Ozzy's FATE

Aortic Thromboembolism Secondary to Hypertrophic Cardiomyopathy in the Feline Patient

Nicole E. Rowbotham

Mississippi State University College of Veterinary Medicine

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Advisor: Aimee Daniel, DVM, MS

Introduction

Hypertrophic Cardiomyopathy (HCM) is a clinically significant heart disease of cats that is encountered frequently in small animal practice. It is characterized by severe left ventricular concentric hypertrophy and secondary left atrial dilation, which results in diastolic failure. HCM is the most common feline cardiac disease and is most often seen in middle-aged male cats. Clinical signs often manifest as acute left sided heart failure and can result in sudden death.[1] Feline Aortic Thromboembolism (FATE) is a potential life-threatening sequela of hypertrophic cardiomyopathy that results from thrombus formation within the left side of the heart. In a study of 127 cats diagnosed with FATE, the breeds that were over-represented include Abyssinian, Birman, and Ragdoll. Additionally, male cats are at a greater predisposition for the development of HCM, and several studies have shown FATE to also be more common in male cats. [4,9] The purpose of this case report is to describe the management of one case of aortic thromboembolism secondary to hypertrophic cardiomyopathy in a 15-year-old Domestic Shorthair cat.

History and Presentation

Ozzy was a 15-year-old neutered male Domestic Shorthair cat who presented to Mississippi State University College of Veterinary Medicine Animal Health Center's Emergency Service on December 29th, 2018 for acute respiratory distress. Ozzy's owners reported that he was acting normally while they were home during the day. Later, his owners left home for approximately two hours, and upon returning, they found Ozzy laterally recumbent, stretched out, vocalizing, panting, and drooling. Ozzy had previously been diagnosed with Diabetes Mellitus and received ProZinc insulin twice daily. He also had a history of chronic renal disease and was fed Hill's Prescription Diet k/d dry diet.

Upon presentation, Ozzy was open mouth breathing and vocalizing. He was hypothermic (temperature: 96.0 F), normocardic (heart rate: 180 beats per minute), and tachypneic (respiratory rate: 90 breaths per minute). His mucous membranes were pink and moist, and his capillary refill time was less than 2 seconds. He was overweight with a body condition score of 6 out of 9. Cardiothoracic auscultation revealed a grade II/VI parasternal systolic murmur. His hindlimbs were pale and cold to the touch. Femoral pulses and withdrawal reflexes were absent in the hindlimbs. He was non-responsive to noxious stimuli. The remainder of his physical examination was unremarkable.

Ozzy's initial presentation of respiratory distress resulted in immediate administration of flow-by oxygen. He was given methadone and acepromazine intravenously for reduction of pain, sedation, and anxiety. Pulse oximetry was measured at 100% on flow-by oxygen and 93% on room air. Electrocardiography (ECG) revealed a normal sinus rhythm. Indirect blood pressure was measured at 245 mmHg on his right forelimb using a Doppler. Hindlimb blood pressure was too low to be assessed, though attempts were made to obtain measurements with a Doppler. Abdominal and thoracic FAST scan were negative for the presence of free fluid. Blood glucose samples were obtained from Ozzy's left forelimb (282 g/dl) and from his left hindlimb (182 g/dl). Due to poor perfusion to his hindlimbs, a large enough blood sample was unable to be obtained for blood lactate levels. Based on the history and physical exam, Ozzy was suspected to have an aortic thromboembolism.

Pathophysiology

As stated previously, Feline Aortic Thormboembolism (FATE) is a potential life-threatening sequela of hypertrophic cardiomyopathy that results in thrombus formation within the left side of the heart that may discharge into the aorta and systemic circulation. Though most often associated with

HCM, all cardiomyopathies serve as a risk factor for FATE. Virchow's triad describes the three conditions that favor thrombus formation: blood stasis or turbulent blood flow, hypercoagulability, and changes to the endothelial surface. Each of these conditions may be present in a cat with HCM, though the exact mechanism of intracardiac thrombi formation is unclear. Most cats that present for FATE have some degree of left atrial enlargement.[4,9] As the left atrium dilates, blood flow slows, resulting in turbulence and the activation of coagulation. Peak blood flow velocity in the left atrial appendage, which is measured by doppler echocardiography, is lower in cats with left atrial thrombi or aortic thromboembolism than those with no cardiac disease. Also, the appearance of spontaneous echo contrast (SEC), or "smoke" in the left atrium is postulated to be a marker of increased risk for FATE.[7] Intracardiac thrombi are often identified on echocardiography in cats with cardiac disease, and 21% of cats with HCM have an identifiable thrombus within the left atrium at necropsy.[9,10]

