Feline Cytauxzoonosis

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Introduction

Cytauxzoonosis is recognized as one of the most fatal diseases to affect both wild and domestic cats. First discovered in the United States in Missouri in 1976, cytauxzoonosis has now spread to the South Central and South Eastern regions of the United States, most commonly seen in the states of Arkansas, Oklahoma, Texas, Georgia, Mississippi, Louisiana, and Florida.[11] While seemingly limited to these regions, there have been recent reports of cases emerging in South America and Europe. The *Cytauxzoon* species present in Europe seems to be different than the organism present in the United States, having a lower incidence of virulence.[10] The virulence of *Cytauxzoon* appears to be dependent on the geographic location.[6] Cytauxzoonosis is transmitted by the bite of both the *Dermacentor variabilis* and *Amblyomma americanum* ticks. When these ticks bite a naive cat, the protozoan *Cytauxzoon felis* is transmitted. What makes *Cytauxzoon felis* unique when compared to other tick-borne organisms is that it causes both an erythrocytic phase and a tissue phase, with the tissue phase inducing severe disease. Historically, cytauxzoonosis was considered to have a 100% mortality rate.[12] However, there are now new treatments available that offer a greater chance of survival for infected cats.

History and Presentation

Cytauxzoonosis most commonly occurs in middle-aged cats, but it can occur in cats of any age, sex, or breed.[2] There is no known association with retroviral infection. Cats with increased exposure to the tick vectors are at higher risk of developing cytauxzoonosis. Infected cats typically have a history of being feral, free-ranging, or having ready access to the outdoors, especially to wooded areas.[5] These cats usually have a history of inadequate application of tick preventative. Cytauxzoonosis is considered to be highly seasonal. Temporal occurrence of clinical disease is usually correlated to periods when tick activity is at its highest. There will be

peaks of presentation during the late spring and early summer months followed by a smaller peak during late summer and early fall.[13] Cats from multi-cat households commonly succumb to clinical disease. However, there is no evidence that *Cytauxzoon felis* is contagious. Instead, this finding is likely due to common exposure to the same tick vectors and the consistent lack of application of tick preventative within the household.[21]

Cats infected with cytauxzoonosis will often initially have nonspecific signs that progress to a more severe form of the disease. Owners may first notice their cats becoming acutely depressed, lethargic, and anorexic, initiating presentation to a veterinarian. Upon presentation, infected cats will show signs of severe dehydration, pallor, and icterus. They will often have tachycardia and tachypnea, with or without marked respiratory distress.[2] Hepatosplenomegaly may be appreciated upon abdominal palpation. Although not pathognomonic, the most consistent finding of infected cats is severe pyrexia, often greater than 106°F.[20] As the disease progresses, patients may experience an altered mentation with abnormal vocalizations as well as neurologic signs including ataxia, seizures, and nystagmus. As infected cats progress into the final stage of the disease, they become hypothermic and reach a moribund state. The clinical course as described occurs acutely. Clinical signs begin 5-14 days after exposure with patients often succumbing to death one week after the onset of clinical signs.[5]

Pathophysiology

Cytauxzoon felis is transmitted directly from the bite of an infected tick vector. Historically, *Dermacentor variabilis* was the only tick documented to transmit the protozoal organism. However, *Amblyomma americanum* is now becoming the more prevalent vector.[14] Once the tick vector attaches, it only takes between 36-48 hours before *Cytauxzoon felis* is transmitted to the naïve cat.[19] Hematological transmission, whether by blood transfusion or

perinatally, will not cause clinical disease.[9,10] This proves that ticks are more than just a mechanical vector, but are an essential part of the *Cytauxzoon felis* life cycle.[11]

