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CASE REPORT

Oculosystemic pneumocystosis in 2 sibling Chihuahuas

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Abstract

Sibling female and male Chihuahuas were evaluated for a 9-month history of tachypnea that failed to respond to fenbendazole, doxycycline, amoxicillin-clavulanate, and prednisone. Physical examination identified tachypnea, hyperpnea, and harsh bronchovesicular lung sounds. Fundic examination disclosed diffuse chorioretinitis, manifested as multifocal chorioretinal granulomas in the female dog and occasional chorioretinal scars in the male dog. Thoracic radiographs indicated moderate to severe interstitial to bronchointerstitial infiltrates in both dogs. Serum and urine antigen and antibody testing in the female dog failed to identify infectious agents, but cytologic assessment of hepatic lymph node, liver, and splenic aspirates identified *Pneumocystis* trophozoites. Infection was confirmed in both dogs by 28S rRNA PCR sequencing from multiple tissue samples. The female dog responded well to trimethoprim-sulfamethoxazole, but the male dog was euthanized because of liver failure, presumably related to antimicrobial treatment.

KEYWORDS
fundic examination, infectious disease, ophthalmology

1 | INTRODUCTION

Pneumocystis is an opportunistic, yeast-like, atypical fungus with species adapted to many mammals. In dogs, *Pneumocystis carinii* formae speciales "*canis*" (*P. canis*) recently has been identified using quantitative PCR and genetic sequencing.[1] *Pneumocystis* pneumonia in the dog appears to be similar to that in humans, where low numbers of organisms, presumed to be commensal in healthy immunocompetent individuals, proliferate in immunocompromised individuals and cause severe pneumonia.[1-3] Use of quantitative PCR to document low cycle thresholds (CT) in dogs with pneumonia has allowed elucidation of this disease process,[1] and rRNA sequencing confirms infection.[2]

Approximately 50 cases of *Pneumocystis* pneumonia have been reported in the veterinary literature, most cases in miniature dachshunds with immunodeficiency involving T and B cells[4] and in Cavalier King Charles spaniels,[5] in which immune deficits are also suspected. An X-linked mutation of a protein involved in both humoral and cell-mediated immunity also has been reported.[6] Diagnosis of *Pneumocystis* pneumonia in dogs has been made primarily by cytologic identification of periodic acid-Schiff- or Grocott methenamine silver (GMS)-stained organisms in tracheal samples, fine needle aspirates of lung, or impression smears of lung samples obtained at necropsy.[7] Disseminated pneumocystosis has been documented rarely in dogs.[7-9] This report describes 2 sibling Chihuahuas with systemic pneumocystosis in which antemortem diagnosis was facilitated by fundic examination and confirmed by cytologic assessment of abdominal aspirates or histopathology. Chorioretinitis has not been previously associated with systemic pneumocystosis in dogs.

Abbreviations: GMS, Grocott methenamine silver; ST, sequence type; TMS, trimethoprim sulfamethoxazole.

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2 | CASE DESCRIPTION

Two 7-month old sibling Chihuahuas were presented to their local veterinarian for routine neutering, which was performed without complication. Five weeks later, both dogs returned for evaluation of tachypnea (respiratory rate, 70-80 breaths/min), with the female (dog 1) more severely affected than the male (dog 2). Both dogs were prescribed doxycycline (5 mg/kg PO q12h for 5 days) and fenbendazole (50 mg/kg PO q24h for 14 days). Tachypnea persisted and prednisone initially was prescribed at 0.3 mg/kg PO q12h, and then q24h before being continued at 0.3 mg/kg q48h. No clinical response was reported by the owner. Six months later, radiographs of dog 1 identified a moderate diffuse, unstructured, interstitial pattern with prominence of the main pulmonary artery. Echocardiography showed main pulmonary artery dilatation, and maximal tricuspid regurgitant velocity of 4.01 m/s suggesting a right ventricular-right atrial pressure gradient of 64 and at least moderate pulmonary hypertension. Sildenafil was prescribed at 1.1 mg/kg PO q8h.

