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CLINICAL REVIEW

CYTAUXZOONOSIS IN CATS
ABCD guidelines on prevention and management

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Overview: *Cytauxzoon* species are apicomplexan haemoparasites, which may cause severe disease in domestic cats, as well as lions and tigers. For many years, cytauxzoonosis in domestic cats was only reported in North and South America, but in recent years the infection has also been seen in Europe (Spain, France and Italy).
Infection: *Cytauxzoon felis* is the main species; it occurs as numerous different strains or genotypes and is transmitted via ticks. Therefore, the disease shows a seasonal incidence from spring to early autumn and affects primarily cats with outdoor access in areas where tick vectors are prevalent. Domestic cats may experience subclinical infection and may also act as reservoirs.
Clinical signs: Cytauxzoonosis caused by *C felis* in the USA is an acute or peracute severe febrile disease with non-specific signs. Haemolytic anaemia occurs frequently; in some cats neurological signs may occur in late stages. The *Cytauxzoon* species identified in Europe differ from *C felis* that causes disease in the USA and are probably less virulent. The majority of infected cats have been healthy; in some cases anaemia was found, but disease as it occurs in the USA has not been reported to date.
Diagnosis: Diagnosis is usually obtained by *Cytauxzoon* detection in blood smears and/or fine-needle aspirates from the liver, spleen and lymph nodes. PCR assays are able to detect low levels of parasitaemia and may be used for confirmation.
Treatment: Currently a combination of the antiprotozoal drugs atovaquone and azithromycin is the treatment of choice. Concurrent supportive and critical care treatment is extremely important to improve the prognosis. Cats that survive the infection may become chronic carriers for life.
Prevention: Cats with outdoor access in endemic areas should receive effective tick treatment.

Introduction

Cytauxzoonosis has been documented in wild felids such as bobcats, Florida panthers and Texas cougars. The first cases in domestic cats were documented in 1976.[1] For many years, cytauxzoonosis in domestic cats was only reported in North America (south eastern and central states and mid-Atlantic regions) and South America, but in recent years the infection has also been documented in Europe.

Agent properties

Cytauxzoon species are apicomplexan haemoparasites (family *Theileriidae*) of wild and domestic cats, which are transmitted by ticks. Several species have been identified. *Cytauxzoon felis* is the main species, with numerous different strains or genotypes[2,3] producing infection and severe disease in domestic cats, lions and tigers. Wild cats (bobcats, mountain lions, ocelots, spotted cats and jaguars) in North and South America can act as reservoir or incidental hosts. Recent studies have shown that domestic cats can also harbour subclinical infections and may act as reservoirs.[4,5] In some endemic areas, the prevalence of subclinical infection in cats may be as high as 30%.[6] Tick vectors for *C felis* are *Amblyomma americanum* and *Dermacentor variabilis*.[7–9]

Other species have been identified: *Cytauxzoon manul* in Pallas cats (Mongolia), *Cytauxzoon* spp in Iberian lynx and domestic cats in Spain,[10] and *C* spp in domestic cats in Italy.[11] The tick vectors for the European species are still not known, but most likely are *Dermacentor* spp or *Ixodes ricinus*.

Epidemiology

It has been hypothesised that infection in domestic cats involved a species jump from bobcats, in which the prevalence of infection may be high in certain geographic areas.[8] Disease shows a seasonal incidence from spring to early autumn,[12,13] associated with peak activity of the tick vectors. There is a significant association between infection and both outdoor access and feral cats in areas where vector ticks are prevalent.[12] No association with gender, breed, age or retroviral status has been found.[11]

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A hyperendemic focus may be found within endemic areas, but is likely due to tick exposure of cats rather than cat-to-cat transmission, which has never been proven.[14,15] In some areas of the USA an increase in cytauxzoonosis diagnoses has been observed in the past decade and it is considered an emerging disease.[13]

In recent years, the infection has also been documented in Europe. Cases have been described in the Iberian lynx (Figure 1)[10,16,17] and in domestic cats[18] in the south of Spain, and in domestic cats in France.[19] Moreover, a case series was reported in north-eastern Italy (Trieste) and two cases in central Italy.[11,20] In the Trieste region, samples from domestic and feral cats showed a 23% prevalence of infection, with a higher prevalence in feral cats (30%). *Cytauxzoon* species in the European cases is different from *C felis*, which produces infection and disease in the USA.

