Histoplasma capsulatum, Toxoplasma gondii, Bartonella henselae and Bartonella clarridgeiae coinfections in an indoor-only Siamese cat

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Abstract

Case summary A 6-year-old male castrated Siamese cat was referred for acute-onset blindness and mydriasis. Physical examination revealed serous retinal detachment with panuveitis and systemic hypertension. Abdominal ultrasound showed suspected dilation of the cisterna chyli and abdominal lymphadenopathy. Aspirates of mesenteric lymph nodes revealed intrahistiocytic yeast organisms with mild-to-moderate pyogranulomatous inflammation. Fungal culture and *ITS1* sequencing of the lymph node aspirates confirmed infection with *Histoplasma capsulatum*. PCR performed on whole blood was positive for *Bartonella henselae* and *Bartonella clarridgeiae*, and *Toxoplasma gondii* IgG and IgM antibodies were detected in serum. The cat was prescribed prednisolone (0.5 mg/kg PO q24h), itraconazole (10 mg/kg PO q24h), clindamycin (13 mg/kg PO q12h), amlodipine (0.625 mg PO q24h), prednisolone acetate 1% drops (q6h) and ophthalmic lubricant for both eyes (q6h). The cat was doing well at home after 2 weeks of prednisolone, itraconazole and clindamycin administration, and no abnormalities were detected on repeat abdominal ultrasound 3 months later. The retinal detachment showed mild-to-moderate improvement at that time, but vision was not regained.

Relevance and novel information This is the first report of coinfection of *H capsulatum, T gondii, B henselae* and *B clarridgeiae* in an indoor-only cat living in a *H capsulatum* non-enzootic area with no known travel history.

Keywords: Infectious; histoplasmosis; toxoplasmosis; bartonellosis

Case description

A 6-year-old male castrated Siamese cat was referred for acute-onset blindness with suspicion of bilateral retinal detachment. The patient was previously healthy and had no other clinical signs apart from dental disease, with multiple extractions performed 7 weeks prior to presentation. The patient was adopted approximately 4 years previously from a rescue center in Colorado, had no known travel history and was a predominantly indoor-only cat with supervised access to a patio. There was another cat and two dogs in the household, which were all reported to be healthy.

On physical examination, the patient's vital signs were normal and an approximately 1×1 cm ulcerative gingival lesion where the left first mandibular molar contacted a previous extraction site was noted. The remainder of the physical examination was unremarkable and the patient's weight was 5.4 kg. The cat was hypertensive (185 mmHg; Doppler) and ophthalmic examination showed bilateral serous retinal detachment with retinal and vitreal hemorrhage (Figure 1a), bilateral mydriasis (Figure 1b) and absent menace and pupillary light reflexes. The

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Figure 1 (a) Retinal detachment with retinal and vitreal hemorrhage. (b) Bilateral mydriasis in a Siamese cat. (c) Panuveitis with hyphemic clot, mydriasis and retinal detachment in the left eye. (d) Cytology of the mesenteric lymph nodes showing intrahistiocytic yeast with mild-to-moderate pyogranulomatous inflammation with *Histoplasma capsulatum* (red arrow)

patient also had aqueous flare with keratic precipitates, with mild hyphema in the left eye (OS; Figure 1c). Tonometry (TonoVet) revealed intraocular pressures of 6 mmHg in the right eye (OD) and 18 mmHg OS.

A complete blood cell count (CBC) showed mild neutrophilia (16.6 × 10^3/μl; reference interval [RI] 2.0–12) and basophilia (400 × 10^3/μl [RI 0–100]).[1] Serum biochemical panel showed hypocholesterolemia (82 mg/dl [RI 95–270]), hypophosphatemia (2.6 mg/dl [RI 3.0–6.0]), hypocalcemia (8.6 mg/dl [RI 9.2–11.1]), hypomagnesemia (1.8 mg/dl [RI 2.0–2.7]), hypoalbuminemia (2.5 g/dl

[RI 3.1–4.4]), low albumin:globulin ratio (0.64 [RI 0.8–1.6]) and hypokalemia (3.67 mEq/L [RI 3.7–5.4]). Total thyroxine was within normal limits, urinalysis was unremarkable, and the cat was seronegative for feline leukemia virus antigen and feline immunodeficiency virus antibodies (SNAP FeLV/FIV; IDEXX Laboratories).

