A Lot on His Mind

A Case of Canine Endocarditis

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Introduction

Infective endocarditis is a fairly uncommon diagnosis in canine patients, and rare in cats.[1] In cases of infective endocarditis, a septic vegetative thrombus occurs on one or more cardiac valves. Although the pathogenesis is not completely understood, disruption of the valvular endothelium and bacteremia are necessary components. Bacteremia may be the result of any infection. Rarely, fungal endocarditis has been reported.[2] Endocarditis is more common among male, middle-aged to older large breed dogs, although it may affect any dog.[1,13] Emboli from the thrombus may dislodge and travel through the bloodstream before lodging in capillaries and arteries. Commonly affected organs of thromboembolism seen in canine patients include the spleen and kidney.[1]

Although frequently described in human patients with infective endocarditis, cerebral infarction secondary to thromboembolism is an uncommon sequela described in canine patients.[1,16,17] This report describes a case of bacterial endocarditis in a canine patient who initially presented as inappetent which progressed to hindlimb lameness and, finally, seizures secondary to cerebral infarction.

History and Presentation

Hardy, an 11 year old male neutered Weimeraner, presented to the Mississippi State CVM Internal Medicine Service on March 1, 2018 for a one-day history of seizures. He also had a two-month history of inappetence which had progressed to hindlimb lameness by the time of presentation to MSU CVM. He presented to his RDVM on January 29, 2018 for inappetence. A CBC revealed a mild thrombocytopenia (132K/μL) and a moderate leukocytosis (28.13 K/μL) with a neutrophilia (20.47 K/μL), monocytosis (5.24 K/μL), and a basophilia (0.16 K/μL). A chemistry panel and the remainder of the CBC were within normal limits. He was treated with a

one week course of Clavamox, five day course of prednisone, and a one week course of Lixotinic supplement. A recheck of his CBC on February 5 showed mild improvement and his platelets were within normal limits. He was continued on Clavamox for an additional week. His clinical signs appeared to improve and he began eating again. However, on February 26, 2018, he returned to his RDVM due to a recurrence of his inappetence. He was prescribed prednisone and sent home. He returned on February 28, 2018 due to a return of his clinical signs. At this time, his owners reported that he was polyuric and polydipsic. A CBC revealed a mild to moderate thrombocytopenia (120 K/ μL) and leukocytosis (29.80 K/μL) with a neutrophilia (22.84 K/μL), severe monocytosis (5.47 K/μL), and a mild basophilia (0.12 K/μL). Hardy was treated with meloxicam and continued on his dose of oral Clavamox. He was hospitalized with his RDVM. While being administered treatments the morning of March 1, Hardy began having seizures. His RDVM suspected he had several the night before while hospitalized. A chemistry panel revealed an elevated ALP (446 U/L) and normoglycemia. Due to the occurrence of seizures, Hardy was referred to MSU CVM Internal Medicine Service.

During transportation to MSU CVM, Hardy had at least one seizure, at which time his owner administered rectal diazepam. On presentation, he was laterally recumbent and comatose. He weighed 31.3 kg, was in normal body condition (BCS 5/9), and his vitals were within normal limits (temperature: 102.5°F, pulse: 160, respiratory rate: panting), however, due to his comatose state, these values may be considered elevated. His mucous membranes were pale pink with a capillary refill time of < 2 seconds. A grade IV/VI left systolic heart murmur was heard on cardiac auscultation. Thoracic auscultation and abdominal palpation revealed no abnormalities. Petechiae were noted along his right flank. The remainder of his physical exam was within

normal limits. Soon after his presentation to MSU CVM, he had a seizure and was administered diazepam, shock boluses of LRS, levetiracetam, and mannitol intravenously.