At 16 months of age, dog 1 was presented to the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis for evaluation of tachypnea and increased respiratory effort of 9 months' duration. Current medications included sildenafil and prednisone. On physical examination, the dog had markedly increased respiratory effort and a respiratory rate of 180 breaths/min, heart rate of 150 beats/min, and rectal temperature of 102.7 °F (39.3°C). Body weight was 4.5 kg with a body condition score (BCS) of 6/9; the dog had marked abdominal distention but no palpable abdominal abnormalities. Harsh breath sounds were auscultated bilaterally, worse over the right hemithorax than the left. Ophthalmic
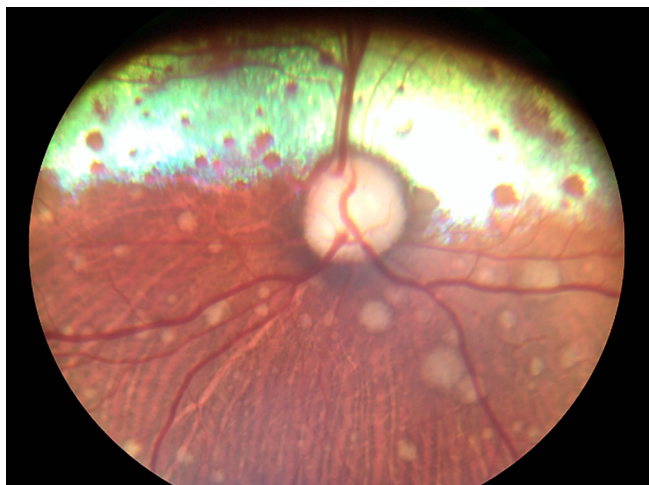

FIGURE 1 Color fundus photograph of the right eye of dog 1 on the day of admission. Multifocal maroon to cream-colored, well-delineated, subtly raised, circular areas are visible throughout the tapetal and non-tapetal fundus. The optic nerve head, retinal and choroidal vasculature appear normal. The apparent tapetal hyperreflectivity in this image is a photographic artifact. The ophthalmic diagnosis was multifocal, highly localized, chronic active chorioretinitis OU.

examination showed a normal anterior segment bilaterally, but fundic examination identified widespread multifocal maroon to cream-colored, well-delineated, raised, circular areas ranging in size from 1/20 to 1/10 of the optic disc diameter in both eyes (Figure 1). Some lesions were surrounded by a narrow rim of tapetal hyper-reflectivity. The optic nerve head, retinal and choroidal vasculature, and general tapetal reflectivity were within normal limits. The ophthalmic diagnosis was multifocal, localized, chronic-active chorioretinitis OU. These lesions appeared granulomatous and were considered consistent with fungal or protozoal chorioretinitis. The dog was placed in an oxygen-supplemented cage (40%-60%), which did not lead to notable improvement in respiratory rate or effort.

A CBC disclosed a moderate regenerative anemia, neutrophilic leukocytosis with a left shift, and thrombocytopenia (see Table S1). Serum biochemistry was unremarkable except for mild hypoalbuminemia with hypoglobulinemia and evidence of severe mixed hepatopathy. Thoracic radiographs identified a diffuse interstitial pulmonary pattern, mild pneumothorax on the left side, and mild main pulmonary artery dilatation. Serum was submitted for assessment of antibodies for *Coccidioides* and *Toxoplasma gondii* and for cryptococcal antigen, and urine was assessed for *Histoplasma* antigen. Itraconazole (5 mg/kg PO q12h) was initiated while test results were pending. Dexamethasone (0.04 mg/kg IV q48h) was given while the dog was hospitalized to taper the dose of corticosteroid administered. The following day, thoracocentesis was performed to manage pneumothorax. Eighty-five milliliters of air were removed, but no change in respiratory rate or effort was observed. Abdominal ultrasound examination identified a mildly enlarged, hyperechoic liver, mild hepatic lymphadenopathy, bilateral nephrocalcinosis (Figure 2), and mild splenic microlithiasis. Hepatic lymph nodes, liver, and spleen were aspirated. Cytologic assessment using Wright-Giemsa staining identified numerous organisms in all samples, each approximately 5 to 8 μm in diameter and containing 4 to 8 nuclei, consistent with *Pneumocystis* (Figure 3). Although Schirmer's tear test results were slightly below normal OS (13 mm/min), they were normal OD (18 mm/min), and the dog was started on trimethoprim-sulfamethoxazole (TMS) at a dosage of 15 mg/kg PO q12h. Results of a 4Dx SNAP test, all serologic tests, and urine *Histoplasma* antigen were negative, and itraconazole was discontinued after 3 days. The dog was discharged on TMS at the recommended dosage of 30 mg/kg PO q12h,[10] and prednisone was tapered.

