A Toxo-ic Level of Immunosuppression

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Introduction

Toxoplasma gondii is best known for causing birth defects and stillbirths in the human fetus when infected during pregnancy. The asexual stages of the organism have been found in a variety of species for over a century, but the discovery in the 1970s that feline species complete the sexual part of the life cycle provided the missing information needed for prevention and control[1]. Although *T. gondii* does not typically result in disease in immunocompetent felids, the implication of cats in transmission has led to a great deal of public concern. This case report describes the presentation and diagnosis of *T. gondii* in a feline patient as well as the pathophysiology of the disease.

History and Presentation

Loki was a 9-year-old, neutered male, domestic shorthair cat that first presented to the Mississippi State University College of Veterinary Medicine Department of Small Animal Internal Medicine on the 20th of January, 2016 and visited many more times over the course of several months for additional diagnostics and treatment. He lived indoors with no other pets, was up to date on core vaccinations, and was not taking any medications.

The presenting complaint was a one year history of tachypnea and throaty upper respiratory sounds, described as wheezes and grunts. There was not a history of dyspnea, respiratory distress, or open-mouth breathing. He had been treated by the referring veterinarian (rDVM) with prednisolone, Depo-Medrol, Metacam, and terbutaline, which resulted in improved, and then a return of, clinical signs. Thoracic radiographs taken at the rDVM revealed thoracic fluid which did not improve after administration of Convenia. His appetite and activity level appeared to be normal. Physical exam findings included harsh lung sounds, bilaterally, and

inspiratory stridor which made auscultation of the heart difficult; however, no loud murmur was noted. It was also noted that his fur smelled of cigarette smoke. There were no other significant exam findings.

Diagnostic Approach / Considerations

The following routine tests were performed: heartworm antibody/antigen (none detected), Baermann fecal exam (no parasites detected), urinalysis, CBC, & chemistry (no significant findings), oral/nasal exam (no polyps or masses seen), aerobic and *Mycoplasma* culture (none detected). Thoracic imaging revealed a severe patchy alveolar pattern in the caudo-dorsal lung fields as well as a bronchial pattern in the ventro-cranial fields. Subsequent imaging demonstrated that this condition progressed to an irregularly distributed mixed pulmonary pattern. CT imaging with contrast showed mild nasal turbinate degeneration, a deviated nasal septum, and severe multifocal alveolar lung disease in the upper and lower lobes. The cause of these abnormalities was not determined.

Cytological examination of an ultrasound guided fine needle aspirate (FNA) from both lungs was non-diagnostic, being epithelial in origin with no signs of inflammation, cancer, parasites, or other infectious organisms. At this point in the diagnostic process, differential causes included long term exposure to environmental irritants, parasites such as *Toxoplasma* or *Aelurostongylus abstrusus*, fungal organisms such as *Histoplasma*, or neoplasia. Given this information as well as the patient's history, a presumptive diagnosis of chronic bronchitis was made.

Next, bronchoscopy revealed the airways were red and inflamed with copious amounts of mucus, as well as diffuse small, white nodules. Cytology of one of the nodules did not have any

significant findings. Bronchoalveolar lavage (BAL) revealed eosinophils, leading to a presumptive diagnosis of eosinophilic airway inflammation with consideration given to allergic inflammation/asthma and immune mediated disease. Also, neoplasia could not be ruled out. Biopsy of lung tissue was recommended, but never performed due to owner concerns regarding potential complications.

Treatment and Management

Treatments given to rule out some possible infectious causes included fenbendazole and azithromycin. Gabapentin was prescribed to improve the patient's comfort level and immunosuppressive doses of prednisolone to address the eosinophilic inflammation, both of which improved the clinical signs observed. A transient hyperglycemia and glucosuria eventually progressed to steroid-induced diabetes mellitus. This was managed with insulin therapy and tapering the dose of prednisolone until it was eventually discontinued, and theophylline was begun. After these changes, the respiratory condition worsened. The respiratory sounds and difficulty increased, coughing episodes began, and there was an episode of open mouth breathing which required emergency stabilization. Also, the patient's appetite decreased and he became more lethargic. He was admitted to the hospital with tachypnea and tachycardia. An additional FNA was performed which was inconclusive due to the low cellularity of the sample. The dose of theophylline was increased, cyclosporine and cetirizine were begun, as well as albuterol and fluticasone inhalants. These changes improved the patient's clinical respiratory signs.

Three weeks later, the patient developed vomiting, soft stools, hematochezia, clear ocular and nasal discharge, and congested upper respiratory sounds. A feline upper respiratory PCR

profile indicated an active FHV-1 infection, while abdominal ultrasound showed evidence of pancreatitis and mild enteritis. The GI signs were resolved with metronidazole and doxycycline, and the respiratory signs improved with lysine and famciclovir, as well as a temporary increase in prednisolone, albuterol, and fluticasone. A month later, the patient began vomiting and it was determined that the diabetes mellitus was over-regulated and in remission. Insulin therapy was discontinued and blood glucose levels monitored regularly.

