious uveitis. Complications go as far as threatening vision, including retinochoroidal scars, vitreous opacity, choroidal neovascularization, cataracts, strabismus, nystagmus, and glaucoma (1).

*Toxoplasma gondii* is a ubiquitous parasite, toxoplasmosis being a widespread infection among peo-

ple on continents with tropical and humid climates, and in areas with many domestic cats, showing a variable prevalence from country to country, depending on hand hygiene, local food habits, contact with water or contaminated food, and contact with contaminated soil.

The incidence of the disease is very high in poor countries and high in developing countries. The CDC (Centers for Disease Control and Prevention in the United States) reports a 22.5% percentage of *Toxoplasma gondii* infection in the population over the age of 12, with a high incidence in humid and

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hot climates. In South America, the percentage reaches up to 80%. A high infection rate is also found in Europe, especially in France, with an estimated rate of 80% (2).

*Toxoplasma gondii* is a strictly intracellular parasite, with the ability to infect any warm-blooded animal, causing chronic infections throughout life. The cat is the definitive specific host for *Toxoplasma gondii*, the human being an intermediate host. The organism has multiple evolutionary forms, the tachyzoite being the proliferating active form found during the acute infection in the intermediate and definitive hosts. It can penetrate any nucleated cell and circulate throughout the body, producing cell lysis, tissue destruction and a strong immune response from the body. Tachyzoites differentiate into bradyzoites under the influence of the host's immune system and form tissue cysts, which are latent forms that may persist indefinitely in the host tissues (central nervous system - especially in the neurosensory retina and striated muscles), without producing an intense inflammatory response. These cysts can rupture, releasing bradyzoites that turn into tachyzoites, thus reactivating the infection, especially in the retina. Tissue cysts are refractory to currently available antiparasitic therapies, which is why *Toxoplasma gondii* infection is not curable. Definitive host infection occurs either by ingestion of tachyzoites from the flesh of intermediate hosts, or by ingestion of oocysts from the soil and/or spread in feline feces. Once the parasite reaches the intestines at the level of enterocytes, it begins to replicate. The specific host, the cat, contaminates the environment with millions of oocysts, and the intermediate host, the human, becomes infected through sources of water, soil, or contaminated food. Transplacental transmission from host with recent infection, and organ transplantation are other pathways of infection (3).

Seroconversion is a problem for pregnant women due to the vertical transmission of the newly acquired acute infection. Seroconversion increases with age. The rate of transplacental infection increases from the first to the third trimester, from 10-25% in the first trimester to 60-80% in the third trimester, but the severity of complications that may occur in the fetus decreases during pregnancy (3).

Although considered a major cause, congenital toxoplasmosis with a presence of about 80% in infected children with retinochoroidal damage, has a relatively low incidence, associated with increased documentation of postnatal infection (often asymptomatic). This supports the hypothesis that the acquired form is more important than it was previously considered. The rate of infection acquired with postnatal eye damage is of 2-20% (4,5).

Ocular toxoplasmosis is a focal retinochoroiditis, a granulomatous inflammation with necrosis of the retina, choroid, but also an inflammation of the vitreous and anterior uveal tract. After fighting inflammation, a retinochoroidal scar remains with proliferation of RPE (retinal pigment epithelium). Histologically, a normal retina may contain intact parasitic cysts. The pathogenesis depends on the immunity of the host and the virulence of the parasite. Extensive eye damage is associated with an immature immune system, present due to altered fetogenesis and embryogenesis (6,7). Immunocompromised individuals have more severe systemic and ocular reactions, as well as a higher risk of infection. They may have a normal retina, even with many cysts present, and an increased risk of reactivation (8).

The gastrointestinal tract is the first defense barrier of the immune system. The immune response includes polymorphonuclear leukocytes, macrophages, B/T lymphocytes, dendritic cells, natural killer NK cells, and the participation of CD4 + and CD8 + T lymphocytes. The T-helper-1 reaction leads to the release of proinflammatory cytokines: interleukin-12, interferon gamma, tumor necrosis factor alpha, and later a T-helper-2 response (9). The virulence of the parasite is another factor which pathogenesis depends on. *Toxoplasma* comprises three typical canonical genotypes (I, II and III) but also atypical recombinant genotypes, with ocular and systemic damage, present in endemic areas such as South America (10).