The life cycle of *Cytauxzoon felis* is a complex one, as there are two distinct phases of infection: the tissue phase and the erythrocytic phase. The phase of infection determines the presence of clinical signs.[7] The bobcat is the reservoir host for *Cytauxzoon felis*. When a tick vector bites an infected bobcat, it ingests merozoite-infected red blood cells, which undergo sexual reproduction in the gut and salivary glands of the tick vector. This results in the formation of an infective sporozoite, which can be transmitted to a naïve cat if bitten by the same tick vector.[10] The sporozoite then infects mononuclear cells within the cat. After infection, the sporozoites undergo a period of asexual reproduction within the macrophages referred to as schizogony. The resulting schizonts produced become so enlarged that they begin to cause vascular obstruction, especially of the venules in the liver, spleen, lung, and lymph nodes.[11] Pulmonary intravascular macrophages can become paralyzed from the abundance of schizonts, triggering the release of pro-inflammatory cytokines.[17] Infection with schizonts can become so widespread throughout the body, it can result in thrombosis, impairment of circulation, tissue hypoxia, failure of gas exchange leading to an interstitial pneumonia, vasculitis, and eventually multi-organ dysfunction syndrome.[4,10] These schizonts are the defining characteristic of the tissue phase, which is the phase that ultimately causes death of the patient.

The second phase of infection is known as the erythrocytic phase. During this phase, the already-developed schizonts cause macrophages to rupture within the circulation. When the infected macrophages rupture, merozoites are released. These merozoites undergo endocytosis by erythrocytes, infecting the red blood cells and additional mononuclear cells. This process is what gives rise to the late stage erythroparasitemia evidenced by the piroplasms seen on the

diagnostic blood smear. As the condition progresses, the piroplasms may cause red blood cell destruction or erythrophagocytosis, ultimately leading to hemolytic anemia.[10]

The clinical development of disease is different in the bobcat than in domestic cats. While bobcats do develop the schizogenous phase of the disease, the disease is self-limiting, with most infected bobcats becoming persistently erythroparasitemic with absence of clinical signs. These are the bobcats that survive to become persistent carriers and reservoirs for future transmission to domestic cats.[11] If domestic cats survive infection, they can remain parasitemic and may too become reservoirs for the infection.[8] If a cat is exposed hematologically to the disease, it can develop piroplasms within the blood without experiencing the schizogenous phase of infection. These cats also have potential to become reservoirs for future infection.[10]

Differential Diagnoses

Diagnosis of cytauxzoonosis is often challenging due to the non-specific history and clinical signs. Differential diagnoses for cats presenting with these clinical signs include *Mycoplasma haemofelis*, cholangitis, cholangiohepatitis, immune-mediated hemolytic anemia, toxoplasmosis, feline infectious peritonitis, pancreatitis, as well as sequelae of retroviral diseases.[2] It is important to rule out these other diseases so that treatment for cytauxzoonosis can be initiated as quickly as possible. Fortunately, the geographic limitations of cytauxzoonosis make it easier to rule the disease in or out. If an ill cat in an endemic state presents with an acute onset of fever, icterus, pallor, splenomegaly, or hepatomegaly, clinical suspicion should be raised for cytauxzoonosis.[2]

Diagnostic Approach

Laboratory Findings

Often, a presumptive diagnosis can be made based on clinical signs and physical exam. However, a full diagnostic work-up is necessary to definitively diagnose cytauxzoonosis. A complete blood count and serum chemistry are initially indicated. A complete blood count will often reveal a pancytopenia, with the presence of leukopenia and thrombocytopenia being unpredictable. If anemia is present, it is most often a normocytic, normochromic non-regenerative anemia due to the acute nature of the condition and the insufficient amount of time for the bone marrow to generate a response to the infection.[21] If a leukopenia is present, it is likely due to the toxic changes present within the bone marrow. Thrombocytopenia is believed to result from increased consumption of platelets. An activated partial thromboplastin time (aPTT) is consistently and markedly prolonged.[2] Serum chemistry will often yield a hyperbilirubinemia due to the presence of extravascular hemolysis and the infiltration of schizont-filled macrophages within the liver. This infiltration may subsequently cause an elevation in liver enzymes, as well. A prerenal azotemia is often present due to severe dehydration of the patient. Hypoalbuminemia, hyperglycemia, and nonspecific electrolyte abnormalities are also commonly present late in the progression of the disease.[10]

