Two Roads Diverged….

Aortic Thrombosis in a Canine

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Introduction

The aortic trifurcation is where the descending aorta branches into the left and right external iliac arteries and the descending aorta continues to branch into the left and right internal iliac arteries (1). The external iliac arteries provide the majority of the blood supply to the pelvic limb. This area of substantial narrowing and branching allows for thrombus formation or embolus lodging in certain disease states. Aortic thrombosis/aortic thromboembolism (ATh/ATE) in canines has become a disease of increasing research in recent years (2). Both terms have been used somewhat interchangeably in the past when diagnosing aortic occlusion in canines, though the etiology described is different between the two. Thrombosis indicates blockage of a vessel by a thrombus that arises at the site of occlusion or *in situ*, while thromboembolism describes an occlusion caused by material that traveled from a more central region of the cardiovascular system. In both cases, vascular occlusion leads to ischemia of structures distal to the thrombus/thromboembolism. ATE is a common occurrence in cats with myocardial disease, particularly hypertrophic cardiomyopathy. In dogs, several concurrent diseases have been linked as potential causes/risk factors for leading to occlusion of the aortic trifurcation due a hypercoagulable state rather than cardiac disease, indicating that ATh is more likely in this species (2).

Diseases linked to ATh in dogs include endocrinopathies, such as diabetes mellitus (DM), hyperadrenocorticism (Cushing's disease), hypoadrenocorticism, and hypothyroidism, systemic inflammatory disease, immune mediated hemolytic anemia (IMHA), neoplasia, protein losing nephropathy/enteropathy (PLN/PLE), parasitism, and heart disease, such as endocarditis (3-5). Physical exam findings in dogs with ATh can range from nonspecific, such as exercise intolerance, pain localizing to the thoracolumbar spine or abdomen, and weakness of the hind

limbs, to signs highly suggestive of an ischemic event to the hind limbs, like pain, hypothermia, lack of palpable pulses, and cyanosis of the hind limbs. They can also present with neurologic deficits similar to dogs suffering from spinal trauma in the thoracolumbar region, which can lead to difficulty in diagnosis/referral to the correct specialist (3).

Diagnosis of ATh is most commonly done through physical exam findings as well as ultrasonographic examination of the abdomen. A thrombus can be identified at the aortic trifurcation, and Doppler evaluation will often show reduced to absent blood flow around the occlusion. Other advanced imaging modalities such as contrast angiogram, commuted tomography, and magnetic resonance imaging have also been described. Serum chemistry evaluation, complete blood count, urinalysis, and coagulation profiles can be used to determine the underlying cause as well as evaluate response to therapy.

Treatment is often multimodal consisting of a combination of thrombolytics (medical or surgical), platelet inhibitors, and anticoagulants to decrease the size of the thrombus; however, treatment of underlying diseases is likely a major factor in preventing recurrence of clinical signs. Prognosis is variable with survival times ranging from days to years, depending on duration of onset, underlying disease factors, and severity of clinical signs (2,3, 5).

History and Presentation

Jack is a 13-year-old, male neutered Jack Russel Terrier who presented to the MSU-CVM Emergency Service on, Thursday, July 18th, 2019 for dragging the left hind limb and having no femoral pulse in his left hind limb. On July 11th, Jack started drinking a lot of water and panting, which was unusual for him. He then started vomiting and having bloody diarrhea. He was taken to his referring veterinarian (rDVM) and was diagnosed with diabetes mellitus. He also had elevated liver and pancreatic enzymes. He stayed for treatment until Tuesday, July 16th. His

appetite was decreased since the onset of his polyuria/polydipsia (PU/PD). His rDVM prescribed Jack mirtazapine 3.75 mg by mouth, twice daily insulin at 4 units, maropitant 16 mg, kaolin pectin at 5 mL every 12 hours, and metronidazole 125 mg twice daily. On the 17th, he began to drag his left hind limb. The morning of the 18th, he ate his first big meal in a week, which consisted of chicken, sliced turkey, and half an egg. He was taken back to his rDVM, where a femoral pulse could not be palpated in the left hind limb, leading to referral to MSU-CVM on emergency.

