Severe Atypical Resistant Form of Ocular Toxoplasmosis Using Combined Therapy: Case Report

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Abstract

Ocular toxoplasmosis, an infection caused by *Toxoplasma gondii*, is the most common cause of infectious posterior uveitis in immunocompetent patients. This paper aims to report the case of a woman with retinitis associated with ocular toxoplasmosis and an intravitreal dexamethasone implant.

A 30-year-old woman was observed during a medical appointment; she consulted for myodesopsias in her left eye. We found uveitis, vasculitis, vitreous opacities, and epiretinal membrane during the initial examination. Blood tests for HIV, Hepatitis, and Epstein Barr were negative, while Toxoplasma antibodies (IgG and IgM) were positive. We performed a vitrectomy in the affected eye, followed by combined treatment with Trimethoprim-Sulfamethoxazole, clindamycin, and prednisolone. Shortly after, macular edema was observed, and we performed an intravitreal dexamethasone implant. Two months later, she developed active retinitis and retinal detachment, for which it was necessary to perform a vitrectomy with silicone oil tamponade. One month later, the infection was controlled, visual acuity improved and stabilized, and the retina was attached.

There is a controversy about the route, initiation, and timing of adjunctive corticoid therapy. In addition, evidence for intravitreal dexamethasone implant is still scarce in the course of infectious uveitis. More studies are needed to define longer-term visual and anatomic results.

Abbreviations

T. gondii: Toxoplasma gondii, BCVA: Best-Corrected Visual Acuity; HIV: Human Immunodeficiency Virus; OCT: Optical Coherence Tomography; ERM: Epiretinal Membrane; WBC: White Blood Cells; PCR: Polymerase Chain Reaction; Ab: Antibody; PPV: Pars Plana Vitrectomy; HCMV: Cytomegalovirus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; Anti-LA: Single-stranded DNA Binding Proteins; Anti-RNP: Anti- Ribonucleoprotein; Anti-RO: Anti-Sjögren's Syndrome Related Antigen A; Anti-SM: Anti-Smith Antibodies; ANA: Anti-Nuclear Antibodies; ACPAs: Anti-Citrullinated Protein Antibodies

Introduction

Toxoplasma gondii (*T. gondii*), an obligate protozoan parasite that can lead to acute or chronic infections, can cause ocular toxoplasmosis in humans [1]. Humans acquire the infection by ingesting the parasite from raw or undercooked meat, direct contact or inhalation of oocysts, organ transplantation from infected donors, and transplacental transmission [1].

Ocular toxoplasmosis is the most common cause of infectious posterior uveitis. The prevalence and clinical course of the disease vary significantly regarding different regions and socioeconomic factors [2–8]. Retina and choroid may become infected by the parasite several weeks to several years after the initial systemic illness [1].

The prevalence of ocular toxoplasmosis and the sources of infection vary depending on the geographic region, climate, eating habits, and hygienic habits of a population. In Colombia, 47% of the population has antibody titers for *Toxoplasma gondii*; it is estimated that 1,000,000 people have retinochoroidal scars; the estimated incidence of ocular toxoplasmosis in Colombia, in immunocompetent patients is three new cases per 100,000 inhabitants per year [28]. The presentation of ocular toxoplasmosis tends to be more severe in South American territories compared to Europe. The difference can be attributed to the South American strains being more virulent type I/III, unlike the European type II. In European countries, for example, Turkey, the seroprevalence of toxoplasmosis is 30%, and ocular toxoplasmosis represents 7.2% of all cases of posterior uveitis in Istanbul [6].

Lesions can be solitary, multiple, or satellite to a pigmented retinal scar [9,10]; the optic nerve head can also be involved [11]. However, clinical diagnosis may be even more challenging in immunocompromised patients, as bilateral involvement, large areas of retinal necrosis, and multifocal chorioretinitis can be found [12–16]. Atypical ocular toxoplasmosis presentations include punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, and rhegmatogenous with serous retinal detachments, among others [15].

Therapy must target both the parasite and host immunity. Typical regimens include Pyrimethamine/Sulfadiazine or Trimethoprim-Sulfamethoxazole and Prednisolone as triple therapy, with the addition of Clindamycin in quadruple treatment for at least 4 weeks–6 weeks [17]. Some authors have reported oral Prednisolone dosages ranging from 1.0 mg/kg/day to 1.5 mg/kg/day, up to a daily maximum of 20 mg/day [17]. However, corticosteroid therapy in patients with ocular toxoplasmosis varies from not using them at all to starting them within three days or a week after anti-parasitic treatment [18]. In addition, other treatments may be necessary, such as intravitreal injections of Clindamycin with or without dexamethasone and posterior vitrectomy with silicone oil tamponade [19].

