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Management of bilateral uveitis in a *Toxoplasma gondii*-seropositive cat with histopathologic evidence of fungal panuveitis

J. Pearce,* E. A. Giuliano,* L. E. Galle,† G. Klauss,‡ J. Ota* and C. P. Moore*

**Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri-Columbia, Columbia, MO, USA; †Veterinary Eye Care, Bessemer, AL, USA; ‡Department of Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, Minneapolis, MN, USA*

Address communications to:
Elizabeth A. Giuliano
Tel.: (573) 882-7821
Fax: (573) 883–5444
e-mail: Giulianoe@missouri.edu

Abstract

A 5-year-old, neutered male Domestic Short-haired cat was referred with a 5-month history of anterior uveitis and cataract in the right eye. Clinical examination confirmed anterior uveitis and immature cataract in the right eye and chorioretinitis in the left eye. Ocular ultrasound showed a retinal detachment in the right eye. Diagnostic testing revealed elevated serum titers for *Toxoplasma gondii*. Anterior uveitis in the right eye and chorioretinitis in the left eye progressed, resulting in blindness despite a 21-day course of clindamycin and aggressive topical medical management of uveitis. The right eye was enucleated and histopathologic evaluation of the globe revealed panuveitis and multiple organisms morphologically consistent with *Histoplasma capsulatum*. Systemic treatment with itraconazole was initiated. Vision returned after 3 months of treatment and complete resolution of the retinal hemorrhages with formation of a flat chorioretinal scar was noted after 6 months of therapy. Itraconazole was discontinued 7 months after starting therapy, at which time the funduscopic appearance of the chorioretinal scar had remained static for 1 month. The cat has remained visual without evidence of disease progression for 6 months following discontinuation of itraconazole.

Key Words: chorioretinitis, fungal disease, *Histoplasma capsulatum*, histoplasmosis, retinal detachment, Toxoplasmosis

INTRODUCTION

Uveitis is a relatively common problem in cats and often results in blindness. Feline uveitis can be caused by many infectious agents or by neoplastic, traumatic, immune-mediated, and other causes. Many cases of feline uveitis are treated as idiopathic as clinical signs, serologic evidence, and histologic lesions pathognomonic for specific causative agents are rarely found. This report details the diagnosis and medical and surgical management of a *Toxoplasma gondii*-seropositive cat with chronic and progressive bilateral uveitis, apparently induced by an organism morphologically consistent with *Histoplasma capsulatum*.

CASE REPORT

A 5-year-old, neutered male, Domestic Short-haired cat was referred with a 5-month history of anterior uveitis and cataract OD. The uveitis did not respond to treatment with topical triple antibiotic solution QID and 1% prednisolone acetate suspension q24h initiated by the referring veterinarian prior to presentation. The cat was the sole pet in the household and had an indoor/outdoor lifestyle. Flea-control medication was applied monthly and vaccinations for rabies, feline panleukopenia, calicivirus and herpesvirus had been performed 6 months prior to referral.

Abnormal findings on complete physical examination were limited to subtle, generalized lymphadenopathy and 2/6 basilar systolic heart murmur auscultated bilaterally. Retroillumination revealed miosis OD. Neuro-ophthalmic examination indicated normal palpebral reflex, corneal sensitivity, and ocular motility OU. Menace response was absent OD and present OS. Dazzle reflex was present OU. Direct and indirect pupillary light reflexes were normal OS, but reduced OD. Abnormalities noted on slit-lamp biomicroscopy included moderate diffuse corneal edema, keratic precipitates, 2/4 aqueous flare[1] with anterior chamber cell, rubeosis iridis, and an immature anterior cortical cataract with pigmented cells adherent to the anterior lens capsule OD. Biomicroscopic examination results were normal OS. Schirmer I tear test values were within the reference range OU (11 mm/min OD and 10 mm/min OS).[2–4] Applanation tonometry (Tonopen-XL®,