In some endemic areas, the prevalence of subclinical infection in cats may be as high as 30%.

Pathogenesis

The life cycle and complex pathogenesis has been well described for this infection.[21] Vector ticks ingest merozoite-infected red blood cells from the natural reservoir host (bobcat, lynx or domestic cat). The parasite initiates a process of sexual replication (gametogenesis) in the tick gut and salivary glands. This leads to the formation of sporozoites, which are the infective form and can be transmitted if the tick attaches to a domestic cat. Sporozoites infect endothelial-associated mononuclear cells and undergo asexual replication within the macrophages; these, in turn, develop into large structures known as schizonts – large enough to occlude blood vessels, especially in the liver, spleen and lungs. Widespread dissemination of schizonts results in parasitic thrombosis, circulatory impairment, tissue infection and a severe systemic inflammatory response, which can lead to multi-organ dysfunction and failure and death within 3 weeks of infection.[22] When schizonts rupture in the circulation, large numbers of merozoites are released, infecting red blood cells and additional mononuclear cells. This is late-stage disease, with erythroparasitaemia (piroplasm structures within red blood cells) which can be readily observed in blood smears, and may lead to haemolytic anaemia and erythrophagocytosis.

Recent studies have evaluated systemic and lung immune responses in cats naturally infected with *C felis* based on serum concentrations of cytokines (TNFα, IL-1β) and serum proteins, immunohistochemical expression of several inflammatory mediators and PCR assay for CD18.[23,24] Both studies demonstrated a marked systemic and lung pro-inflammatory response that can contribute to the pathogenesis of the disease; the response was even more pronounced in cats that died compared with survivors.[23,24]

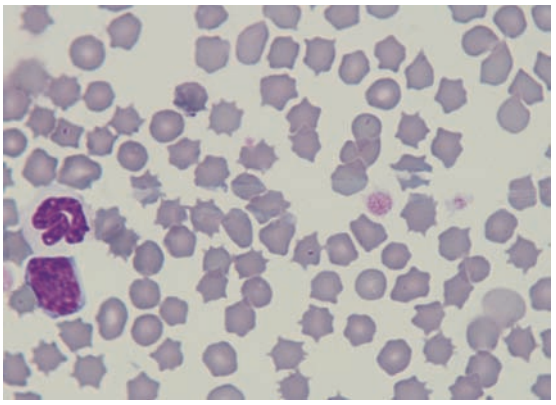

Figure 1 Merozoites within red blood cells in an Iberian lynx from southern Spain. *Courtesy of Professor Josep Pastor, Veterinary School of Medicine, Universitat Autònoma de Barcelona, Spain*

European Advisory Board on Cat Diseases

The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

The latest version of the cytauxzoonosis in cats guidelines is available at www.abcdcatsvets.org and www.abcd-vets.org

Clinical presentation

Cytauxzoonosis (*C felis*) in the USA is typically an acute or peracute severe febrile disease. Clinical signs are non-specific and consist of depression, anorexia, high fever, icterus, dyspnoea, tachycardia, generalised pain and vocalisation. Signs of haemolytic anaemia are frequent (pale mucous membranes, pigmenturia, splenomegaly, hepatomegaly). Some cats may present or evolve to late-stage disease with neurological signs (ataxia, seizures, nystagmus), hypothermia, moribund state and coma. Many cats die within 1 week of the onset of clinical signs.[14,25] Veterinarians practising in an endemic area must suspect cytauxzoonosis when faced with any cat with an acute severe disease.

Frequent clinicopathological signs include non-regenerative anaemia, leukopenia with toxic changes, thrombocytopenia, hyperbilirubinaemia, bilirubinuria and an increase in liver enzymes. These changes are associated with erythrophagocytosis and systemic inflammatory response syndrome (SIRS). Coagulation times are usually prolonged due to disseminated intravascular coagulation. Other biochemical abnormalities include hypoalbuminaemia, hyperglycaemia, pre-renal azotaemia, and electrolyte and acid–base disturbances associated with the SIRS state.[14,25]

Diagnostic imaging reveals non-specific signs consisting of hepatosplenomegaly on abdominal radiography and/or ultrasound, and a pulmonary interstitial–alveolar pattern on thoracic radiography.