The current study aims to report the course of an atypical case of ocular toxoplasmosis that did not respond to traditional treatment and worsened after the suspension of oral corticoid therapy and intravitreal Dexamethasone implant.

Case Presentation

A 30-year-old woman who resides in Bogota, Colombia, traveled to Turkey 10 months ago and consulted our clinic for one month about the evolution of myodesopsias in her left eye. Our initial examination showed that her Best-Corrected Visual Acuity (BCVA) was 20/20 in her right eye and 20/80 in her left eye. In the fundus of the left eye, there was evidence of vitreous opacification of the vitreous cavity, healthy papilla, and ghost vessels in the upper sector with inflammatory presence. Posterior uveitis was suspected, so we indicated one drop four times a day of Prednisolone at 1%.

Given the high probability of posterior uveitis, immunodeficiency and infection by opportunistic microorganisms were ruled out. Blood tests showed Toxoplasma IgG antibodies (+) (5384 UI/mL) and IgM antibodies (+) (1.38 UI/mL) (Table 1, Table 2). In the angiography, it is impossible to demonstrate details of the fundus due to media opacity; however, blood vessels with staining of their walls and late leaks of the dye are observed, with findings highly suggestive of uveitis and retinal vasculitis (Figure 1). Moreover, severe vitreous opacities of low reflectivity, without evidence of vitreous detachment, were reported in the ultrasound (Figure 2).

Table 1: Paraclinical Investigation.

Paraclinical Investigation	Results without vitrectomy	Results post vitrectomy
White blood cells	14.67 x 10 ^ 3/ul	14.67 x 10 ^ 3/ul
Ab IgG *Toxoplasma gondii*	5384.00 UI/mL	5806.00 UI/mL
Ab IgM *Toxoplasma gondii*	1.38 UI/mL	1.26 UI/mL
PCR aqueous humor *Toxoplasma gondii*	-	0.21 mg/L (positive)
PCR aqueous humor *Mycobacterium tuberculosis*	-	Not detectable
PCR aqueous humor CMV	-	Not detectable
PCR aqueous humor herpes simplex virus 1 and 2	-	Not detectable
Ab HIV	0.19 U/ml	0.24 U/ml
Syphilis Serology test	0.10 U/ml	0.13 U/ml
Anti-Epstein Barr Ab IgG	274 U/ml	274 U/ml
Anti-Epstein Barr Ab IgM	< 10 U/ml	< 10 U/ml
Ab HAV	< 3 U/ml	
Hepatitis B surface antigen	0.37 U/ml	0.41 U/ml
Ab IgG HCMV	252.00 U/ml	315.00 U/ml
Ab IgG Rubeola	230 U/ml	250 U/ml

Table 2: Immune indicators.

