Monk's Malevolent Malady

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Introduction

Feline cytauxzoonosis is a disease that occurs in wild and domestic felids and is caused by the protozoan blood parasite *Cytauxzoon felis,* with the bobcat serving as the reservoir host. Transmitted by *Amblyomma* and *Dermacentor* tick species, this protozoan produces a short-term illness followed by a carrier state in the reservoir host.[1] However, when this organism is transmitted to domestic cats, it generally causes a more severe and often fatal disease process. *Cytauxzoon felis* manifests with an erythrocytic phase and a schizogenous tissue phase that develops in macrophages within many organs of the body including the lungs, spleen, liver, and lymph nodes.[2] History and clinical presentation of infected cats can strongly suggest feline cytauxzoonosis, but definitive diagnosis is typically made by morphologic identification of piroplasms within erythrocytes with or without schizonts in macrophages observed on blood smear.[1] Treatment with atovaquone and azithromycin coupled with supportive therapy is currently considered the standard of care. Most patients diagnosed with this disease decline rapidly and have high mortality rates despite timely and aggressive treatment.[3]

History and presentation

Monk was a 3-year-old male neutered Domestic Shorthair cat who originally presented to Mississippi State University College of Veterinary Medicine's Community Veterinary Services on October 2, 2020 for a two-day history of lethargy. Monk's owner noted that on October 1, 2020, Monk seemed sluggish, not engaging in his normal activities, and sleeping more often at home prompting his owner to present him for further examination. Monk had not experienced any vomiting, diarrhea, anorexia, or trauma at home. Monk was a mostly indoor cat with access to the outdoors. There was an outdoor feral cat that had been noticed around the home. Monk had a prior history of having a mandibular canine removed with surrounding osteomyelitis noted and treated with antibiotics. Monk has been previously examined for upper respiratory infections and had one

episode of tongue ulceration and hypersalivation. On presentation to MSU-CVM, Monk was not receiving any regular medications and was up to date on vaccinations and parasite preventatives.

On presentation, Monk was quiet, alert, and responsive. He weighed 5 kg (11 lbs) and had a body condition score of 6/9 (5 is ideal). His heart rate was 180 beats per minute, respiratory rate was 40 breaths per minute, and his rectal temperature was markedly elevated at 108F. Upon cardiopulmonary auscultation, there were no crackles or wheezes appreciated in his lungs and no murmurs or arrhythmias detected in his heart. His abdomen was very tense and mildly painful upon palpation. His eyes were clear with normal dazzle and menace response. Several areas of moderate gingivitis were noted on oral examination. His mucus membranes were pink and slightly tacky with a capillary refill time was under 2 seconds. Monk's coat was clean and free of external parasites. The remainder of his physical exam findings were within normal limits.

History, Presentation, and Diagnostic approach

Infected cats often have access to the outdoors and are possibly reported to have been bitten by a tick. Occurrence is often seen in seasons when tick activity is higher. While some clinical signs and laboratory findings can be indicative of cytauxzoonosis, a definitive diagnosis generally requires microscopic identification of the organism.[4,1] The most common clinical signs seen initially are acute lethargy, high fever, and anorexia which are mostly nonspecific.[5] More severe clinical signs such as icterus, profound lethargy, and generalized pain are often not seen until later in the disease process. On physical exam, infected cats often have pale mucous membranes and jaundice. Other signs which may be present can include tachycardia, tachypnea, and hepatomegaly and/or splenomegaly.[5] A high fever (often greater than 105) is often a consistent clue which should place *Cytauxzoon felis* on the differential list. As the disease progressively worsens, additional signs which may be seen include abnormal

mentation/neurological status as well as vocalization, and eventually a decline in temperature with a significant decline in clinical status.

Abnormalities commonly seen on complete blood count often shows pancytopenia, including a profound leukopenia with evidence of toxic neutrophilic changes, severe thrombocytopenia, and an anemia with a lack of regenerative response. Chemistry findings are generally not specific, but hyperbilirubinemia, hypoproteinemia, and hyperglycemia are often observed.[5] Increased liver enzymes and azotemia (prerenal) can also be seen. Coagulation testing can be prolonged. Diagnostic imaging changes that can be observed with Cytauxzoonosis include hepatomegaly, splenomegaly, and an interstitial to alveolar pulmonary pattern.[3]