Thoracic radiographs were unremarkable, but abdominal ultrasound showed suspected dilation of the cisterna chyli with mesenteric and iliac lymphadenopathy. Aspirates of the mesenteric lymph nodes revealed low-to-moderate numbers of intrahistiocytic yeast organisms

(round-to-ovoid, measuring approximately 2–4 μm), with a thin clear halo, containing a basophilic (often lateralized) internal structure and rarely displaying budding, with mild-to-moderate pyogranulomatous inflammation (low-to-moderate numbers of macrophages, and a slightly increased number of neutrophils and plasma cells; Figure 1d). The lymphoid population was mixed, with small-sized lymphocytes predominating and low numbers of intermediate-to-large lymphocytes. Fungal culture of the lymph node aspirates confirmed infection with *Histoplasma capsulatum*. The aspirates were also evaluated for DNA from *Bartonella* species and *Toxoplasma gondii* using conventional PCR assays (positive or negative results provided) available commercially at an American Association of Veterinary Laboratory Diagnosticians certified laboratory (Veterinary Diagnostic Laboratory, Colorado State University), which were negative. These tests are based on previously reported assays.[2,3] However, DNA from *B henselae* and *Bartonella clarridgeiae* was amplified from whole blood. While *Bartonella* species IgG was not detected in serum, the *T gondii* titers for IgG and IgM were 1:256 and 1:64, respectively (Veterinary Diagnostic Laboratory, Colorado State University). Urine was submitted for quantitative detection of *Histoplasma* and *Blastomyces* species antigen (MiraVista Diagnostics), which were positive at 0.55 ng/ml (RI 0.20–20.00) and positive but below the limit of quantification (RI 0.2–14.7), respectively.

The cat was administered amlodipine (0.625 mg PO q24h [Amlodipine Besylate; Ascend]) to control hypertension, clindamycin (13 mg/kg PO q12h [Clindamycin Hydrochloride; Zoetis]) to treat the *T gondii* infection, generic itraconazole capsule (10 mg/kg PO q24h [Itraconazole; Amneal]) to treat the *H capsulatum* infection, prednisolone (0.5 mg/kg PO q24h [PrednisTab; LLOYD]) to reduce systemic inflammation and prednisolone acetate ophthalmic solution 1% (one drop OU q6h; SANDOZ) to reduce uveal inflammation and the likelihood of anterior lens luxation. An ophthalmic lubricant (one drop OU q6h [I-Drop Vet Plus; I-MED Animal Health]) was also used. Systolic blood pressure was normal the following day (140 mmHg; Doppler) and the cat was discharged to the owners.

Three weeks later, a serum biochemistry panel was performed to monitor liver enzyme activity due to itraconazole administration and was found to be unremarkable. There was a mild improvement in the retinal detachment, but uveitis persisted and there was no return of vision. Hyphema of the left eye resolved approximately 8 weeks following initial presentation (Figure 2). Systemic prednisolone was discontinued after 3 months, but the patient continued to be administered itraconazole, amlodipine and prednisolone acetate. There were no new physical examination findings, but the cat became

Figure 2 Resolution of the hyphema of the left eye approximately 8 weeks following initial presentation. Mild plaque of an old hemorrhage and fibrin on the anterior lens capsule is visible. There is also the presence of early fibrosis of the lens capsule in the left eye

severely hypertensive (215 mmHg; Doppler) despite therapy, and the amlodipine dose was increased (to 1.25 mg PO q24h). One week later, the physical examination was still normal and blood pressure was normal (125 mmHg; Doppler). No abnormalities were noted on the CBC and serum biochemistry panel. Repeat abdominal ultrasound showed resolution of previously suspected dilation of the cisterna chyli and abdominal lymphadenopathy. *Histoplasma* species antigen was not detected in the urine and PCR on whole blood for *Bartonella* species was negative. *T gondii* IgG (1:256) and IgM (1:128) were still detected in serum, and the *Bartonella* species IgG assay was still negative at that time. At the time of manuscript submission (10 months after diagnosis), the cat was still blind with absent menace OU and bilateral retinal detachment but otherwise systemically well.

Discussion

Retinal detachment in cats is commonly associated with systemic hypertension, hyperthyroidism and kidney disease, as well as infections such as mycobacterial infection, cryptococcosis and histoplasmosis.[4,5] Chorioretinitis in cats has been commonly reported with toxoplasmosis, cryptococcosis and histoplasmosis.[4] This case report describes serous retinal detachment and panuveitis in a predominantly indoor cat with systemic hypertension and evidence of coinfections with *H capsulatum, T gondii, B henselae* and *B clarridgeiae*. Owing to the detection of *H*

capsulatum by cytology of the mesenteric nodes, culture and urine antigen assay, the infection was confirmed, and this organism was most likely associated with some of the clinical manifestations in this case.[6] However, whether the fungus was directly involved with the ocular findings is unclear as chorioretinitis was not apparent, and aqueous or vitreous paracentesis was not performed. Based on the blood pressure findings over time without detection of other common causes of hypertension, it is possible some of the ocular changes (retinal detachment) were related to essential hypertension that occurred concurrently. The role of *T gondii* and the two *Bartonella* species in the clinical findings is less clear as both these genera commonly infect cats without causing clinical signs of disease.