Non-cardiac related causes of aortic thromboembolism have been identified. Neoplasia, most notably pulmonary carcinoma, can result in tumor embolism.[3,4] Previously diagnosed hyperthyroid cats that became euthyroid had echocardiographically normal hearts at the time of aortic thromboembolism which may conclude that thyroid disease poses a risk for FATE independent of thyrotoxic cardiac changes.[9] Any disease that causes a hypercoagulable state can conceivably result in thrombus formation and result in FATE. Ozzy's previously diagnosed chronic renal failure may have also contributed to low antithrombin via protein losing nephropathy; however, a serum chemistry was not performed on Ozzy antemortem to identify hypoalbuminemia.

Clinical signs associated with FATE are a result of acute ischemic injury of the tissue distal to the occluded artery. The location of the occlusion may vary due to vascular anatomy and the size of the embolus. Because large thrombi can form within the left atrium, the most common location of embolus occlusion is the aortic trifurcation. This is known as a "saddle thrombus" and results in a presentation for

acute bilateral hindlimb lameness, paraplegia, or paraparesis. Unilateral hindlimb presentation is possible with smaller thrombi that lodge more distal in the vascular tree. It is also possible for a unilateral forelimb presentation to occur if a smaller thrombi embolizes into the right or left subclavian arteries. Affected limbs are usually painful, evident by patients' vocalizing, panting and excitement. In cats with no radiographic evidence of congestive heart failure (CHF), 89% were tachypneic or open-mouth breathing as a result of pain rather than respiratory distress. Radiographic or necropsy evidence of CHF has been reported in approximately half of cats with FATE.[10]

Depending on the degree of ischemia, paw pads and nail beds may appear pale or cyanotic. Motor function is more likely to be present when FATE presents in the forelimb or unilaterally in the hindlimb.[9] Most cats are in distributive and/or cardiogenic shock at time of presentation due to the ischemia and subsequent release of vasoactive substances downstream from the occlusion or the underlying cardiac disease. Hypothermia is often present as a manifestation of shock and poor systemic perfusion. Pulses are weak or nonpalpable on affected limbs, and the musculature is frequently firm due to ischemic myopathy by 10 to 12 hours post embolization. Hyperglycemia is frequently observed, likely secondary to cortisol and epinephrine release resulting from stress.[8,9]

Diagnostic Approach and Considerations

Diagnosis of limb ischemia is straightforward and can be characterized by the "five P's": pulselessness, pain, pallor, paresis, and poikilothermia. However, confirming that the ischemia is the result of aortic thromboembolism can be difficult due to the possibility of partial obstructions. Doppler can be used to evaluate arterial blood flow in cats with plegia and nonpalpable pulses; however, arterial blood flow cannot exclude FATE as a diagnosis because of the possibility of partial occlusions.

Neurologic differential diagnoses should be ruled out in any case of acute appendicular signs. Differentials include diseases of the spinal cord including intervertebral disk disease, spinal neoplasia, embolism, trauma or foreign body, peripheral neuropathies, and acute intracranial disorders including toxicity, trauma, shock, neuroglycopenic crisis, and embolism. [10]

Many cats have underlying cardiac disease and consequently, may have a heart murmur or arrhythmia. These physical exam findings, in conjunction with the presenting appendicular signs, often bolster support of the FATE diagnosis. However, absence of a murmur or arrhythmia should not deter one from the diagnosis of FATE, as up to 43% of cats diagnosed with FATE will have no cardiac abnormalities on auscultation.[4, 9] In fact, in up to 89% of cats with FATE, acute appendicular signs are the first indication of any underlying cardiac disease.[4]

Comparing central venous blood samples with blood samples from an affected limb can also support the diagnosis of FATE. Venous glucose of an affected limb will be significantly lower than central venous glucose in cats with appendicular aortic thromboembolism. Venous lactate in an ischemic limb will be significantly higher than central venous lactate. Serum chemistry will often reveal azotemia, acidosis, and electrolyte abnormalities (often hypocalcemia, hyperphosphatemia, hypokalemia, hyperkalemia, and hyponatremia). Increased serum aspartate aminotransferase is almost always seen due to muscle ischemia. Serum creatine phosphokinase is often markedly elevated. [9] Routine coagulation tests are generally unremarkable.[2]

Radiography, ultrasonography, angiography, and nuclear scintigraphy may all be used to provide further information when other diagnostic modalities have failed to identify a cause for ischemia. These imaging modalities may also serve to determine whether the obstruction is local rather than embolic in nature.