On presentation, Jack was bright, alert, and stable. He weighed 8.6 kg and had a body condition score of 7/9. His vital parameters were within normal limits (T=102.0 °F, P=136 beats/min, and R=32 breaths/min), and a grade 3/6 left sided heart murmur was evident. His mucous membranes were pink but tacky, and his capillary refill time was less than 2 seconds. He was missing his 1st and 2nd upper left incisors (201 and 202). He was estimated to be 5% dehydrated. There was no pain noted on abdominal palpation. The left hindlimb had a very weak femoral pulse and was colder than any other limbs. Jack was not using the left hindlimb. The right hindlimb had a normal femoral pulse. The rest of the general physical exam was unremarkable. An intravenous (IV) catheter was placed, and he was placed on Lactated Ringer's solution at 27 mL/hr (maintenance) and methadone at 0.2 mg/kg IV every 6 hours for pain. He remained stable throughout the night of arrival, and was bright, alert, and responsive the following morning; however, his deficits had progressed to decreased proprioception in both hind limbs, measured through paw flipping. At this time, his right femoral pulse was also diminished.

Diagnostic Approach

Diagnosis of ATh is most often made on physical exam and abdominal ultrasound (2), but serological tests and advanced imaging can aid in diagnosis and prognostication. Increased lactate and decreased glucose in affected limbs compared to peripheral blood values indicate anaerobic metabolism due to hypoxemia. Since PLN is the most common cause associated with ATh in dogs (2), UA and UPC should also be performed. Urinalysis is also of great diagnostic value in other potential causes of ATh. Neoplastic conditions have been associated with ATh, so evaluation for metastasis via thoracic radiographs and abdominal ultrasound is also indicated. Further diagnostics can be used pending identification of underlying conditions (urine culture and sensitive for DM, for example) as needed. Coagulation profile, D-dimers, antithrombin, and fibrinogen should also be measured to determine effect of treatment(6), but PT and aPTT have shown variable changes in dogs with ATh. In dogs with ATh, antithrombin will likely be decreased, fibrinogen decreased, and D-dimers increased. Decreased antithrombin leads to a hypercoagulable state, because it acts to decrease the activity of thrombin, which converts fibrinogen to fibrin. D-dimers are products of fibrinolysis and will be elevated in the presence of a thrombus. If lactate in affected limbs is abnormal, serial lactate over multiple days can be used to monitor for return of blood flow to the limb. Recently, thromboelastography (TEG) has become a potential tool for evaluating hypercoagulability, though availability of this diagnostic tool is limited.

On the night of presentation, blood was taken from the left hind limb and compared to systemic values from jugular venipuncture. The left hind had an increased lactate (8.8 mmol/L) and decreased glucose (243 mg/dL) compared to systemic values (1.2 mmol/L and 300 mg/dL

respectively). Blood was obtained for complete blood count (CBC), serum biochemistry, and iSTAT, and urine was obtained for urinalysis. CBC showed a moderate neutrophilic leukocytosis (19883 cells/μL). iSTAT showed hyperglycemia (276 mg/dL). Chemistry revealed a similarly elevated glucose, as well as moderately high ALT (1376 U/L), markedly high ALP (10690 (U/L), marked hyperbilirubinemia (2.7 mg/dL), moderately hypercholesterolemia (839 mg/dL), and severely elevated CK (4161 U/L). Urinalysis showed a 1+ proteinuria, with negative SSA, and a 4+ glucosuria. The hyperglycemia along with glucosuria are diagnostic for diabetes mellitus. Thoracic and abdominal radiographs, abdominal ultrasound, and echocardiogram were performed the following day, July 19th. Abdominal radiographs showed no major abnormalities, and thoracic radiographs showed no cardiomegaly or pulmonary parenchymal change. Abdominal ultrasound revealed a severe pancreatitis, that was possibly necrotizing. Blood flow was not able to be evaluated at that time due to Jack's comfort level and panting. It was during ultrasound that a fentanyl CRI was started at 3 mcg/kg/hour, which improved his pain. In the aortic trifurcation, there was a thrombus that measured 0.7 cm x 1.7 cm, residing mostly in the right external iliac artery but extending over to the left side as well. There was minimal blood flow around the thrombus. He had some evidence of age-related changes to the kidneys, and his adrenal glands were normal in size bilaterally at this time. Echocardiogram revealed moderate mitral valve and mild tricuspid valve regurgitation, as well as mitral valve thickening. He also had mild aortic regurgitation, but this was attributed to increased pressure due to his thrombus. There was smoke in left ventricle as well. At this time, Jack was diagnosed with ATh likely due to severe pancreatitis (possibly necrotizing) and/or DM.

