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Ocular Toxoplasmosis: No Stranger to the Masquerade Ball

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Abstract

Purpose: This article illustrates multiple atypical manifestations of ocular toxoplasmosis masquerading as acute retinal necrosis and vitreoretinal lymphoma. **Methods:** Two case presentations are discussed, and the body of pertinent literature is reviewed and discussed. **Results:** In these cases, an extensive workup and attention to history lead to the correct diagnosis and management. **Conclusions:** Aggressive cases of ocular toxoplasmosis may present in a variety of phenotypes that may mimic other vision- and potentially life-threatening conditions, particularly in a milieu of inadequate endogenous and exogenous antimicrobial defenses.

Keywords

acute retinal necrosis, masquerade, ocular toxoplasmosis, retina, uveitis, vitreoretinal lymphoma

Introduction

Toxoplasma gondii is an intracellular protozoan parasite that commonly infects humans and other warm-blooded animals through contact with felids (cats, the only known definitive host), ingestion of cyst-laden food and water, or transplacental transmission, resulting in the disease state toxoplasmosis. The seroprevalence is estimated to be 23% in the United States, where approximately 2% of those infected are thought to have ocular involvement, while seroprevalence and ocular involvement are significantly higher in endemic regions such as Latin America and sub-Saharan Africa.[1,2]

Although most infections are subclinical and may become latent in individuals who are immunocompetent, those who are immunocompromised are more likely to suffer flu-like symptoms in addition to others such as vision loss, encephalitis, and even death.[3] Ocular manifestations may result from a primary or acquired infection or reactivation of latent toxoplasmosis months or years following infection and most often include unilateral posterior uveitis and retinochoroiditis with characteristic single or, less commonly, multiple yellow-white chorioretinal foci with or without adjacent chorioretinal scarring and overlying vitritis. Associated examination findings may include anterior uveitis, papillitis, cystoid macular edema (CME), vasculitis, scleritis, and rarely confluent retinal necrosis.[4] Given its prevalence, unsurprisingly toxoplasmosis is the most common cause of infectious posterior uveitis in the United States and worldwide.[1,5] More atypical and aggressive presentations can manifest in settings of relative immune system dysfunction and may lead to delayed diagnosis, particularly when masquerading as other urgent, vision-threatening ophthalmic conditions that require prompt empiric treatment and/or rely on time-intensive confirmatory diagnostics. Here we present 2 such cases.

Methods

Case 1

The first case is that of a 69-year-old woman with no pertinent medical history and an ocular history of distant bilateral radial keratotomy and pseudophakia. Four months before presentation she developed new floaters in her right eye and was diagnosed with unilateral chronic posterior uveitis by an outside retina specialist.

After an initial workup that included a QuantiFERON (Qiagen Sciences, Inc) gold test as well as those for rapid plasma reagin and *Treponema pallidum* particle agglutination, Lyme immunoglobulin M (IgM) and immunoglobulin G, HLA-B27, antinuclear antibody, lysozyme, and erythrocyte sedimentation rate returned unremarkable findings, she was treated with