Treatment and Management

Therapy of FATE is directed at survival of the patient rather than preserving the affected limbs. During the initial crisis, providing analgesia, improving systemic perfusion, and treating CHF, if present, are the primary objectives. Typically, little is done in hopes to restore limb function because of the significant risks associated with attempted thrombus dissolution.

During initial treatment, analgesia is of utmost importance when treating cats with aortic thromboembolism due to the severe pain associated with ischemic injury. Intravenous administration of an opioid is reasonable for FATE. Acepromazine is occasionally given in conjunction with an opioid to decrease anxiety and for its vasodilatory effect which is thought to potentially improve arterial flow to the ischemic limb; however, use of this drug is controversial due to its potential to exacerbate shock. [6,10]

Oxygen supplementation is indicated for all patients with FATE that present with respiratory signs, whether those signs are due to CHF, anxiety, or pain. Tachypnea does not reliably predict the presence of CHF; therefore, cats with FATE should not be treated for CHF unless confirmed by radiography. Treatment of CHF includes use of a diuretic, most commonly furosemide, which may worsen systemic perfusion by reducing circulatory volume and vasodilation. If CHF is present, furosemide and venodilators should be used as needed for the individual patient. Thoracocentesis may be indicated in cats with pleural effusion. [9]

Efforts should be made towards improving systemic perfusion as early as possible. Because poor perfusion in these cases may be due to a combination of distributive and cardiogenic shock, correcting perfusion can be challenging. Fluid therapy is indicated in dehydrated patients who are not in CHF; conversely, significant caution should be used when administering fluids to a patient in CHF. Positive ionotropes may be helpful, particularly when echocardiography shows decreased systolic function. It is

important to note that externally warming hypothermic patients will cause peripheral vasodilation and worsen perfusion of vital organs; therefore, correction of hypothermia should only be done after addressing systemic perfusion.[10] Rectal temperature and heart rate inversely impact prognosis as these factors reflect a compromised hemodynamic state. Cats with rectal temperatures above 98.9 F have a 50% probability of survival.[9]

Anticoagulant therapy with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or aspirin should be initiated during the short-term management of FATE as it reduces the risk of intracardiac thrombus formation. It is also speculated that anticoagulants prevent thrombus extension, which decreases the potential for further reduction of arterial blood flow. UFH prevents the involvement of antithrombin (AT) and heparin cofactor II in the coagulation cascade by catalyzing their binding to various coagulation factors. Efficacy has not been established, so monitoring of activated partial thromboplastin time (aPTT) and/or activated clotting time (ACT) is indicated throughout treatment. LMWH enhances antithrombin's inhibition of activated factor X and other coagulation factors to prevent the development of new thrombi and the dissemination of existing thrombi. LMWH is effective, has reduced need for monitoring, and results in fewer bleeding complications than other anticoagulants. Because LMWH is cleared through the kidney, dosing may need to be adjusted in patients with renal compromise, like Ozzy.[5] Aspirin (acetylsalicylic acid) is a cyclooxygenase inhibitor that decreases vasoconstriction and platelet aggregation in response to injury by irreversibly inhibiting the production of thromboxane A2 in platelets. Experimentally, aspirin has been shown to improve collateral circulation in cats that were treated versus those not treated, but no controlled trials have been evaluated for efficacy in the acute management of FATE in cats. Aspirin is recommended at a dose of 5mg/kg administered every 72 hours.[5]

