Clot off Guard

A Case Report of Aortic Thromboembolism in the Canine

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Introduction

Aortic thromboembolism, often appropriately termed “saddle thrombus” due to the thrombus becoming lodged at the aortic bifurcation, is a well-known entity in the feline patient. Though documented in both cats and dogs, it is significantly less common and thus less commonly described in dogs. In most basic terms, thrombosis is the pathologic formation of a blood clot within a vessel, while an embolus occurs when a thrombus breaks off and obstructs the blood flow to a distal location.[1]

Classically, the feline patient presents with acute onset of paraparesis or paraplegia, pain, hypothermia of the distal extremities, absent or weak femoral pulses, and footpad pallor. Feline aortic thromboembolism is most commonly associated with underlying heart disease, particularly hypertrophic cardiomyopathy, though other less common etiologies have also been reported. The pathogenesis of a thromboembolic event secondary to cardiac disease involves thrombus formation in the left heart followed by embolization of the thrombus to the distal aorta. Occlusion of blood flow in the distal aorta leads to acute pelvic limb ischemia and paresis. Given the severity of associated pain, the frequent presence of significant underlying heart disease, and low efficacy of treatment, most patients are humanely euthanized. Intensive nursing care, time, and luck can sometimes lead to clinical recovery, but even with initial survival, recurrence is common. Prognostic indicators at presentation that are negatively associated with survival include decreased rectal temperature, bradycardia, and multiple limb involvement.[2]

Canine aortic thrombosis is less thoroughly documented in the current veterinary literature. Some studies suggest that dogs more often have a chronic or insidious onset of clinical signs related to pelvic limb dysfunction compared to the acute onset typically seen in cats. There is a much more extensive list of possible etiologies for a hypercoagulable canine patient. With

coagulopathies commonly encountered in critical illness, disease processes such as immune-mediated illness, neoplasia, systemic inflammation and sepsis, cardiac disease, endocrine disease, protein-losing states, and infectious diseases have all been implicated as potential underlying causes of aortic thrombotic disease in dogs. Locomotor dysfunction with neurologic deficits have been described as a consequence of aortic thromboembolism in dogs.[3,4] Both acute and chronic onset have been reported; clinical signs include exercise intolerance, hind limb paresis, absent femoral pulses, cold extremities, and pain. Survival rate of afflicted dogs is reportedly better than that in cats, but overall prognosis and recurrence rate have not been thoroughly investigated.[5]

A wide variety of differential diagnoses come to mind when a "down dog" presents for evaluation, but unlike in cats, saddle thrombus is not always on the list, much less at the top. In contrast to dogs who present for paraparesis of primary neurologic origin, a thorough and attentive physical examination by a general practitioner can yield enough clinical evidence to heighten suspicions of a saddle thrombus. The following case demonstrates how a thorough and informed physical exam can be crucial in the presumptive diagnosis of aortic thromboembolism in dogs. By recognizing key findings on a basic physical exam and readily available patient-side diagnostic tests, small animal general practitioners can confidently diagnose this disease and thus provide accurate diagnostic, treatment, and referral options for these patients and their owners.

History and Presentation

Little Bear was an 11-year-old male neutered Rottweiler mix dog who was referred to the Neurology service at the Veterinary Specialty Center (VSC) on November 8, 2018 for evaluation of being down in the hind end. He had been boarding at his primary veterinarian since November 3, 2018 and was reportedly normal upon admission to that facility. He was first noted by kennel

staff to be limping on his right pelvic limb on November 6th. By the following day, he had progressed to ambulatory paraparesis. He was noted to have a decreased appetite on the evening of November 7th, which was unusual for him. Little Bear had a history of right cranial cruciate ligament rupture 3 years prior that had been medically managed with strict cage confinement and anti-inflammatory medications. He was not on any medications other than monthly preventatives at the time of presentation, and no other clinical abnormalities were reported by the owners. He had no recent history of gait abnormalities, exercise intolerance, polyuria, or polydipsia. On the morning of November 8th, Little Bear was found by kennel staff to be unable to use his pelvic limbs and was thus referred to Neurology for evaluation.

