Congestive Heart Failure

A Chordae Tendineae Rupture Case Report

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DVM Class of 2017

Clinicopathologic Conference

September 30, 2016

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Introduction:

The third most common cause of death in small breed dogs is congestive heart failure (CHF) secondary to mitral valve disease—the most common acquired heart disease in dogs, horses, and humans.[1-5] Clinical signs of mitral valve disease are seen in 30% of dogs over 13 years of age.[5] The most common causes of mitral valve insufficiency include mitral valve endocardiosis, valve prolapse, dynamic outflow obstruction, ruptured chordae tendineae (CT) and dilated cardiomyopathy.[6] CT rupture may be more common than originally thought with a reported prevalence of 16% in dogs with mitral valve disease, and can be caused by substantial pre-existing mitral regurgitation, remodeling of the heart, or abnormally high tension on CT.[4,7,8]

Canine heart disease is classified into four basic stages by the American College of Veterinary Internal Medicine (ACVIM), which help determine the course of treatment required for the individual patient. Stage A is an animal without an identifiable structural disorder of the heart who is at high risk for development of acquired valvular disease. Stage B patients have not developed clinical signs of heart failure despite structural changes to the heart. Stage C indicates a dog with past or current signs of failure associated with structural heart disease. Stage D patients have end-stage disease with clinical signs of heart failure that are refractory to standard therapies. These classifications can assist the clinician in defining a standard therapy for each stage of disease and identifying risk factors for valvular degeneration, allowing treatment before major structural changes occur.[9]

History and Presentation:

Canine mitral valve disease frequently does not elicit clinical signs until the onset of CHF, when owners may report a moist cough or exercise intolerance.[5] Left, apical, systolic heart murmurs that are typically detected at routine wellness exams can be consistent with mitral valve

disease in dogs greater than one year of age. Increased intensity of the murmur has been shown to parallel the severity of disease.[4,5] An animal with CHF frequently presents with cough, acute dyspnea, tachypnea, and crackles on thoracic auscultation.[10]

Gizmo, a 15-year-old, male Shih Tzu, presented to the Mississippi State University College of Veterinary Medicine for heart failure on May 17, 2016. That morning he had begun showing signs of respiratory distress, including labored breathing and bilateral nasal discharge, and was taken to the referring veterinarian. Gizmo was not on any medications and was not up to date on vaccines, heartworm prevention or flea prevention. Upon arrival at the referring clinic, Gizmo's temperature was 96° F, and heart sounds were not audible on auscultation. He was then referred to MSU-CVM Internal Medicine Service for further diagnostics and treatment.

Upon presentation, Gizmo was anxious, but alert and responsive. He was hypothermic (98.0° F) and dyspneic with a respiratory rate of 56 breaths per minute. Heart rate was within normal limits. Thoracic auscultation revealed crackles bilaterally and a grade V/VI left systolic heart murmur. Bilateral, clear, frothy nasal discharge was seen. FAST scan of the thorax revealed no free fluid in the pericardial sac or thoracic cavity. Differential diagnoses at the time of presentation included cardiogenic pulmonary edema (as with CHF), heartworm disease, bacterial pneumonia, hypoalbuminemia resulting in pulmonary edema, non-cardiogenic pulmonary edema, pulmonary thromboembolism, pulmonary neoplasia, and metastatic neoplasia. Gizmo was started on furosemide and oxygen supplementation while further diagnostics were performed.

Diagnostic Approach:

Diagnosis of CHF is based on clinical signs, physical examination, radiographic findings, and echocardiography.[5,11,12] Thoracic radiographs are important for staging and long-term monitoring of canine valvular heart disease by assessing heart size, pulmonary vessels, and lung parenchyma. Pulmonary edema causes an interstitial pattern on radiographs by increasing the opacity of the parenchyma and thickening bronchial walls. Furthermore, as edema worsens, the unstructured appearance coalesces to an alveolar pattern. Distribution of these patterns is important since cardiogenic pulmonary edema is typically perihilar and caudodorsal with a patchy distribution, and is often associated with distended pulmonary veins.[12] Echocardiography is required to definitively identify the cause of CHF, such as an insufficient mitral valve or other structural abnormalities.

Initial diagnostics for Gizmo included SNAP 4Dx Plus, complete blood count (CBC), and serum chemistry. SNAP was negative for heartworm antigen, ehrlichiosis, Lyme disease, and anaplasmosis. CBC and chemistry showed mild neutrophilia (17220/ul, reference range 3500-14200), increased BUN (28mg/dl, reference range 8-24), hypoalbuminemia (2.4 g/dl, reference range 2.5-3.9) and hyperphosphatemia (6.8 mg/dl, reference range 2.5-5.0). The hypoalbuminemia was not severe enough to cause pulmonary edema, so this was ruled-out as a cause of respiratory distress. In addition, SNAP test results ruled-out heartworm disease. Although diagnostic imaging was still required for definitive diagnosis, CHF secondary to mitral valve disease was the working diagnosis.