Mentor O & O Inc., Norwell, MA, USA) with topical anesthesia revealed hypotony OD (4 mmHg) and normal intraocular pressure OS (13 mmHg).[5–7] Neither cornea retained fluorescein stain. Indirect ophthalmoscopy, following mydriasis OU (1% tropicamide, Bausch & Lomb Pharmaceuticals, Tampa, FL, USA) identified a focal, raised, mottled, brown, hyporeflective chorioretinal lesion within the lateral midperipheral tapetal fundus OS measuring 4 optic disk diameters (DD) horizontally, and 4.5 DD vertically (Fig. 1). Multifocal white, strand-like vitreal opacities ranging from 0.25 to 1 DD in size were closely associated with the chorioretinal lesion. Funduscopic examination OD was impossible because of extensive corneal opacities and cataract. Marked anterior uveitis, immature cataract and blindness OD, and chorioretinitis with associated vitritis OS were diagnosed based upon ophthalmic examination findings and history.

Initial diagnostic testing included complete blood count, serum biochemical profile (SBP) total serum thyroxine concentration, and urinalysis. Results were unremarkable except for mild lymphopenia ($1.12 \times 10^3/\mu L$; reference range 1.5–$7 \times 10^3/\mu L$) and eosinophilia ($1.72 \times 10^3/\mu L$; reference range $0–1.5 \times 10^3/\mu L$). Lymphopenia was considered a stress response to primary disease.[8] Mild eosinophilia was probably normal individual variation for this cat, but could have been caused by parasitism, hypersensitivity, bacterial infection or neoplasia.[8] Thoracic radiographs showed no evidence of metastatic neoplasia or fungal disease but did reveal a slightly enlarged cardiac silhouette with 'valentine' shape on dorsoventral view, suggestive of hypertrophic cardiomyopathy. Systolic blood pressure, measured oscillometrically, was within reference range at 120 mmHg.

Ocular ultrasound was performed OD and showed complete retinal detachment (Fig. 2). ELISA testing for antibodies against feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) antigen was negative (SNAP® FIV/FeLV test, Idexx Laboratories Inc., Westbrook, ME, USA). Serum antibody titers against *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Cryptococcus neoformans* (Immuno-Mycologics Inc., Norman, OK, USA) were negative. Western immunoblot testing for *Bartonella henselae* (FeBart western-immunoblot, National Veterinary Laboratory Inc., Franklin Lakes, NJ, USA) did not indicate antibody production. Serum antibody titers for *Toxoplasma gondii* (*Toxoplasma gondii* IFA test kit, Zeus Scientific Inc., Raritan, NJ, USA) were suggestive of active toxoplasmosis (IgM 1 : 256; IgG 1 : 4096).[9,10] Lymph node aspirates revealed small, mature lymphocytes admixed with larger reactive lymphocytes. Organisms and neoplastic cells were not detected and lymph node aspirates were interpreted as cytologically reactive. Serum antibody and reverse transcriptase PCR testing[11] for enteric coronaviruses were not performed because of low positive predictive value of these tests in patients lacking clinical signs of systemic or hematologic disease due to feline infectious peritonitis (FIP).[12,13] A subretinal aspirate or anterior chamber paracentesis OD was offered but declined by the owners because of cost and invasiveness of the procedure. Abdominal radiography and ultrasound and further investigation of cardiac disease, including an electrocardiogram and echocardiogram, were recommended, but declined by the owners because of cost.