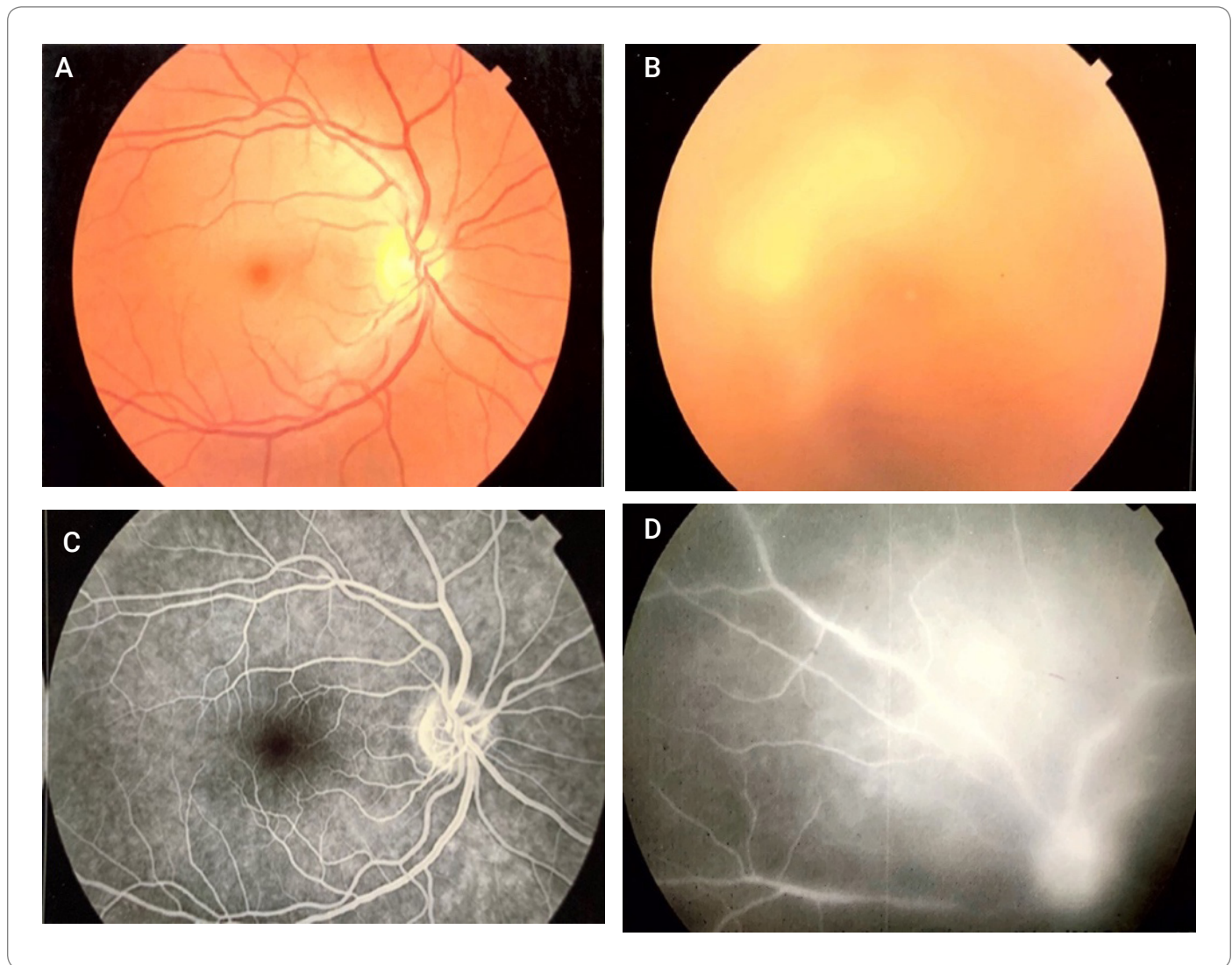| Antibody					
Anti-LA	**Anti-RNP**	**Anti-RO**	**Anti-SM**	**ANA**	**ACPAs**
12.4 U/mL	2.20 u/mL	1.00 u/mL	0,80 u/mL	Neg	< 7.0 u/mL
Lymphocyte					
Total lymphocyte count CD4	Total lymphocyte count CD8	Total lymphocyte count CD3	Lymphocyte ratio CD4/CD8	Lymphocyte CD4	Lymphocyte CD8
244	266	529	66.8	30.9%	33.6%

Figure 1: A) Color Fondus Photography Right eye, normal; **B)** Color Fondus Photography Left eye, Severe vitritis; **C)** Angiography Right eye; **D)** Angiography Left eye.

Results

A Pars Plana Vitrectomy (PPV) in the left eye was performed, and a sample of the vitreous humor was taken to carry out diagnostic tests. Within the intraoperative findings, multiple vitreous opacities and retinal vascular sheathing in temporal and superior vascular arcades. After surgery, we found vitritis with no retinal detachment, so we started a combined oral treatment with Trimethoprim 160 mg -Sulfamethoxazole 800 mg twice daily, Clindamycin 300 mg four times a day, and Prednisolone 5 mg once a day. Optical Coherence Tomography (OCT) showed a hyper-reflective macular lesion and a foveal Epiretinal Membrane (ERM) with a macular thickness of 317 µm (Figure 3A).

After four weeks of antibiotic treatment with Trimethoprim 160 mg -Sulfamethoxazole 800 mg twice daily, and Clindamycin 300 mg four times a day without clinical improvement, we decided to perform an intravitreal Dexamethasone 700 µg implant in the left eye. However, the visual acuity continued to deteriorate during the following four weeks, going from 20/40-2 to 20/70-2. Macular thickness increased up to 393 µm, and macro- and microcysts appeared in OCT (Figure 3B).