Diagnostic Approach/Considerations

While Hardy was being stabilized, diagnostics were started. An iSTAT revealed metabolic acidosis with mild respiratory compensation. Glucostix and iSTAT showed normal glucose levels. A CBC and chemistry panel revealed severe thrombocytopenia (estimate: 64 K/μ), a moderate neutrophilia (18786/μL), mild hyperchloridemia (124.1 mmol/L), moderate to severe hypocapnia (13.8 mEg/L), mild azotemia (BUN: 30 mg/dL, creatinine: 1.52 mg/dL), mildly elevated ALP (452 U/L), and moderately elevated CK (1539 U/L). Lactate was elevated at 4.7 mmol/L. He was mildly hypertensive (145/83 mmHg, MAP: 104 mmHg) and an ECG revealed sinus tachycardia. A 4Dx SNAP test was performed and all parameters were below detectable limits. Packed cell volume and total protein were within normal limits. A FAST scan of his abdomen showed no free fluid and his SpO_2 was 98%. A tick-borne disease PCR panel was sent off to North Carolina State University and was negative for all diseases on the panel.

Thoracic radiographs showed an unstructured interstitial pattern, worse in the caudal lung fields, consistent with pulmonary edema secondary to seizures. Abdominal radiographs indicated mild hepatomegaly, a flattened caudal pole of the left kidney, osteophyte formation of the coxofemoral joints, and spondylosis deformans at L7-S1. Abdominal ultrasound showed multiple hyperechoic structures along the gallbladder mucosa, hyperechoic hepatic parenchyma, and mottled splenic parenchyma. An echocardiogram revealed a large, irregularly marginated, hyperechoic structure on the septal leaflet of the mitral valve and valvular insufficiency consistent with a vegetative endocarditis lesion. There was also valvular insufficiency of the

tricuspid valve, likely due to myxomatous degeneration. Following the findings of the echocardiogram, blood was submitted for blood culture, *Bartonella* culture, and *Bartonella* PCR.

The day after presentation, Hardy was transported to the Veterinary Specialty Center where he underwent an MRI. This scan showed multiple areas of hemorrhage and suggested vasogenic and cytotoxic edema.

Pathophysiology

The findings of Hardy's diagnostic imaging, physical exam, and bloodwork suggested that he had chronic vegetative mitral valve endocarditis which resulted in cerebral thromboemboli and infarction, thus leading to his seizures. The pathogenesis of infective endocarditis in dogs and humans is not fully understood.[1] It has been proposed that the valvular endothelium is disturbed, forming a thrombus. This thrombus is then colonized by bacteria secondary to a bacteremia, causing further proliferation of the lesion. However, inherent virulence factors of bacterial species associated with infective endocarditis may allow for adhesion to valves prior to thrombus formation.[7] The location of vegetative lesions on the side of valves receiving the highest force from blood flow suggests that trauma to the valves from this flow may increase the likelihood of bacterial adhesion and disturb endothelial integrity.[1] Bacteremia associated with infective endocarditis may result from any infection in the body, and the inciting cause is not often identified. Potential original insults include any systemic infection, abscess, urinary tract infection, or skin wound.[1,2] The role of periodontal disease in the genesis of infective endocarditis is controversial, but severe periodontal disease has been associated with a higher incidence of endocarditis.[15] Bacterial species reported to cause endocarditis include *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, *Pseudomonas aeruginosa*, *Corynebacterium* spp., and *Erysipelothrix rhusiopathiae*.[1,2] *Bartonella* spp. are reported to cause infective

endocarditis, but the incidence of *Bartonella* endocarditis may be regionally specific.[1,2,8,9] Fungal endocarditis has been rarely reported.[2] The most commonly affected valves in dogs are the mitral and aortic valves, with the pulmonic and tricuspid valves much less frequently affected.[13] Thrombus formation on the mitral and aortic valves predisposes patients to thromboembolism, in which portions of the vegetative lesion break off and travel through the bloodstream, lodging in smaller arteries and capillaries.[13] In most canine patients, the kidney and spleen are the most commonly affected organs of thromboemboli.[13]

Although brain involvement is described in dogs with endocarditis, it is less common than involvement of other organs.[10] Emboli from the valvular lesion travel through the arterial blood supply and lodge in smaller arteries or capillaries in the brain, causing an arterial infarction. In less severe cases, collateral circulation may make up for some of the deficits; however, once arterial blood supply to the brain has been completely occluded for 4-5 minutes, the functional damage to neural tissue is irreversible. Energy deficits lead to lactic acidosis, free radical formation, and cytotoxicity. This causes necrosis of neural tissue and a breakdown of vascular integrity within the brain.[6] Liquefactive necrosis within the brain and breakdown of blood vessels results in hemorrhagic infarcts. Additionally, inflammation can cause a breakdown of the blood brain barrier, increasing exposure to pathogens and causing an influx of inflammatory cells within the neural tissue.[6] Cerebrovascular disease in dogs usually affects the forebrain, as was seen in Hardy's case.[11] Damage to the cerebral tissue resulted in his seizures and declining mental status.

