Anaplasma phagocytophilum
infection of domestic cats: 16 cases from the northeastern USA

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Abstract

Objectives Anaplasma phagocytophilum is an Ixodes species-transmitted rickettsial organism that is occasionally associated with clinical abnormalities in humans, ruminants, horses, dogs and cats. While serological evidence of A phagocytophilum exposure is common in cats in Ixodes species endemic areas, reports of clinical feline anaplasmosis are few. The objective of this study was to describe the clinical and laboratory abnormalities and treatment responses in 16 cats with A phagocytophilum DNA amplified from blood.

Methods Commercial laboratory electronic records were searched to find cats that had A phagocytophilum DNA amplified from their blood. Once cases were identified, the primary care veterinarian was interviewed and the medical records were reviewed.

Results The cats ranged in age from 4 months to 13 years (mean 4.1 years, median 2 years). All cats lived in Ixodes scapularis endemic areas and had potential for exposure. All cats were lethargic, 15 (94%) had elevated body temperature (>39.4°C) and 14 were anorexic on initial physical examination. Other less common clinical findings included hepatosplenomegaly, ataxia, conjunctivitis and elevation of the nictitating membranes. Blood from 11 cats was evaluated by complete blood cell count; abnormalities included lymphopenia in seven (64%) cats, thrombocytopenia in seven (64%), morulae in neutrophils of three (27%), neutropenia in three (27%) and leukopenia in two (18%). Treatment responses were reported for 14 cats, and the clinical abnormalities in these cats resolved when doxycycline was administered.

Conclusions and relevance This is the first published report describing A phagocytophilum morulae in neutrophils of naturally infected North American cats with infection confirmed by PCR. A phagocytophilum infection should be considered in cats evaluated for lethargy, anorexia and fever living in Ixodes species endemic areas.

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Introduction

Anaplasma phagocytophilum is a rickettsial organism that causes granulocytic anaplasmosis in cats, dogs, horses, ruminants and humans. The organism was first described in 1932 in Scottish sheep,¹ and then reported to affect horses, dogs, cats, cattle, camelids and humans. The worldwide distribution of A phagocytophilum follows the geographic distribution of the primary vector, Ixodes species.² In North America, the organism is transmitted by Ixodes scapularis in the Northeast and Midwest, and by Ixodes pacificus in the West.³ Infections are highest in the late spring and autumn when both nymph and adult ticks are most mobile.⁴ Transmission to mammals occurs within 24–48 h of tick attachment.⁵,⁶
Once transmitted, *A phagocytophilum* infects neutrophils forming intracellular inclusions (morulae), which can be observed via light microscopy on a Romanowsky or Wright-Giemsa-stained blood smear. In North America, morulae have been identified in the neutrophils of naturally exposed dogs, horses, humans and experimentally infected cats. In Europe, morulae of *A phagocytophilum* have been described in ruminants, cats, horses and dogs. There are multiple papers describing anaplasmosis in dogs. The first reports of granulocytic anaplasmosis in naturally infected cats primarily reported non-specific clinical signs of lethargy, anorexia, fever and dehydration. Clinicopathologic abnormalities in infected cats often include neutrophilia, lymphopenia and hyperglycemia with or without thrombocytopenia. Diagnosis of *A phagocytophilum* can be made based on clinical suspicion, a history of exposure to *Ixodes* species, identification of morulae within neutrophils, positive serologic results, PCR results and response to treatment. Naturally infected cats produce serologic antibodies to *A phagocytophilum* and in the acute phase of infection may form morula inclusions in neutrophils identifiable on a blood smear. There are 20 reported cases identifying morulae in naturally infected cats in Europe: 15 cats in Italy, two cats in Poland and one cat each in Sweden, Switzerland and Finland. To date, only five naturally infected cats with *A phagocytophilum* have been described in North America.

The objectives of this study were to collect retrospectively and describe the clinical and historical findings in cats that were positive by PCR for *A phagocytophilum* DNA in their blood, and to describe treatment and response. We were also able to characterize intracellular morulae identified in neutrophils on microscopic examination of peripheral blood smears.