Pathophysiology

For the purposes of this case study, general pathogenesis of ATh, as well as DM and pancreatitis as etiologies of ATh,will be discussed. Hemostasis is the process that maintains regulated blood flow through the vascular system after endothelial or vessel damage (7-9). Vascular damage results in exposure of collagen in the vessel wall and release of tissue factor, and one or both of these mechanisms can cause platelet activation (by direct attachment to collagen or by activation of thrombin, which is present in the blood, by tissue factor (TF)). Platelet activation by TF does not require endothelial damage, however; so, disruptions in this mechanism can trigger clotting without direct vascular damage. To generate thrombin, TF binds with coagulation factor VIIa, which then interacts with factor Xa to generate thrombin from prothrombin. Thrombin then activates platelets in the area causing them to clump together and activate other platelets, leading to a platelet plug. As coagulation continues, thrombin activates fibrinogen to fibrin which stabilizes the platelet plug to form a true thrombus, or blood clot. The final stage of hemostasis involves the dissolution of the blood clot once the vascular damage has healed. Fibrin actually acts as an anticoagulant by absorbing excess thrombin to prevent spread of the clot. A protein called antithrombin III is also present, which binds and inactivates thrombin. Plasmin or fibrinolysin, causes actual lysis of the clots and is often stored within the clot as plasminogen until surrounding endothelium releases tissue plasminogen activator. Once plasminogen transforms into plasmin, lysis of the clot occurs. These processes are often happening simultaneously throughout the vasculature, and disruptions in levels in the above enzymes can lead to a hypercoagulable patient. Several disorders leading to hypercoagulabilty have been documented, including DM. DM has also been linked to artherosclerosis which has also been found in dogs with ATh. Pro-inflammatory states like pancreatitis can lead to

thrombosis due to increased activated tissue factor, increased platelet activation, vasculitis, and increased fibrinogen concentration (4).

Treatment and Management

Treatment of ATh is multimodal and should focus on reducing the thrombus size as well as preventing further thrombi and treating the underlying disease, which may be the most important factor in preventing thrombus recurrence. Options for direct treatment of the thrombus include thrombolytics, platelet inhibitors, and anticoagulants (10). Other treatments depend on etiologies leading to the thrombus formation. Thrombolytic options include medical, surgical, and the use of interventional medicine/radiological procedures. There is limited evidence on thrombolytics in dogs with naturally occurring disease, despite canines used in multiple preclinical human medicine. As thrombolytics were not used in Jack's case, they will not be discussed here.

Platelet inhibitors work by disrupting platelet function by multiple mechanisms. The most well known of these is salicylic acid (aspirin). Aspirin works by irreversibly inhibiting cyclooxygenase, decreasing prostaglandin synthesis, including thromboxane A_2 in platelets, which is a potent platelet activator. Clopridogrel (Plavix) is another platelet inhibitor of a different class, $P2Y_{12}$ ADP receptor antagonists. It works by directly modifying the receptor on the platelet and blocking platelet activation and aggregation (2).

Anticoagulants like heparin work by enhancement of antithrombin., which decreases conversion of fibrinogen to fibrin by thrombin, thus reducing thrombus formation. There are 2 types of heparin used in veterinary medicine unfractionated heparin (UFH) and low molecular weight heparin (LMWH). LMWH has less unwanted protein binding and more predictable excretion since it is primarily excreted renally, but it is more costly. Since it is renally excreted

there is increased risk of adverse events due to accumulation and increased relative anticoagulant, in patients with chronic renal disease (11,12). There is a new group of anticoagulants that work directly by inhibiting factor Xa (FXa) or thrombin. Rivaroxaban is a direct FXa inhibitor, that has been shown to demonstrate a concentration-dependent anticoagulant effect (13).

Treatment of DM involves management of hyperglycemia through insulin administration, nutritional support, and close monitoring for signs of hyper-/hypoglycemia. Treatment of pancreatitis involves pain management, nutritional support with a low-fat diet, and aggressive fluid therapy to maintain hydration.

Case Outcome

The afternoon of July 19th, Jack was started on enoxaparin (LMWH) at 0.8 mg/kg subcutaneously (SQ) every 8 hours, clopidogrel at 2 mg/kg orally every 24 hours, and his insulin dose was changed to 2 units of Vetsulin subcutaneously every 12 hours after eating (1 unit if not eating). Jack's fluid rate was increased to 54 mL/hr, which is twice maintenance based on his body surface area. His fentanyl CRI was increased to 4 mcg/kg/hour to have stronger pain control, and he was started on maropitant at 1 mg/kg intravenously every 24 hours. A Freestyle Libre® was placed to allow for continues glucose monitoring during his stay. He developed dark green diarrhea the night of the 19th and was also hyperthermic (104 °F), but his hyperthermia resolved after changing the site of his intravenous catheter. Throughout the night, his glucose ranged from approximately 250-425 mg/dL. On the 20th, urine was collected for UPC and urine culture, neither of which showed significant abnormalities. Lactate was measured in his hind limbs that morning with values of 5.1 and 4.9 mmol/dL in his left and right limbs, respectively. The left hind was decreased from 8.8 mmol/dL compared to the day before. The evening of July