Treatment and Management

Treatment for infective endocarditis is focused on aggressive antimicrobial therapy. A culture and sensitivity based on blood culture would be the ideal method of deciding on an

antimicrobial regimen. However, most patients need to begin treatment immediately due to the severity of their illness, and blood cultures are often negative, making empiric therapy the best treatment option[1,2] Broad spectrum antimicrobial therapy may be started empirically. Because bacteria have colonized the thrombus, high levels of bactericidal agents are needed to penetrate deep into the vegetative lesion.[2] Parenteral antimicrobials should be used for the first 4-7 days. Once the patient is stable, oral medications may be utilized. These will often need be given for several months following hospitalization.[2] It can be difficult to sterilize the thrombus, and if it is done, valvular insufficiency often still remains.[2] Valve replacements, though gold standard in human medicine, are very rare in veterinary medicine, although they have been reported.[4,5]

Treatment for cerebral ischemic infarction centers on maintaining cerebral perfusion pressure and minimizing inflammation. There is no evidence to support the use of glucocorticoids in ischemic cerebrovascular events.[6] Although ischemic cerebral incidents are caused by a thrombotic event, thrombolytics are discouraged in human patients, due to increased risk of hemorrhage and association with a higher mortality rate.[12,16] Antithrombotic therapy has shown some benefit if given very early in the course of disease in veterinary patients, but should not be used in cases when hemorrhage is suspected.[6] Supportive care and management of sequelae, such as seizures, are also important.[2,6] Other sequelae of endocarditis include congestive heart failure and arrhythmias and should be considered when formulating a treatment regimen.[1]

Hardy was treated with cefoxitin, doxycycline, enrofloxacin, and ampicillin/sulbactam for broad spectrum antimicrobial coverage the first day of hospitalization. He was given dexamethasone for anti-inflammatory purposes and maintained on LRS. Seizure control initially included rescue doses of diazepam and a levetiracetam constant rate infusion. When he

continued to have seizures, a midazolam constant rate infusion was added. This controlled his seizures for a short time, but eventually a propofol constant rate infusion was needed to fully control his seizures.

Case Outcome

Due to the severity of Hardy's illness and grave prognosis, his owners elected to humanely euthanize him. At necropsy, infective endocarditis of the mitral valve was confirmed. Culture of the valve revealed growth of *Escherichia coli*, *Enterococcus faecium*, and *Pseudomonas aeruginosa*. A blood culture showed growth of *Corynebacterium* spp. A large hemorrhagic infarct was present in his cerebrum from the left rostral frontal lobe to the hippocampus at the level of the occipital lobe, crossing midline. Both white matter and grey matter were affected. The multifocal nature of the hemorrhage is suggestive of multiple arterial infarcts within the brain. A chronic arterial infarction was present in the kidney, possibly secondary to a thromboembolism earlier in the disease process, or from some unknown etiology. Necropsy also confirmed the pulmonary edema and hepatocellular vacuolar degeneration suspected from diagnostic imaging. Incidentally, a pheochromocytoma was present in an adrenal gland, and the intestines showed signs of enteritis.

The prognosis associated with endocarditis is poor to grave. Negative prognostic indicators associated with infective endocarditis include thrombocytopenia, increased creatinine, thromboembolism, and renal complications.[13,14] Hardy had evidence of all of these prognostic indicators. Early diagnosis and aggressive treatment may give patients the best chance at a positive outcome. Due to its often nonspecific signs, endocarditis should always be considered as a rule out for a patient with chronic lethargy, inappetence, lameness, fever, or newly diagnosed heart murmur.

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