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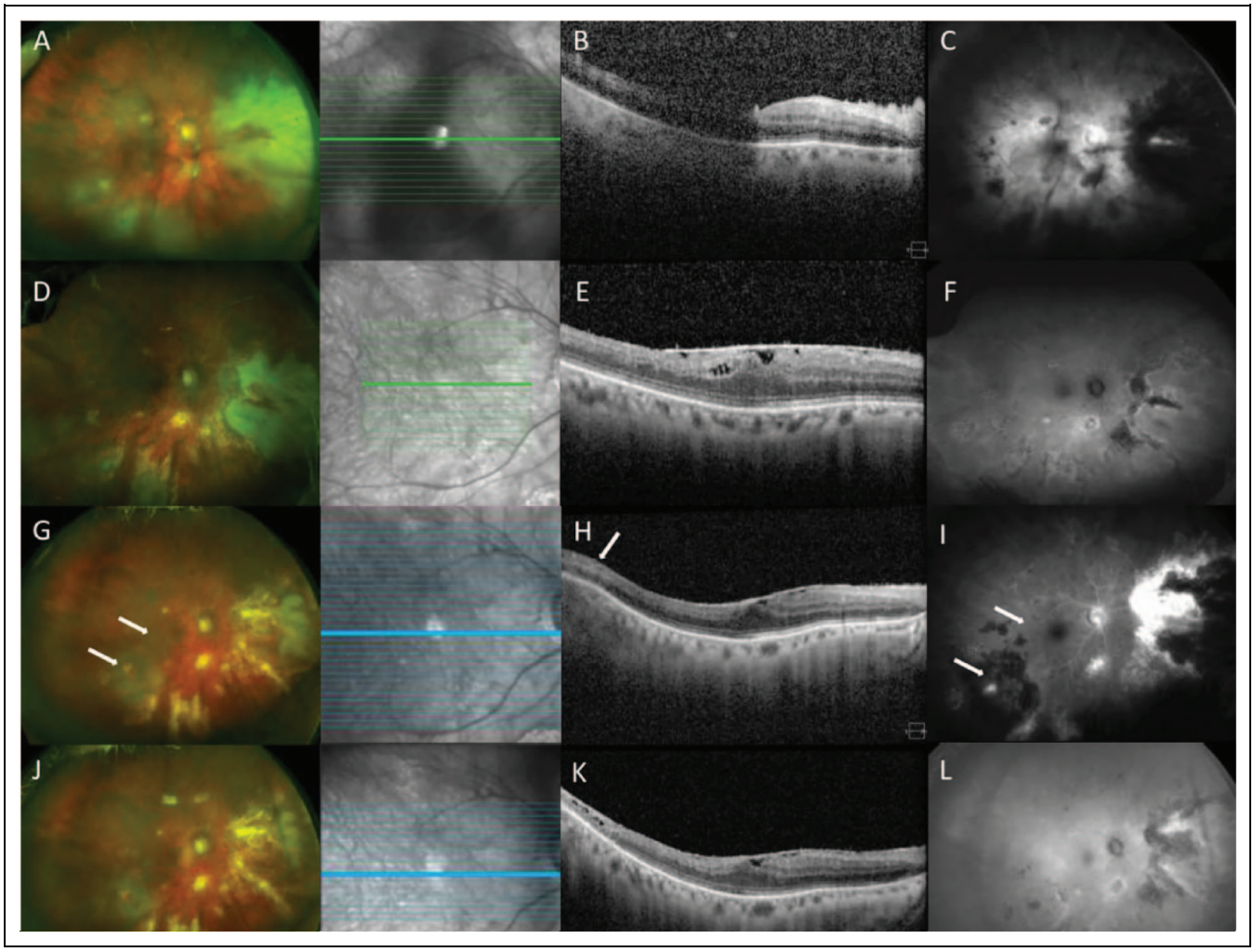

Figure 1. (A) On presentation, Optos color scanning laser ophthalmoscopy (SLO) showed vitritis and multifocal retinal whitening and vascular changes. (B) Optical coherence tomography (OCT) was attenuated because of vitritis and showed collections of cells and inflammatory debris settling on the internal limiting membrane. (C) Fluorescein angiography demonstrated occlusive vasculitis with peripheral ischemia, early hypofluorescence, and late hyperfluorescence corresponding with regions of retinal whitening. (D) At postoperative month 1 after pars plana vitrectomy and Ozurdex removal, Optos color SLO showed scarring in the regions of prior retinal whitening. (E) OCT showed a new epiretinal membrane. (F) Fundus autofluorescence showed mixed hypoautofluorescence and hyperautofluorescence corresponding to the peripheral chorioretinal lesions. (G) On recurrence at 6 months postoperatively, Optos color SLO showed new retinal whitening temporally (arrows). (H) The margin of this reactivation was seen as full-thickness retinal hyperreflectivity and blurring of normal choroidal vasculature in the temporal macula (arrow). (I) Fluorescein angiography revealed window defects and blocking located nasally and temporally, with subtle hypoperfusion and loss of normal retinal vasculature markings found temporally in the region of retinochoroiditis reactivation (arrows). (J) A month later following retreatment, the regions of retinal whitening improved on Optos color SLO. (K) Corresponding atrophy and degenerative cystic changes are noted on OCT. (L) Fundus autofluorescence shows heterogenous autofluorescence in the affected regions.

