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Cytauxzoon felis

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Introduction

Cytauxzoon felis was first reported in the United States in 1976[1] .Since this discovery in Missouri, the protozoa has been identified in domestic cats (*Felis catus*) across the southeast[1]. Many *Cytauxzoon* species have already been identified across the globe (*C. sylvicaprae, C. strepsicerosi, C. taurotragi, C. manul*)[1,2]. It is a blood parasite of the Theileriidae family whose definitive host in the U.S. is the bobcat (*Lynx rufus*) [1, 3]. The parasite is transmitted by the lonestar tick (*Amblyomma americanum*) and experimentally by the American dog tick (*Dermacentor variablilis*) [1, 3, 4].

The significance and awareness of cytauxzoonosis is becoming more prevalent as the range of the vector widens and concurrent willingness for owners seeking medical treatment for their pets increases. Historically felines diagnosed with cytauxzoonosis were given a death sentence[1, 2]. This likely has not changed dramatically, but there are increasing reports of successful treatment

History and Presentation

Young cats with outdoor access are most commonly infected. However, there is no age or sex predilection for *C. felis*. An astute owner may report vague signs such as lethargy or anorexia. As the disease progresses, the cat can become dehydrated, develop pale mucous membranes, respiratory distress and extreme pyrexia (105-107° F). Due to the extravascular hemolysis, icteric mucous membranes, sclera and skin may be evident[1, 5].

Cats are fastidious groomers and as such, ticks are removed readily by the feline. Owners rarely report finding a tick embedded in the skin, with or without prevention on board. Even in

outdoor cats, owners rarely report seeing ticks on their cats and ticks are rarely seen on cats upon presentation[1, 6].

Pathophysiology

Cytauxzoon felis is a protozoal blood parasite of the apicomplexan phylum. The apicoplast organelle is used to invade erythrocytes of the host. The host's red blood cells are ingested by the Lonestar or American dog tick. Once in the gastrointestinal tract of the arthropod vector, the merozoites inside the erythrocytes undergo gametogenesis. The new zygotes produce kinettes which are then thought to migrate to the salivary gland of the tick. Kinettes form sporoblasts and ultimately sporozoites, which are released from the salivary gland of the tick during its blood meal[1, 7].

The time from contact transmission to cytauxzoonosis is approximately ten days. During this phase, sporozoites enter the host's tissue and are engulfed by macrophages, known as schizonts. This schizongenous phase is when asexual reproduction occurs leading to expansively large macrophages (up to 250µm) [1, 2]. The schizonts disseminate throughout the host. They become lodged in the vessels of the host's organs, especially the spleen and liver, as well as lymph nodes. As such, splenomegaly, hepatomegaly and lymphadenopathy can be palpated. As the host's body attempts to fight off this infectious disease, incredible pyrexia can occur, leading to lethargy, anorexia and dehydration. Overall, massive tissue involvement can lead to multiple organ dysfunction syndrome (MODS) and death[1, 2, 5, 7].

Simultaneously, the large schizonts occlude capillaries leading to micro thrombi which is very serious in the pulmonary parenchyma of cats because the lung is their shock organ. Cats

may suffer from acute respiratory distress syndrome (ARDS) and/or pulmonary edema. Pleural effusion and other third spacing, such as pericardial effusion and renal edema can occur in the later stages due to disseminated intravascular coagulation (DIC) [1,2,5,7].

Once the schizonts rupture from macrophages, the merozoites are free to pierce the membrane of red cells via their apicoplasts. The merozoites undergo fission multiplication and are seen microscopically with Giemsa or Wright stain. They appear in the erythrocyte with an offset dark blue nucleus and oval shape and are usually not seen in circulation until a few days after the onset of the first clinical signs (lethargy, fever, etc.). These piroplasms have a classic 'signet ring' morphology[1]. However, this is not pathognomonic, as other blood parasites such as *Babesia spp.* and *Mycoplasma spp.* also produce piroplasms and all can be pleomorphic. The destruction of the red cells causes extravascular hemolytic anemia, another hallmark of cytauxzoonosis. Host antibodies bind to *C. felis* antigens on the red cell, marking them for destruction. Pale, icteric mucous membranes, sclera and/or skin can be mild to moderate. A mild to moderate, normochromic, normocytic, non-regenerative anemia as well as leukopenia reflects this acute devastation[1, 2, 5, 7].