Ocular toxoplasmosis was tentatively diagnosed based on clinical findings and results of diagnostic tests. Treatment objectives included amelioration of uveitis OD and chorioretinitis and vitritis OS, as well as suppression of *T.-gondii* organisms. Topical anti-inflammatory medications prescribed to treat anterior uveitis OD included prednisolone acetate ophthalmic suspension q8h (1% prednisolone acetate ophthalmic suspension USP, Alcon Laboratories Inc., Fort Worth, TX, USA) and flurbiprofen ophthalmic solution q12h (Ocufen® 0.03% flurbiprofen ophthalmic solution, Allergan Inc., Irvine, CA, USA). Atropine (1% atropine sulfate ophthalmic ointment USP, Fougera Inc., Melville, NY, USA) was administered q12h to induce mydriasis and cycloplegia and to stabilize the blood–aqueous barrier.[14] Topical anti-inflammatory medications and atropine were not applied OS based on absence of anterior uveitis in this eye. Clindamycin hydrochloride, an antibiotic with static antiprotozoal properties and which suppresses the tachyzoite stage of *T. gondii*,[15] is the most widely used antimicrobial for feline toxoplasmosis[9,10] and was selected in this case. Clindamycin has been shown to successfully resolve *T. gondii*-induced anterior and posterior uveitis in cats.[13,15] This patient was treated with 13 mg/kg clindamycin hydrochloride (60 mg/mL oral suspension, Wedgewood Pharmacy, Swedesboro, NJ, USA) PO q12h for 21 days.[9] Oral L-lysine (L-lysine 500 mg tablets, Source Naturals®, Scotts Valley, CA, USA) was administered at 500 mg q12h in an attempt to limit reactivation of feline herpesvirus following systemic absorption of topically administered corticosteroid.[16] Systemic anti-inflammatory medication was not initially prescribed because a presumed primary infectious cause for the uveitis had been identified. Systemic nonsteroidal anti-inflammatory medications were not administered because the presumed primary cause of uveitis was being treated and because these medications are not labeled for use in cats.

On recheck examination (21 days following initial presentation), slit-lamp biomicroscopy revealed decreased keratic precipitates, 1/4 aqueous flare with anterior chamber cell, and posterior synechia involving the dorsal and ventral 1/3 of the pupil margin OD. Progression of the chorioretinitis lesion OS was documented (lesion measured 4.5 DD horizontally and 5 DD vertically). Prednisolone acetate (q8h) and atropine (q24h) were administered topically OU because of improvement of anterior uveitis OD, and potential for anterior extension of worsening chorioretinitis OS.[17] Flurbiprofen was continued OD q12h. Meloxicam (Metacam® meloxicam 1.5 mg/mL oral suspension, Merial Inc., Duluth, GA, USA) was instituted at 0.1 mg/kg PO q24h for 3 days in an attempt to control worsening posterior uveitis OS and following owner consent for off-label use of this medication. Additional diagnostic testing was not pursued at this time, as anterior uveitis OD had improved with treatment and as meloxicam had been prescribed to treat the worsening posterior uveitis OS.

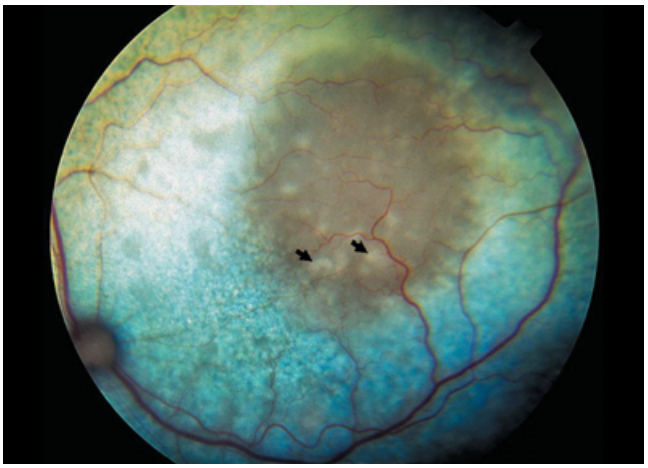


Figure 1. Fundus photograph of the left eye at presentation. A focal, raised, mottled chorioretinal lesion is apparent within the lateral mid-peripheral tapetal fundus. Also note the multifocal white vitreal opacities closely associated with the chorioretinal lesion (arrows).