a 0.7-mg dexamethasone intravitreal implant (Ozurdex) injection. Her floaters consistently worsened and were soon accompanied by progressive unilateral vision loss, prompting referral to our eye institute. At the time she was taking prednisolone acetate 1% every 2 hours in the affected eye and had 3 weeks of neck stiffness. She reported a history of cold sores treated with acyclovir, her last outbreak of which was 8 to 10 years prior, as well as a history of childhood chicken pox. She had no known consumption of undercooked meat, cat exposure, recent travel, or systemic immunosuppression.

Her examination was significant for counting fingers (CF) visual acuity (VA) at 3 feet (1 m) in her right eye and 20/20 in her left. Intraocular pressures were normal. Her right eye conjunctiva was white and quiet, though she had multiple inferior keratic precipitates, 3+ anterior chamber (AC) cell, 2 to 3+ posterior vitreous haze, multifocal patches of retinal whitening ranging from less than 1 disc diameter (DD) to 5×8 DD, as well as attenuated and occluded retinal vasculature. Her left eye examination and imaging were unremarkable. In her right eye, ultra-widefield (UWF) scanning laser ophthalmoscopy (SLO)

showed hazy media and reflected the multifocal patches of retinal whitening and vascular changes that had been noted on examination, as well as multiple smaller foci near the arcades, none of which involved the macula (Figure 1A). Optic coherence tomography (OCT) of the macula was attenuated because of her vitritis and showed collections of cells and inflammatory debris settling on the internal limiting membrane (Figure 1B). UWF fluorescein angiography (FA) demonstrated occlusive vasculitis with peripheral ischemia, early hypofluorescence, and late hyperfluorescence corresponding with regions of retinal whitening, with leakage most notably located nasally (Figure 1C).

Case 2

A 75-year-old woman with a medical history of pneumonia of unknown origin 8 months prior (now resolved), an ocular history of photorefractive keratectomy 20 years prior, and presumed unilateral toxoplasma retinochoroiditis of the left eye diagnosed 3 years earlier presented to us when she developed decreased vision and new floaters in her left eye. She owned cats and denied travel abroad. At the time of her presumptive diagnosis of OT 3 years earlier, she was treated successfully with oral clindamycin, azithromycin, and low-dose prednisone. She experienced a reactivation following an intravitreal corticosteroid injection for CME the following year and was treated with multiple clindamycin IVIs. A year prior to presentation she underwent PPV with membrane peel for an ERM in the left eye during which vitreous PCR samples returned negative for HSV, VZV, and toxoplasma. Following cataract surgery her vision improved to 20/40. Her CME persisted despite use of difluprednate 0.05% and bromfenac 0.07%.

Two months before presentation, she had documented inactive retinitis and received an IVI of aflibercept 3 times a day. She developed worsening ipsilateral floaters and blurred vision and was seen a month later by another outside retina specialist who noted a quiet anterior segment, vitritis, and disc and peripheral vascular leakage on FA. She was diagnosed with presumed toxoplasma retinitis reactivation and was recommended to increase her difluprednate to every 2 hours. Although her CME resolved a week later, she experienced continued unilateral vision loss, prompting her presentation to University of California, Los Angeles.

On examination her vision was 20/20 OD, CF at 2 feet (0.6 m) OS with intraocular pressures of 18 and 10 mm Hg, respectively. Her examination and imaging in the right eye were unremarkable. Her anterior segment examination of the left eye was notable for 2 to 3+ AC cell and 3+ flare. Her posterior segment was notable for 1+ AV cell, 2-3+ vitreous haze with blurred disc margins, central-involving macular edema and retinal whitening (previously her lesions had been peripheral), and numerous white lesions along her arcades and periphery with a larger region of confluent retinal whitening temporally. UWF SLO reflected the vitritis and multifocal retinal whitening that had been noted on examination (Figure 2, A and B). OCT of the macula showed disorganization of the retinal layers with inner retinal hyperreflectivity (Figure 2C).