A blood smear is indicated in a pancytopenic patient suspected of having *Cytauxzoon felis.* This can provide a diagnosis if the piroplasm is seen in red blood cells, as this organism has a characteristic "signet ring" appearance. A limitation to the blood smear providing the diagnosis is that cats can show clinical signs of the disease well before the erythrocytic phase of disease. To increase the chances of finding the organism if the initial blood smear is negative is to perform the blood smear daily in a patient highly suspicious for *Cytauxzoon felis.*

Additional testing to gain a diagnosis of *Cytauxzoon felis* can include cytology of aspirates taken from abnormal organs as well as PCR testing. Abnormal organs which may be affected by *Cytauxzoon felis* and have the best chance to provide a diagnosis often include the lungs, liver, and spleen. Others can include lymph nodes as well as bone marrow.[1] Infected macrophages may be visualized in these aspirates, supporting a diagnosis. Additionally, there is PCR testing for *Cytauxzoon felis* infection that is commercially available and is currently the most sensitive and specific method for detection of infection. Nevertheless, a positive result could be found in a recovered carrier cat and thus PCR cannot be used to differentiate between

an acutely infected cat and a recovered carrier.[1] Another limitation of this test is the amount of time it can take to get results in a severely affected cat, making it not as useful for patients with acute and severe clinical signs. Treatment should not be delayed while waiting for results if cytauxzoonosis is clinically suspected.

Monk's nonspecific clinical signs upon presentation to MSU-CVM on October 2, 2020 prompted a more in-depth diagnostic approach to investigate infectious, neoplastic, and immune-mediated etiologies for his fever. Monk's initial complete blood count showed a mild leukopenia of 4160 cells/ul (5500-20000) characterized by a moderate lymphopenia of 416 cells/ul (1500-7200), and a mild thrombocytopenia of 192000 cells/ul (200000-700000) with some Dohle bodies and Howell-Jolly bodies noted. Chemistry revealed a mild hyponatremia of 146.7 mmol/L (148-159), mild to moderate hypokalemia of 2.98 mmol/L (3.50-5.50), mild hyperglycemia of 220 mg/dl (70-160), mild hypocalcemia of 8.1 mg/dl (8.2-10.6), mild hypophosphatemia of 2.0 mg/dl (2.6-5.7), mildly decreased serum osmolality of 291 mOsm/kg (295-320), and mild hypomagnesemia of 1.8 mg/dl (1.9-2.6). Urinalysis showed a mild proteinuria with occasional granular casts with no overt evidence of an active sediment. An FIV/FeLV SNAP test was performed to rule out the most likely viral etiologies and was below detectable limits for FIV antibodies and below detectable limits for FeLV antigen. Thoracic radiographs did not yield any clinically relevant abnormalities. Abdominal radiographs disclosed some gas in the small bowel with clinical consideration given to aerophagia, enteritis, inflammatory bowel disease, and round cell neoplasia. Abdominal ultrasound revealed gall bladder sludge, thickening of some of the small intestine, mildly enlarged ileocecal and colic lymph nodes, hyperechoic and mildly enlarged kidneys, as well as mildly thickened bladder wall with some sludge present in the urinary bladder. Differentials for these findings were unchanged from those mentioned for the

radiographic changes with the addition of the consideration of a urinary tract infection with possible pyelonephritis. While abdominal radiographs and ultrasound could be supportive of gastrointestinal lymphoma or inflammatory bowel disease, the complete lack of gastrointestinal signs along with inconsistencies with history and presentation make these etiologies less likely. Due to the findings on abdominal ultrasound and to rule out urinary tract disease as a source of fever, a urine culture was submitted on the morning of October 3, 2020. Urine culture did not yield any bacterial growth at 24 or 48 hours. Monk was admitted to the small animal hospital and was maintained on intravenous lactated ringers solution at 60 ml/kg/day with 20 mEq of KCl supplementation and was started on unasyn (30 mg/kg IV Q8) and clindamycin (12.5 mg/kg IV Q12) to preemptively address possibility of a bacterial urinary tract infection and toxoplasmosis, respectively. He was also administered maropitant (1 mg/kg IV Q24) to prevent nausea and buprenorphine (0.01 mg/kg IV Q12) for pain control. At this time, Monk was maintaining a good appetite.