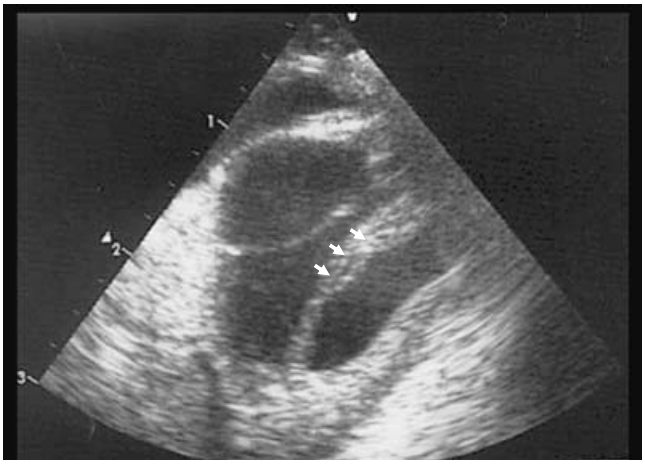
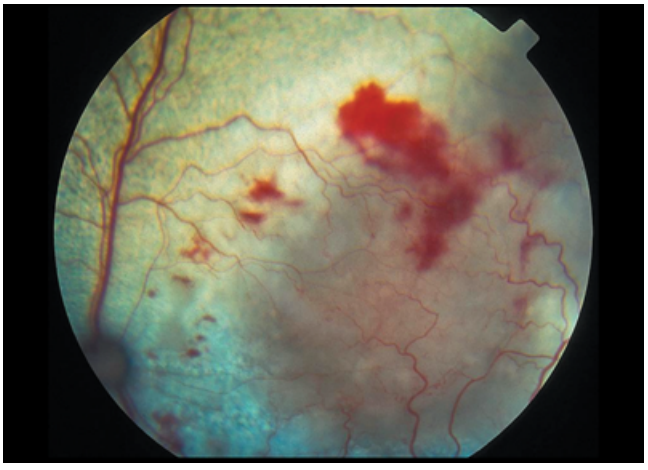


Figure 2. Ocular ultrasound image of the right eye at presentation. Complete retinal detachment is present with thickening of the detached retina (arrows).



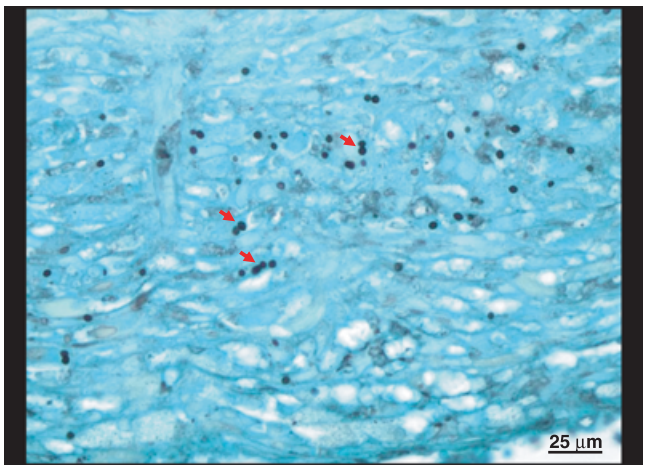


Figure 4. Photomicrograph of a section through the dorsal choroid OD revealing intracellular budding yeast-like organisms measuring approximately 3 µm and consistent with *Histoplasma capsulatum* (red arrows). Grocott's methenamine silver stain.