Results

Case 1

The presentation was most compatible with an infectious origin. The differential diagnosis included viral retinitis (herpes simplex virus [HSV], varicella-zoster virus [VZV], and less likely, cytomegalovirus [CMV]), ocular toxoplasmosis [OT], syphilis, bartonella, and fungal or bacterial endogenous endophthalmitis, with autoimmune and malignant causes considered less likely given her vision's deterioration on steroids. An AC paracentesis was performed and aqueous humor sent for HSV, VZV, and CMV polymerase chain reactions (PCRs). Intravitreal injection (IVI) of foscarnet 2.4 mg/0.05 mL was administered in the clinic for the presumptive clinical diagnosis of acute retinal necrosis (ARN), and the patient was admitted for intravenous acyclovir with neurology and infectious disease consultations. Serum laboratory test results including complete blood count, erythrocyte sedimentation rate, C-reactive protein level, and HIV were all unremarkable. Results from tests that were performed at an outside laboratory for Toxoplasma antibodies were initially pending.

A lumbar puncture showed no evidence of meningitis, and magnetic resonance imaging of the brain and orbits with and without contrast showed unilateral retinal thickening and enhancement without signs of acute retro-orbital or intracranial vasculitis, meningitis, encephalitis, or ring-enhancing lesions. On hospital day 2 (HD2) the viral PCRs of the aqueous fluid returned negative findings, although given a persistently elevated clinical suspicion for viral retinitis, on HD3 the patient received her second IVI of foscarnet once daily. That day the test results for toxoplasma IgM and immunoglobulin G returned and were positive, and the patient was placed on oral double-strength trimethoprim-sulfamethoxazole (TMP-SMX/trimethoprim-sulfamethoxazole 160-800 mg) twice daily. A vitreous tap was sent for evaluation of toxoplasma PCR. Three days later (HD6) her vision was subjectively improved but remained CF, and she received her first clindamycin 1 mg/0.05 mL IVI. The following day her vision improved to 20/400 (at near, eccentric) and she noted improving floaters. On HD9 the vitreous toxoplasma PCR returned positive, and acyclovir was discontinued. She received her second clindamycin IVI, and was discharged on oral trimethoprim-sulfamethoxazole.

Two weeks after presentation, vision remained CF at 3 feet (1 m), her AC reaction had resolved, her vitritis and retinal whitening improved, and she received a third clindamycin IVI. Prednisolone acetate 1% drops were tapered to 4 times a day. She was followed weekly, had an improving posterior segment examination, was given 3 subsequent clindamycin IVIs, and her vision fluctuated between 20/500 and CF in the setting of persistent vitreous opacities. Six weeks after presentation she was taken for a pars plana vitrectomy (PPV) with Ozurdex