Upon presentation to VSC, Little Bear was dull but responsive. He was normothermic (temperature: 101.2 F), moderately tachycardic (pulse rate: 160 beats per minute), and mildly tachypneic (respiratory rate: 40 breaths per minute). Little Bear weighed 32.2 kg (70.84 lbs) with an overweight body condition score of 7/9. Notable physical exam findings included an absent palpable femoral pulse in the right pelvic limb and a very weak, intermittent femoral pulse in the left pelvic limb. Both pelvic limbs were cold to the touch, atonic, and painful with merely gentle palpation. A full neurological exam revealed lack of motor function of the right pelvic limb and very minimal motor function in the left pelvic limb, as well as absent postural reactions in both pelvic limbs. Reflexes and muscle tone were absent in the right pelvic limb and decreased to absent in the left pelvic limb. Throughout the exam, Little Bear intermittently dribbled pink-tinged urine, suspected to be pigmenturia.

Diagnostic Approach

Given Little Bear's physical and neurological exam findings, aortic thromboembolism was the top differential diagnosis which was then corroborated using simple in-house

diagnostics. Doppler blood pressures were taken on both the thoracic limbs and pelvic limbs and then compared to one another. Thoracic limb blood pressures were within normal limits, but pelvic limb blood pressure could not be detected, supporting lack of appreciable blood flow to these extremities. Another diagnostic tool utilized in this case included comparative blood glucose levels. Blood sampled from the right thoracic limb had a blood glucose of 97 mg/dL, while blood sampled from the right and left pelvic limbs measured 73 mg/dL and 63 mg/dL, respectively. This difference is expected with aortic thromboembolism, as the diminished circulating blood flow leads to lack of appropriate delivery of glucose and other nutrients.[5] Additional diagnostics, including complete blood count, chemistry panel, thoracic radiographs, and abdominal contrast computed tomography were offered to the owners but ultimately declined. Give the high clinical suspicion of an aortic thromboembolism and associated poor prognosis, Little Bear's owners elected humane euthanasia and necropsy exam.

Although a working diagnosis of aortic thromboembolism can be made primarily on clinical presentation and a concurrent history of a predisposing condition, definitive antemortem diagnosis requires assessment of the caudal abdominal vessels via ultrasonography or advanced imaging. Selective iodine contrast medium angiography is regarded as the gold standard for diagnosis of canine aortic thromboembolism.[6] When owners are willing to pursue additional diagnostic testing, several modalities may be utilized with varying success. Abdominal ultrasonography is potentially the least invasive and thus most useful to identify the aortic thrombus, as well as color Doppler to determine blood flow. However, depending on the size as well as age of the thrombus, their characteristics change and can be technically difficult to image.[7, 8]

Pathophysiology

Although an exhaustive discussion of coagulation is beyond the scope of this paper, a basic review of the coagulation cascade is imperative for understanding the pathophysiology of aortic thromboembolism. The interactions and balance between the coagulation cascade and its counterregulatory mechanisms are complex. Coagulation is the result of activation of proteases, with the end product being thrombus formation and cross-linking of fibrin at the site of injury. Just as the formation of a stable fibrin clot is important in achieving hemostasis, dissolution of clots by fibrinolysis is also imperative. Plasmin formed by plasminogen is the major fibrinolytic enzyme responsible for breaking down fibrinogen and fibrin, which yields fibrin degradation products.[9] Protein C, protein S, antithrombin, and fibrinolytic enzymes are anticoagulants that are naturally present in the body. These molecules ensure that thrombin formation and fibrin deposition occur only when necessary.[9,10]

Pathologic thrombosis is often a fatal complication of hypercoagulable diseases, occurring in approximately 25% of patients.[12] Virchow described three factors that contribute to thrombosis: hypercoagulability, vascular injury, and blood stasis. Anticoagulant properties of cells and negative feedback mechanisms are instrumental in appropriately regulating thrombus formation by limiting clot formation to the site of injury while preventing excessive thrombus formation and thus inappropriate vascular occlusion.[12,13] Several pathological entities can overwhelm these regulatory mechanisms, including increased generation of prothrombotic elements via induction of inflammatory pathways, direct production of tissue factor or similar prothrombotic substances, and platelet activation. Inhibition of anticoagulation mechanisms via decreased antithrombin, thrombomodulin, tissue factor pathway inhibitor production, or endothelial dysfunction have also been documented. Inhibition of thrombolysis via depression of the fibrinolytic system can also occur.[14]