At reevaluation, 12 days after starting TMS, the owner reported that dog 1 had a decreased respiratory rate of 48 breaths/min. The multifocal chorioretinal lesions throughout the tapetal and nontapetal fundus were more well-circumscribed, no longer appeared raised, and were darker, suggestive of resolving inflammation and early development of chorioretinal scars OU (Figure 4). Blood test results were unchanged to mildly improved (see Table S1), prednisone was decreased to q48h, and TMS was continued at the same dosage.

At this reevaluation, the owner also presented the male sibling (dog 2) for evaluation of tachypnea. On physical examination, the dog had a respiratory rate of 100 to 160 breaths/min with increased lung sounds in all fields. Fundic examination identified 2 dark,

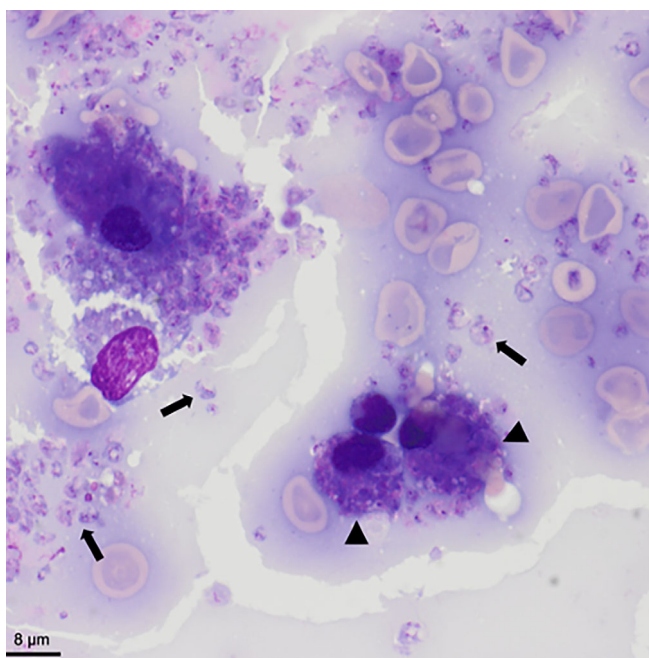**FIGURE 2** Ultrasound imaging on dog 1 on the day of admission demonstrating severe nephrocalcinosis.

FIGURE 3 Cytologic findings from aspiration of the peri-hepatic lymph node from dog 1 (×50); (Wright Giemsa staining). Many individualized and aggregated *Pneumocystis* organisms (black arrows) are present alongside macrophages containing intracytoplasmic organisms (black arrowheads).

FIGURE 4 Color fundus photograph of the right eye of dog 1 10 days after initiating antibiotic and anti-inflammatory treatment. Note that, relative to Figure 1, the multifocal chorioretinal lesions throughout the tapetal and non-tapetal fundus are better circumscribed, no longer appeared raised, and are darker, suggestive of resolving inflammation and early development of chorioretinal scars. The optic nerve head, and retinal and choroidal vasculature remain normal.