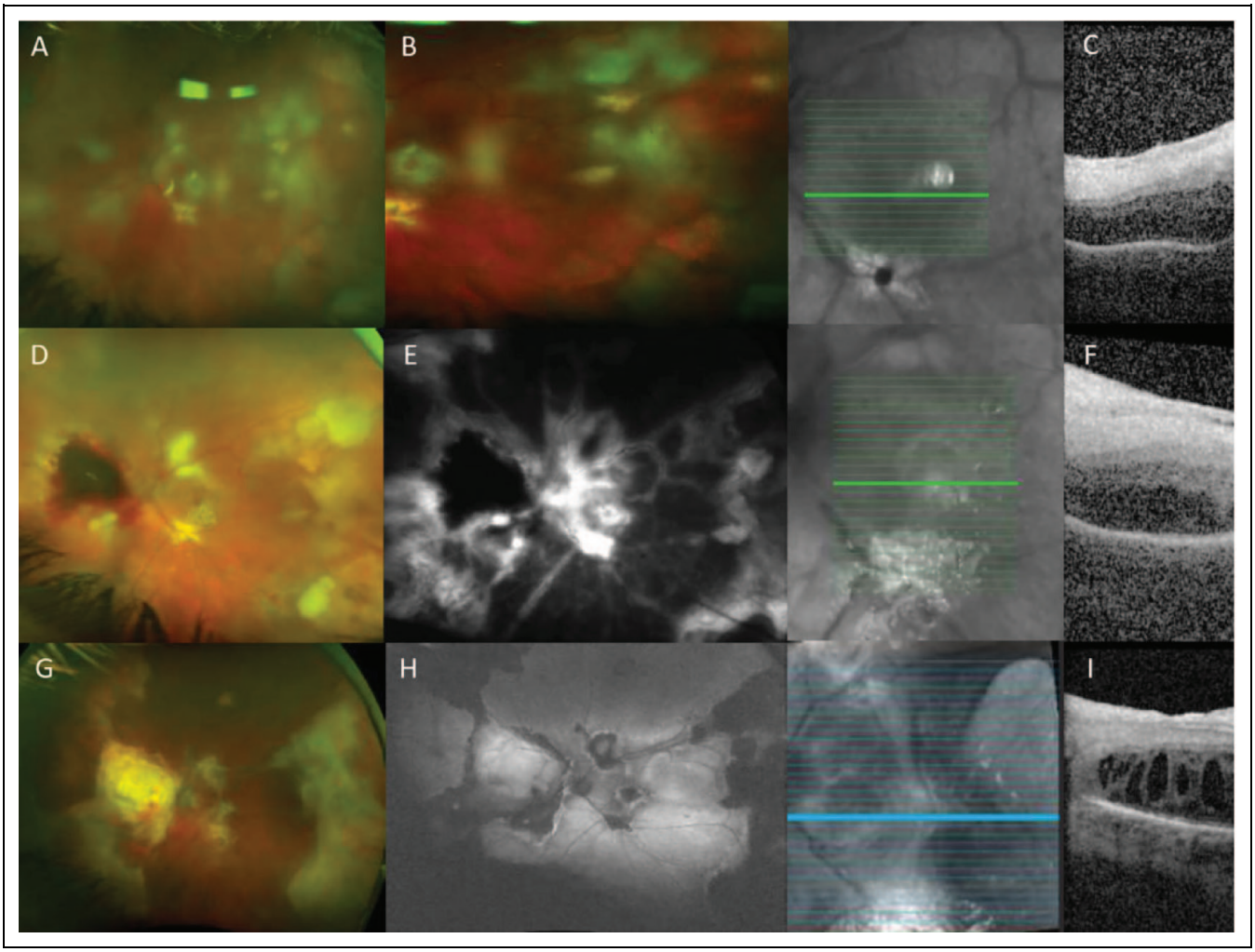

Figure 2. (A and B) On presentation, Optos color scanning laser ophthalmoscopy (SLO; widefield and closeup) showed vitritis and multifocal retinal whitening with confluence temporally. (C) Optical coherence tomography (OCT) demonstrated hyperreflectivity of the inner retina with disorganization of normal retinal layers. (D and E) Ultra-widefield color SLO and fluorescein angiography at postoperative week 1 after pars plana vitrectomy and chorioretinal biopsy demonstrate consolidation of retinal lesions and occlusive vasculitis with peripheral ischemia and leakage, respectively. (F) OCT at this time point shows full-thickness hyperreflectivity of the fovea. (G and H) SLO color and autofluorescence images at postoperative month 6 show scarring and concentric hypoautofluorescence and hyperautofluorescence in the regions of prior retinal whitening. (I) Concurrent OCT shows subtle improvement in the foveal and inner retinal hyperreflectivity and organization, although interval cystoid macular edema is noted.

removal, air-fluid exchange, and a seventh clindamycin IVI. Six weeks postoperatively trimethoprim-sulfamethoxazole was discontinued as her inflammation subsided. Her retinal lesions remained quiescent for 6 months postoperatively and her VA was 20/100 with lingering 1+ AC cell, 0.5+ anterior vitreous (AV) cell, and a new epiretinal membrane (ERM; Figure 1, D-F). She subsequently experienced an acute recurrence with subjective vision decline, VA 20/150, 2+ AC/1+AV cell, and new regions of retinal whitening temporally encroaching on the macula (Figure 1, G-I). Trimethoprim-sulfamethoxazole was restarted and she was treated with another series of 3 clindamycin IVIs for a total of 10, with improvement in her vision to 20/125, resolution of AC cell, reduction in AV cell to 0.5+, and stabilization of her posterior segment examination within the following 2 months (Figure 1, J-L). Her left eye remained uninvolved.