Another month later, the patient presented with a declining condition over the last several days. The clinical signs included hypothermia, dyspnea, tachypnea with abdominal effort, severe PU/PD, lethargy, decreased appetite, weight loss, dull/depressed demeanor, dehydration, pale mucous membranes, elongated capillary refill time, increased lung sounds in all fields, and bilateral wheezes and crackles. An ultrasound exam revealed multiple pockets of pleural effusion and pulmonary edema throughout the lung fields. Thoracic radiographs indicated the previously identified interstitial/alveolar pulmonary pattern had worsened as well as retraction of the lobes from the dorsal margin of the thoracic cavity. The lung patterns, pleural effusion, and pulmonary edema observed were most likely due to infectious pneumonia secondary to what was observed to be eosinophilic disease and immunosuppression. A CBC test revealed lymphopenia, and increased numbers of segmented neutrophils. Measurement of blood chemistry showed an electrolyte imbalance, as well as elevated BUN, creatinine, total protein, CK, and bilirubin. The patient was hospitalized overnight, and the next day he was hypothermic, did not have palpable femoral pulses, and began showing signs of respiratory distress and fatigue. Euthanasia was performed because of the patient's declining condition.

Case outcome

Necropsy findings showed that all lobes of the lungs were severely affected by chronic interstitial pneumonia. This resulted in widespread hypertrophy of terminal bronchiolar smooth muscle and cuboidalization of the alveolar septal walls. Also present were areas of necrosis, indicated by consolidation by cellular debris and absence of any visible tissue elements. Many areas of widened and inflamed septal walls contained neutrophils, lymphocytes, and plasma cells, while the lumina were filled with necrotic cellular debris, degenerate neutrophils, and proteinaceous fluid. Amongst these areas of inflammation and necrosis were 2-3µm, falciform-shaped organisms with a small dense nucleus. These were identified as *T. gondii* tachyzoites, which were found singly or in clusters within airways, alveoli, septa, macrophages, or Type II pneumocytes. Although lung tissue contained the most significant numbers of organisms, tachyzoites were also found in other tissues affected by localized necrosis, such as the tongue and diaphragm.

Pathophysiology

Infection of humans and animals by *T. gondii* typically occurs when encysted organisms are ingested through the consumption of affected animal tissues. Infection also occurs when sporulated oocysts are ingested, typically through contact with contaminated soil, food, or water. Sporozoites emerge from oocysts, while bradyzoites emerge from the encysted stage, and develop into tachyzoites which disseminate throughout the body. Clinical signs result from inflammation, tissue destruction, and necrosis that is the result of intracellular growth and rupture by tachyzoites. Also, the deposition of immune-complexes in affected tissues, and possible subsequent development of hypersensitivity, may also contribute.[2] In cats, the tissues

most commonly infected include the lungs, eyes, central nervous system, and muscles, with the lungs typically being the primary organ affected by both first-exposure and reactivated infections.[3]

The consideration was made that the presenting clinical signs were the result of *T. gondii* infection, but it is more likely that the high numbers of tachyzoites detected are the result of emergence of a latent infection following immunosuppression therapy. This patient presented in January 2016 with a one year history of respiratory difficulty and was treated until September. The duration of the symptoms, the nature of the clinical signs observed, and the diagnostic testing performed suggest the diagnosis of asthma / allergic inflammation to be correct and the treatments administered to be prudent. The proliferation of *T. gondii* is likely the unfortunate side effect of the necessary levels of immunosuppressive prednisolone administered.

Cell mediated immunity is the primary mechanism of defense against *T. gondii* infection. Because of this, immunosuppression increases susceptibility to infection and also to re-emergence of a latent infection. In cats, immunosuppression leading to infection with *T. gondii* is usually because of FeLV/FIV infection, cyclosporine therapy, or the administration of immunosuppressive levels of corticosteroids, such as what occurred with this patient.[4] This is supported by the serology pattern observed. Prior to euthanasia, a serum sample was submitted for measurement of *T. gondii* titers. The results were received later and reactive IgG levels were measured at 1:512, while there was no detectable level of reactive IgM. High or rising IgG levels, together with low to no IgM is characteristic of emergence of a latent infection.[5]

Also, the lifestyle (indoor only, fed a commercial diet) of this patient immediately prior to presentation does not provide an opportunity for a recently acquired infection. Much about the history of this patient is unknown, making it impossible to theorize how it would have

initially encountered the organism. However, seroprevalence to *T. gondii* can be as high as 100% in some areas,[6] so it is not unreasonable to believe that this patient may have been infected previously.

Although cats with antibody titers above 1:64 are unlikely to be shedding oocysts,[7] the high burden of tachyzoites present in such patients is a public health concern that veterinarians should be aware of. Tachyzoites are highly infectious and can be found in saliva, sputum, urine, tears, and semen. In spite the fact that horizontal transmission to humans exposed to these materials has not been documented[8] there is still a potential risk of infection to those individuals working with the patient as well as the clinical samples, tissues, and fluids from the patient. As with all potentially zoonotic cases, care must be taken to protect staff from accidental transmission.

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