22nd, a weak pulse was felt in his right hind limb, and that limb was slightly warmer to the touch. Electrolytes remained normal via venous blood gas analysis, but he had become mildly acidotic. He was started on 7.5 mg/kg of metronidazole orally for diarrhea, to be given every 12 hours. On July 21st, Jack had become resistant to oral medication, so he was switched to intravenous metronidazole at the same dose. He had not eaten since his presentation to the hospital, so a naso-esophageal (NE) feeding tube was placed and he was started on a low-fat liquid diet at 1/3 maintenance. Over the weekend of the 20th and 21st, he showed increased ability to use his hind limbs, though he could still not place them properly.

The morning of July 22nd, he was doing well, but was hyperthermic again, so his catheter site was changed again. Repeat abdominal ultrasound were performed, which revealed that the thrombus was still present, but Doppler did show some blood flow around the thrombus on the right side. No blood flow was seen on the left side. The pancreas still showed inflammation but had good blood flow, decreasing the chance of necrotizing pancreatitis. At this time, his right adrenal gland was noted to be enlarged (0.94 cm), which was normal on his first ultrasound, adding hyperadrenocorticism as a possible cause of his ATh. The morning of July 23rd, Jack's front left paw was swollen, the same leg in which the IV catheter was placed. The IV catheter was removed and the swelling of the paw reduced. He was placed on 0.1 mg/kg methadone SQ every four hours, and IV fluids and IV fentanyl were discontinued. Jack was able to start standing and using his hind legs to walk when he was taken outside, and his attitude was much brighter. Blood for a DIC panel was submitted to Cornell, and values were returned on July 24th: aPTT elevated at (18.1 s), PT normal (13.6 s), fibrinogen elevated (885 mg/dL), antithrombin decreased (59%), and d-dimer elevated (616 ng/mL). These were used as baseline values to evaluate long term effectiveness of treatment. On July 24th, Jack was started on mirtazapine to

see if it would help increase his appetite, and he also started physical rehabilitation as well with cold laser therapy and an assortment of motion therapy for his hind legs, He developed mucopurulent nasal discharge, so Clavamox was started at 14.5 mg/kg every 12 hours. On July 25th, his appetite began to improve, but he still needed feeding via NE tube to achieve his daily caloric needs.

Jack was discharged on Friday, July 26th, after receiving rehabilitation therapy in the morning as well as removal of his NE tube. He was sent home with enoxaparin (0.8 mg/kg SQ every 8 hours), clopidogrel (2 mg/kg PO every 24 hours), Vetsulin (2U SQ every 12 hours at meal time), metronidazole (7.5 mg/kg PO every 12 hours), Tylenol 4 (1 mg/kg PO every 8 hours), mirtazapine (1.1 mg/kg PO every 24 hours), omeprazole (1 mg/kg PO as needed), and rivaroxaban (0.6 mg/kg PO every 24 hours to begin when enoxaparin was finished). Over the next few months, Jack had several rechecks. On August 2nd, his Freestyle Libre® was evaluated, and his Vetsulin dose was increased. On August 16th, no adjustments were made. On August 30th, an ACTH stimulation test was performed, and his cortisol levels were 1.1 μg/dL pre-stimulation and 23.2 μg/dL post-stimulation, which is consistent with hyperadrenocorticism. The DIC panel was also repeated and showed improvement: aPTT 16.5 s (mildly elevated), PT 15.8 s (mildly elevated), fibrinogen 406 mg/dL (normal), antithrombin 115% (normal), and D-dimers 104 ng/mL (normal). At this time, clopidogrel and rivaroxaban were discontinued, and trilostane was started at 1 mg/kg orally every 12 hours. On September 27th, he returned for repeat ACTH stimulation testalong with Doppler blood pressure, which indicated adequate control and normal blood pressure (pre-stimulation cortisol-2.6 μg/dL, post-stimulation-7.7 μg/dL, and BP-120 mmHg). He also had signs of a skin infection at this time and was started on cefpodoxime. His Vetsulin dose was increased to 5 U twice a day with food. At this visit, he was ambulating

normally and doing well at home. Over the next few months, he returned with the only changes being adjustments to his Vetsulin dose. His last recheck with MSU-CVM was November 6th, and he was doing well at that visit.