Case 2

The differential diagnosis included fulminant reactivation of OT—although a prior laboratory workup had been negative for OT and this presentation was atypical given perivascular whitening, recent CME, multifocality of the retinitis in an ostensibly immunocompetent host— vitreoretinal lymphoma, viral retinitis, syphilis, fungal and bacterial retinitis, and tuberculosis. Autoimmune causes such as sarcoidosis were considered less likely given her decompensation on steroids. An extensive workup, including for complete blood count, HIV, rapid

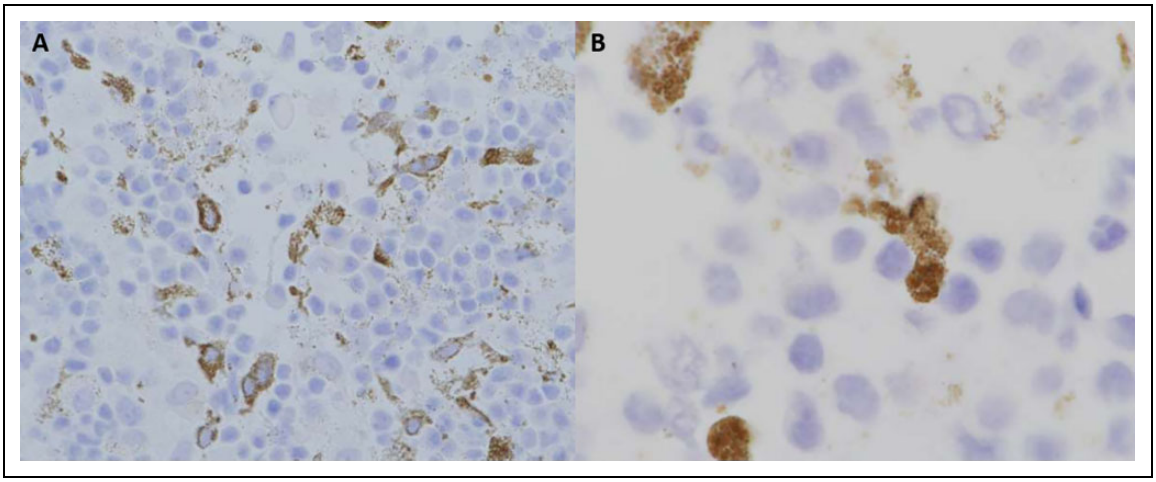

Figure 3. A toxoplasma immunostain at (A) 40× and (B) 100× magnification shows numerous organisms (tachyzoites, stained bronze) identified within host cells.

plasma reagin, QuantiFERON gold, toxoplasma IgM (IgG was not re-sent because the patient was previously IgG+ on multiple outside tests) level, HSV and VZV serum PCR, *Pneumocystis carinii* titers, chest x-ray, and levels of Coccidioides antigen, Bartonella IgG and IgM, angiotensin-converting enzyme, lysozyme, and antineutrophil cytoplasmic antibodies, and HLA-A29 genotyping, was unremarkable.

Shortly following presentation, the patient underwent PPV with chorioretinal biopsy and silicone oil placement, with vitreous samples sent for HSV, CMV, toxoplasma PCRs, and bacterial and fungal cultures. She was given oral atovaquone 750 mg 3 times a day for empiric treatment of toxoplasmosis, which was increased 1 week later to 4 times a day per infectious disease recommendations, with an expected course of at least 3 months. UWF FA 1 week postoperatively revealed occlusive vasculitis with significant retinal ischemia and leakage (Figure 2, D and E). The biopsy revealed chronic granulomatous inflammation with focal necrosis, mixed B and T cells, and numerous toxoplasma tachyzoites within host cells (Figure 3).