**Materials and methods**

Cats that had *A phagocytophilum* DNA amplified from a blood sample assayed by the laboratory (Antech Diagnostics, Lake Success, NY, USA) between May 2009 and May 2011 were identified by an electronic record search. The laboratory uses EDTA-anticoagulated blood samples to attempt to amplify DNA of *A phagocytophilum*, *Bartonella henselae*, *Bartonella clarridgeiae*, *Bartonella quintana*, *Ehrlichia* species, *Mycoplasma haemofelis*, *Candidatus Mycoplasma haemominutum*, *Candidatus Mycoplasma turicensis*, *Rickettsia rickettsii* and *Rickettsia felis* using a proprietary PCR assay (FastPanel) with the standard operating procedures of the laboratory. The main Genbank sequence identification used for the proprietary primer design for *A phagocytophilum* was gb CP006618.1. The sensitivity of the multiplex primer systems was analyzed using titrated, synthesized DNA sequences in bacterial plasmids. These synthetic targets contained exact sequence matches to the primer sequences at the exact sequence distances found in the intended reference target sequences. An internal validation study was performed and assays were determined to be sensitive to 20 copies of their synthetic DNA targets.

The attending veterinarians were then contacted by telephone to obtain clinical information from the case records. Data abstracted from the medical record included history (duration of signs, outdoor activity, tick exposure, use of acaricides and geographic location), physical examination findings, clinicopathologic data, date of the PCR test, diagnostic imaging at the time of diagnosis, treatments administered and response to treatment. Clinicopathologic data came from multiple diagnostic laboratories. Numerical data were evaluated using manually calculated standard descriptive statistics (range, mean, frequency).

**Results**

Between May 2009 and May 2011, 4334 blood samples from cats were submitted for PCR testing at the commercial laboratory. *A phagocytophilum* DNA was amplified from the blood of 40 (0.92%) samples. Historical and clinical data were available for 16 cats.

Of the 16 cats, six were spayed females, nine were neutered males and one was an intact male. The median age of the cats was 2 years (mean 4.1 years; range 4 months to 13 years). All cats had access to the outdoors and resided in areas considered endemic for *Ixodes* species. Of the 16 cats, four had been prescribed fipronil (Frontline and Frontline Plus; Merial) and two had been prescribed selamectin (Revolution; Zoetis).

The cats resided in Connecticut (n = 7), New Jersey (n = 3), New York (n = 3), Massachusetts (n = 2) and Vermont (n = 1). The month of diagnosis was June (five cats), May and October (three cats each) and one cat each in April, July, August, September and November. Duration of clinical signs prior to presentation to a veterinarian was reported for five cats (median 2 days; mean 2.8 days; range 1–7 days). Four cats were presented more than once to a veterinarian prior to diagnosis of *A phagocytophilum* infection and initiation of specific treatment. Lethargy (16 cats) and elevated body temperature (15 cats) were the most common abnormalities reported the day the blood sample was collected for performance of the PCR assay (Table 1). The body temperatures for the 15 febrile cats ranged from 39.6–41.5°C, with a mean of 40.3°C.

Of the 16 cats, only one was concurrently positive for DNA of other agents (*M haemominutum* and *B clar-ridgeiae*). Results of a complete blood count and serum biochemical panel were available for 11 cats, performed on or immediately before the day the PCR assay was submitted. Abnormalities are listed in Table 2. These 11 cats often included neutrophilia, lymphopenia and hyperglycemia with or without thrombocytopenia. Diagnosis of *A phagocytophilum* can be made based on clinical suspicion, a history of exposure to *Ixodes* species, identification of morulae within neutrophils, positive serologic results, PCR results and response to treatment. Naturally infected cats produce serologic antibodies to *A phagocytophilum* and in the acute phase of infection may form morula inclusions in neutrophils identifiable on a blood smear. There are 20 reported cases identifying morulae in naturally infected cats in Europe: 15 cats in Italy, two cats in Poland and one cat each in Sweden, Switzerland and Finland. To date, only five naturally infected cats with *A phagocytophilum* have been described in North America.

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cases had blood smears reviewed by medical technicians and some were additionally reviewed by a board-certified veterinary clinical pathologist (PE). In three cases, cytoplasmic inclusions were identified in 5–20% of neutrophils. The inclusions were basophilic and intracytoplasmic with a coarsely granular texture ranging in size from 1–2 µm (Figure 1), consistent with morulae of *Ehrlichia* species or *Anaplasma* species. As the inclusions were not seen in other leukocytes, it was concluded they were most likely those of *A. phagocytophilum*, which was confirmed by PCR assay. The three cats with morula identified were all hyperthermic. One had a body temperature above the mean (41°C), while the other two had lower body temperatures at 39.8°C and 40.2°C at the time of examination. Urinalyses were performed in four cases and proteinuria was identified by dipstick in two cases; quantitative results are not available.

