# Feline Cytauxzoonosis

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## INTRODUCTION

Cytauxzoonosis is a disease of wild and domestic cats caused by the protozoan *Cytauxzoon felis*. *C. felis* exists in the felid host in two main forms: the piroplasm, or erythrocytic phase, is the form that parasitizes red blood cells and is relatively non-pathogenic; the schizont, or tissue phase, is a separate form that is found in macrophages, affects essentially any tissue and is responsible for the clinical manifestations of the disease.

## TRANSMISSION

The agent is transmitted by ticks that acquire the infection by feeding on parasitemic infected hosts. *Amblyomma americanum* (the Lone Star tick) is the principal vector and the distribution of *C. felis* parallels the geographic distribution of this tick. Experimentally, *Dermacentor variabilis* (the American dog tick) has also been shown to be a capable vector but the contribution of this tick in natural infection is unclear. The organism can infect any felid but not other mammals. Bobcats, in which infections are usually mild or subclinical, can become persistently infected carriers and are the major reservoir host. Domestic cats that survive the acute illness can remain persistently parasitemic and, experimentally, have been shown to be capable of transmitting infection via the tick vector but the role of domestic cats as a reservoir host in natural infections is uncertain.

In the transmission cycle, ticks ingest parasitized red blood cells (piroplasm form) during feeding on a parasitemic host. Organisms released in the tick gut differentiate into macrogamonts and microgamonts which unite to form a zygote (sexual reproduction). The zygote differentiates into an ookinete, which replicates by asexual reproduction. Ookinetes penetrate the gut wall, then migrate to and enter salivary gland cells, where asexual reproduction (merogony) occurs. Resulting sporozoites are released into the tick saliva via budding from the cell surface of infected salivary cells and are inoculated into the new host when the tick feeds. In the felid, inoculated sporozoites enter phagocytic mononuclear cells then, in the phagocyte, reproduce by schizogony and binary fission. Merozoites bud from schizonts to eventually fill and distend the host cell, then are released into blood or interstitial fluid. Free merozoites enter red blood cells by endocytosis then replicate into a variety of piroplasm forms, establishing parasitemia.

Infection can be transmitted experimentally by inoculation of cats with schizont-containing tissue or with blood collected during the acute phase of illness, when schizont-containing mononuclear cells may be circulating. Transfusion of blood from recovered cats transmits the piroplasm form and does not result in disease, which requires schizonogy, but does establish a persistent erythrocytic parasitemia.

## OCCURRENCE

In the United States, cytauxzoonosis occurs primarily in southeastern, south central and mid-Atlantic states, paralleling the distributions of the vector *Amblyomma americanum* and the primary reservoir host, the bobcat *Lynx rufus rufus*. In domestic cats, there is no evident age, sex or breed predisposition and likelihood of infection is not related to retroviral status. Disease is usually seen in outdoor or indoor/outdoor cats in wooded rural or suburban areas, presumably because of increased chance of exposure to ticks that have fed on an infected bobcat. Disease is highly seasonal and generally seen in the spring through summer months when the tick vector is most active, rarely occuring in the period from November to March.

## PATHOGENESIS

It is the schizont form of *C. felis,* residing intracellularly in phagocytic mononuclear cells, that is responsible for causing clinical illness. These parasitized cells become greatly enlarged and vascular obstruction by these large parasitized cells is believed to be the major pathophysiological mechanism of cytauxzoonosis. Occlusion of small venules and capillaries may occur in any tissue but is seen most dramatically in the lung, liver and spleen. Lymph nodes are also prominently affected. Vascular obstruction leads to hypoxic tissue injury and release of inflammatory cytokines and other damaging substances from cell death and rupture may precipitate systemic inflammatory response syndrome and, with endothelial disruption, promote DIC and multiple organ failure. Hemolysis triggered by presence of piroplasms in RBCs may be seen later in acute disease but contributes little to the pathogenesis of the disease: hemolysis resolves in cats that survive and hemolytic anemia is not noted in chronic carriers, which have persistent erythrocytic parasitemia.

## CLINICAL FINDINGS

Cytauxzoonosis in domestic cats is a severe acute febrile illness with a high mortality rate. Onset of clinical signs occurs 1-2 weeks after tick transmission. Initial signs are non-specific; often, owners report sudden onset of marked lethargy and anorexia in a previously healthy cat. The disease progresses in severity in hours to days and cats may show vocalization, weakness, icterus, respiratory distress, abnormal mentation and sometimes seizures. Fever ($103^0$-$107^0$F, often > $106^0$F ) is a consistent finding. Dehydration, pale or icteric mucous membranes, tachypnea, tachycardia and mild to moderate enlargement of lymph nodes, spleen and liver may be found on physical examination. The nictitating membrane is frequently bilaterally elevated and hyperemic. Many cats are reluctant to move and object to being touched as if they have generalized pain. Cats may become dyspneic, hypothermic and/or comatose in the terminal stages of the disease. The disease has a rapid course and many cats die within days of onset of clinical signs.

## LABORATORY AND IMAGING FINDINGS

Abnormalities in the CBC are common and include varying combinations of cytopenias: neutropenia (often profound) with toxic changes to neutrophils, lymphopenia, thrombocytopenia and, in later stages of disease, non-regenerative anemia which may become profound in the terminal phase of illness. Cell counts return to normal in cats that recover: chronically parasitemic carriers do not show chronic anemia despite having piroplasms evident in RBCs. Hyperbilirubinemia is commonly present on the serum chemistry profile. Elevations of ALP and ALT are less common and mild to moderate in severity. Hypoalbuminemia, usually mild, is common, especially later in the disease. Some cats show prolongation of aPTT and PT and DIC is considered to be a common complication of this illness. Splenomegaly, hepatomegaly and/or lymphadenomegaly may be evident on abdominal imaging studies. In cats with respiratory signs, thoracic radiographs commonly show a diffuse interstitial pulmonary pattern or, less commonly, an alveolar pattern and/or pleural effusion.