well-circumscribed, non-raised circular lesions, each surrounded by a narrow zone of tapetal hyper-reflectivity in OD (Figure 5). Tapetal reflectivity was otherwise normal, and the fundus of OS was within normal limits. The ophthalmic diagnosis was focal areas of resolved chorioretinitis (i.e., chorioretinal scars). Thoracic radiographs identified a diffuse homogenous m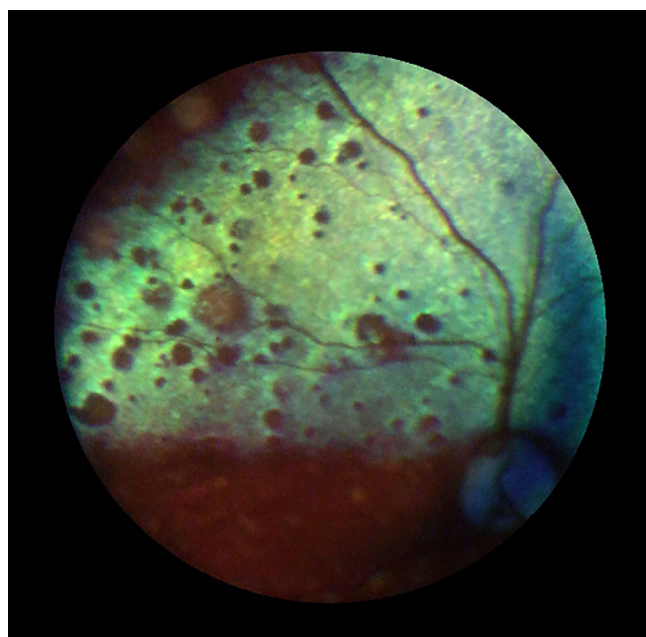oderate interstitial pulmonary pattern and increased soft tissue opacity in the perihilar region suspicious for hilar lymphadenopathy (Figure 6). These findings were considered suggestive of pulmonary pneumocystosis as diagnosed in the sibling dog. Schirmer's tear test results were normal and the dog was prescribed TMS at 27 mg/kg PO q12h. Eleven days later, the owner

reported that the dog's tachypnea had resolved but it acutely developed anorexia, became limp, and was transported to an emergency clinic, where the dog was reported to be eupneic but obtunded and nonresponsive. Physical examination disclosed a head tilt to the left, anisocoria with miosis OS, and decreased direct and consensual pupillary light reflexes. No menace response was observed but palpebral reflexes were intact OU. The, dog was mentally inappropriate,

nonambulatory, and unable to support itself. The findings were consistent with intracranial hemorrhage and the owners elected euthanasia.

Necropsy examination of dog 2 identified subarachnoid hemorrhage and severe pulmonary disease consistent with granulomatous interstitial pneumonia (Figure 7). All lung lobes were firm and mottled with sharp borders. Multifocal to coalescing pale pink to tan nodules up to 1-mm thick expanded the pleura overlying all lung lobes. The tracheobronchial lymph nodes were diffusely, mildly enlarged. Histopathologic examination of lung, spleen, and lymph nodes identified many spherical structures 5 to 10 μm in diameter with thin black rims and clear to gray central regions that were GMS-positive, consistent with *Pneumocystis* spp. Histopathologic evaluation of the right eye identified mild to moderate mixed inflammatory panuveitis consisting primarily of lymphocytes and plasma cells with rare lymphocytes and plasma cells also seen within the retina. Fungal organisms were not seen with GMS staining. Evaluation of the liver indicated acute, severe hepatic necrosis.

Methanol-fixed aspirates from the liver and hepatic lymph node from dog 1, and impression smears of liver, hilar lymph nodes, and lung obtained at necropsy from dog 2 were submitted to Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Italy for PCR assessment of *Pneumocystis* DNA as previously described.[1] Previously-stained material was scraped from the slide's surface and suspended in 300 μL phosphate-buffered saline. The DNA was extracted using a commercial spin kit (DNAeasy Blood & Tissue Kit; QIAGEN, Germany) following the manufacturer's recommendations. The qPCR assay was performed using SYBR Green technology (StepOnePlus; Applied Biosystems, Foster City, CA) and 2 sets of primers for screening and identity sequencing confirmation as follows:

FIGURE 5 Color fundus photograph of the right eye of dog 2 at initial presentation. Note the two dark, well-circumscribed, non-raised circular lesions in the far nasal tapetal periphery (black arrows). Each was surrounded by a narrow zone of tapetal hyper-reflectivity, although this finding is not evident in the more ventral lesion in this photograph because of the angle of illumination. Both lesions were considered to be chorioretinal scars consistent with focal areas of resolved chorioretinitis. The general tapetal reflectivity, optic nerve head, and retinal and choroidal vasculature of the right eye were normal. No abnormalities were detected in the left eye.