Treatment information was available for 15 cats. An antibiotic other than doxycycline (enrofloxacin, clindamycin, amoxicillin with clavulanic acid or ampicillin) was administered to eight cats prior to amplification of *A. phagocytophilum* DNA from blood; for two cats more than one antibiotic was used. Once PCR assay results confirming the presence of *A. phagocytophilum* DNA were available, all 15 cats were administered doxycycline orally. Dosing information was available in four cats (5 mg/kg PO, once or twice daily). Clinical abnormalities resolved after initiating doxycycline therapy in the 14 cats with a known response to treatment. The duration of doxycycline administration varied from 21–45 days, with most cats treated for 21 days.

Table 1  Clinical abnormalities reported for 16 cats the day blood was submitted and proven to contain *Anaplasma phagocytophilum* DNA

<table>
<thead>
<tr>
<th>Clinical abnormalities</th>
<th>Number of cats (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Fever</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14 (88)</td>
</tr>
<tr>
<td>Ocular signs (bilateral ocular discharge, elevated nictitating membranes, mild conjunctivitis)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Table 2  Clinicopathologic abnormalities in cats infected with *Anaplasma phagocytophilum*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Median*</th>
<th>Value or range</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC (×10^9/l)</td>
<td>1</td>
<td>NA</td>
<td>2.3</td>
<td>3.5–16.0</td>
</tr>
<tr>
<td>RBC (×10^12/l)</td>
<td>2</td>
<td>NA</td>
<td>5.88–10.23</td>
<td>5.92–9.93</td>
</tr>
<tr>
<td>Hematocrit (l/l)</td>
<td>2</td>
<td>NA</td>
<td>0.186–0.245 (18.6–24.5%)</td>
<td>0.29–0.48 (29–48)</td>
</tr>
<tr>
<td>Platelets (×10^9/l)†</td>
<td>7</td>
<td>120</td>
<td>68–187</td>
<td>200–500</td>
</tr>
<tr>
<td>Neutrophils, PMNs (×10^9/l)</td>
<td>2</td>
<td>NA</td>
<td>1600–2430</td>
<td>2500–8500</td>
</tr>
<tr>
<td>Lymphocytes (×10^9/l)</td>
<td>6</td>
<td>498</td>
<td>86–936</td>
<td>1200–8000</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>2</td>
<td>NA</td>
<td>10.3–15.6 (186–281 mg/dl)</td>
<td>3.5–9.4 (64–170)</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>1</td>
<td>NA</td>
<td>144</td>
<td>145–158</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>1</td>
<td>NA</td>
<td>10.09 (390 mg/dl)</td>
<td>1.94–5.69 (75–220)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>1</td>
<td>NA</td>
<td>9.28 (13 mg/dl)</td>
<td>10.0–25.7 (14–36)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>1</td>
<td>NA</td>
<td>40 (4.0 g/dl)</td>
<td>25–39 (2.5–3.9)</td>
</tr>
</tbody>
</table>

* *A median was not able to be generated when fewer than three animals had the abnormality
† Platelet clumping precluded an accurate determination of a platelet count in all seven cats. Five of the seven cats were estimated to have adequate platelets.

WBC = white blood cells; RBC = red blood cells; PMN = polymorphonuclear neutrophil; NA = not available
including subcutaneous or intravenous crystalloid fluids (seven cats), histamine-2 receptor blocker (famotidine; two cats), appetite stimulant (mirtazapine; one cat) and/or analgesics (buprenorphine and oxymorphone; two cats).