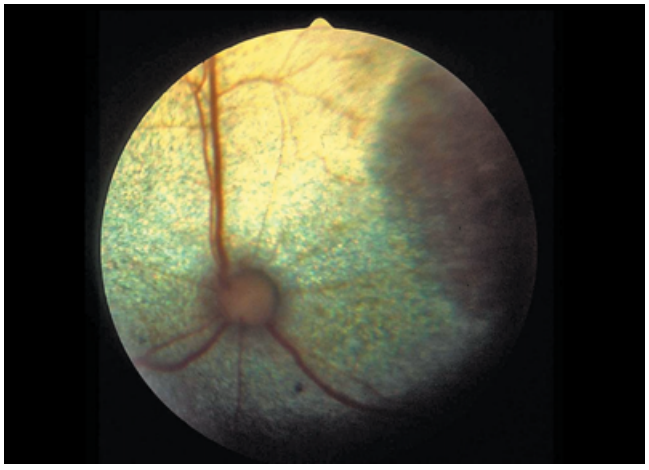


Figure 5. Fundus photograph of the left eye 6 months after initiating itraconazole treatment. A flat chorioretinal scar remains in the lateral mid-peripheral tapetal fundus.

Recheck examination 1 week later (day 28) showed active uveitis with increased (2/4) aqueous flare with anterior chamber cell, and a 2-mm superficial axial corneal ulcer OD. Funduscopy OS revealed marked dorsolateral extension of the chorioretinitis lesion (dimensions were 7 DD horizontally and 9 DD vertically), as well as multifocal retinal hemorrhage (Fig. 3) and a ventral exudative retinal detachment. Menace response was absent OU. Dazzle response was absent OD and present OS. Systolic blood pressure was again within normal range at 120 mmHg. Serum titers for *T. gondii* were repeated and supported clearance of active infection[9,18,19]

Figure 3. Fundus photograph of the left eye on day 28. Marked dorsolateral extension of the chorioretinitis and multifocal retinal hemorrhages are present.

(IgM titer decreased to < 1 : 64; IgG unchanged at 1 : 4096). Because of progressive vision loss, anterior chamber centesis OD (with cytology, culture and sensitivity, and C-value analysis), subretinal aspirates OU (with cytology, culture and sensitivity, and *T.-gondii* PCR), and enucleation OD to provide a specimen for histopathologic diagnosis were discussed with the owner. The owner elected to pursue enucleation OD because prognosis for vision was grave and the cat was experiencing discomfort because of uncontrolled uveitis.

Subconjunctival enucleation was performed under general anesthesia. Following enucleation but prior to formalin fixation, 0.5 mL of aqueous and 0.7 mL of subretinal fluid was aspirated and submitted for cytologic evaluation, which revealed suppurative inflammation without evidence of infectious organisms or neoplasia. Evaluation of subretinal fluid for *T. gondii* by PCR[20] (Veterinary Diagnostic Laboratory, University of Missouri, Columbia, MO, USA) was negative.

Because positive serologic evidence of *T.-gondii* infection does not necessarily prove a diagnosis of clinical ocular toxoplasmosis, the Goldmann-Witmer coefficient (C-value = [*T.-gondii* antibody (aqueous) × total antibody (serum)]/[*T.-gondii* antibody (serum) × total antibody (aqueous)] was calculated using quantified *T.-gondii* IgM and IgG and total IgM and IgG values from serum and remaining aqueous humor from the enucleated globe.[13,21] A C-value of 0.72 was obtained. Calculated C-values < 1 are consistent with *T. gondii*-specific antibody leakage into aqueous humor from serum, and inconsistent with clinical ocular toxoplasmosis.[21]

At recheck examination 13 days following enucleation OD (day 42 following initial evaluation), the surgery site was healed, skin sutures were removed, and lesions OS were unchanged. Histopathologic evaluation of the enucleated globe revealed lymphosuppurative and granulomatous panuveitis. Grocott's methenamine silver stain identified intracellular budding yeast organisms measuring approximately 3 μm in diameter, morphologically consistent with *Histoplasma capsulatum* within the uveal tract (Fig. 4). Serologic testing for *H.-capsulatum* antigen (Histoplasma antigen test, MiraVista Diagnostics, Indianapolis, IN, USA) was performed as a means to monitor response to treatment and because previous *H.-capsulatum* antibody testing was negative. *H. capsulatum*-specific antigen was not detected. Polymerase chain reaction testing for *H.-capsulatum* DNA was performed on DNA extracted from fixed sections of ocular tissue (Viromed Laboratories/Labcorp, Minnetonka, MN, USA) in an effort to identify the fungal organism. No *H.-capsulatum* DNA was detected. Abdominal ultrasound to detect dissemination of fungal organisms to abdominal organs was offered but declined by the owners as the cat lacked systemic signs of disease and as it would not change the therapeutic course. Therapy with itraconazole (50 mg/mL liver-flavored oral suspension, Wedgewood Pharmacy, Swedesboro, NJ, USA) was initiated at 11 mg/kg PO q24h.[22,23]