Cytauxzoon species infection reported in European cats (Italy, Spain, France) is probably less virulent than *C felis* infection. The majority of infected cats have been healthy, showing only low-level erythroparasitaemia (merozoites within red blood cells) as an incidental finding. In some cats anaemia was described and one cat died after severe disease of a short duration, but no schizont structures were found in tissues, so cytauxzoonosis was not confirmed.

Diagnosis

In clinical practice, diagnosis is usually obtained by identification of *C felis* in blood smears and/or fine-needle aspirates from the liver, spleen and lymph nodes using rapid Romanowsky-type stains.

Observation of schizont-infected myeloid cells on blood and/or tissue smears is the diagnostic test of choice because it confirms acute disease. These are seen as very large (50–250 μm diameter) single cells with an eccentric nucleus containing a single prominent nucleolus. The cytoplasm contains variable numbers of basophilic particles (a few to thousands), which are developing merozoites. These cells may be confused with platelet clumps. The sensitivity of blood smears may be low, so fine-needle aspirates and cytology of liver, spleen, lymph nodes and lungs are indicated if blood smears are not diagnostic in a suspected case.

Observation of merozoites (piroplasms) within red blood cells in thin blood smears prepared with Romanowsky-type stains is supportive of a diagnosis of cytauxzoonosis. However, it does not confirm acute disease as merozoites can be an incidental finding in healthy cats, and may also be observed in cats that have survived acute infection or those with clinical signs of another disease. Piroplasms are usually round to oval structures, 1–2 μm in diameter, with a dark purple eccentric nucleus within a pale blue cytoplasm (signet ring shaped), but in some cases may be more elongated with a bipolar nucleus (Figure 2). One to four merozoites may be observed within individual red blood cells. Sensitivity is not very high, as merozoites appear late in the course of the disease; they are either absent or present in very low numbers in probably more than 50% of cats with acute disease. Blood smears should be performed daily because merozoites can appear over the course of the disease. The distal edges of a blood smear are the best place to look for them.

PCR assays have been developed to confirm the presence of *C felis* and other *Cytauxzoon* species,[10,11,14] but so far they are not useful as a quick diagnostic tool in practice. It is recommended though that samples from suspected cats are submitted to appropriate laboratories to further confirm the infection. Low levels of parasitaemia can only be detected by PCR assay.[5] In one clinical trial, parasitaemia was determined by qPCR and at significantly lower levels in surviving cats versus non-surviving cats, so qPCR results might be of prognostic value.[26]

EBM grades
The ranking system for grading the level of evidence of various statements within the treatment and prevention sections of this article is described on page 574 of this Special Issue.

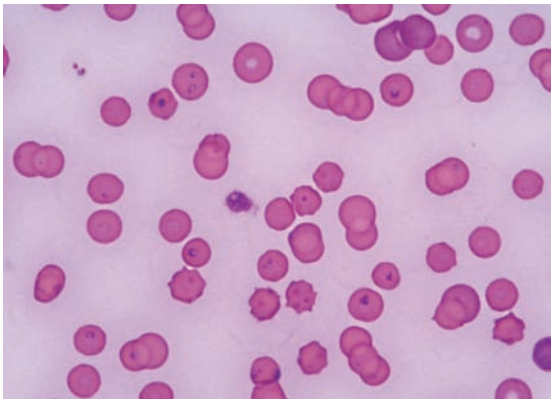

Figure 2 Merozoites within red blood cells in a cat from Trieste (Italy). *Courtesy of Dr Erika Carli and Dr Laia Solano-Gallego, Clinica Veterinaria Privata San Marco, Padova, Italy*

Cat-to-cat transmission of cytauxzoonosis has never been proven.