**Discussion**

Cats in endemic areas are commonly exposed to *A phagocytophilum* based on antibody prevalence rates. For example, in Connecticut, antibodies against *A phagocytophilum* were detected in 38% of 93 feline sera tested by enzyme-linked immunosorbent assay (ELISA). A survey of different areas of the USA showed a prevalence ranging from 0–13.0%, with an overall prevalence of 4.3%. Lastly, antibody prevalence rates in healthy cats and cats with clinical signs (fever, lethargy, inappetance) living in Maine were 3.6% and 15.4%, respectively. The study described here is the largest *A phagocytophilum* molecular study from feline blood samples reported to date. In contrast to the above-reported prevalence rates, the prevalence rate of 0.92% in this study (40/4339 cats) is lower. The prevalence reported here likely underestimates the true prevalence rate in specific regions and populations of cats. The samples were submitted for a commercial PCR assay and included samples from all regions of the USA, not exclusively *Ixodes* species endemic areas. Some veterinarians may have submitted the PCR assay for reasons not specific to *A phagocytophilum*. The test may have been performed to screen healthy cats as blood donors or to test cats with clinical syndromes not likely to be induced by *A phagocytophilum*. All 16 of the cats identified in this study were positive for *A phagocytophilum* DNA in blood, were from an endemic area, had potential exposure to *Ixodes* species, and the majority had clinical and laboratory evidence of anaplasmosis, as well as apparent responses to doxycycline. Only one cat had molecular evidence of other infectious agents that may have responded to tetracyclines. Thus, we believe that anaplasmosis was the likely diagnosis for these cats. However, the major limitations to the study include the variability in the diagnostic workup, the lack of clinicopathologic data from all cats and differences in clinical management amongst cases. As the study was retrospective, information regarding *A phagocytophilum* titers or resolution of laboratory abnormalities after treatment could not be determined.

To date, cats with suspected anaplasmosis in the USA have only been described in the Northeast. In contrast, granulocytic anaplasmosis in dogs and humans have been reported in the Midwest, West and Northeast. Causes of this inconsistency in geographic distribution between cats and dogs/humans may include insufficient data, differences in the genetic strains that infect these species and the range of the organism that affects different species. The seasonal distribution of feline infections mimics that seen in other species, with the greatest incidence in the late spring and early autumn. This coincides with the greatest nymphal and adult tick activity.

The primary clinical abnormalities of lethargy, elevated body temperature and anorexia are consistent with those found commonly in other infected cats, dogs and humans. Whether the other reported abnormalities presented in Table 1 are related to *A phagocytophilum* infection is unknown and could not be ascertained in this retrospective study. The ocular changes reported were non-specific and likely the result of systemic inflammation. Abdominal discomfort was reported in 4/16 cats but the cause was not determined. Radiographic hepatosplenomegaly was found in one cat in this study but as hepatic and splenic aspirates were not performed the cause is not known.

With the exception of identifying intracytoplasmic morulae within neutrophils, the clinicopathologic abnormalities are non-specific for infection with *A phagocytophilum*. In this study, anemia was identified in two cats. The cat with the lowest hematocrit (0.186 l/l, 18.6%) was a 4-month-old kitten. As kittens normally have a lower hematocrit than adult cats, the anemia in this case was not as severe as would be expected if present in an adult cat. Anemia has only been described in one other report of cats infected with *A phagocytophilum*. Lymphopenia has been previously identified and in this report was seen in six (55%) cats. Although thrombocytopenia was reported in 7/11 cases, all seven samples had clumped platelets, which falsely decreases the automated platelet counts. The absence of confirmed thrombocytopenia in this study is inconsistent with previous reports where 3/5 cats were reportedly thrombocytopenic; however, one of the three samples had clumped platelets. A more recent report of *A phagocytophilum* infection in three cats in Poland described thrombocytopenia in all three, though no evaluation of platelet clumping was performed. Though thrombocytopenia is a commonly reported finding of *A phagocytophilum* infection in dogs, it may not be as common in cats. Automated platelet counts can falsely lower platelet counts owing to the tendency of feline platelets to aggregate in vitro; therefore, more studies are needed to determine if a true thrombocytopenia exists and how frequently this abnormality occurs. Mild hyperglycemia was identified in two cats and attributed to a normal physiologic stress response. Other mild and non-specific serum biochemical changes were only seen in one cat each, the consequences of which cannot be elucidated based on these few abnormalities.

Morulae were identified in neutrophils in 3/11 (27%) cases in this report, with inclusions in approximately 4–20% of neutrophils. Identification of these inclusions prompted submission of blood for the commercial PCR.
test, confirming the diagnosis of *A. phagocytophilum* infection. Morulae appear as basophilic intracytoplasmic inclusions that must be carefully differentiated from Döhle bodies. Morulae have been described repeatedly in dogs, horses, sheep and other ruminants. European cats and specific pathogen-free cats infected with wild-caught *I. scapularis*. But, to our knowledge, this is the first report of intracellular morulae being seen in the neutrophils in naturally infected North American cats. The identification of morulae demonstrates the importance of manual examination of a blood smear from any patient where granulocytic anaplasmosis is considered a differential diagnosis.