Conclusion

This case offers a good representation of possible clinical signs associated with ATh as well as the importance of proper diagnosis when neurologic deficits occur. In this case, there was evidence of limb ischemia on physical exam, but that is not always the case. So, though not very common, ATh should be included as a differential in patients presenting with exercise intolerance, pain referenced to the back or abdomen, and/or neurologic deficits such as paresis or proprioceptive deficits in one or both hind limbs, especially in dogs without other signs of disease to these body systems. Palpation of limbs and femoral pulses should be a part of routine physical examination. There are multiple modalities available for diagnosis, but definitive diagnosis often occurs via physical exam and Doppler ultrasound. Additional diagnostics are usually warranted based on other concurrent/underlying disease processes and to monitor efficacy of therapy. There is no current standard treatment for ATh, because treatment involves modification of coagulation state of the patient, as well as treatment of underlying disease. Anticoagulants such as enoxaparin and anti-platelet drugs such as aspirin or clopidogrel are the most commonly used medications in veterinary medicine. Though prognosis is variable due to the multitude of etiologies that can lead to ATh in canines, favorable outcomes can be achieved with prompt effective treatment of underlying disease.

References

1. Dyce, K. M., Sack, W. O., & Wensing, C. J. G. (2010). Textbook of veterinary anatomy (4th ed., pp. 248-252). St.Louis, Mo: Saunder Elsevier.
2. Williams, T. P. E., Shaw, S., Porter, A., & Berkwitt, L. (2017). Aortic thrombosis in dogs, *J Vet Emerg Crit Care*; 27 (1): 9-22. https:doi.org/10.1111/vec.12527
3. Gonclaves, R., Penderis, J., hange, Y. P., Zoia, A., Mosley, J., & Anderson, T. J. (2008). Clinical and neurological characteristics of aortic thromboembolism in dogs, *J Small Anim Pract*; 49, 178-184.
4. Laforcade, A. De. (2012). Diseases Associated with Thrombosis. *Top Companion Anim Med*; 27(2), 59–64. https://doi.org/10.1053/j.tcam.2012.07.002
5. Ralph, A. G., Saunders, A. B., Hariu, C. D., & Nabity, M. (2011). Spontaneous echocardiographic contrast in three dogs, *J Vet Emerg Crit Care;* 21(2), 158–165. https://doi.org/10.1111/j.1476-4431.2011.00624.x
6. Kuzi, S., Segev, G., Haruvi, E., & Aroch, I. (2010). Plasma Antithrombin Activity as a Diagnostic and Prognostic Indicator in Dogs: A Retrospective Study of 149 Dogs, *J Vet Intern Med;* 24, 587–596.
7. Hall, J. E., & Guyton, A. C. (2016). Hemostasis and Blood Coagulation. In Guyton and Hall Textbook of Medical Physiology (13th ed., pp. 483–492). Philadelphia: Elsevier.
8. Furie, B., & Furie, B. C. (2008). Mechanisms of Thrombus Formation. *N Engl J Med*; 359 (9):938-949
9. Smith, S. A., & Dacvim, M. S. (2009). The cell-based model of coagulation, *J Vet Emerg Crit Care;* 19(1), 3–10. https://doi.org/10.1111/j.1476-4431.2009.00389.x

10. Smith, S. A. (2012). Antithrombotic Therapy. *Top Companion Anim Med*, 27(2), 88–94. https://doi.org/10.1053/j.tcam.2012.08.002

11. Hirsh, J., Anand, S. S., Halperin, J. L., & Fuster, V. (2001). Guide to Anticoagulant Therapy : Heparin-a statement for healthcare professionals from the American Heart Association. *Ciculation*; 103(24), 2994–3018.

12. Farooq, V., Hegarty, J., Chandrasekar, T., Lamerton, E. H., Mitra, S., Houghton, J. B., … Wood, G. N. (2004). Serious adverse incidents with the usage of low molecular weight heparins in patients with chronic kidney disease. American Journal of Kidney Diseases, 43(3), 531–537. https://doi.org/10.1053/J.AJKD.2003.11.012

13. Conversy, B., Blais, M., Dunn, M., Gara-boivin, C., Carioto, L., & Jérôme, R. E. (2013). Rivaroxaban demonstrates in vitro anticoagulant effects in canine plasma, *Vet J;* 198(2), 437–443. https://doi.org/10.1016/j.tvjl.2013.08.001