Thoracic radiographs and echocardiogram were performed to characterize the pulmonary and cardiac disease and to identify valvular origin of the grade V/VI systolic murmur.

Radiographic impressions included an unstructured interstitial pulmonary pattern, consistent with cardiogenic pulmonary edema, and left atrioventricular enlargement, suggestive of mitral endocardiosis. Echocardiogram confirmed severe mitral valve insufficiency with a large jet of regurgitation, thickened leaflets and irregular movement of leaflets which prolapsed into the left atrium (flail leaflet). The flail leaflet also suggested ruptured CT, which would have been consistent with the acute onset of clinical signs. Aortic valve leaflets were thickened, likely due to chronic myxomatous degeneration, and mild insufficiency was present at the pulmonic valve.

Pathophysiology:

Congestive heart failure in small breed dogs is most commonly initiated by mitral valve regurgitation and the resultant remodeling of the heart. To understand the pathway from regurgitation to CHF, the anatomy of the mitral valve must first be understood. The mitral valve apparatus consists of four major components: leaflets, annulus, CT and papillary muscles of the left ventricle.[4,5,7] As discussed earlier, causes of mitral valve insufficiency include valve prolapse and CT rupture.[6] Prolapse of the leaflets occurs secondary to elongated or ruptured CT. An important primary cause of rupture is endocardiosis, with redundant, thickened valvular tissue leading to an abnormally floppy valve.[7,13] Endocardiosis and thickened valves are commonly associated with mitral valve insufficiency.

Mitral valve insufficiency causes regurgitation of stroke volume back to the low pressure left atrium and remodeling of the heart walls. Remodeling of the heart attempts to compensate for decreased stroke volume but becomes a cascade of continued dysfunctional changes with no return to normal stroke volume. Stretching of the mitral annulus from remodeling and progressive left-sided cardiomegaly increases the regurgitant orifice and regurgitant volume. A

vicious cycle ensues in an attempt to compensate for dysfunctional changes by further remodeling.[5,14] The majority of remodeling occurs prior to the onset of clinical signs, with the most rapid changes occurring in the six months prior to onset of CHF.[3,14] Animal models for mitral regurgitation—induced by chordae rupture—consistently lead to CHF with left-sided dilation from low pressure volume overload.[2] Low pressure volume overload also leads to degradation of collagen between cardiomyocytes which then attracts calcium leading to mineralization of the intercellular connections.[13,14] As remodeling continues, aortic output steadily decreases, which eventually lessens blood volume entering the pulmonary vein and left atrium, causing increased pulmonary pressure, pulmonary venous congestion and interstitial leakage with the end product of pulmonary edema and the onset of clinical signs of CHF.[15] The lymphatics cannot compensate for the accumulation of transudate in the extravascular space of the lung, and the edema worsens. Respiratory distress caused by pulmonary fluid overload is the cause of death in acute onset CHF.[6]

Although CT rupture is considered to be spontaneous, mechanical fatigue and previously discussed structural changes of the mitral valve apparatus play a major role in CT rupture and the resultant hemodynamic changes.[7] CT are essential to mitral valve function and operate as tethers to prevent flail and prolapse of the valve leaflets into the left atrium.[4,5,7] Studies on the mechanical fatigue of CT in porcine mitral valves have shown CT at the leaflet margin are significantly smaller in cross-section than basal CT. Likewise, septal leaflet CT are thinner than those anchoring the parietal leaflet. The thinner nature of these makes CT at the margin of the septal leaflet most prone to rupture.[8] The tip of the septal leaflet is the most common location for regurgitation.[1] Rupture of CT most often leads to non-compensated, severe hemodynamic

changes that include decreased end diastolic volume, decreased aortic stroke volume, and increased left atrial and ventricular end diastolic pressure.[2]