Two months after the implant, macular thickness increased up to 434 µm, suggesting active retinitis (Figure 4).
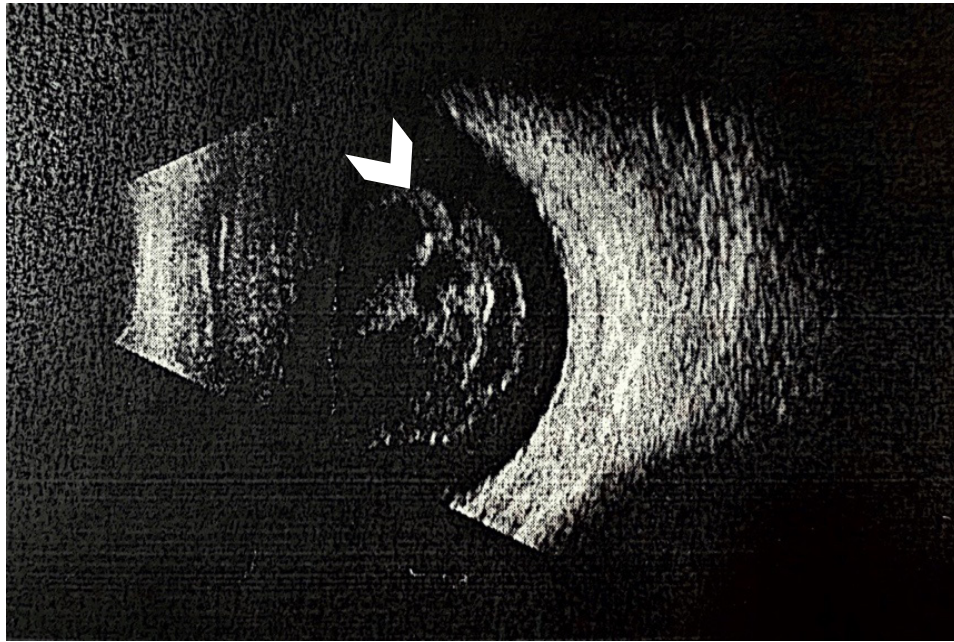
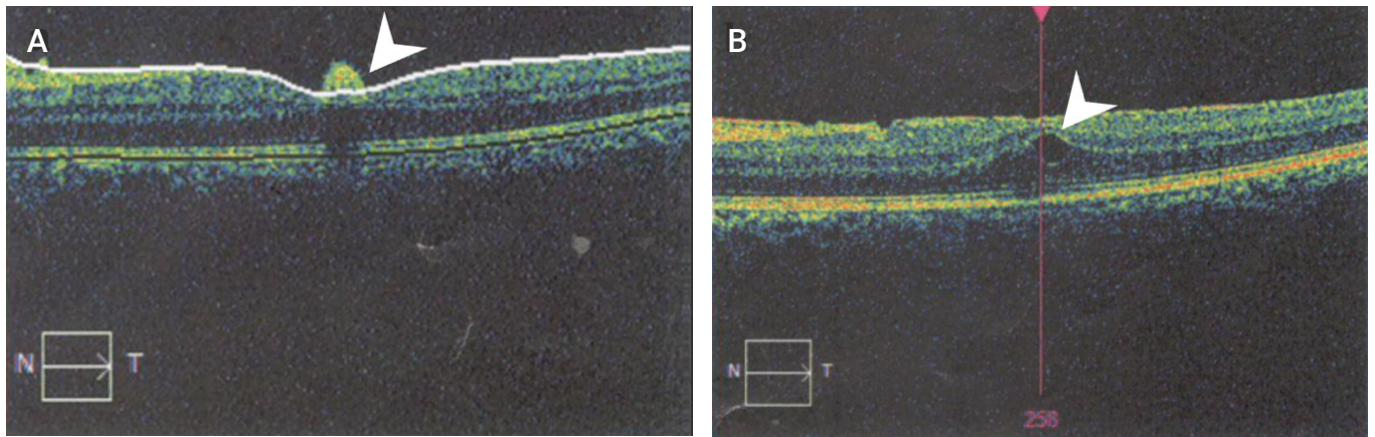**Figure 2:** Initial ultrasonography. Vitreous opacities.