Diseases known for predisposing canine patients to a hypercoagulable state include diabetes mellitus, glomerular disease, hyperadrenocorticism, cardiac disease, neoplasia, disseminated intravascular coagulation (DIC), and sepsis.[6] Little Bear's necropsy disclosed histopathologic evidence of chronic glomerulonephritis, which was presumed to be responsible for his hypercoagulable state and subsequent aortic thromboembolism. Given this finding, the remainder of this discussion will focus primarily on the pathophysiology of glomerulonephritis specifically as it relates to aortic thromboembolism. Most often, glomerular disease is the result of immune complexes that become lodged in the glomerular capillary walls. These immune complexes stimulate glomerular cell proliferation and thickening of the capillary walls, leading to glomerular hyalinization and sclerosis. Once a glomerulus has been irreversibly damaged by glomerulonephritis, the entire nephron becomes non-functional.[15]

There are several known causes of glomerulonephritis, but often no specific etiology can be identified. Although there are a wide range of theories and postulations as to the exact cause of glomerulonephritis leading to a hypercoagulable state, it is generally accepted that drastic loss of antithrombin III into the urine plays a consistently significant role. Antithrombin III works with heparin to inhibit proteases, including clotting factors II, IX, X, XI, and XII. Under normal physiologic conditions, antithrombin III plays an important role in modulating thrombin and fibrin production.[16] Other theories to explain the role of glomerulonephritis in hypercoagulability include mild thrombocytosis, hypoalbuminemia-related platelet hypersensitivity, altered fibrinolysis, and increased proportion of large molecular weight clotting factors in comparison to regulatory proteins.[16]

Disruption of normal glomerular filtration in glomerular disease leads to protein loss. The resulting protein-losing nephropathy allows low molecular weight plasma proteins such as

albumin at 69,000 Da and antithrombin ranging from 58-65,000 Da in size to pass through the filtration barrier into the urine. Interestingly enough, protein C with a molecular weight of 62,000 Da is not consistently low in patients with protein-losing nephropathies, suggesting that molecular size may not be the only factor influencing glomerular protein loss. Protein C is strongly negatively charged, which may be why it does not pass through the filtration barrier as easily.[8]

Clinical signs of aortic thromboembolism in dogs vary depending on the degree of occlusion of the distal aorta by the thrombus. Exercise intolerance or intermittent unilateral hindlimb paresis or lameness may be the only reported clinical signs. More often than cats, dogs tend to present chronically affected, speculated to be due to better collateral circulation in the region of the caudal abdomen and pelvic limbs. Depending on the underlying cause of aortic thromboembolism, chronically affected dogs can have a better overall prognosis. Dogs that present with acute and dramatic clinical signs such as paraplegia, as in Little Bear's case, have a poorer chance of survival.[6, 7,8]

Diagnostic Approach and Considerations

With Little Bear's acute, progressive presentation and high suspicion for aortic thromboembolism based on physical exam, several diagnostic options for not only definite diagnosis of aortic thromboembolism but also screening for an underlying disease entity were offered to the clients. A serum chemistry panel, a complete blood count, and urinalysis would have been helpful in increasing or decreasing the suspicion for several rule outs for diseases predisposing dogs to hypercoagulability, such as hyperadrenocorticism, diabetes mellitus, immune-mediated hemolytic anemia, protein-losing enteropathy or nephropathy, inflammatory processes such as pancreatitis and sepsis, neoplasia, and cardiac disease.[4] Had it been performed,

serum chemistry is also expected to have reflected the degree of muscle damage caused by the ischemic myopathy via elevations in CK and AST.[3] Other diagnostics recommended included thoracic radiographs to screen for cardiac disease and pulmonary metastatic neoplasia, an abdominal ultrasound to assess blood flow through the distal aorta, and an abdominal CT scan with contrast for three-dimensional visualization of the caudal abdominal vessels. These diagnostics were unfortunately declined by the clients. Readily available diagnostics utilized in this case included thorough physical and neurological exams, Doppler blood pressures, and comparative blood glucose of the fore and hindlimbs. With this information quickly and easily obtained, an accurate clinical diagnosis was identified despite the lack of additional diagnostics.