Recheck examinations and SBP to monitor alanine aminotransferase and alkaline phosphatase elevation secondary to itraconazole-induced hepatotoxicity[22,23] were scheduled monthly. Retinal reattachment, flattening of the chorioretinitis lesion, and partial resolution of retinal hemorrhages OS were evident after 1 month of itraconazole therapy. Positive menace response was evident OS 2 months after initiation of itraconazole. Complete resolution of the retinal hemorrhages and a flat chorioretinal scar were noted after 6 months (Fig. 5). Itraconazole was well tolerated with a favorable clinical response to therapy and normal serial SBP evaluations and was discontinued 7 months after starting therapy, at which time the funduscopic appearance of the chorioretinal scar had remained static for 1 month.[24,25]

DISCUSSION

Feline uveitis can be caused by numerous infectious agents or have neoplastic, traumatic, immune-mediated, idiopathic,[26] or many other causes.[27] In this case, the patient's age, lymphadenopathy, history, and lifestyle (indoor/outdoor) made an infectious cause most likely. Based on history, clinical signs, serum antibody titers, and failure to demonstrate other etiologies, this cat's uveitis initially was attributed to toxoplasmosis. The presence of positive serum antibody titers to *T. gondii* and correlation between titer and uveitis are controversial in cats without systemic signs of infection. However, seroprevalence of *T. gondii* is higher in cats with anterior uveitis than in those without anterior uveitis.[28] In this case, detection of decreasing serum *T. gondii* IgM antibody titer after administration of clindamycin suggested the presence of active toxoplasmosis at the initial presentation. Although this patient had an IgM/IgG C-value of < 1, which is inconsistent with ocular toxoplasmosis, this was calculated using samples collected following administration of prednisolone. Therefore, this test result cannot be accurately interpreted because glucocorticoid administration can significantly decrease intraocular *T. gondii*-specific antibody production.[21] Also, the effect on C-value of surgical manipulation of the globe, in this case prior to collection of aqueous humor, is unknown. Failure to amplify *T.-gondii* DNA from the subretinal fluid of the patient could be interpreted to mean that *T. gondii* was not involved with the ocular disease.[29] However, PCR results using aqueous humor are commonly negative in cats with experimentally induced *T.-gondii* infection and validation of this assay for subretinal fluid has not been performed. In addition, it is possible that this cat was infected with both *T. gondii* and fungus and that, while clindamycin administration led to the negative *T.-gondii* PCR result, ocular inflammation persisted because of the fungal infection. Unfortunately, ocular tissue was not later available for determination of the presence of *T.-gondii* DNA.

Following ocular histopathology OD, *H. capsulatum* was established as the most likely cause of uveitis OU and this was supported by the patient's response to systemically administered itraconazole. Although *H.-capsulatum* antibody production was not observed in this case, false-negative serologic tests have been reported in feline histoplasmosis.[24] An antigen test also was negative. The *H.-capsulatum* antigen