## CASE PRESENTATION

A 42-year-old Caucasian female patient from an urban area presented to the Ophthalmology Center of Regina Maria Health Network in Bucharest for decreased visual acuity in the right eye, with an onset of approximately 15 years, with loss of central vision, to evaluate the eye and establish the usefulness of a local treatment.

The patient had no significant personal pathological and hereditary-collateral antecedents. Visual acuity testing revealed acuity of 0.5 nc (50% uncorrectable) in the right eye with no affirmative central vision, and 1fc (100% uncorrected) in the left eye.

Upon examination of the anterior pole of the eye, discrete cortical crystalline densifications were identified in both eyes, while in the rest of the anterior pole both eyes were normal. Intraocular pressure was normal at the time of evaluation: OD = 14 mmHg, OS = 16 mmHg. Upon examination of the posterior pole of the eye by digital format photography with the VuEye portable retinophotograph, the following were identified: right eye: OD papilla pla-

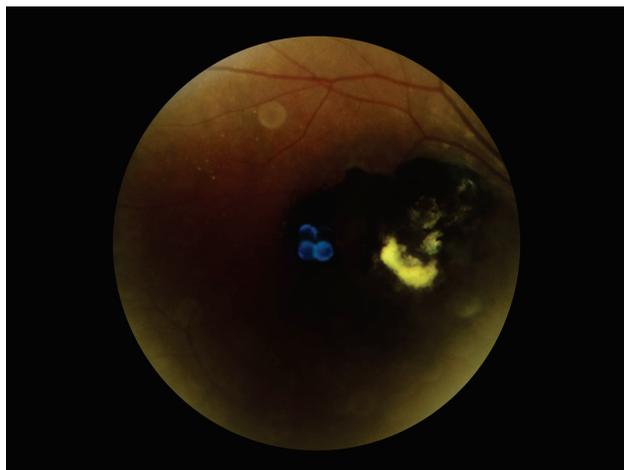
na with clear outline, physiological excavation, macula with yellow lesion  $\frac{1}{2}$  DD (disc diameter) delimited at the edge by a hyperpigmented lesion (hyperpigmentation of RPE = retinal pigment epithelium) of approximately 8DD total enlargement, with visibility of the choroid in the upper part of the lesion near the optic nerve, without vascular inflammation (Figures 1, 2). The left eye had a normal fundus examination.

Laboratory tests performed by two working methods are recommended: ELFA (enzyme-linked immunofluorescence assay) and ECLIA (electrochemiluminescence-based immunoassay). The results obtained after testing were: IgG positive anti-Toxoplasma antibodies: ELFA 3,178 UI/ml; ECLIA 1,257 U/ml and IgM negative anti-Toxoplasma antibodies: ELFA 0.37 Index; ECLIA 0.6 Index. Reference values are depending on the working method. Toxo-IgG ELFA < 4 UI/ml: Negative; 4-8 UI/ml: Equivocal;  $\geq 8$  UI/ml: Positive. ECLIA < 1 UI/ml: Negative; 0.5-1 UI/ml: Equivocal;  $\geq 3$  UI/ml: Positive. Toxo-IgM: ELFA < 0.55 Index: Negative; 0.55-0.65 Index: Equiv-

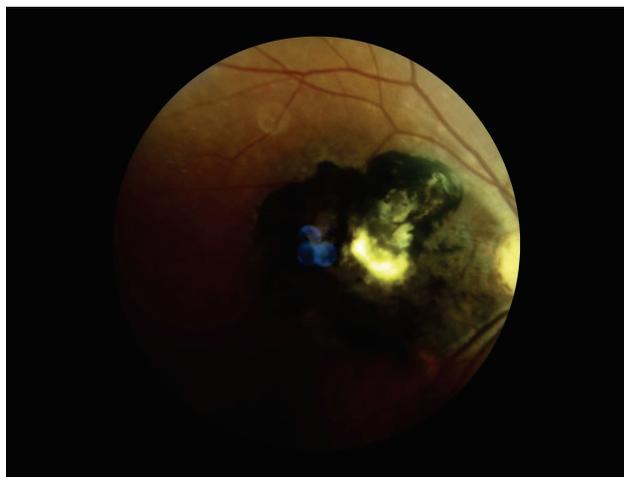
ocal;  $\geq 0.65$  Index: Positive; ECLIA < 0.8 Index: Negative; 0.8-1: Index: Equivocal;  $\geq 1$  Index: Positive.