Treatment

Historically, cytauxzoonosis has been considered a fatal disease, with mortality approaching 100%. With the recent advances in treatment and/or differences in strain pathogenicity, this is no longer true, although the prognosis remains guarded in some cats.[27,28]

Supportive and critical care treatment (intensive fluid and oxygen therapy, antithrombotic therapies such as unfractionated heparin 200 U/kg SC q8h, blood products, antibiotics, analgesics) is extremely important to keep the cat alive while the antiprotozoal drugs and immune system do their work. Many cats deteriorate during the first days and often die; but, if they survive, a gradual improvement is seen over the ensuing days.[26]

A variety of antiprotozoal drugs have been used in case reports or experimental studies (diminazene, imidocarb dipropionate, thiacetarsamide sodium, tetracycline, parvaquone, buparvaquone) but efficacy has not been proven [EBM grade IV].[27–29]

Imidocarb had been the drug of choice for many years, although it was not known if it provided any advantage over supportive care alone. However, an open-label randomised prospective clinical trial demonstrated better survival rates (60% vs 26%) with the combination of atovaquone (15 mg/kg PO q8h) and azithromycin (10 mg/kg PO q 24h) compared with imidocarb (3.5 mg/kg IM once) in 80 cats with acute disease.[26] Mortality was high (41/80 cats). Most cats died during the first 3 days after presentation, only three cats dying after the third day of treatment. Supportive treatment was the same in all cats, comprising fluid therapy and heparin. This study suggests that this antiprotozoal combination plus supportive treatment is the current approach of choice [EBM grade I].[26] In some cats, a nasooesophageal tube may be needed to administer drugs and enteral feeding.

Cats surviving the acute infection may become chronic carriers for life, with piroplasms within the red blood cells. These cats act as reservoirs and may transmit the infection through tick vectors.

A recent study failed to demonstrate efficacy of diminazene at higher doses (4 mg/kg IM) for 5 consecutive days in eliminating or reducing the parasite burden in chronic carrier cats. Moreover, multiple adverse effects appeared, so this treatment is not recommended [EBM grade III].[30]

Prevention

There is currently no vaccine against *C felis*, although preliminary studies are being conducted.[31]

Prevention is based on living indoors or use of effective tick treatment in cats with outdoor access. Efficacy of an acaricide collar (imidacloprid 10% plus flumethrin 4.5%) for prevention of *C felis* transmission has been proven in a controlled prospective clinical trial. Two groups of cats (with and without a collar) were exposed to ticks (*A americanum*) infected with *C felis*. No cats with a collar, vs 90% of the cats with no collar, were infected [EBM grade II].[32]

Testing for the presence of *Cytauxzoon* species in feline blood donors is advised. Although inoculation of merozoites within red blood cells in a blood transfusion does not lead to the development of schizont structures and disease, cats can become chronic carriers and an infection reservoir.

Prognosis

The prognosis for cats with cytauxzoonosis in the USA should be considered guarded to fair, if proper intensive care is provided and atovaquone is available. It has been suggested that different *C felis* strains may vary in pathogenicity, as some cats have survived after not receiving antiprotozoal drugs.[2,27,33] It is recommended that cats are treated in well-equipped hospitals where the best supportive treatment can be provided.

Veterinarians practising in an endemic area must suspect cytauxzoonosis when faced with any cat with an acute severe disease.

Cytauxzoon infection in Europe reportedly has a good prognosis: so far, only cats with subclinical infection or signs of mild disease (anaemia, diarrhoea), possibly unrelated to the infection, have been documented.[11,20]

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Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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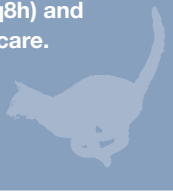
KEY POINTS

- Cytauxzoonosis has been reported worldwide, both in domestic cats and wild cat species.
- The parasite is transmitted via ticks, and the prevalence of infection is higher in cats with outdoor access and in feral cats.
- In the USA, cytauxzoonosis is typically an acute or peracute, severe febrile disease. Non-regenerative haemolytic anaemia is often present, as are neurological signs, followed by death in nearly 100% of cases.
- Cats infected with *Cytauxzoon* spp have been reported in southern Europe, but clinical signs in those cats were mild and possibly unrelated to the infection.
- In practice, diagnosis is often based on blood smears and/or fine-needle aspirates from the liver, spleen and lymph nodes using rapid Romanowsky-type stains.
- PCR assays have been developed to confirm the presence of *C felis* and *Cytauxzoon* species, but are not useful for a quick diagnosis in practice.
- Current treatment of choice is a combination of atovaquone (15 mg/kg PO q8h) and azithromycin (10 mg/kg PO q24h), as well as fluids, heparin and supportive care.
- Surviving cats may become chronic carriers.
- Prevention is based on living indoors or use of effective tick treatment in cats with outdoor access.



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