

**Cytauxzoon felis infection in cats in the mid-Atlantic states: 34 cases (1998–2004)**

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Cytauxzoon felis is associated with both a tissue (or schizogonous) phase and an intraerythrocystic phase that correlate with the clinical signs of severe circulatory impairment and hemolytic anemia, respectively. Typical clinical manifestations include signs of depression and lethargy, anorexia, fever, and jaundice. Cats often rapidly succumb to the disease, dying within < 1 week from initial onset of clinical signs. However, some cats survive infection with C felis and, after clinical recovery, may remain nonclinical carriers for months to years.

Initial diagnosis can be made by microscopic visualization of round signet ring–like piroplasms within erythrocytes or schizont-laden macrophages in tissue aspirates, impression specimens, or peripheral blood smears. Because the tissue phase occurs prior to the erythrocytic phase, some cats can be severely ill but not have detectable parasites in their RBCs. The diagnosis can also be confirmed by characteristic histopathologic findings following necropsy. The pathophysiology of feline cytauxzoonosis mainly involves occlusion of small vessels with large histiocytic, schizont-filled macrophages in the lungs, spleen, and liver.

Originally reported in domestic cats from southwestern Missouri in 1976, cytauxzoonosis has since been reported in many of the south central and southeastern states. To the authors’ knowledge, there are no previously published reports of C felis infection in the mid-Atlantic region of the United States. Prior to 1998, the NCSU-VBDDL had not diagnosed C felis infection in cats or had consultations requested in relation to cytauxzoonosis in cats in North Carolina. Over the past several years, the NCSU-VBDDL has consulted with increasing numbers of veterinarians or owners regarding C felis infections in cats in North Carolina, Virginia, and South Carolina. Consequently, the purpose of the study reported here was to describe the demographic and clinical characteristics of cytauxzoonosis in cats in the mid-Atlantic states and compare the C felis 18S rRNA gene sequences from affected cats with sequences reported from affected cats in other regions of the United States.

**Criteria for Selection of Cases**

Medical records of C felis–infected cats that were identified by either the NCSU-VBDDL or by state animal-disease diagnostic laboratories located in Virginia, North Carolina, and South Carolina from May 1998 through June 2004 were reviewed. For a cat to be included in the study, the following eligibility criteria had to be met:

1. The cat was domestic or pet and not a bobcat or wild cat species
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**Objective**—To describe the demographic and clinical characteristics of feline cytauxzoonosis in the mid-Atlantic states and compare the Cytauxzoon felis 18S rRNA gene sequences from affected cats with sequences reported from affected cats in other regions.

**Design**—Retrospective case series.

**Animals**—34 cats with C felis infection.

**Procedure**—Medical records of cats in which C felis infection was diagnosed from May 1998 through June 2004 were reviewed; data collected included signalment, month of diagnosis, geographic location, clinicopathologic abnormalities, medical treatments, outcome, and necropsy findings when applicable. Cytauxzoon felis DNA was amplified, cloned, and sequenced from 4 of these cats and compared with previously reported C felis DNA sequences.

**Results**—Of 34 C felis–infected cats, 28 resided in North Carolina, 3 resided in South Carolina, and 3 resided in Virginia; in 32 cats, a diagnosis of C felis infection was made in April through September. Pancytopenia and icterus were the most common clinicopathologic abnormalities. Thirty-two cats either died or were euthanatized, and 2 cats survived. At 5 veterinary hospitals, multiple cases were identified, and 4 multicat households had > 1 cat infected with C felis. The 18S rRNA gene sequences characterized in organisms obtained from 4 cats were nearly identical to C felis DNA sequences reported from other US regions.

**Conclusions and Clinical Relevance**—Data indicate that veterinarians in the mid-Atlantic region of the United States should consider C felis infection in cats that become ill with fever, icterus, and pancytopenia or bicytopenia, especially in the spring and summer months. (J Am Vet Med Assoc 2006;228:568–571)

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Cytauxzoonosis is a protozoal disease of cats that is caused by *Cytauxzoon felis*. The organism is believed to be transmitted from bobcats, the primary reservoir host, to domestic cats via a tick vector. Because of the typical induction of a rapidly fatal illness, the domestic cat has been considered an accidental, dead-end host for this infectious agent. The typical clinical manifestation of feline cytauxzoonosis mainly involves occlusion of small vessels with large histiocytic, schizont-filled macrophages in the lungs, spleen, and liver.

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included in the study; detection of either schizonts within macrophages or merozoites within erythrocytes was required on examination of tissues or of a blood smear. It should be noted that without molecular testing, \textit{C. felis} cannot be definitively distinguished from \textit{Babesia felis} when only the intraerythrocytic phase of the organism is identified. However, \textit{B. felis} has never been identified in the United States and that organism was considered unlikely to be the cause of illness in these cats.

**Procedures**

For each cat that met the entry criterion, the following information was reviewed when available: signalment, month of diagnosis, geographic location, clinicopathologic abnormalities, medical treatments, outcome (survival vs nonsurvival), and necropsy findings when applicable.