Figure 3: Optical Coherence Tomography (OCT); **A)** Post-vitrectomy, hyper-reflective macula, epiretinal membrane, macular thickness: 317 μm; **B)** Post-dexamethasone implant, macrocyst, macular thickness: 393 μm.
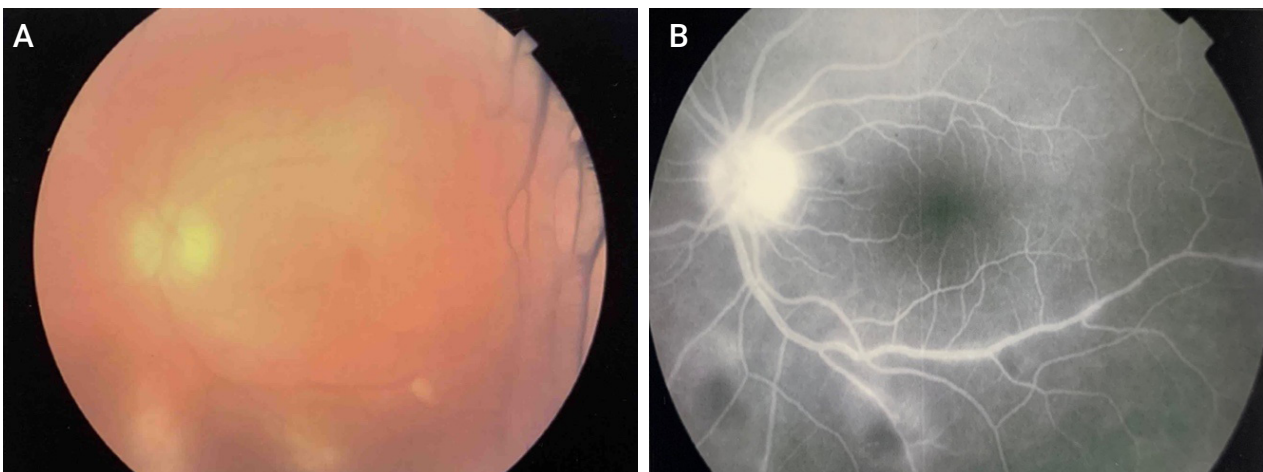

Figure 4: A) Color Fondus Photographypost- dexamethasone implant. Active Retinitis Left eye; **B)** Angiography post- dexamethasone implant. Active Retinitis. Left eye.

We initiated a combined scheme with 40 mg intramuscular Methylprednisolone, one drop three times a day of diclofenac, and Trimethoprim 160 mg -Sulfamethoxazole 800 mg twice daily, Clindamycin 300 mg four times a day for another six weeks. At this time, blood tests showed Neutrophilic leukocytosis (WBC: 14,670, neutrophilia: 80%) and higher levels of Toxoplasma-IgG (5806 UI/mL), with negative C-reactive protein (0.21 mg/L) (Table 1). Polymerase Chain Reaction (PCR) analysis of aqueous humor confirmed the presence of *T. gondii*; mycobacteria, cytomegalovirus, and herpes simplex virus 1 and 2 PCR were negative, the Elecsys® Toxo IgG IgG avidity test was also performed, which yields a high percentage (90%).

After a month of the last antibiotic scheme, BCVA decreased up to 20/100. The vitreous had mild cellularity (flare +3) according to standardized rating scales for uveitis, so we decided to give an intravitreal injection of Clindamycin 1 mg, followed by a subconjunctival dose of Dexamethasone 8 mg after vision decreased to hand motions a week later. Unfortunately, despite many therapeutic efforts, vitritis was still evident on ultrasound.

Given the inadequate response to treatment and the persistence of symptoms, the patient consulted another uveitis specialist, who stopped corticoid treatment gradually. Shortly after, vision decreased rapidly in one month, and the patient came back to our clinic, where we restarted therapy with oral Prednisolone 1 mg/kg, topic prednisolone one drop four times a day, Pyrimethamine 75 mg a day for three days, followed by 35 mg every week and Folic acid 25 mg a day.

One month after taking the Clindamycin injection, no improvement in visual acuity was evident. The ultrasound showed retinal detachment (Figure 5), so we performed a second vitrectomy. Within the intraoperative findings, inferior fibrosis was evident, and total retinal detachment. An inferior relaxing retinectomy was performed, perfluorocarbon was injected, endolaser was performed on the posterior edge of the retinectomy and in lower quadrants, and finally, injection of silicone oil was fully applied to the retina. After this, visual acuity slowly improved up to 20/60, the retina was attached entirely, and infection was controlled (Figure 6).