Blood Smear

The simplest and most common method of definitively diagnosing cytauxzoonosis is visualizing *Cytauxzoon felis* on a peripheral blood smear. A Giemsa or Romanowsky-based stain is the preferred method for differentiating *Cytauxzoon felis* from other erythrocytic parasites and artifacts.[5] The piroplasms present in a cytauxzoonosis infection have a characteristic appearance of a signet-ring. The piroplasms are approximately 1-3 micrometers in diameter with a thick, round nuclear area at one aspect of the ring structure.[11] While the

piroplasms are most often in the signet ring shape, it is important to remember that they can appear in the shape of a safety pin, tetrad, or chains as well.[2]

While a blood smear can be diagnostic, this diagnostic test has its limitations. Because the erythrocytic phase follows the schizogenous phase, infected cats typically have clinical signs long before piroplasms appear in the peripheral bloodstream. Up to 50% of piroplasms may be absent at initial clinical presentation.[2] It is, therefore, of utmost importance to repeat peripheral blood smears daily if there is a high suspicion of cytauxzoonosis, as significant increases in circulating organisms can occur in just 24 hours.[11] A schizont can potentially be visualized within an infected macrophage along the feathered edge of a smear, but this is not as common as visualizing the piroplasm. Additionally, not all cats with identifiable piroplasms have clinical infection. This may be the result of a previous infection which the patient survived and then became a reservoir for the disease.[10]

Cytologic Evaluation

If there is strong clinical suspicion of cytauxzoonosis, but organisms are unidentifiable on a peripheral blood smear, fine needle aspirates of tissue may be performed and followed by cytologic evaluation. Tissue samples of liver, lung, and spleen are likely to yield the most diagnostic results, but lymph node and bone marrow aspirates may prove to be successful as well. In clinical disease, these organs will be infected with large schizogenous macrophages that adhere to the vascular endothelium.[11] These will appear as enlarged macrophages with a prominent nucleolus surrounded by distended cytoplasm. The schizonts will begin as a small, lobulated, blue structure within the cytoplasm then progress until small basophilic granules can be seen within the schizont, ultimately resulting in vascular obstruction and thrombus formation.[5]

PCR

A PCR assay can assist in confirming a diagnosis of cytauxzoonosis, especially in patients with low erythroparasitemia. The assay is highly sensitive and specific in identifying the 18S rRNA gene sequences associated with piroplasms of *Cytauxzoon felis*. This PCR based test can detect erythroparasitemias that are up to 1000-fold lower than the limit of detection that can be achieved by examining a peripheral blood smear and can detect genetic differences of varying organisms.[1] In recent years, an additional assay has been developed that focuses on amplification of the cox3 mitochondrial gene rather than the 18S ribosomal gene. This assay is proven to be even more sensitive than the 18S gene in the diagnosis of cytauxzoonosis, resulting in earlier detection of clinical disease and differentiation between acute and chronic infection.[16]

Imaging

Imaging is often not necessary for the diagnosis of cytauxzoonosis. However, hepatosplenomegaly can be consistently expected on abdominal radiographs. Thoracic radiographs may reveal pulmonary changes consistent with edema, congestion, or consolidation resulting from an interstitial pneumonia. It is not uncommon for a cat infected with cytauxzoonosis to have pericardial effusion and, as a result, generalized cardiomegaly on radiographs.[5]