Differential Diagnoses

As mentioned previously, other blood parasites should be considered rule outs when suspecting *C. felis*. These include *Mycoplasma haemofelis* (previously *Haemobartonella felis*) and *Babesia felis* (Africa and India). Retroviral diseases should always be considered not only as a cause of this disease, but as a complication during treatment. These include feline leukemia (FeLV) and feline immunodeficiency virus (FIV). The mutated version of a corona virus, feline

infectious peritonitis (FIP), should be considered, especially when no other cause can be found[1, 5, 8].

In regards to rule outs for hyperbilirubinemia or bilirubinuria, the following differential diagnoses should be considered: cholangitis/cholangiohepatitis, pancreatitis, feline triaditis syndrome, immune-mediated hemolytic anemia, heartworm disease, hepatotoxin, hepatic neoplasia, disseminated intravascular coagulation (DIC) and/or bites from brown recluse spiders, snakes, or bees. Without icterus, there are many rule outs for fever of unknown origin (FUO): abscessation, infectious causes listed above, pyothorax, bartonellosis (*Bartonella henselae*), plague, tularemia and rarely: prostatitis, diskospondylitis, closed pyometra, septic arthritis, and bacterial endocarditis[1, 5, 8].

Diagnostic Approach

A complete physical exam and excellent history must be obtained prior to any diagnostics. Two common diagnostic paths are undertaken based on vital parameters. The first, FUO, comes from pyrexia (103-107° F). The second, anemia, comes from pale and/or icteric mucous membranes. Routine bloodwork, (CBC and serum biochemistry) should include scrutinizing a blood smear. If no piroplasms are seen upon presentation, a blood smear should be evaluated daily as merozoites increase in numbers as the disease progresses. Outdoor cats are at risk of retroviral infections and heartworm disease from mosquitos, so testing for FeLV and FIV is warranted. However, interpreting heartworm tests can be difficult[1, 5, and 8].

Diagnosing cytauxzoonosis in an ill cat can be challenging. Consider three potential scenarios: 1) piroplasms cannot be seen on blood smear, but the cat is showing typical signs of

cytauxzoonosis, 2) piroplasms are identified on blood smear and the cat is showing typical signs of cytauxzoonosis or 3) piroplasms are seen on peripheral blood smear, but the cat is showing clinical signs unrelated to cytauxzoonosis[1]. *Cytauxzoon felis* is the only blood parasite that has a schizontogenous cycle and is pathognomonic[1, 4, 5].

A real-time PCR for *C. felis* is widely available. However, turn-around time is about a week and does not prove active infection. To determine this versus a carrier state of *C. felis*, schizonts must be identified. These are rarely seen in peripheral blood. Obtaining a blood sample from the ear margin may increase the likelihood of finding monocytes engorged with schizonts. Similarly, a fine-needle aspirate (FNA) of peripheral lymph nodes may yield engorged macrophages. Performing an ultrasound-guided FNA of the liver and spleen may be more successful. Routine bloodwork and clotting times should be obtained beforehand to assess the risk of internal hemorrhage during the FNA procedure as well as determining other potential pre-anesthetic risks[1, 4, 5].

Treatment and Management

Supportive care is critical and pharmaceutical treatment needs to be instituted immediately if *C. felis* is suspected, even when diagnostics are pending. Additionally, minimizing handling should be balanced with adequate monitoring of the patient as stressful events often result in rapid decompensation of these delicate patients. The lungs are the shock organ for felines and care must be taken not to fluid overload the patient iatrogenically. This is especially important as this disease can lead to micro thrombi in the alveoli as well as third spacing due to hypoalbuminemia. Early placement and long-term use of a nasoesophageal (NE) tube might seem very stressful for cats. However, control of nutrition and medication

administrations is better tolerated with one in place to reduce the risk of aspiration pneumonia and wasted product with force feeding. The anti-protozoal drug, atovaquone, is an expensive, bright yellow, citrus flavored liquid that causes hypersalivation in the cat due to its highly bitter taste. Stress is significantly reduced not only for the patient, but for the staff when a feeding tube is placed. An NE tube is ideal in these hematologically unstable patients due to its low profile nature[1, 3, and 5].