1. PneuSSU189 (5′-CTTTAGTTCGTGTTGTGAAATG-3′) and PneuSSU362 (5′-TAAGGGTCATGAGGACTTGTC-3′) targeting a short fragment (130-150 bp) of the mitochondrial small subunit (mtSSU) rRNA.
2. In house primers 26S (56-73 for 5′-TAACGGCGAGTGAASCGG-3′ and 26S 329-311rev 5′-TACTTGTKCGCTATCGGTC-3′) targeting a portion (230/240 bp) of the D1/D2 region of 28SLSU rRNA.
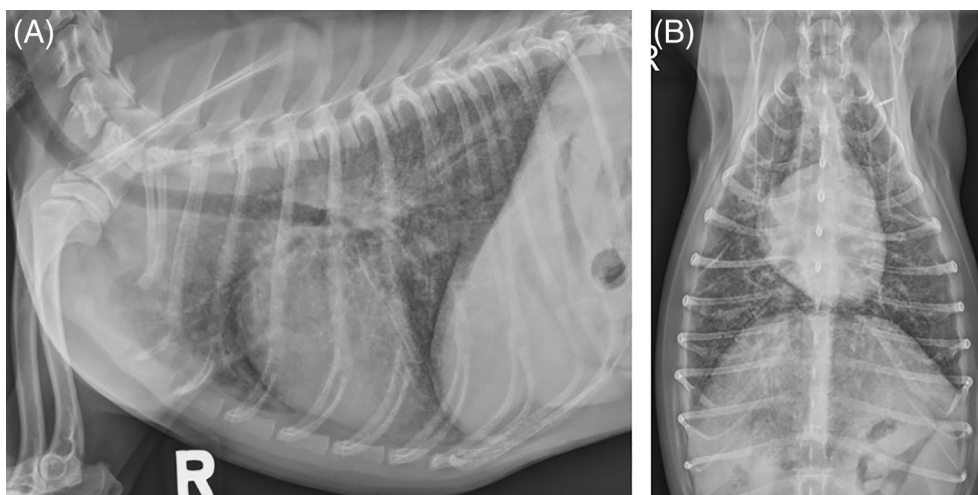

FIGURE 6 Right lateral (A) and dorsoventral (B) thoracic radiographs of dog 2 identified a diffuse homogenous moderate interstitial pulmonary pattern and increased soft tissue opacity in the perihilar region suspicious for hilar lymphadenopathy.

Negative (sterile water) controls and *Pneumocystis canis* (KU986903) positive-control DNA were included for each assay. *Pneumocystis* DNA was amplified from all samples with both PCR protocols and *Pneumocystis canis* was confirmed by sequencing of the 28SLSU rRNA portion. Phylogenetically, 2 different *Pneumocystis* sequence types (ST) were identified. The ST1 sequences from liver and hilar lymph node samples from both dogs were identical and
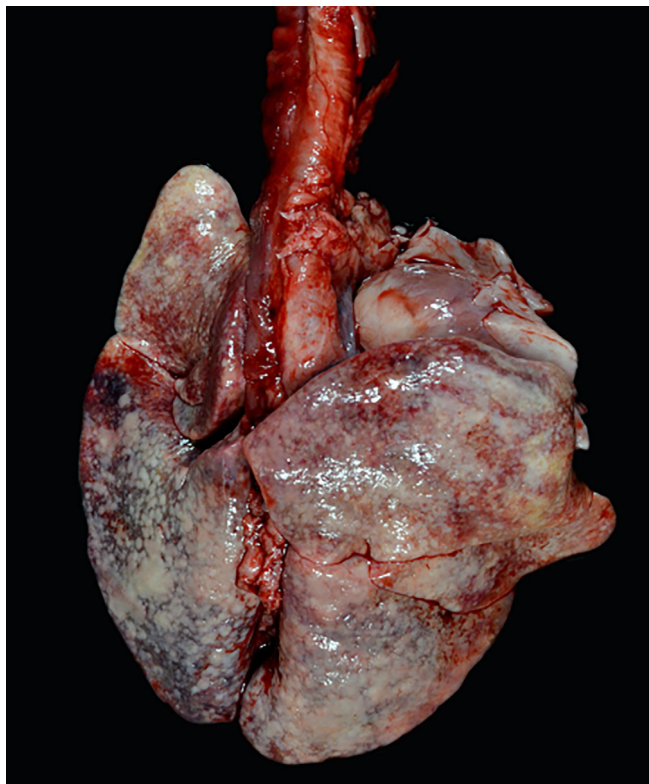
showed 99% homology to the *P. canis* strain (MT780538) in the GenBank database. The ST2 sequence from the lung of dog 2 was 20 bp different from ST1. Both ST1 and ST2 grouped in the *Pneumocystis canis* clade (Figure 8).