Laboratory results were interpreted as a previous infection (older than 2 years). The diagnosis of chronic *Toxoplasma gondii* infection, without activation at the time of presentation to the doctor, was confirmed.

The main factors that influenced the decision not to treat retino-choroiditis have been the following: the immunocompetent status of the infected patient (normal blood count, IgM negative anti-toxoplasma antibodies by the two methods ELFA and ECLIA), the inactivity of the lesion (absent optic disc edema or macular edema, lack of vitreous involvement, constant visual acuity (assessed after diagnosis for 6 months post-diagnosis), stationary clinical context and adverse effects of antiparasitic therapy and corticosteroids. The patient was evaluated 12 months after diagnosis: visual acuity of 0.5 nc (50% uncorrectible) in the right eye with lack of central vision, visual acuity of 1fc (100% uncorrected) in the left eye were constant, with no signs of iridocyclitis or vitreous and maintaining constant retino-choroidal lesion in location and size. The patient remains under regular ophthalmologic observation with: determination of visual acuity, biomicroscopy, tonometry, periodic retinophotography of the fundus, optical coherence tomography (OCT), angio-OCT to exclude the presence of macular edema and / or optic nerve edema, and also ultrasound to exclude vitreous inflammation, vitreous or retinal detachment. Current status is stationary, both clinically and biologically.



**FIGURE 1.** Fundus examination by posterior pole retinophotography: yellowish-white macular lesion  $\frac{1}{2}$  DD, with RPE hypertrophy edges, upper nasal corrosion



**FIGURE 2.** Fundus examination: macular lesion of approximately 8DD surface without vascular changes

## DISCUSSIONS

The particularity of the case consists in minimal symptoms at onset: blurred vision in the right eye, without manifestations of the previous uveitis type (eye pain or photophobia, symptoms of eye floaters), with no lesions identified in the retina, choroid, vitreous or anterior pole indicating an active infection. In addition, it is intriguing the early onset correlated with a late diagnosis: the debut of symptoms about 15 years before, with a diagnosis established in adulthood, although the patient came from an urban environment. Also, the patient stated the lack of contact with the cat, the skin lesions produced by it, the lack of contact with animal feces, the lack of ingestion of contaminated food or water and admitted to have respected hand hygiene, so it is unknown the source of the infection.

In immunocompetent individuals, most cases of postnatal acquired toxoplasmosis are asymptomatic. Some cases present symptoms such as altered general condition, fever, lymphadenopathy, and a small number of cases develop pneumonia, enceph-

alitis, myocarditis, and hepatitis (11). In immunocompromised individuals, the infection is more aggressive, causing a life-threatening systemic condition, frequently toxoplasmosis encephalitis.

Ocular disease in combination with postnatal toxoplasmosis is rare in people with a competent immune system, but reactivation of parasitic cysts can cause chorioretinitis lesions at any time during life. The retinochoroidal lesion presents a white-yellow color, similar to an exudate, which produces retinal edema around it. The active lesion most often appears at the edge or in the vicinity of an old retinochoroiditis scar, as a satellite lesion. An active exudative lesion in the absence of a retinochoroidal scar is possible, although less common - this being an isolated focal lesion (12). The infection affects the thickness of the retina, followed by an inflammatory reaction of the choroid, an inflammatory infiltrate in vitro, which is present invariably. Opacities and vitreous bands are present. The active lesions determine a cloudy, foggy vitreous, with the appearance of a “headlight in the fog”. Perivascularly, there is a more frequent puncture of the venules, and periarterial lipid exudates are present (Kyrieleis arteriolitis) (11). Perivascular lesions are the cause of vascular occlusions, retinal edema, and retinal hemorrhage. Active toxoplasma lesions cause both macular edema and optic nerve edema. Anterior granulomatous or non-granulomatous iridocyclitis occurs in the anterior part of the eye. Intraocular pressure is increased in 10-30% of infected people, leading to glaucoma (13). Retinal and choroidal scars show a degree of pigmentation by hyperplasia or hypertrophy of retinal pigment epithelium, being clinically polymorphic and can enhance visualization of the sclera below.

Congenital toxoplasmosis is present in 80% of cases of newborns with parasitic infection and retinochoroidal lesions, often macular and even bilateral “spoke-wheel” type. Satellite or isolated focal lesions may be present immediately at birth or later in life. Atypical lesions including reduced vitreous, with serous retinal detachment, macular star pattern, and optic disc edema, are also possible. Extensive and bilateral multifocal active lesions may also be present. Another atypical form includes anterior uveitis, optic neuritis, retinal vasculitis, but no retinochoroiditis with necrosis. Atypical forms are rare in postnatal infections (13).