Based on Monk's clinical presentation, history, and initial diagnostics; greater consideration was given to cytauxzoonosis or toxoplasmosis as primary differentials. On October 3, 2020, an iStat was performed to continue to monitor his bloodwork values. It revealed a persistent mild hyponatremia of 146 mg/dl (148-159) with the previous hypokalemia resolving at 4 mg/dl (3.5-5.5). A blood smear was obtained and stained with Diff-quick for an informal pathology review of Monk's blood. There were no overt abnormalities appreciated at that time, but cytauxzoonosis was still highly suspected. Monk continued to receive supportive treatment in hospital as previously described except for discontinuing the KCl supplementation and starting transdermal mirtazapine (1/8 inch strip on ear pinna Q24) to encourage his appetite. On the morning of October 4, 2020, Monk began to decline clinically, becoming increasingly lethargic

and anorexic. An iStat was performed and revealed a hypokalemia of 3.1 mg/dl (3.5-5.5) and a mild hyponatremia of 146 mg/dl (148-159). A packed cell volume (PCV) and total protein (TP) were run and showed a PCV of 28% (30.0-46.0) and a TP of 5.4 g/dl (6.0-7.5) with icteric serum noted. Complete blood count revealed a progressive leukopenia of 2410 cells/ul (5500-20000) characterized by a significant neutropenia 819.4 (2500-12800) and a moderate lymphopenia 771.2 cells/ml (1500-7200). A mild anemia was now present, based on a decreased hematocrit of 25.6% (30.0-46.0) with an elevated MCHC at 34.9 g/dl (24.0-34.0). Additional findings on complete blood count included a severe thrombocytopenia at 22000 cells/ul (200000-700000) and a mild hypoproteinemia at 5.1 g/dl (6.0-7.5). Chemistry analysis showed a moderate hyponatremia of 144.7 mmol/L (148-159), mild hypokalemia of 3.23 mmol/L (3.50-5.50), mild hyperglycemia of 173 mg/dl (70-160), mild hypocalcemia of 7.5 mg/dl (8.2-10.6), a mildly elevated ALT of 86 U/L (7-60), a mildly decreased ALP of 9 U/L (10-42), moderate hyperbilirubinemia of 2.7 mg/dl (0.1-0.5), a mild hypoproteinemia of 5.1 g/dl (5.5-6.4) characterized by a hypoalbuminemia of 1.8 g/dl (2.2-3.2) and a hypoglobulinemia of 3.3 g/dl (4.1-6.0), a mild hypocholesterolemia of 83 mg/dl (95-200), a moderately elevated creatinine kinase of 9920 U/L (50-225), hypophosphatemia of 2.5 mg/dl (2.6-5.7), mildly decreased serum osmolality of 285 mOsm/kg (295-320), and mild hypomagnesemia of 1.8 mg/dl (1.9-2.6). Due to the low platelet count, coagulation times were run and revealed a prolonged prothrombin and partial thromboplastin times of 14.8 seconds (5-10) and 29.2 seconds (15-25) respectively. A new blood smear was submitted for pathology review with classic “signet ring” shaped piroplasms appreciated in several erythrocytes throughout the slide, confirming a diagnosis of feline cytauxzoonosis. Most of the findings on bloodwork including thrombocytopenia, leukopenia, hypocalcemia, hyperglycemia, hyperbilirubinemia, and hypoproteinemia are often

associated with the pathophysiology of Cytauxzoonosis infection. Given Monk's prolonged coagulation parameters, Monk was administered a plasma transfusion after being blood typed as Type A. A nasogastric tube was also placed to be able to provide nutrition to Monk as he was not eating on his own and to aid in ease of oral medication administration.

Pathophysiology

The more severe clinical presentation seen in domesticated cats infected with *Cytauxzoon felis* is associated primarily with the schizogenous tissue phase of parasite development during which parasite-distended mononuclear cells leads to the obstruction of blood vessels.[4] It is evident that the schizont tissue phase is not as prolific among reservoir hosts. The red blood cell phase of the parasite seems to be dominant in reservoir hosts and produces a much milder illness that results in a carrier state with a persistent erythrocytic parasitemia.[5] This allows for a tick vector to transmit the disease from carriers to clinically healthy domestic cats and other susceptible felids.