Postmortem Evaluation

Anatomically, an infected cat will have pallor, icterus, and hepatosplenomegaly as identified on physical exam. Red, enlarged lymph nodes may be present as well as edematous lungs. Petechial and ecchymotic hemorrhages may be found on multiple organs and the vasculature may be enlarged as a result of obstruction.[5] Pleural, pericardial, and abdominal

effusions are less common findings, but can be present in some patients. Histologic evaluation of post-mortem tissues will have a similar appearance to tissues evaluated on cytology. Schizont-containing macrophages are most commonly found within the lumen of the vessels in the liver, lungs, and spleen, but any organ can be affected. Evidence of ischemia may be apparent in the brain and heart.[11]

Treatment and Management Options

The single most important therapy for a cat infected with cytauxzoonosis is supportive therapy. Intravenous fluid therapy with a balanced crystalloid is necessary to correct dehydration, preserve intravascular volume, and maintain tissue perfusion. If the patient is at risk for disseminated intravascular coagulation (DIC), a blood transfusion with whole blood, packed red blood cells, or an oxyglobin based solution may be initiated. To prevent the occurrence of DIC, heparin therapy is often initiated prophylactically at 200 U/kg subcutaneously every 8 hours. Adjunct use of antibiotics including ampicillin, enrofloxacin, and doxycycline has been documented, though they do not directly assist in the treatment of the *Cytauxzoon felis* organism.[2] Nutritional management is a crucial part of supportive care in infected cats. A nasogastric or esophagostomy tube is often placed upon hospitalization in order to provide partial parenteral or enteral nutrition as well as to decrease stress of administering medications multiple times daily.[5]

A variety of antiprotozoal drugs have been implemented in the treatment of cytauxzoonosis, though efficacy has proven to be questionable. Imidocarb dipropionate was used as the treatment of choice for years. Two 2.0-3.5 mg/kg doses should be given intramuscularly, one week apart.[3] If imidocarb diproprionate is used, it is important to administer atropine or glycopyrrolate prior to the imidocarb diproprionate to counteract its cholinergic

effects, including salivation, lacrimation, and vomiting.[2] Treatment with atovaquone at 15mg/kg orally three times daily for ten days and azithromycin at 10mg/kg orally once daily for ten days is now proven to be more successful compared to treatment with imidocarb diproprionate, with a 60% survival rate compared to a 26% survival rate respectively.[3]

Prevention

Since *Cytauxzoon felis* is solely transmitted by the bite of an infected tick, prevention is based on methods of decreasing or eliminating contact with ticks. The most reliable methods of decreasing contact with ticks are limiting access to the outdoors and regular application of acaricides. Application of a Seresto collar (Imidacloprid 10% and Flumethrin 4.5%) has proven to have a 100% success rate for the prevention of attachment of *Amblyomma americanum* ticks, thus eliminating the ticks' ability to feed and transmission of *Cytauxzoon felis*.[15] While cats generally have a reduced propensity for metabolizing pyrethroid-esters, metabolism of the flumethrin does not require glucoronidation, allowing safe usage of Seresto collars in cats.[18]

Prognosis

Cytauxzoonosis historically has a mortality rate of nearly 100% occurring days after onset of illness.[21] Despite the implementation of supportive care and antifungal medication, cytauxzoonosis continues to have high fatality with only 10% of infected cats surviving infection.[7] Due to the grave prognosis and rapid progression, it is important to diagnose the disease as quickly as possible in order to implement supportive measures or humanely end the suffering of infected cats.[6]

Conclusion

Feline cytauxzoonosis is a fatal disease that is becoming increasingly prevalent in the Southeastern United States where the *Dermacentor variabilis* and *Amblyomma americanum* ticks are most prevalent. The easiest way to diagnose *Cytauxzoon felis* is by visualizing the characteristic signet-ring shaped piroplasms on a peripheral blood smear. Unfortunately, by the time changes to erythrocytes are visualized, shizonts have already invaded the tissue and caused vascular obstruction. Several treatment modalities are available for cytauxzoonosis, but none have proven to have great success. Due to the severe mortality rate, it is of utmost importance for cats to remain on proper tick preventative, especially in endemic areas.

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