Dog 1 was re-evaluated after receiving TMS for 4 weeks (30 mg/kg PO q12h) and prednisone (0.2 mg/kg PO q48h). Owner-recorded respiratory rate was <40 breaths/min. On physical examination, respiratory rate was 40 to 80 breaths/min and lung sounds were slightly increased bilaterally. Schirmer tear test results were normal OU and fundic lesions were unchanged from the previous visit. Thoracic radiographs indicated a diffuse unstructured interstitial pulmonary pattern that was substantially improved compared with previous radiographs. A CBC (see Table S1) identified resolving regenerative anemia, thrombocytosis, and an improved white blood cell count. Biochemically, worsening of liver enzyme activities was noted, but serum albumin and globulin concentrations had improved. The most likely cause for the hepatopathy was TMS-induced hepatotoxicity. Given the dog's clinical improvement, TMS, prednisone, and sildenafil were discontinued and at 6-week reevaluation, the dog was clinically normal.

FIGURE 7 Postmortem appearance of the lungs and trachea of dog 2. The lungs were diffusely firm and failed to collapse. The pleura was diffusely covered by pale tan to white, firm plaques, and nodules. Multifocal, firm, white nodules (granulomas) expanded the pulmonary parenchyma.

3 | DISCUSSION

Pneumocystis is an opportunistic, atypical fungal organism that can be found in the airways of normal dogs,[1] but which causes systemic disease (typically pneumonia) in some cases.[1,2,4-9] For this reason and because history was unavailable on the parents and siblings of the 2 dogs, it was impossible to identify the original source of *Pneumocystis*. Potential sources include transplacental transmission or colonization by aerosolization between dogs housed in the same environment.[2,3] It is unclear if pneumocystosis was the cause of tachypnea noted initially in the dogs described here or if the organism disseminated after chronic corticosteroid administration. Although multisystemic disease has been observed only rarely in dogs,[8,9] it is well-established in immunosuppressed human patients.[11-14] It is also possible that infection in these 2 sibling dogs developed secondary to innate immune dysfunction.[6] Infection with *Pneumocystis* was shown to result in antibody class
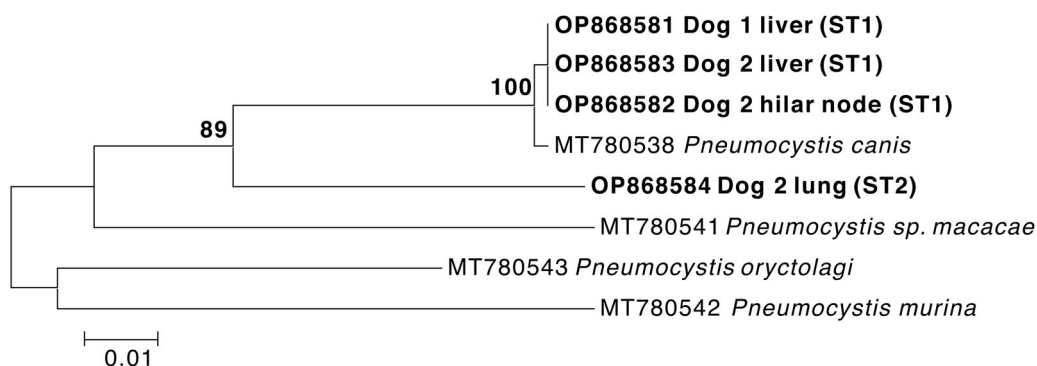