Waxing and waning pyrexia, along with continued destruction of red cells, require intravenous fluids and potentially blood product transfusions. Unlike other causes of hemolytic anemia, *C. felis* antigens do not require immune suppression to prevent antibody formation and immunosuppression may be actually be detrimental during the recovery period. Similarly, the use of NSAIDs is not recommended based on poor outcomes[1]. The current recommended protocol specific to treating *C. felis* is the anti-protozoal, atovaquone (15mg/kg PO TID) and the anti-microbial, azithromycin (10mg/kg PO SID). Medications should preferably be given with food having a high fat content and for a ten day duration[1, 5].

Atovaquone is expensive and not kept in most animal hospitals. Maintaining a good relationship with local human pharmacies may help facilitate acquisition of the drug. In lieu of atovaquone, imidocarb diproprionate can be given intramuscularly at 2 to 5 mg/kg and again in one to two weeks. Atropine at 0.04mg/kg subcutaneously must be given beforehand to reduce cholinergic side effects of imidocarb. Survivability with imidocarb averages about 25% and was used for decades prior to the use of atovaquone and azithromycin[1, 5,9,10].

Diminazene aceturate is undergoing research with potential success at treating *C. felis*. It is an intramuscular injection dosed at 2mg/kg that is repeated after one week. Currently, it is not available in the U.S. market nor is it FDA approved[5].

Additional supportive care may include, but is not limited to isotonic crystalloid fluid therapy with potassium chloride supplementation (20 to 40 mEq/L), pain management (buprenorphine 0.01mg/kg IV q8h), anti-coagulation drugs (enoxaparin 1.5mg/kg SC q24h or heparin 100-300IU/kg SC q8H), anti-emetics (maropitant 1mg/kg IV q24h and/or ondansetron 1mg/kg IV q8h). Additional anti-biotics may be required depending on white blood cell derangement or complications such as aspiration pneumonia. Oxygen supplementation may be needed as well with signs of respiratory distress due to aspiration pneumonia, ARDS, or bronchoconstriction (an adverse side effect from imidocarb) [9].

At this time, it is unknown exactly how long the tick must attach to the host in order to transmit the sporozoites. Recent data from Thomas, et al. suggests transmission may occur as early as 36 hours and potentially quicker with increased ambient temperatures. Therefore, eliminating tick exposure and using repellants is the best method of prevention for the cytauxzoonosis when compared to acaricides[11, 12].

Expected Outcome and Prognosis

Survival rates have significantly improved since the discovery of cytauxzoonosis. Previous rates of zero percent have more than doubled with atovaquone/azithromycin therapy, but the prognosis is still guarded (65% survival) [1, 5]. Even with the right pharmaceuticals, this disease wreaks havoc on the patient's body and intense supportive care must be implemented to prevent mortality during the long days to weeks of hospitalization. Prognosis is grave with hypothermic, moribund patients that have severe icterus and anemia[1, 5].

Improvement should begin soon after the initial five to seven days of critical illness. Signs include regaining appetite, grooming, appropriate thermoregulation, improved mentation and/or affection. Normalization of hematologic and biochemical abnormalities resolve over one to two months, with the exception of piroplasms persisting on blood smear analysis. This may continue for the life of the cat and survivors are considered carriers with or without evidence of merozoites in red blood cells. These cats are also considered to have protective immunity and a normal lifespan after survival from infection[1, 5, and 13].

Conclusion

Cytauxzoon felis is a costly and often devastating disease. Prognosis is usually guarded with treatment and grave without. However, a historically fatal disease is now survivable thanks to the research from Cohn, et al. proving that the combination of atovaquone and azithromycin is efficacious[1]. In addition, the fact that *C. felis* exists in feral cat populations suggest that there is a less pathogenic strain. Some cats will survive without treatment and remain as carriers[1, 13]. Therefore, realistic expectations should be discussed with clients to facilitate informed decision-making. Rapid, aggressive treatment versus euthanasia must be considered on a case by case basis.

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