The pathogenesis and life cycle for this infectious process is well described in domestic cats. *Amblyomma americanum* and *Dermacentor variabilis* are the tick vectors that ingest red blood cells infected with merozoites from a reservoir host or disease carrier such as a bobcat, lynx or domestic cat. Sexual replication of the protozoon takes place in the digestive system and salivary glands of the tick vector.[4] Sporozoites are produced during this process which are the infective form of the parasite and can be transmitted via the tick during a blood meal to a currently healthy domestic cat. Once in the naïve cat, sporozoites infect mononuclear cells and undertake asexual replication within the host macrophages.[5] This process, called schizogeny, forms schizonts within macrophages that become large enough to occlude blood vessels in multiple organs and especially in the liver, spleen and lungs. When schizonts rupture in the circulation, large numbers of merozoites are released, infecting red blood cells and additional

mononuclear cells.[5,1] This is now considered the second phase of the disease, called the erythrocytic phase. The parasite now in the red blood cell is referred to as a piroplasm. This is late-stage disease, in which piroplasms can often be readily observed in blood smears, and hemolytic anemia and erythrophagocytosis can develop.[4,1] Widespread dissemination of schizonts results in the development of a parasitic thrombosis, circulatory problems, and a severe systemic inflammatory response, which can lead to organ failure and death within 3 weeks of infection.[5] The primary disease mechanism that is involved in the end stage of Cytauxzoonosis infection is generally due to the hematological changes associated with the high numbers of schizont swollen mononuclear cells that act as thrombi leading to disseminated intravascular coagulation and multi-organ failure.[4,1]

Treatment options and prevention

Several different medications have been instituted as treatment options for infection with *Cytauxzoon felis*. While the efficacy of various therapies has been tested in many different studies, there has most recently been one drug combination that has shown much promise and successfully decreased mortality rate of these cases.[5] At this time, it is evident that targeted supportive care is key for initial support and can prolong survival time after infection but does not necessarily improve mortality rates. Dehydration, electrolyte abnormalities, anemia, thrombocytopenia, fever, and coagulation derangements often occur with cytauxzoonosis and must be addressed appropriately. Appropriate nutrition must also be maintained if the patient becomes inappetant/anorexic and could include placement of a feeding tube. A feeding tube would also help facilitate administration of oral medications.

Historically, efficacious therapy has been attempted for *Cytauxzoon felis* infection using a variety of medications, including several antibiotics as well as antiprotozoal agents but most of these agents have proved to be ineffective. Treatment with imidocarb dipropionate (3.5 mg/kg

IM) has been used in previous studies with very limited success.[5] The most recent literature supports the administration of atovaquone at 15 mg/kg orally every 8 hours coupled with azithromycin at 10 mg/kg orally every 24 hours as the standard of care.[4]

In a 2011 study, eighty cats found to be acutely infected with *Cytauxzoon felis* were evaluated to determine the efficacy of a combination treatment of atovaquone and azithromycin compared to treatment with imidocarb dipropionate.[3] The inclusion criteria included cats that had been diagnosed based on clinical signs such as fever, lethargy, and anorexia as well as positive identification of piroplasms on blood smear. The treatment groups were determined using an imbalanced blocked randomization of 2:1 (atovaquone and azithromycin vs imidocarb, respectively), yielding 53 cats to be treated with atovaquone and azithromycin and 27 cats to be treated with imidocarb.[3] All of the cats in the study received IV fluids, heparin, and other supportive care, such as pain medications and esophagostomy tube placement was implemented according to the attending veterinarian's discretion.[3] Atovaquone was administered at a dose of 15 mg/kg PO Q8 for 10 days with azithromycin administered at a dose of 10 mg/kg PO Q24 for 10 days. Cats that received imidocarb were pretreated with atropine (0.05 mg/kg) SC 15 minutes before injection of 3.5 mg/kg imidocarb dipropionate IM once and then again 7 days later.[3] The results of the study demonstrated a survival rate of 60% in the atovaquone and azithromycin (A&A) group compared to a 27% survival rate observed in the imidocarb treatment group. Cats with a lower parasitemia, higher white cell count, and lower total bilirubin were more likely to survive.[3] The A&A treatment protocol has been shown to effectively decrease mortality rate and is currently considered standard of care.[1] However, the success of this treatment protocol is heavily dependent upon early detection and prompt treatment of disease with mortality rates still often approaching 100%.

There is evidence that supports the existence of a less virulent strain of *Cytauxzoon felis* prevalent in the region of Arkansas, Oklahoma, and parts of Missouri. In a 2015 study, prevalence of *Cytauxzoon felis* infection in clinically healthy cats was examined. Blood samples were collected from 902 healthy domestic cats between October 2008 and April 2012. *Cytauxzoon felis* DNA was detected in 56 of 902 cats that were sampled.[6] The high prevalence of *Cytauxzoon felis* reported in this study suggests that infected domestic cats surviving acute infection are likely reservoirs of infection for naive felines. In another study, 18 cats that became acutely infected with *Cytauxzoon felis* as determined by presence of characteristic piroplasms on blood smear were evaluated.[2] All 18 of these cats survived the acute infection phase without receiving any treatment known to have efficacy against *Cytauxzoon felis* and developed a carrier state. These cats presented almost identically to cats with typical feline cytauxzoonosis apart from having slightly lower fevers on initial examination.[2] Both studies support the possibility of a less virulent strain of *Cytauxzoon felis* in the population.