Findings from vitreous cultures and viral PCRs were negative. On postoperative day 10 the vitreous toxoplasma PCR returned positive results, confirming the diagnosis of toxoplasmosis retinochoroiditis reactivation. At postoperative month 6 her vision was hand motion with a silicone-oil fill. Her disc edema and retinal whitening improved, although a focus of whitening corresponding to full-thickness foveal involvement remained with interval development of CME (Figure 2, G-I). Topical prednisolone was continued while atovaquone was discontinued because of clinical lesion quiescence.

Conclusions

Widespread retinal infection with multifocality and large lesions is highly atypical for OT; however, for such a phenotype, OT must be included high in the differential diagnosis as demonstrated by the 2 presented cases. As single, fewer than 2 or 3 DD lesions of retinal whitening are the norm for OT, numerous and/or confluent lesions larger than this may mimic other vision-threatening ophthalmic conditions such as bacterial or fungal endogenous endophthalmitis,[6] and viral retinitis.[7] In a retrospective case series of 154 patients with OT in the Netherlands, 4 of the 18 cases with "extensive" (>3 DD) lesions were initially diagnosed as acute (viral) retinal necrosis based on clinical examination, as was our first case.[4] Balansard et al[8] likewise observed OT masquerading as ARN in 10 of 16 (63%) patients who presented with nonviral ARN phenotypes over 5 years at a Paris hospital. Nine of 10 were systemically immunocompromised.

While there are no reports in the literature of OT masquerading as vitreoretinal lymphoma as in our second case, Mittra and colleagues[9] in 1999 reported a case of bilateral, metastatic vitreoretinal non-Hodgkin B-cell lymphoma with a phenotype mimicking multifocal OT chorioretinitis (multiple small <1 DD white chorioretinal lesions with associated AC and vitreous cell) in a patient with HIV. Retinal biopsy was likewise performed to confirm the diagnosis.

While clinical examination has long been considered the diagnostic criterion standard in the majority of OT cases, laboratory testing becomes particularly helpful in atypical presentations. In suspected cases, modern biologic tests run on serum, vitreous body, and/or aqueous humor samples are able to confirm the diagnosis in the vast majority.[10] Three main tests are currently utilized, including direct toxoplasma DNA gene amplification with PCR (sensitivity 27%-75%, specificity 100%),[11,12] ratio comparison of ocular to serum toxoplasma antibody load (via the Goldmann-Witmer coefficient [GWC], sensitivity 29%-81%, specificity 83%-100%),[10,12] and qualitative comparisons of antibodies produced in ocular compartments and serum through the immunoblot technique (sensitivity 53%-98%, specificity >95%).[10,12]

The differential utility of these tests may vary depending on which time point in the disease course they are used, host immune status, and degree of inflammation PCR is generally more useful early on and in immunosuppressed patients in

whom the parasite may run more rampant, and GWC and immunoblot are more useful later on in the disease course and in immunocompetent hosts when and in whom antibodies are more plentiful, respectively.

Employed together, these tests are very sensitive (85%-97%) and specific (93%).[13,14] The ability to run all 3 in addition to viral PCR in atypical cases may be limited by sample volume (GWC alone may necessitate > 100 μL), occasionally requiring multiple samples as in our first patient, or a larger vitreous sample, as in our second. Depending on the recombinant antigens used to detect specific immunoglobulins, serologic testing via immunoassays may be up to 95% to 100% sensitive and specific for IgG and IgM, which can help definitively rule out OT in IgG-negative cases (notably, a negative IgM does not rule out OT as demonstrated in our second case).[15] IgM, often thought a marker of acute disease, may persist up to 2 years in a subset of patients, making IgG avidity for recombinant antigens a better proxy for disease chronicity, with higher avidity seen in chronic infections.[12]

Although OT has a proclivity for the posterior pole, involved in more than 50% of cases, visual outcomes are generally favorable in cases without foveal or optic nerve involvement.[16] In the subset of cases involving these vital structures, visual prognosis can be grim.[8] In one Dutch cohort of 154 patients with OT, 24% developed legal blindness ($\leq$20/200) in at least 1 eye over a mean follow-up period of 5.8 years.[4] The poor visual outcomes in this subset were because of macular lesions (80%), retinal detachment (13%), and optic nerve atrophy (7%). Unopposed steroid exposure was associated with worse visual outcomes.