detection test is most sensitive in human patients with disseminated or acute pulmonary histoplasmosis[30] and false negatives are common in experimental subjects with a low fungal burden.[31] Although this case did not appear to have disseminated fungal disease or a large fungal load, the diagnosis of ocular histoplasmosis could not be excluded on the basis of this negative result. The negative PCR result for *H.-capsulatum* DNA on the fixed enucleated eye of this cat was an interesting finding. As PCR methods for identifying *H.-capsulatum* DNA are not currently validated or accepted as accurate in human or veterinary patients, clinical interpretation of this result was difficult.[31] Molecular diagnostic methods such as PCR are thought to be the most sensitive tests for identification of many infectious organisms. However, in mice affected with histoplasmosis, PCR evaluation for *H. capsulatum* was not significantly more sensitive than silver stains for identification of the organism.[32] Also, fixation of the tissue may have caused DNA denaturation and cross-linking, resulting in the absence or significant reduction of extracted DNA. The possibility that an unknown fungal organism morphologically similar to *H. capsulatum* caused ocular disease in this patient also exists. Diagnosis by isolation of the organism from cultures provides the strongest evidence for infection with *H. capsulatum* in humans and animals.[31] Unfortunately, fungal culture was not performed in this case because fixation of tissue made culture impossible following histopathologic identification of fungal organisms.

Histoplasmosis is caused by the saprophytic, mycelia-producing, soil fungus *Histoplasma capsulatum*.[33] The organism is endemic in the Ohio and Mississippi river valleys of the USA.[24] Infection occurs when microconidia in the air are inhaled, phagocytosed by pulmonary macrophages, and disseminated beyond the lungs by reticuloendothelial system macrophages.[34] In cats, a clinically silent infection of the lungs and associated lymph nodes may occur in endemic areas, with the disease becoming obvious only once dissemination occurs.[33] Lungs, gastrointestinal tract, lymph nodes, spleen, liver, bone marrow, eyes, and adrenal glands are affected most commonly.[25,35,36] Histoplasmosis appears to be more prevalent in young cats, with no gender-related predilection.[33,35] In this cat, organisms were histologically localized in the eyes, with only lymph node reactivity evident clinically and cytologically in those nodes sampled. This presentation was unusual because of limited evidence of disseminated disease and lack of evidence of respiratory disease. In reported cases of feline ocular histoplasmosis, respiratory disease is usually concurrent.[25,37–39] A retrospective study of deep mycotic infections in cats indicated that patients with limited focal disease (cutaneous or ocular) at presentation often had disseminated infections at necropsy.[35]

Three different forms of ocular disease due to *H. capsulatum* have been reported in humans.[40] The most common form is called presumed ocular histoplasmosis syndrome and consists of choroidal scarring, peripapillary atrophy, and choroidal neovascularization with absence of systemic symptoms.[41] The other two forms are usually seen in immunocompromised individuals and manifest as solitary chorioretinal granuloma or endophthalmitis with diffuse uveal and retinal involvement from disseminated histoplasmosis.[40] Ocular disease in this cat was similar to the endophthalmitis form OD and solitary granuloma form OS. Immunosuppressive factors are thought to have a minor role in predisposing cats to *H.-capsulatum* infection, but concurrent infection with FeLV, FIV, or FIP has been reported.[25,35] In immunocompromised humans, opportunistic infections with *H. capsulatum* and *T. gondii* can occur in the heart, lungs, and ocular tissues.[42–44] To the authors' knowledge, no reports exist of concurrent seropositivity to, or infection with both *H. capsulatum* and *T. gondii* in any species.

Itraconazole was selected for treatment of this patient based on efficacy and relative safety in cats compared to other available antifungals.[23,45] Itraconazole is a triazole antifungal and the free-azole nitrogen competes for oxygen at the catalytic heme iron atom of cytochrome P-450 enzymes and prevents synthesis of ergosterol in fungal cell membranes, increasing cell wall permeability and inhibiting fungal growth.[46–48] Although fluconazole has better penetration into the eye and central nervous system than itraconazole, it is less effective for treating histoplasmosis in people[49] and has not been studied extensively in cats. Long-term outcome for this patient after initiation of itraconazole was good with amelioration of fundic lesions and return of functional vision OS, without evidence of progressive systemic disease.

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