Seeing the devastating nature of this disease process with such a high mortality rate warrants the emphasis of parasite prevention in reducing the incidence of disease. Current literature suggests that tick prevention is a very effective method for the prevention of clinical disease with *Cytauxzoon felis.* A 2013 study investigated the effectiveness of a Imidacloprid10%/ Flumethrin 4.5% Collar (Seresto®) in preventing transmission of cytauxzoonosis in a group of 20 cats. The 20 cats were equally randomized to either a treated or non-treated control group based on their susceptibility to ticks.[7] Cats with low, medium, and high risk were equally distributed among both groups. Treated cats were fitted with 10% imidacloprid/4.5% flumethrin collars on day 0 of the study and both groups were then infested with *Cytauxzoon felis*-infected *A. americanum* on day 30 of the study. Transmission of

Cytauxzoon felis was confirmed by examining blood of cats using DNA extraction followed by PCR amplification with piroplasm-specific primers.[7] Ticks did not attach to any of the cats treated with 10% imidacloprid/4.5% flumethrin but they did attach and feed on all the non-treated control cats. *Cytauxzoon felis* was transmitted to 90% of non-treated control cats and was not transmitted to any of the treated cats.[7] This study emphasizes the importance of appropriate tick control to prevent ticks from attaching, feeding, and transmitting *Cytauxzoon felis*.

Case outcome

Upon confirming a diagnosis of feline cytauxzoonosis on October 4, 2020, oral treatment with azithromycin at 10 mg/kg every 24 hours and atovaquone at 15 mg/kg every 8 hours was started immediately. Due to Monk's progressively worsening anemia and severe thrombocytopenia noted on a complete blood count performed on October 5, 2020, a blood transfusion was discussed with the owner as an option as an attempt to allow time for Monk to respond to treatment in addition to rapidly addressing his need for replacement blood products. Monk's owner agreed to a blood transfusion. Monk's blood was submitted for a major cross match and the donor blood cells were found to be compatible for the blood transfusion. Shortly after beginning the whole blood transfusion, Monk's condition began to decline rapidly and he started to vocalize, became increasingly hypothermic, and was experiencing dyspnea. Given Monk's progressively deteriorating condition, the owner elected to have Monk humanely euthanized at that time. Monk was first sedated with 2 ml of Propofol IV and was then administered 3 ml of euthanasia solution IV. Death was verified via cardiopulmonary auscultation to confirm loss of heartbeat and lack of corneal reflex. Monk's owner elected to have Monk cremated with ashes returned.

References

1. Sherrill, Meredith K., and Leah A. Cohn. "Cytauxzoonosis: Diagnosis and treatment of an emerging disease." *Journal of Feline Medicine and Surgery*. (2015) 17: 940-948.
2. Meinkoth J, Kocan AA, Whitworth L, et al. "Cats surviving natural infection with Cytauxzoon felis: 18 cases (1997–1998)". *J Vet Intern Med* (2000) 14: 521–525.
3. Cohn. L. A. et al. "Efficacy of Atovaquone and Azithromycin or Imidocarb Diproprionate in Cats with Acute Cytauxzoonosis". *Journal of Veterinary Internal Medicine*. (2011) 25, 55-60.
4. Lloret, Albert et al. "Cytauxzoonosis in Cats: ABCD guidelines on prevention and management". *Journal of Feline Medicine and Surgery*. (2015) 17, 637-641.
5. Meinkoth J, Kocan AA. "Feline cytauxzoonosis". *Vet Clin North Am Small Anim Pract* (2005) 35: 89–101.
6. Rizzi, Theresa E. et al. "Prevalence of *Cytauxzoon felis* infection in healthy cats from enzootic areas in Arkansas, Missouri, and Oklahoma". *Parasites & Vectors*. (2015) 8:13.
7. Reichard, Mason V. et. al. "Efficacy of an Imidacloprid 10%/Flumethrin 4.5% Collar (Seresto®, Bayer) for Preventing the Transmission of *Cytauxzoon felis* to Domestic Cats by *Ambylomma americanum*". *Parasitol Res*. (2013) 112: S11-S20.