Efforts have been made to establish screening tests to identify hypercoagulability in dogs with known predisposing diseases. Platelet count, activated clotting time, and coagulation panels are more useful in identifying hypocoagulable patients, thus an easy and non-invasive diagnosis of hypercoagulability is difficult. Diagnostic procedures used to detect formed thrombi, such as angiography and ventilation/perfusion (V/Q) scans, are more invasive and involve inherent risk to the patient.[10] These tests also lack the ability to identify hypercoagulable states prior to the formation of a gross thrombus. Laboratory tests to detect fibrin and D-dimer are commonly used to assess patients with thrombotic syndromes, but once again are not predictors of clot formation. Nonspecifically, thrombocytosis and high fibrinogen may be associated with thromboembolism but are not consistently present in all cases. Some clinicians have proposed that hypercoagulability can be suggested with a shortened prothrombin time or active partial thromboplastin time, but there is no published evidence to support this.[11]

Thromboelastography (TEG) is a method of testing efficiency of blood coagulation utilized primarily in human medicine to identify platelet disorders, coagulation factor

deficiencies, DIC, thrombotic disorders, and fibrinolytic pathway defects. TEG produces a tracing of the coagulation process in whole blood, reflecting the kinetics and tensile strength of a fibrin clot and its subsequent fibrinolysis. This test thus has the potential to identify patients with physiologic conditions that favor thrombosis. A few recent studies have utilized TEG in animal models.[11]

Treatment and Management

Many of the treatment protocols for thrombosis in veterinary patients have been extrapolated from human medicine.[17] There are stringent limitations to treatment in veterinary patients, as the safety and efficacy of some drugs utilized are largely unknown. A multimodal approach consisting of anti-thrombotics, anticoagulant therapy, thrombolytics, and possibly surgical intervention is often considered. Surgical thrombectomy has only been sporadically reported in veterinary medicine, and thus is not always utilized in the treatment of aortic thromboembolsim.[14] Treatment with antithrombotic drugs or anticoagulants addresses suppression of thrombogenesis, while thrombolytic medications or surgical thrombectomy are utilized to break up existing thrombi. Minimally invasive procedures utilized in human medicine, such as catheter-directed thrombolysis, balloon dilatation or angioplasty, vascular stenting, and emboli trapping devices, are logistically not currently possible in veterinary medicine.[14, 15]

Medical management is often attempted in veterinary patients, though success is variable. Thrombolytic medications target the clot directly to accelerate fibrinolysis, but may also lead to bleeding tendencies, pulmonary thromboembolism, and reperfusion injury. A few reports in the veterinary literature describe the use of tissue plasminogen activator, streptokinase, and urokinse in canine and feline patients with generally poor survival rates.[15] Following thrombosis intervention, anticoagulation management becomes essential to prevent recurrent clot formation.

Most importantly, any underlying condition identified must be addressed. Warfarin has been classically utilized in human patients, and use in veterinary patients is reported. Warfarin has a narrow margin of safety due to extrapolation of doses and various factors that can influence its *in vivo* effects, thus it is typically no longer recommended for use in veterinary patients. Unfractionated heparin requires antithrombin for its anticoagulant effect. The heparin-antithrombin complex inactivates several coagulation factors, most notably thrombin and Xa. Though largely preferred in human medicine, veterinary use of low-molecular weight heparin, such as enoxaparin, is hindered by lack of an established dosing regimen. Clopidogrel, an irreversible ADP antagonist, is a potent antiplatelet medication that further reduces the risk of vascular events. Both single agent use and various combination therapies have been documented with success, though no consensus in treatment has been established.[15, 16]

Overall, dogs presenting with aortic thromboembolism have a reported 50-60% chance of survival. Acute and severe signs are both poor prognostic indicators, as milder, more chronically affected dogs have a much better chance of survival.[6]

Case Outcome

Given the presumptive diagnosis of aortic thromboembolism and associated poor prognosis, Little Bear's case concluded in humane euthanasia with necropsy, which ultimately confirmed the suspected clinical diagnosis. A 9 cm thromboembolism was identified in the distal aorta, extending into the external iliac arteries bilaterally. Other notable necropsy findings included the gross and histopathologic characteristics of his kidneys. Both kidneys were grossly pale, firm, and multifocally irregularly contoured, with a fine granular appearance in the renal cortex. Histopathology confirmed glomerulonephritis and glomerulosclerosis, characterized by severe fibrosing and lymphoplasmacytic interstitial nephritis. Analysis of ocular fluid confirmed

the presence of azotemia with a BUN of 119 mg/dl and a creatinine of 3.4 mg/dl. With the severity of locomotor deficiencies present, euthanasia was an appropriate treatment decision.

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