FIGURE 8 Phylogenetic tree based on portions of the 28S LSU sequences of various members of the *Pneumocystis* genus including samples from 2 sibling Chihuahuas with oculosystemic pneumocystosis. *Pneumocystis murina* sequence was used as an outgroup. The tree was constructed using the Maximum Likelihood Method. Bootstrap values shown at the main nodes represent the probabilities based on 1000 replicates. ST, sequence type.

switching, with ineffective immunoglobulin G production in favor of an immunoglobulin M response.[5] Although immune function testing (e.g., serum electrophoresis to investigate hypoglobulinemia or B- and T-cell markers on liver aspirates) was not undertaken here because of financial constraints, the finding that dog 2 was infected by 2 separate isolates of *Pneumocystis canis* could support a role for immunosuppression or dysfunction.

An etiological diagnosis in dog 1 was facilitated because fundic examination directed investigation toward disseminated infectious disease, which ultimately was confirmed by ultrasound-guided abdominal organ aspirates. Similarly, in humans with pneumocystosis early fundic examination is encouraged,[15] and consistent signs are considered to be a clue to disseminated pneumocystosis.[12] In dog 1, cytologic examination of aspirates was undertaken from multiple intra-abdominal sites because of suggestive fundic lesions, despite no overt pathology identified ultrasonographically. Fine needle aspiration of abdominal tissues obviated the need for airway sampling under general anesthesia.

To our knowledge, this report represents the first description of presumed chorioretinal pneumocystosis in dogs. Fundic lesions were extensive and similar to the multifocal yellow choroidal lesions reported in humans with *Pneumocystis* choroidopathy.[12,15] These lesions regressed within 12 days of starting fungicidal treatment with TMS in dog 1, as has been reported in humans.[16] Also, in dog 2, panuveitis was identified histologically, providing further support for oculosystemic disease. In humans, fundic lesions have been described variously as choroidopathy,[12] choroiditis,[15,17] or simply choroidal lesions.[15] This terminology points to 2 important clinical and histologic features of these lesions in humans: (a) they lack clinical evidence of notable inflammation and (b) they seem to be located more within and affect to a greater degree the choroid than the retina. These features were overtly evident in dog 1, in which we noted well-circumscribed, choroidal lesions without funduscopically evident overlying retinal detachment, edema, hemorrhage, or cellular infiltrate. Confirmation of this apparently disparate choroidal vs. retinal involvement in future cases should be better defined using advanced imaging, such as optical coherence tomography. Regardless, this relatively uncommon combination of fundoscopic features might be used to increase suspicion of *Pneumocystis*.

Metastatic renal calcification in dog 1 could have been related to corticosteroid use, but dystrophic calcification has been reported in bronchioles and cardiac tissue that expressed *P carinii* antigens.[9] Pulmonary microcalcification is described rarely in atypical *Pneumocystis* pneumonia in human immunodeficiency virus infection[18] and could have contributed to the marked tachypnea observed in dogs of our study, but microcalcification was not apparent in histologic samples from dog 2.

Four weeks of treatment with TMS resulted in good clinical resolution in dog 1, but potentially resulted in fatal hepatic necrosis in dog 2. It is also possible that disseminated pneumocystosis or prednisolone administration contributed to the hepatopathy in dog 2. Hepatotoxicity is a known complication of TMS and has been

reported with a variety of drug dosages and durations of treatment.[19] In dogs with *Pneumocystis* pneumonia, 8 to 12 weeks of treatment resulted in recovery when infection was identified promptly,[4,5,7,20] but less information is available in dogs with systemic pneumocystosis. Our report indicates that clinical signs of systemic pneumocystosis can be rapidly ameliorated by TMS administration, but monitoring for evidence of hepatotoxicity is essential.

CONFLICT OF INTEREST DECLARATION

Lynelle Johnson's employment was instrumental to creation of this work but did not bias presentation of results. Dr. Johnson's book royalties and speaker honoraria are not directly involved in the cases described. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.