Management of bilateral uveitis in a \textit{Toxoplasma gondii}-seropositive cat with histopathologic evidence of fungal panuveitis

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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 \textit{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 \textit{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, \textit{Histoplasma capsulatum}, histoplasmosis, retinal detachment, \textit{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 \textit{Toxoplasma gondii}-seropositive cat with chronic and progressive bilateral uveitis, apparently induced by an organism morphologically consistent with \textit{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\textsuperscript{1} with anterior chamber cell, rubecosis 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 OD (11 mm/min OD and 10 mm/min OS)\textsuperscript{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).  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 mid-peripheral 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 × 10³/µL; reference range 1.5–7 × 10³/µL) and eosinophilia (1.72 × 10³/µL; reference range 0–1.5 × 10³/µL). Lymphopenia was considered a stress response to primary disease. Mild eosinophilia was probably normal individual variation for this cat, but could have been caused by parasitism, hypersensitivity, bacterial infection or neoplasia. 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). 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 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). 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 toxoplasmosis were 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.
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.

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Laboratories/Labcorp, Minnetonka, MN, USA) in an effort to monitor response to treatment and because previous therapy with itraconazole (50 mg/mL liver-flavored oral suspension, Wedgewood Pharmacy, Swedesboro, NJ, USA) was supported by the patient’s response to systemically administered clindamycin. Although H.-capsulatum DNA was not involved with the ocular disease. No H.-capsulatum DNA was detected. Abdominal ultrasound to detect dissemination of fungal organisms to abdominal organs was offered but not performed. In addition, it is possible that this cat was infected with both T. gondii and fungus and that, while clinically responsive to treatment and because previous therapy with 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

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 (Vironed 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 hepatotoxicity22,23 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, or many other causes.27 In this case, the patient’s age, lymphadenopathy, history, and lifestyle (indoors/outdoors) 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 toxoplasmic infection. 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...
producing, soil fungus following histopathologic identification of fungal organisms. This case because fixation of tissue made culture impossible. Prevalent in young cats, with no gender-related predilection. The organism morphologically similar to H. capsulatum DNA. The possibility that an unknown fungal link, resulting in the absence or significant reduction of evidence for infection with H. capsulatum. Diagnosis by isolation of the organism from cultures provides the strongest 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. 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. The organism is endemic in the Ohio and Mississippi river valleys of the USA. Infection occurs when microconidia in the air are inhaled, phagocytosed by pulmonary macrophages, and disseminated beyond the lungs by reticuloendothelial system macrophages. 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. Lungs, gastrointestinal tract, lymph nodes, spleen, liver, bone marrow, eyes, and adrenal glands are affected most commonly. Histoplasmosis appears to be more prevalent in young cats, with no gender-related predilection. 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. 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.

Three different forms of ocular disease due to H. capsulatum have been reported in humans. 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. 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. 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. In immunocompromised humans, opportunistic infections with H. capsulatum and T. gondii can occur in the heart, lungs, and ocular tissues. 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. 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. Although fluconazole has better penetration into the eye and central nervous system than itraconazole, it is less effective for treating histoplasmosis in people 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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