## DIAGNOSIS

Cytologic examination of blood smears or tissue aspirate samples is the most common method of diagnosis. Identification of piroplasms in RBCs confirms infection and compatible history and clinical findings support a diagnosis of acute disease (recovered carrier cats will also show this erythroparasitemia but clinical signs and other abnormalities are absent). Piroplasms are classically seen as 1-3 micrometer intraerythrocytic signet ring-shaped bodies with a thick round nuclear region at one end of the ring but several other shapes are also seen: safety-pin, tetrad and linear/comma shapes. Differentials for *C. felis* erythroparasitism include *Babesia*, other *Cytauxzoon* species, *Mycoplasma* spp.,

stain precipitate overlying RBCs and Howell-Jolly bodies (RBC nuclear remnants). Sequential examination of blood smears if piroplasms are not found in cats suspected to have cytauxzoonosis may yield positive results on subsequent days: level of parasitemia is low initially but increases as the disease progresses. Up to 50% of cats are negative for piroplasms at the onset of clinical disease. Identification of schizonts in mononuclear cells identifies acute disease (schizogony occurs in acute infections and is not present in recovered carriers). These schizont-laden phagocytes are commonly found in tissue aspirate samples of spleen, liver, lung, or lymph node but may also be seen on blood smears, often on the feathered edge of the smear. Schizonts form earlier in infection than piroplasms and therefore may be identified in infected cats that are piroplasm-negative. PCR assay of whole blood for detection of *C. felis* DNA provides the most sensitive test for cytauxzoonosis. PCR tests identify presence of infection and will be positive in chronic carriers as well as in acute disease. These assays are useful for screening cats for identification of potential carriers as well as diagnosis of acutely ill cats, although the time delay in obtaining a PCR test result limits the utility of the test in informing treatment choices for acutely ill cats suspected to have cytauxzoonosis. Likewise, serologic testing for antibodies to *C. felis* can identify previous infection in recovered cats but is not practical in confirming acute disease as cats may die prior to appearance of specific antibody.

At necropsy, enlarged edematous spleen, liver and lymph nodes and consolidated lungs are commonly identified and generalized icterus is frequently present. Marked venous distension, especially of abdominal veins, is often evident on gross examination. Pleural and pericardial effusion may be present and petechial and ecchymotic hemorrhages in various tissues and on serosal surfaces of organs may be seen in patients with DIC. Histologically, enlarged mononuclear cells distended by schizonts and merozoites are seen throughout tissues, especially the spleen, liver and lung, within tissue spaces or within venules and capillaries, causing partial or complete obstruction of vascular structures. Lymph nodes and bone marrow often show marked numbers of parasitized mononuclear cells. Tissues may show hypoxic changes secondary to vascular obstruction by parasitized cells.

TREATMENT

Treatment of cytauxzoonosis includes administration of antiprotozoal drugs and aggressive supportive care. The antiprotozoal therapy of choice is a combination of atovaquone (Mepron@ Glaxo-SmithKline) 15mg/kg q8h and azithromycin 10mg/kg q24h PO for 10 days which has shown a 50-60% survival rate versus the less effective imidocarb dipropionate (Imazol@ Schering-Plough) which showed a 25-26% survival rate. Imidocarb has been used at 2-5mg/kg IM q4-7 days for 2 doses but is generally considered to have poor efficacy in treating cytauxzoonosis. Diminazene aceturate, which is not available in the United States but can be requested through the FDA for importation for compassionate use, has shown efficacy in some reports but the delay inherent in acquiring this drug precludes practical use in treating acute cytauxzoonosis. Neither diaminazene nor imidocarb reduce or eliminate the erythrocytic form of *C. felis* and, with persistence of piroplasms, recovered cats may remain clinically normal yet serve as a source of infection for naive ticks. Treatment with atovaquone/azithromycin does not uniformly eliminate infection but does reduce parasitemia sufficiently that most treated cats are negative for piroplasms on blood smear examination and PCR.

Intensive supportive care with judicious use of IV fluids, RBC transfusion as needed during the hemolytic phase, management of DIC and enteral feeding through a nasoesophageal or esophageal feeding tube (cats are usually anorexic or hyporexic during acute illness and early recovery) is critical for optimizing outcomes. Pain may be addressed with buprenorphine; NSAIDs and glucocorticoids are less advisable agents for controlling pain and fever.

## PROGNOSIS

Most domestic cats infected with *C. felis* become critically ill and die. With intensive treatment, mortality rates may be reduced from nearly 100% to (at best) 40%. Treated cats that do not survive generally die within a day of initiating treatment. There are rare cases in which cats are found to be positive for *C. felis* piroplasms with no history of clinical illness or having recovered from a milder form of clinical disease. It is theorized that there may be less pathogenic strains of *C. felis* to explain the diminished impact of infection in these cats, which is supported by the findings that survival rates may regionally be higher than expected independent of treatment.

## PREVENTION

There is currently no vaccine available or under development. Prevention centers on avoiding tick bites by consistent use of acaricides (topical fipronil, flumethrin collars) and keeping cats in endemic areas indoors to reduce exposure. Recovered carrier cats should also be protected with acaricides and indoor confinement to reduce the risk of transmission of their infection to naive ticks. Treatment with atovaquone-azithromycin may also be beneficial in reducing transmission by reducing the parasitemia.