At present, the patient is in annual check-ups; on the last May of 2022, BCVA was evident in the left eye of 20/60, which is a visual acuity better than expected, given the complications and sequelae of severe inflammation. In addition, there has been no recurrence in a fundus with a fully engaged retina with 360-degree peripheral gliosis bands and multiple mainly inferior laser scars with gliosis surrounding retinectomy, without signs of active retinitis.
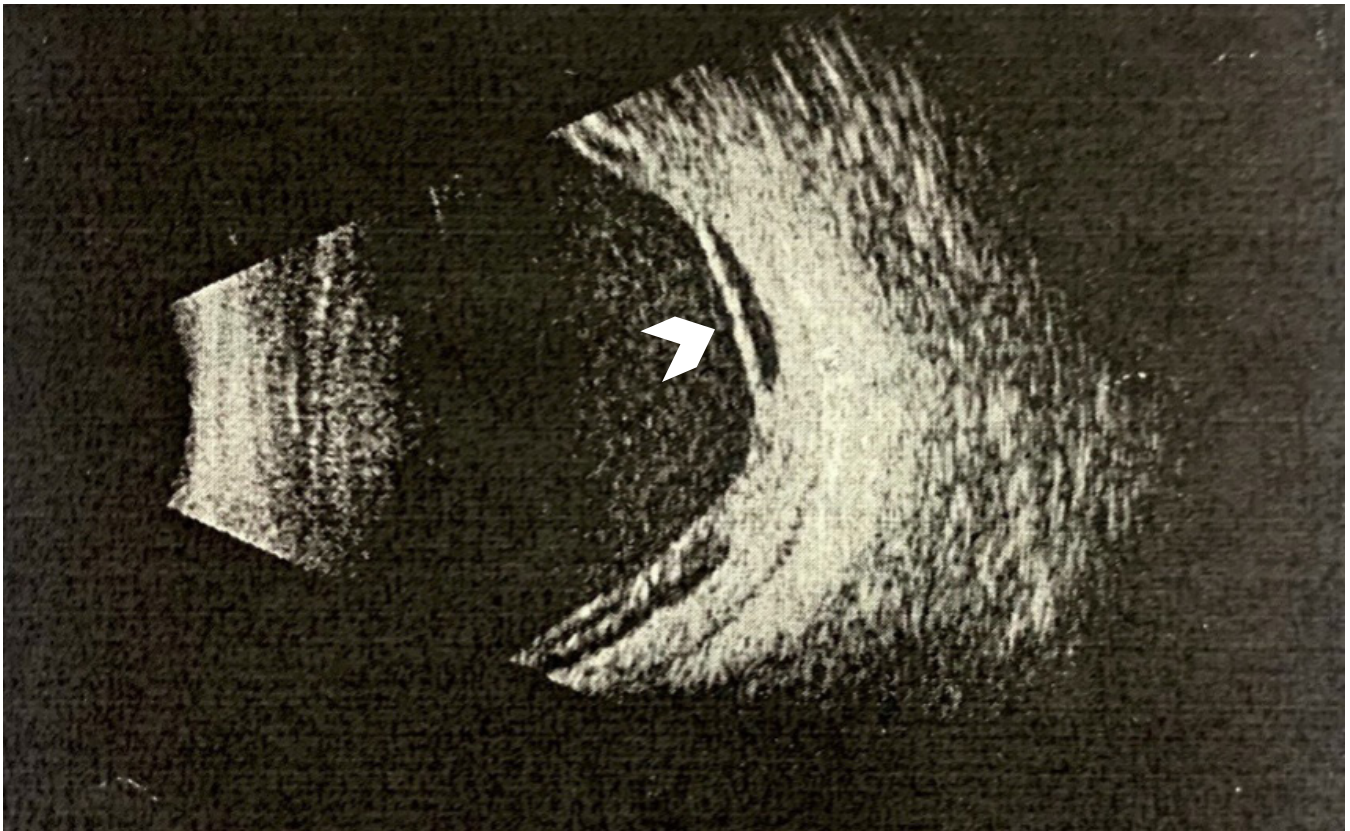