Initiation of thrombolytic therapy with tissue type plasminogen activator (TPA) and streptokinase (SK) for the acute treatment of FATE is controversial and has minimal supportive scientific data.[10] It is typically not recommended for cats with FATE.[5] TPA lyses clots by activating plasminogen to form plasmin and degrade fibrin. SK is a protein produced by a beta-hemolytic streptococci that binds freely circulating plasminogen and been shown to lyse thrombi in cats experimentally.[5] Thrombolytic treatment has many potential side effects, such as bleeding and distal embolization and the potential to cause fatal reperfusion injury.[5,10]

Long-term treatment for these patients consists of treating the underlying disease. With HCM, treatment is aimed at reducing left ventricular end diastolic pressure (LVEDP), correcting arrhythmias, improving myocardial oxygenation, and preventing pulmonary edema. Furosemide is the diuretic of choice in emergencies due to its ability to reduce LVEDP. To treat the diastolic failure of HCM, beta blockers and calcium channel blockers may be used to slow the heart rate and enhance ventricular relaxation.[1]

Thromboprophylactic drugs may be used in long-term treatment of FATE. Aspirin is commonly recommended for cats at risk of aortic thromboembolism at a dose of 5mg/cat administered orally every 72 hours as there is no need for monitoring, but efficacy is questionable. Thienopyridine derivatives, such as clopidogrel and ticlopidine, are reasonable alternatives to aspirin that irreversible antagonize ADP receptors on platelet membranes and interfere with primary and secondary platelet aggregation. Warfarin has been used in cats at risk of FATE, anecdotally.[10] Further research is necessary to determining the most efficacious method of long-term thromboprophylaxis.

FATE typically results in severe hemodynamic compromise, acid-base imbalance, and electrolyte abnormalities; thus, prognosis is generally poor. Reported rates of survival are 33-45%, and humane euthanasia is often elected.[10] For those who do survive, a complete return of function may be possible for

the affected limbs, depending on the severity. The presence of motor function and having only one limb affective support a better prognosis, but neurologic function of the limb may not completely return.[9] Ischemia may cause tissue necrosis and possibly result in the need for wound management, skin grafting, or amputation. Tendon contracture may also occur. Recovery times may be as long as months, but permanent limb damage is rare.[8] Concurrent CHF during an acute aortic thromboembolism has been shown to have no significant effect on survival to discharge but does have significant effect on long-term survival after discharge. The median survival time of cats with CHF who survived FATE was 77 days opposed to the median survival time of 223 days for cats without CHF who survived FATE.[9] Recurrence of aortic thromboembolism is 24% to 45% of cats treated with various anticoagulants and typically prompts euthanasia.[10]

Ultimately, the best treatment is prevention. Once a diagnosis of HCM has been made echosonographically, the presence of an enlarged left atrium and/or a "smoke" sign within the left atrium should prompt the initiation of thromboprophylactic therapies to decrease the risk of FATE.

Case Outcome

Due to the poor prognosis associated with the diagnosis of aortic thromboembolism, Ozzy's owners for elected humane euthanasia with necropsy. Necropsy confirmed the suspected clinical diagnosis. The heart was markedly enlarged, weighing 35.1 grams, which is consistent with HCM. Upon cross section, the left ventricular free wall and the septal wall were both markedly thickened (septal wall= 1 cm, left ventricular free wall= 1.5 cm), leaving a slit-like left ventricular lumen. The left atrium was dilated, and the associated auricular wall was thin. Histologically, the myofibers were often swollen and displayed frequent right-angled branching (myofiber disarray). There were multifocal foci of fibrosis,

most severe in left ventricular free wall. The turbulent blood flow and cardiac emboli within the markedly dilated left atrium predisposed Ozzy to thromboemboli formation. A 1.5 cm long thrombus was noted in the caudal abdominal aorta and was lodged at the aortic bifurcation which caused the lack of blood flow and impaired function to both hindlimbs. The presence of chronic pulmonary edema and hepatic congestion indicated that Ozzy was in biventricular heart failure.

Additional notable necropsy findings include small cell lymphoma of the small intestines, atrophy and fibrosis of the gastric mucosa, and changes to the kidneys consistent with the historical diagnosis of chronic renal disease. Parathyroid hyperplasia was also noted and likely a result of secondary renal hyperparathyroidism. Necropsy confirmed that euthanasia was a reasonable decision due to the severity of Ozzy's cardiac disease, his comorbidities, and the poor prognosis associated with aortic thromboembolism.

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