Co-exposure with *B. burgdorferi* and *A. phagocytophilum* occurs in dogs, horses, cats, humans and wildlife as both agents have the same vector and can share mammalian hosts. Different prevalences of co-exposure in cats have been reported in different geographical areas. In one study in Connecticut, 16% of cats had evidence of co-exposure to *B. burgdorferi* and *A. phagocytophilum*, whereas in a study in Maine, 5.1% of ill cats and 2.4% of healthy cats had exposure to both infectious agents. The clinical impact of co-exposure or co-infection with *B. burgdorferi* and *A. phagocytophilum* is unknown in cats. In this study, as specific testing was not performed, we could not determine whether *B. burgdorferi* infection contributed to the clinical disease in the cats described.

As previously discussed, only one cat in this study had proven coinfections (*B. clarridgeiae* and *Candidatus M. haemominutum*). This cat was not anemic, and as hemoplasmas do not always cause clinical illness, the effects of these co-infections is unknown.

As a retrospective study, there was variability in the treatment of each case. Fifteen of the 16 cats were treated with doxycycline once an infection with *A. phagocytophilum* was identified. Where a dose was recorded, cats received 5 mg/kg q12h. The duration of treatment with doxycycline was variable (21–45 days) and clinician dependent. As a retrospective study it is a limitation that an explanation for the duration of treatment is unknown. The majority of cats were treated for 21 days; those that were treated for 45 days were all seen at the same practice. Previous reports in cats have recommended treatment with 5 mg/kg doxycycline PO q12h for 28 days. The ideal duration of treatment with doxycycline in cats is unknown and warrants additional study. One cat received enrofloxacin prior to testing. The cat initially improved with treatment, but had recurrence of clinical signs and tested positive, demonstrating the importance of identification of this infection and appropriate treatment. All other non-tetracycline antibiotics were administered after sample collection while awaiting test results. Owing to the retrospective nature of this study it is unknown if cats responded to non-tetracycline treatment prior to the availability of results. When response to treatment with doxycycline is recorded, all responded without recurrence of clinical signs.

Information regarding persistent or recurrent infections in cats is not available from this study. Persistent infections have been described in dogs, horses and sheep where experimentally induced clinical disease was acute and self-resolving with persistent yet cyclical non-clinical bacteremia. Studies are needed to determine if feline anaplasmosis is a self-resolving disease and to determine if clinical persistent infections occur.

In this report all the cats were in *Ixodes* species endemic areas with outdoor access. Routine use of tick preventative in dogs can reduce the incidence of *A. phagocytophilum* transmission. Six cases in this report had a history of parasiticide application; however, the last date of product application is unknown. Based on this information, cats living in an *Ixodes* species area with exposure to *Ixodes* species might benefit from monthly treatment with an effective and safe parasiticide.

It is unknown if recurrent infections occur in cats and the most appropriate duration of doxycycline treatment in cats for treating anaplasmosis is still to be elucidated. Other reports have shown feline exposure to *A. phagocytophilum* without known clinical disease; additional studies are needed to identify how common subclinical infections occur. To date, all cats in the USA with clinical disease have been reported in the Northeast, despite the fact that *A. phagocytophilum* is also present in the Midwest and West. Studies evaluating feline infection of different strains or geographical variants of *A. phagocytophilum* are needed to determine if one strain is more successful at infecting cats than others and which strains cause clinical disease.

**Conclusions**

*A. phagocytophilum* infection should be included on a differential diagnoses list for any cat that lives in an *Ixodes* species endemic area with potential tick exposure and presents with acute or intermittent, vague symptoms of lethargy, fever and anorexia. *A. phagocytophilum* infection can be identified by documenting DNA in peripheral blood by PCR prior to antibiotic administration or by identifying morulae within neutrophils on a direct blood smear examination. Exposure can be documented by demonstrating the presence of antibodies with ELISA and indirect fluorescent antibody serology; a fourfold change in convalescent titers after 14 days indicates an active infection. Treatment without signs of recurrence has been successful with tetracyclines.

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