Figure 5: OCT post-clindamycin injection. Retinal detachment. Severe vitreous opacities, vitreous remnants in the periphery, tractional retinal detachment inferotemporal.
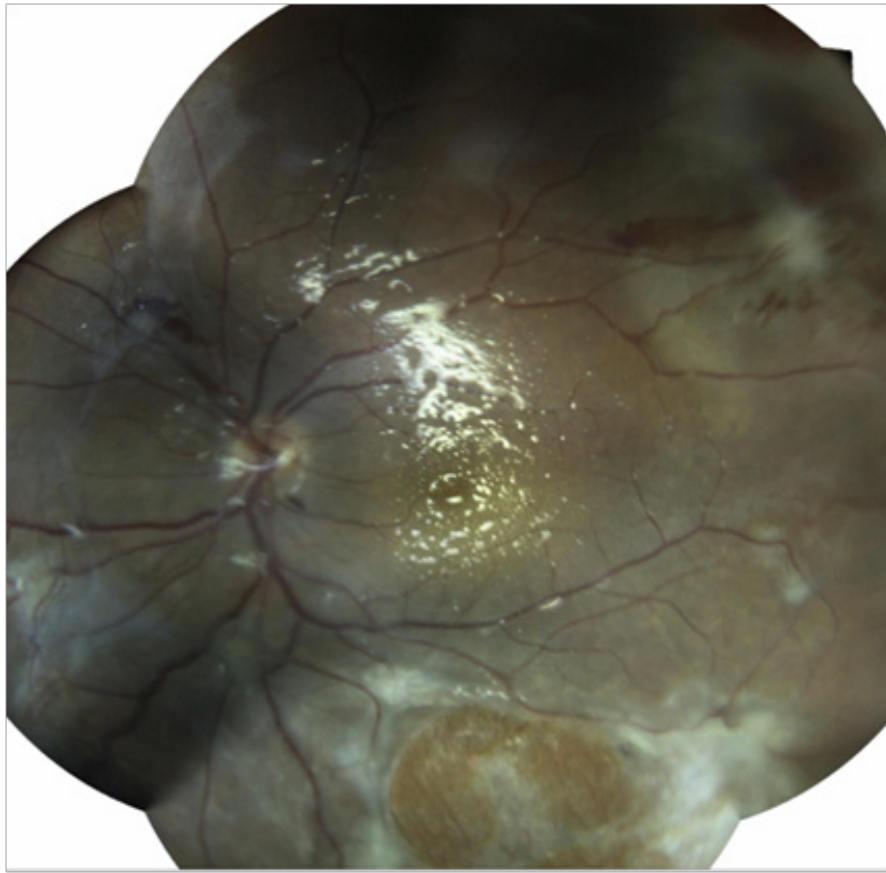
Figure 6: Post-second vitrectomy. Silicon oil and retinectomy in toxoplasmic focus.

Discussion

The development of a fulminant and resistant form of ocular toxoplasmosis has been reported. In a case like this, treatment should focus on three aspects: to block the multiplication of the parasite during active chorioretinitis, to stop the necrotizing inflammation, and to minimize damage over the retina and optic nerve [20].

The most used therapeutic regimen for ocular toxoplasmosis consists of Pyrimethamine and Sulfadiazine, plus corticosteroids. In selected cases, Trimethoprim/Sulfamethoxazole plus oral Prednisolone or intravitreal Clindamycin and Dexamethasone injections may be alternative treatment options [21].

When used, corticoids are usually started simultaneously or 24 hours–72 hours after initiating antibiotic therapy [20,22–24]. However, whether given systemically or periocularly, corticosteroids should always be administered with a shield of antiparasitic drugs [25].

In a cross-sectional survey of uveitis specialists, 17% responded that they initiated corticosteroid management in immunocompetent patients regardless of clinical findings [33]. The other physicians refer to the use of corticosteroid therapy in specific cases, like vitreous inflammatory severe reaction (71%). The American Academy of Ophthalmology concluded that there was no evidence from randomized controlled trials to support or refute the effectiveness of adjunctive steroid therapy for treating ocular toxoplasmosis [18]. However, the use of this therapy is supported by the knowledge that the use of corticosteroids suppresses inflammation and therefore decreases damage to ocular tissue [17].

Nevertheless, there is a long-lasting controversy around the use of corticosteroids in ocular toxoplasmosis. Some authors [22] have reported that iatrogenic immunosuppression induced by corticosteroid monotherapy may lead to an aggressive course and severe complications of ocular toxoplasmosis, such as retinochoroiditis. Conversely, as visual damage in toxoplasmosis has been attributed to direct inflammation by the parasite, corticosteroids could be beneficial given their anti-inflammatory properties [26]. Furthermore, intravitreal dexamethasone implants may be safe and effective alternatives in macular edema secondary to uveitis from several infectious etiologies, toxoplasmosis included [27].

