American Canine Hepatozoonosis

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February 24, 2017

Introduction

Canine hepatozoonosis is a well-known and widely distributed disease. The two pathogens that are the most recognized are *H. canis* and *H. americanum*. The brown dog tick, *Rhipicephalis sanguineus*, is the vector for *H. canis*, and the disease is much less severe. As disease began spreading across the southeastern United States, it was determined that the symptoms were much more severe than expected in dogs infected by *H. canis*. Through research, it was found that there was a variation in in the 18S rRNA gene, so the new disease was designated *H. americanum*. (Li and al.) The most suitable host for *H. americanum* is *Amblyomma maculatum*, the Gulf Coast tick. It is believed that most cases in the United States are caused by *H. americanum*. Cases of *H. canis* had not been reported in North America until recently. (Little and al.)

History and Presentation

The patients that are infected with *H. Americanium* often have a very vague and non-specific history. The owners may or may not have seen any ticks on the dog, but there is usually a history of improper tick control or being able to roam a large area. Depression is often the first noticeable sign followed by reluctance to move, stiffness, and an attitude change. The owners may note some weight loss and muscle atrophy that is normally obvious, especially around the head. Copious amounts of mucopurulent ocular discharge will be apparent to the owners. A decrease in tear production is also present due to the amount of inflammation in the extraocular muscles. (Panciera and Ewing)

Upon presentation, the patient is usually febrile with bone and muscle pain, most apparent over the cervical and lumbar spine, present on the physical exam. Radiographs may reveal bilateral and symmetrical periosteal bone proliferation. The proliferation is usually present

on the proximal long bones, but can be present on other bones. It looks very similar to hypertrophic osteopathy. A chemistry panel may show a mild elevation in alkaline phosphatase, as well as a hypoalbuminemia and hyperglobulinemia. Active disease is usually characterized by an extreme elevation of neutrophilic leukocytosis. It can occur before clinical signs or right in conjunction with them. An ongoing infection can result in polyuria and polydipsia, related to renal amyloidosis or glomerulonephritis, leading to renal failure. Uveitis or retinal scarring may be present on an ophthalmic exam. (Panciera and Ewing)

Grossly, there are few lesions that can be observed. The previously mentioned muscle atrophy is the most noticeable. Some subcutaneous edema could be present in the distal limb, more commonly in the dogs that are recumbent or moving very little. Occasionally, peritoneal effusion is present from a protozoal myocarditis. (Panciera and Ewing)

Pathophysiology

The most common route of transmission is through ingestion of an infected tick; though newer reports are showing that ingestion of an infected mammal is another route of transmission. Transstadial transmission is documented experimentally to show that ticks will carry the disease from the larval stage, through the nymph stage and into the adult stage. This widens the amount of potential hosts, that will infect dogs and other canines. (Panciera and Ewing)

The life cycle of *H. americanum* begins with the Gulf Coast tick ingesting gamont-containing leukocytes. The organism goes through sexual reproduction in the tick, zygotic meiosis and sporogony follow. The intermediate hosts, the dog, ingest the infected tick that has the oocyst present that will rupture and release sporocysts that will excyst in the presence of bile into the gastrointestional tract. This process will release the infectious sporozoites, which penetrate intestinal epithelial host cells and are transported to other sites with a preference to

skeletal muscle. An “onion-skin cyst” is formed in the muscle that is made of concentric layers of mucopolysaccharide, which protects the sporozoite from the host’s immune response. Within the cyst, sporozoites will mature to meronts. The cyst will lie dormant for varying lengths of time, but will eventually rupture releasing merozoites. When the cysts ruptures, a severe inflammatory reaction occurs resulting in a pyogranuloma at the site of the previous cyst. The merozoites invade circulating neutrophils and monocytes where develop into gamonts that can be ingested by feeding ticks to continue the life cycle. (Sykes)

Differential Diagnoses

Due to the non-specific signs of *H. americanium*, there are several differential diagnoses. It is crucial to make sure and rule-out all other causes of fever and non-specific pain due to how critical early treatment of hepatozoonosis is to the survival of the patient. The diagnosis and treatment of hepatozoonosis is very specific, which makes it difficult to gain a diagnosis until several others are ruled out. These differentials can include intervertebral disc disease, immune mediated polyarthritis, discospondilytis, or any other spinal abnormality. Other tick born diseases can present in a similar fashion, including ehrlichosis, Rocky Mountain Spotted Fever, and Lyme disease.