The clinical diagnosis of ocular toxoplasmosis is sustained, like in our case, by laboratory investigations represented by serological tests that in most cases reveal only the presence of IgG antibodies of *Toxoplasma gondii*. A significant titer of IgG and IgM antibodies indicates a recently acquired disease, and their absence excludes *Toxoplasma gondii* as the cause (8). Congenital toxoplasmosis is diag-

nosed by the presence of IgM antibodies and/or IgA antibodies and/or elevated IgG antibody levels after the first year of life. In uncertain cases, an in vitro or aqueous humor PCR test helps confirm *Toxoplasma gondii* infection (8).

Differential diagnosis includes infectious, non-infectious, and tumor causes. Infectious causes in differential diagnosis can be bacterial such as: syphilis, tuberculosis, bartonellosis, Lyme disease; viral: herpes virus, cytomegalovirus, West Nile virus, Zika virus; fungal: candidosis, aspergillosis; parasitic: toxocara). The non-infectious causes are those associated with systemic diseases: Behcet's disease, sarcoidosis, or not associated with systemic diseases: serpiginous choroiditis, multifocal choroiditis and panuveitis, punctate inner choroidopathy, unilateral acute idiopathic maculopathy. The neoplastic causes are mainly vitreoretinal lymphoma. In newborns with suspected congenital disease, it is mandatory to exclude infections from TORCH acronym (toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis) (14).

The main factors influencing the decision to treat active retinochoroiditis are: the immune status of the infected organism, the location and size of the active lesion, the presence or absence of optic or macular disc edema, the degree of involvement of vitreous (vitritis), visual acuity, clinical evolution, special situations such as those of pregnant patients, adverse effects of antiparasitic therapy and corticotherapy. Retinochoroiditis may be self-limiting in some immunocompetent patients. In immunosuppressed patients with active retinochoroidal lesions, therapy is mandatory because of the high risk of vision loss and complications associated with infection.

Newborns with congenital toxoplasmosis are treated in the first year of life, regardless of the existence of retinochoroidal lesions. Pregnant women with seroconversion require antiparasitic therapy, even in the absence of eye damage, in order to reduce vertical transmission. Confirmation of fetal infection by PCR analysis of amniotic fluid or ultrasound requires specific antiparasitic treatment. In the absence of eye damage, reactivations during pregnancy can be monitored in an early stage, due to a reduced risk of fetal infection (15).

The main antiparasitic therapies include: sulfadiazine and pyrimethamine as standard therapy, clindamycin, azithromycin, spiramycin, sulfamethoxazole. The treatment also includes folic acid administration and oral corticosteroid therapy with prednisone at a dose of 1 mg/kg body weight/day, as well as topical ocular treatment with corticosteroids, mydriatic and antiglaucoma medication to lower intraocular pressure. As ophthalmological therapy, the following are also suggested: laser

photocoagulation of extramacular lesions, cryotherapy, and pars plana vitrectomy (16).

Primary prophylaxis is essential for seronegative women, during pregnancy and before pregnancy, as well as for immunosuppressed patients. Prophylactically, it is recommended to avoid cats or contact with their feces, or to use gloves when cleaning litter, to frequently wash hands after contact with soil, food, meat, and cats, to avoid eating unprepared or insufficiently cooked meat, to consume boiled or filtered water, to intensely wash fruits and vegetables before eating (15).

Ocular toxoplasmosis with retino-choroidal lesions is recurrent in two-thirds of patients. Reactivations are more common in congenital forms than in acquired forms and occur in the first year after a previous episode. The prognosis is influenced by the host's immune system, age, and the location of

eye lesions. Significant decrease in visual acuity occurs in the context of vitreous opacity, optic atrophy, macular edema, extensive retinochoroidal scars, retinal detachment, and choroidal neovascularization (7).

## CONCLUSIONS

Toxoplasmosis represents an infectious disease with a wide range of signs and symptoms, ocular toxoplasmosis being one of the most difficultly diagnosing disorders. Although it usually is asymptomatic and rarely affects immunocompetent adults, it is essential to screen and capture the moment of maternal infection during pregnancy in patients with negative IgGs in order to treat the infection, to minimize or even prevent transplacental passage.

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