The most unique finding in this case is the documentation of *H capsulatum* in a primarily indoor cat in a state generally considered to be non-enzootic. *H capsulatum* is a soil-borne fungal pathogen that is endemic to the Mississippi and Ohio River valleys, and the route of transmission is primarily by inhalation of spores from soil, particularly those contaminated by bird and bat droppings.[7] Histoplasmosis in indoor-only cats is less common than in cats with outdoor access; however, transmission to indoor-only cats through potted plants or unfurnished basements has been described.[8] Nevertheless, the agent has been detected in Montana, another Rocky Mountain state,[9] and so may be more common in this region of the USA than previously believed. It is also possible that the organism was present in potting soil or other materials such as wood shavings that originated in enzootic areas; this cat had supervised access to a patio and could have been exposed to the organism there. Another possibility is that the cat could have been infected prior to adoption, but since this was 4 years ago, it seems less likely. The weakly positive result of the *Blastomyces* species quantitative antigen was attributed to cross-reactivity with *Histoplasma* species antigen. As multiple drugs were used in the management of this case, it is hard to determine which was related to the clinical improvement. However, as the urine *H capsulatum* test became negative and the mesenteric lymphadenopathy resolved, it is likely that itraconazole had the expected treatment effect.

T gondii infection in cats in the Rocky Mountain states is common and can infect cats housed indoors if the owners feed undercooked meat or transport hosts enter the home and are ingested by the cats.[10] Most cats that are infected with *T gondii* have no clinical signs of disease, but ocular manifestations with uveitis, iritis or chorioretinitis are common when illness occurs.[11,12] As *T gondii* is not thought to be eliminated from the body after primary infection, the detection of IgG and IgM antibodies confirms the agent infected the cat described here, but it is impossible to determine the role the agent played in the clinical findings. *T gondii* DNA was not amplified from the aspirates from the mesenteric nodes, suggesting it was not involved with that manifestation of disease. Amplification of *T gondii* DNA in aqueous humor collected by aqueous paracentesis could have been performed to further document the role of the agent in the ocular manifestations of disease but was not carried out in this case.[11] The *T gondii* IgG titer could have been present for years in this cat, but IgM generally is recognized during acute or activated disease, suggesting a potential role in the clinical findings. After treatment, IgM titers can increase transiently, likely from naive B-cell activation by *T gondii* antigens released from tissue cysts. Clindamycin is an appropriate drug for the treatment of clinical feline toxoplasmosis.[13–15] However, it is unknown whether the positive treatment response in the cat described here related to the administration of this drug or the others that were prescribed. As clindamycin is a static drug, *T gondii* antibody titers do not necessarily decrease with successful therapy as the agent persists in tissues and recurrence is possible.[14]

Bartonella species are vector-transmitted, blood-borne, intracellular, Gram-negative bacteria that can cause disease in mammals, with cats being recognized as the main reservoirs for some species.[16,17] While fleas are the most common vectors for both *Bartonella* species detected in this cat, current infestations were not detected.[18] However, infection could have occurred previously, and low-grade bacteremia could have persisted for months. Some cats, dogs and people with *Bartonella* species infection have antibodies below the detectable limit of the assay, particularly if concurrent immunodeficiencies occur. *Bartonella* species DNA was not amplified from the aspirates from the mesenteric lymph nodes, suggesting that the agent was not involved with that manifestation of disease. As discussed for *T gondii*, aqueous paracentesis for *Bartonella* species PCR assay could have been used to further evaluate the role of *Bartonella* species in the ocular manifestations of disease.[11] While clindamycin is not generally used for treatment of *Bartonella* species infection in cats,[19] this drug may have an effect against some strains of the bacterium. As culture and antibiotic susceptibility testing was not performed, whether this antibiotic had a treatment effect in this cat is unknown. However, *Bartonella* species DNA was not amplified from blood from a post-treatment sample, suggesting a possible clindamycin treatment effect. While doxycycline or quinolones may have been more effective for *Bartonella* species infection, we chose to start with clindamycin alone initially because of *T gondii* infection.[20]

H capsulatum, T gondii and *Bartonella* species can infect otherwise healthy cats and coinfections with *T gondii* and *Bartonella* species are common in outdoor cats that hunt and have fleas.[21] However, detection of all three

agents in one indoor cat seems unusual and could possibly suggest immune deficits may have been present. Persistence of *T gondii* IgM has been common in cats with immunodeficiency.[14] These findings could suggest an inadequate B lymphocyte response in this cat. A primary immunodeficiency could be considered, although this is rare in cats and immune profiling is currently not commercially available for cats.[22] CBC did not reveal any changes to the white blood cell counts in this patient; however, CBC does not provide information about white blood cell function. Functional assays can be used to further assess neutrophil and lymphocyte function, but these tests are only available in certain research laboratories.[22] Primary immunodeficiencies, although rare, exist in cats. A recent paper reported an autosomal recessive leukocyte adhesion (CD18) deficiency in a cat.[23] Whether immune function deficits existed cannot be determined with the available data. However, the rapid response to therapy suggests that any immune deficits that may have occurred were minimal.

Conclusions

The patient was successfully treated with an antihypertensive agent, anti-inflammatory agents and antimicrobial agents, and at the time of writing, was being treated with itraconazole with no systemic signs of coinfections with *H capsulatum*, *T gondii* and *Bartonella* species. However, the patient failed to regain vision in either eye. This case report reinforces previous reports suggesting that even cases believed to be indoor-only without a pertinent history of exposure should be screened for infectious agents if deemed appropriate by the clinical presentation. In addition, more specific diagnostic tests to assess immunocompetency in cats are needed.

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