Whole-blood samples were available for \textit{C. felis} 18S rRNA gene amplification and sequencing from 4 cats that died or were euthanatized as a result of a \textit{C. felis} infection and 1 \textit{C. felis}–infected cat that survived; the latter was evaluated via PCR assay 2 years after recovery from infection. The DNA was extracted from the whole-blood samples by use of a commercial kit, according to the manufacturer’s instructions. Amplification of the nearly full-length 18S rRNA genes was performed as previously described with minor modifications. In brief, each 50-µL reaction contained 1× PCR buffer II, 1.25 units of \textit{Taq} polymerase, 3 µL of DNA template, 1.5 mM MgCl₂, 25 pmol of each primer, and 200 µM each dNTP. Cycling conditions were 95°C for 5 minutes, followed by 50 amplification cycles (95°C for 1 minute, 55°C for 1 minute, and 72°C for 1.5 minutes), and a final extension step at 72°C for 5 minutes. To prevent PCR amplicon contamination, sample preparation, reaction setup, PCR amplification, and amplicon detection were all performed in separate areas. A positive control sample (blood obtained from a \textit{C. felis}–infected cat) and negative control samples (blood obtained from noninfected cat and sterile water) were used in all processing steps, including the DNA extraction. After electrophoresis in a 1% agarose gel containing ethidium bromide (0.1 µg/mL), all PCR products were detected by transillumination with a UV light.

The PCR products were cloned into a plasmid vector and \textit{Escherichia coli} was transformed following the protocol of the supplier. For each sample, at least 3 recombinants were selected on the basis of the blue-white color of colonies. Plasmid DNA from each clone was isolated with the plasmid DNA isolation kit according to the manufacturer’s instructions. Recombinant plasmid DNA was sequenced bidirectionally with infrared fluorescent-labeled primers by use of an automated DNA sequencer. Sequencing reactions were set up following the manufacturer’s protocol. The sequencing reaction conditions consisted of an initial denaturation of 2 minutes at 92°C, followed by 40 sequencing cycles (15 seconds at 92°C, 15 seconds at 54°C, and 15 seconds at 72°C), and a hold stage at 9°C on a thermal cycler. The DNA sequences generated in this study were aligned and compared with known \textit{C. felis} 18S ribosomal DNA sequences (GenBank accession Nos. L19080 and AF399930) by use of a computer program.

**Results**

Medical records of 34 cats with cytauxzoonosis were identified, and all met the entry criterion. \textit{Cyttauxzoon felis} infection was diagnosed histologically or cytologically through identification of schizonts within macrophages and merozoites within erythrocytes in 23 cats; the diagnosis was made on the basis of detection of merozoites within erythrocytes in the remaining 11 cats. Twenty-eight cats were from North Carolina, 3 were from South Carolina, and 3 were from Virginia (Figure 1). Interestingly, 5 veterinary clinics were responsible for the diagnosis of cytauxzoonosis in 18 cats. In addition, 4 multicat households had 2 cats each in which cytauxzoonosis was diagnosed. Of the 31 cats for which age was reported, the mean age was 4 years (age range, 2 months to 14 years). Fourteen cats were sexually intact males, 10 were sexually intact females, 6 were neutered males, and 1 was a spayed female; the sex of 3 cats was not reported. In 11 of the 34 medical records, it was noted that those cats had access to outdoor areas; in each of the remaining records, there was no entry regarding the cat’s environment. There was a notation in the records about tick attachment at the time of diagnosis for only 2 cats, and 1 other cat had a history of tick attachment noted 2 years prior to diagnosis. Infection with \textit{C. felis} was diagnosed in 32 of the 34 (94%) cats in the months of April through September (Figure 2).

Laboratory data from initial evaluations were available for 12 cats, although not all variables were assessed in all cats. The mean ± SD Hct for 11 cats was 24 ± 5.9% (reference range, 31% to 50%). The mean WBC count for 11 cats was 3,900 ± 2,600 cells/µL (reference range, 5,400 to 23,600 cells/µL). Results of platelet counts were

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Figure 1—Geographic location of 34 cats infected with \textit{Cyttauxzoon felis} in the mid-Atlantic region of the United States. Affected cats were identified either by the NCSU-VBDDL or by state animal disease diagnostic laboratories located in Virginia, North Carolina, and South Carolina from May 1998 through June 2004. The location of each \textit{C. felis}–infected cat is identified by a dot.
The most common finding was large schizont-laden macrophages located within the lumens of small vessels. These infected macrophages were most commonly identified in the liver (18/19 cats), pulmonary vasculature (16/19), spleen (14/19), kidneys (13/19), and pulmonary parenchyma (11/19).

Nearly full-length (approx 1.7 kilobases) C felis 18S rRNA genes were amplified from whole-blood samples collected from 4 cats that either died or were euthanatized. No 18S rRNA amplicons were detected in the blood sample collected from a cat that survived infection. Amplicons were not detected in the negative control samples. The C felis 18S rRNA gene sequences from cats residing in the mid-Atlantic states were ≤ 99.9% homologous to sequences reported for cats that died as a result of C felis infection and cats that survived C felis infection (GenBank accession Nos. L19080 and AF399930, respectively).