In this case, we appreciate the two sides of the same coin: when oral corticoid doses were decreased and treatment was stopped, visual acuity diminished dramatically, but when we restarted prednisone and injected intravitreal dexamethasone, vitritis worsened and evolved to necrotizing retinitis with secondary retinal detachment.

Seemingly, silicone oil tamponade was the best treatment for

secondary complications of the infection as well as the way to control the infection. Indeed, although retinal detachment is a relatively rare complication of ocular toxoplasmosis, previous reports suggest that once this condition appears, it may require several therapies, including multiple surgical procedures and systemic and intravitreal medications [19].

Moreover, it is very important to identify if uveitis is of infectious etiology or not since it allows timely treatment and offers a better prognosis for the patient. Uveitis syndromes can be diagnosed by a combination of medical history, physical examination, laboratory, and imaging [29,30]. However, there are clinical dilemmas in which it is difficult to determine the etiology, such as atypical or severe presentations of the disease, among others. A diagnostic and therapeutic vitrectomy is useful in these cases [29].

Based on a retrospective study in which seventy-five patients (84 eyes) with posterior uveitis who underwent PPV were selected and followed up retrospectively from 2005 to 2009, it was evidenced that visual acuity and inflammatory activity showed marked improvement after PPV, with an improvement in visual acuity from 20/200 to 20/80 after one year (Snellen, $P \leq 0.001$) [30].

Vitrectomy allows clarification of the posterior cavity, and some specialists believe it can favorably influence the evolution of uveitis, although this point is debatable [30]. In a case series of 8 patients who underwent vitrectomy for toxoplasmosis, a patient with active retinochoroiditis was identified and treated with antibiotics and corticosteroids for many months. However, the vitreous opacities and inflammation persisted, and due to the marked inflammation and decreased visual acuity, a vitrectomy was performed. No recurrence was identified in a 20-year follow-up, according to the previous case, and in the case of our patient, it can be inferred that vitrectomy is an excellent therapeutic and diagnostic method in severe cases of vitritis, given the marked improvement in visual acuity reported, the decrease in recurrence and the inflammatory process, as well as the question that it is probably involved in removing factors that could be involved in inflammatory processes and recurrence [31].

Regarding the route of infection, it can be deduced that it was a recently acquired ocular toxoplasmosis, that is, less than a year of contagion; because both IgG and IgM antibodies were positive, IgM antibodies became negative after a year of infection [32]. However, having an avidity test more outstanding than 30%, it can be concluded that the infection was in a period higher than four months. Therefore, we can infer that there is the same risk of acquiring the infection in Colombia and on the trip reported by the patient to Turkey, in which there is no notion of exposure to any identifiable risk factor. However, despite that, it is within the estimated window period for infection (between 4 months and a year).

Given the high prevalence of this disease in Colombia and Turkey, it is difficult to determine the site of infection. However, due to

the severity of the disease presentation, it can be concluded that it was a highly virulent infection (type I/III and atypical), which is more common in South American territories.

Conclusions

The goal of treating ocular toxoplasmosis is to reduce the risk of visual loss and the multiplication of the parasite during the active state, the inflammation, and the sequelae produced by it. It is usually managed with antibiotic therapy; however, in the case of severe vitritis and poor response to antibiotics, it is necessary to evaluate and use other less conventional management.

In the presentation and management of our patient's disease, we identified various controversies, firstly, the performance of posterior vitrectomy as a therapeutic and diagnostic method. As we highlighted in the literature and as evidenced in the reported case, posterior vitrectomy in cases of severe vitritis is extremely useful to rule out complications and severe lesions that are not possible to visualize due to the opacity of the media, as well as to make an opportune diagnosis and treatment directed to the etiological agent.

Secondly, regarding corticosteroid therapy, as mentioned above, there is controversy about the route, initiation, and timing of adjunctive corticoid therapy. In addition, evidence for intravitreal dexamethasone implant is still scarce in infectious uveitis. More evidence and more studies are needed to determine the resolution time, the improvement of visual acuity, and the response to therapy since it is not known, as well as studies that establish a therapeutic regime to avoid risks and iatrogenicity with its use.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained for this publication.

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