Diagnostic Approach

A presumptive diagnosis can be made off of clinical signs combined with neutrophilic leukocytosis and periosteal bone proliferation. The diagnosis can be confirmed off of identification of an intracellular gamont in peripheral blood leukocytes using a Romanowsky stain. It is difficult to find them because of the low levels of parasitemia. They are only present in less than 0.1% of the circulating monocytes and neutrophils. The gamonts appear as a basophilic oval shaped cytoplasmic inclusion. (Ewing and Panciera)

Muscle biopsy is another test that can be used. The biopsies can be taken from the biceps femoris or the semitendinosis muscle. The classic lesion can be described as an onion skin cyst. They are made of layers of mucopolysaccharide material in a concentric pattern that surround a parasitized host cell, forming a large cyst structure. The cyst is imbedded between fibers of skeletal muscle. When a cyst is ruptured the merozoites that are released will cause a pyogranulomatous inflammatory reaction. The granuloma that is formed will have intracellular parasites and inflammatory cells. (Ewing and Panciera)

There has been development of an indirect enzyme-linked immunosorbent assay. It is a minimally invasive tool that was first thought to be highly sensitive and specific. New research has shown that false positives can be detected from the exposure to an *Amblyomma* tick. Some residual tick tissue may be present, affecting the test. (Ewing and Panciera)

A real time polymerase chain reaction test has been developed that extracts DNA from EDTA-whole blood. The PCR checks for a fragment of the *Hepatozoon* 18S rDNA gene and can detect as few as seven copies per milliliter of blood. There is a very high specificity and it will differentiate between *H. americanum* and *H. canis*. (Li and al.)

Treatment and Management Options

Initially, treatment includes supportive care and correcting any significant abnormalities that will prevent the patient from improving, such as dehydration, cachexia, and hypoproteinemia. Non-steroidal anti-inflammatories should be used to control pain throughout the length of clinical signs. Multimodal therapy is used to treat the overt disease. No medications are currently effective at eliminating the tissue stages of the disease. The therapy is a combination of trimethoprim-sulfadiazine at 15 mg/kg every 12 hours, clindamycin at 10 mg/kg every 8 hours, and pyrimethamine at 0.25 mg/kg every 24 hours for two weeks. (Baneth) This

protocol will eliminate the merozoite stage, and that will decrease the pyogranulomatous inflammation by removing the organisms. The patient will have to stay on an anticoccidial drug (decoquinate) for at least two years to help reduce the chance of a relapse occurring. New studies are showing that with the use of PCR testing the patient may not have to stay on decoquinate chronically. A negative PCR in conjunction with resolution of clinical signs is shown to be when the drug can be discontinued; however, it is safe to continue long term. Relapses are much less common with this protocol than with others. Other antiprotozoal drugs, such as imidocarb dipropionate or toltrazuril, can be transiently effective but relapses usually occur. (Potter and Macintire)

Prevention

Prevention is based solely on ways to decrease or eliminate contact with ticks. Regular application of ascaricides and tick repellants, as well as environmental parasiticides can help reduce the contact with ticks. Hepatozoonosis has not been shown to be transmitted through blood transfusions the way that other tick born disease are, most likely due to the complex life cycle. (Baneth) Experimental transmission has been achieved through consumption of an infected mammal, so dogs should not be fed raw meats or allowed access to animal organs. (Potter and Macintire)

Prognosis

If diagnosis is confirmed early in the disease process and therapy is began relatively quickly, the prognosis is excellent. Long term administration of decoquinate is imperative to prevent reinfection. If any doses are missed or the drug stopped all together, the prognosis drops. With secondary complications to the disease process, such as protein-losing nephropathy, usually related to delayed diagnosis and treatment the prognosis falls to guarded to poor.

Conclusion

American canine hepatozoonosis is an emerging disease that is getting more and more common in the endemic areas of the southeastern United States, and other areas where the Gulf Coast tick is present. Clinicians need to recognize the disease early in order to increase the chance of a good prognosis. Clinical signs will develop between four and ten weeks post exposure, and will get worse the longer the disease goes untreated. Use of the common physical exam, blood work, and radiographic abnormalities will help lead to a presumptive diagnosis. Even though the gold standard of diagnosis is muscle biopsy, other methods, such as PCR, can be used to gain a definitive diagnosis.

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