Discussion

To the authors’ knowledge, the present study involved the largest case series of naturally infected cats reported to date and brings to light some findings that are important for veterinary practitioners. First, these C felis–infected cats all resided in the mid-Atlantic states, a region in which C felis infections in cats had not been previously reported. Therefore, clinicians in these regions have not frequently included the disease as a differential diagnosis for cats with a sudden onset of lethargy, fever, and jaundice. It is not clear whether these cases represent changes in the distribution, prevalence, or transmission of C felis in the mid-Atlantic states or whether there is increased recognition of cytauxzoonosis by veterinary clinicians and diagnosticians. The large number of cases reported by only 5 clinics suggests that familiarity with the clinical signs of the disease may contribute to enhanced recognition and diagnosis of cytauxzoonosis. Alternatively, there may be hyperendemic foci of C felis transmission as evidenced by the detection of infection in more than 1 cat in multicat households. There is potential support in the literature for possible hyperendemic foci of C felis in regions in which cytauxzoonosis is known to be endemic. The earliest report of C felis infection included 2 cats from households in which several cats were presumed to have died as a result of cytauxzoonosis. Since that report, there have been at least 2 other publications2,10 in which several cats from the same household or same geographic location were reported to have C felis infections. In addition, to enhance awareness of C felis transmission, findings of the present study highlight several other helpful indicators of cytauxzoonosis, including signalment (young male cats), outdoor lifestyle with presumed exposure to ticks, and a history of sudden onset of illness generally consisting of fever and jaundice. The seasonal distribution of disease onset identified in our study (the diagnosis was made in nearly all of the cats from late spring to early fall) is associated with the activity of most tick species in the mid-Atlantic region, including Dermacentor variabilis. It is of interest that ticks were detected on only 2 cats at the time of examination. This may reflect failure to examine cats carefully for tick
infestation, failure to record the detection of ticks in the medical records, rapid removal of ticks by the grooming behavior of cats, or an alternative means of disease transmission.

The clinicopathologic findings in these cats were similar to those described for *C. felis*–infected cats in other regions of the United States in that pancytopenia and hyperbilirubinemia were the most common hemato-
logic and serum biochemical abnormalities. In the present study, most of the cats died or were euthanatized; only 2 *C. felis*–infected cats survived, and no particular treatments appeared to influence outcome. The outcomes for these 2 cats along with an increased number of reports of cats surviving *C. felis* infection go against the longstanding dogma that the disease is always fatal in domestic cats. Although the prognosis is grave, aggressive treatment of affected cats is an option that can be considered and offered to clients as an alternative to euthanasia. Treatment of cytauxzoonosis generally consists of supportive care involving IV fluid therapy and administration of antimicrobials (presumably to prevent development of septicemia) and heparin (to prevent thrombus formation and development of disseminated intravascular coagulation). Because most of the pathologic changes associated with cytauxzoonosis are associated with the occlusion of small blood vessels, some clinicians have speculated that aggressive supportive care, including fluid therapy and treatment with heparin, may be important therapeutic interventions. An early diagnosis of the schizogenous phase of infection may prompt clinicians to begin aggressive treatment. When parasites are not detected in blood smears, early diagnosis can be best achieved via cytologic examination of fine-needle aspirate specimens collected from organs such as the liver, spleen, or lungs. The high percentage of parasites identified histologically in these organs suggests that sample collection from these sites is the most appropriate for organism identification. The use of antipiroplasm drugs, such as imidocarb diprophionate and diminazene aceturate for the treatment of cats with *C. felis* infection, remains somewhat controversial because their effect on patient survival is questionable and these drugs are not approved by the FDA for use in cats. Further investigation of the use of antipiroplasm agents for the treatment of cytauxzoonosis in cats is warranted.

On the basis of 18S rRNA gene sequences derived as a component of the present study, the *C. felis* organisms responsible for deaths among cats in the mid-Atlantic region are not genetically distinct from the other North American *C. felis* strains that have been sequenced. It is important to note that in some instances, rRNA gene analyses are not able to differentiate closely related species, subspecies, or strains. The possibility remains that more virulent strains of *C. felis* exist, but their discrimination may require sequencing of more variable genes or the use of more sensitive discriminatory techniques such as genetic fingerprinting.

Findings of the study reported here indicate that the mid-Atlantic region of the United States is a location in which *C. felis* is endemic. Therefore, clinicians in this region should consider *C. felis* infection in cats that die suddenly or are examined because of sudden onset of fever, lethargy, pancytopenia, neutropenia, thrombocytopenia, or icterus. Particular vigilance is indicated if a practice is located in a region in which *C. felis* infection has been diagnosed previously in cats. Because there is no consistently effective treatment of *C. felis*–infected cats, prevention remains one of the most important aspects of disease control. Prevention of cytauxzoonosis should include keeping cats indoors, routine application of acaricides approved for use in cats, and daily removal of ticks from cats that have outdoor access.

References