OT may be treated with oral and/or intravitreal medical therapy. Multiple randomized controlled trials have demonstrated equivalent efficacy of IVI of clindamycin 1 mg and dexamethasone 0.4 mg (average 1-2 rounds of injections) in achieving disease resolution with comparable recurrence rates at 2 years (6%-15%) when compared with conventional oral therapy (COT)—pyrimethamine, sulfadiazine, folinic acid—with an oral prednisone taper.[17,18] No adverse drug reactions were observed in the IVI cohorts compared with COT, in which hepatitis, rash, and thrombocytopenia arose in subsets, supporting the conclusion that IVI therapy carries a better safety profile. Time to resolution of disease activity was 2.5 ± 1 week with no adverse drug reactions in another similar IVI cohort.[19]

In addition to COT, oral TMP-SMX, azithromycin, and atovaquone have all been found effective in treating OT. A randomized study comparing oral azithromycin 500 mg $\times 1$ followed by oral 250 mg daily with a prednisone taper to 1 double-strength TMP-SMX tablet twice daily found similar efficacy including VA improvement, lesion size and vitritis reduction, as well as response time.[20] Azithromycin in place of sulfadiazine has also been found to have equivalent efficacy to COT with fewer adverse effects when used alone or in tandem with pyrimethamine, although time to disease inactivity may be longer with azithromycin.[21,22] A phase 1 trial of oral atovaquone 750 mg 4 times a day for OT in immunocompetent patients found a satisfactory response beginning 1 to 3 weeks following initiation of treatment, with VA stabilized or improved in all 17 patients (median 20/200 to 20/25) at an average follow-up of 10 months without significant adverse reactions to the drug.[23]

There remains no consensus on steroid use in OT. A recent systematic review found wide variation in adjuvant steroid use for OT with no randomized controlled trial–based evidence for or against their use, for guiding their timing of initiation, or optimal dosing and duration.[24] While it is unsurprising that unopposed steroid use, especially depot IVI (eg, triamcinolone or dexamethasone), has been associated with fulminant OT presentations, as was seen in case 1, so too occasionally have intravitreal steroid injections even when administered along with standard-of-care systemic antiparasitics.[25]

Depot steroids should thus generally be avoided in patients with suspected active OT, as should any unopposed steroid use, even topical, as illustrated in case 2. OT recurrences are not uncommon and rates may be lowered by secondary prophylactic medication regimens. A prospective, randomized clinical trial of 124 patients with recurrent OT given TMP-SMX (160-800) every 3 days (n = 61) or observed (n = 63) showed a lower rate of recurrence at 20 months in the treatment group (6.6% vs 23.8%, $P = .01$).[26] Similarly, a randomized trial (n = 141, 1:1) comparing a well-tolerated 1 tablet of double-strength TMP-SMX every 2 days with placebo for 311 days found a significantly lower recurrence rate in the treatment cohort at 6 years (1.4% vs 27.5%).[27]

While most cases of OT do not require surgical intervention, vitrectomy may be performed in a subset to aid in diagnosis and/or restore vision in cases of retinal detachment, ERM, vitreous hemorrhage (eg, due to choroidal neovascularization or hemorrhagic vasculitis), or persistent inflammatory opacities. In one study of 15 patients treated with PPV for various OT sequelae, vision improved in all cases, as it did in our first case.[28] While vitrectomy did not lead to vision improvement in our second case, it did confirm the diagnosis and guide management.

In summary, we present 2 cases of atypical toxoplasmosis characterized by widespread retinal involvement with both multifocality and large lesion sizes. OT must be considered in the differential diagnosis of widespread or multifocal retinal opacification, alongside other infectious, inflammatory, and neoplastic conditions to avoid delayed treatment. In these cases, proper diagnosis and management relies heavily on history and laboratory testing.

Although response to medical therapy is classically favorable unless fovea or optic nerve are involved, visual outcomes may be especially guarded in fulminant cases, making rapid diagnosis and prompt therapeutic intervention critical.

Ethical Approval

Ethical approval was not required by our institution for this 2-case report and review of the literature.

Statement of Informed Consent

The patients provided written consent for the inclusion of their clinical information and images in this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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