Endocrine pathways are suggested to play a role in progression of heart disease. Although the role of hormones is controversial, they become the target of mainstay therapies for heart disease management.[14] Initially, decreased blood pressure leads to an increase in sympathetic tone and the release of norepinephrine. Stimulation of the β-1 receptors by norepinephrine increases heart rate and contractility. The β-1 receptors are down regulated within a few days, but norepinephrine continues to be released in increasing amounts as heart failure worsens.[11] The renin-angiotensin-aldosterone system (RAAS) is stimulated by renal hypoxemia which is a result of decreased renal blood flow associated with heart failure. Renin release from the juxtaglomerular apparatus initiates aldosterone release from the adrenal cortex. Aldosterone increases sodium and water reabsorption in the distal tubules of the nephron which increases blood volume, venous pressure, and preload. Ultimately, the result is increased workload on an already failing heart. Additionally, RAAS stimulation increases formation of angiotensin II, a potent vasoconstrictor which will increase vascular resistance and afterload. Antidiuretic hormone (vasopressin) release is stimulated by the increased plasma osmolality of heart failure and has similar effects as RAAS. The results of these pathways can play a significant role in remodeling and attempting to compensate in acute or chronic CHF. As such, these endocrine pathways become a focus for therapies following diagnosis.[11,16]

Treatment and Management:

Therapy for CHF is aimed at altering hemodynamic changes, and does not alter structural changes that may have already occurred at the onset of clinical signs. Treatment protocols are based on stage of clinical disease as established by ACVIM "Guidelines for the Diagnosis and

Treatment of Canine Chronic Valvular Heart Disease". Furosemide is the diuretic of choice, with dosing dependent on severity of clinical signs. In the case of life-threatening pulmonary edema, furosemide can be administered as a constant rate infusion after an initial bolus. Once diuretic therapy has been initiated, the patient should be allowed free access to water in order to limit dehydration secondary to therapy. Other side effects of aggressive diuretic therapy include hypokalemia, dilutional hyponatremia and renal damage.[9,11] Anecdotal evidence along with hemodynamic and experimental evidence supports use of pimobendan in heart failure patients, although its efficacy in an acute crisis is not thoroughly studied. Oxygen supplementation, removal of effusions, and sedation (particularly with opioids) are also recommended based on individual case evaluation. In patients refractory to standard therapy for heart failure, more aggressive therapy to reduce pulmonary edema and alter hemodynamics may be necessary. Additional furosemide may be administered as well as an additional (off-label) dose of pimobendan. Potentially useful drugs for refractory cases (in addition to ACE inhibitors and pimobendan) include sodium nitroprusside, hydralazine, or amlodipine. Bronchodilators are recommended as an adjunct therapy.[9]

After completing diagnostic imaging, Gizmo was moved to the Intensive Care Unit for treatment of CHF with suspected ruptured CT. Initial treatment was focused on stabilizing the patient and addressing hemodynamic changes. Furosemide was the loop diuretic of choice for reduction of pulmonary edema, dosed at 2 mg/kg intravenously every 12 hours and for rescue in respiratory distress. Albuterol puffs were administered via canine aerosol chamber every 6 hours for their bronchodilatory effects. Pimobendan (0.25 mg/kg PO Q12H) and enalapril (0.5 mg/kg

PO Q12H) were added to the treatment regimen following official diagnosis of CHF due to mitral valve insufficiency.

Gizmo required continuous oxygen supplementation throughout hospitalization to maintain blood oxygen saturation (SpO_2) greater than 94%; he was kenneled in a temperature and humidity-controlled oxygen cage and supplemented with flow-by oxygen when out of the cage. Furosemide was administered five times for rescue over a five-hour period with the last dose of 4 mg/kg IV. Since Gizmo's total dose of furosemide was 12 mg/kg without sustained improvement of respiratory signs, nitroglycerin was applied topically to the inner pinna every 6-8 hours to reduce preload via vasodilation in addition to established therapy. Blood pressure was monitored by Doppler every 6 hours to ensure pressures were not too low prior to nitroglycerin application, and gloves were worn at all times when handling Gizmo to prevent potential acute hypotension of exposed personnel. Gizmo remained stable overnight without any episodes of tachypnea or dyspnea.

The following morning, Gizmo's harsh lung sounds had mild improvement, and recheck radiographs showed moderate improvement in the unstructured interstitial pattern. Dosing of furosemide was increased from 2 mg/kg IV every 12 hours to 2 mg/kg IV every 6 hours with no rescue doses needed. Gizmo's appetite was decreased to absent, so ondansetron (0.5 mg/kg IV Q8H) was prescribed to limit nausea. Enalapril, pimobendan, albuterol and nitroglycerin were continued as previously prescribed.

Nitroglycerin was discontinued on the third day due to severe hypotension (<60 mmHg, systolic). Hypotension was persistent throughout hospitalization. Gizmo became unable to maintain a normal body temperature, and hot packs were added to his kennel to provide warmth. His temperature was monitored closely, and the packs were warmed every four hours to maintain

Gizmo's body temperature greater than 98.5° F. Unasyn (30 mg/kg IV Q8H) was added to the drug protocol on day three in the event that undetected respiratory infection was limiting improvement of clinical status. Throughout hospitalization, radiographs showed moderate improvement of pulmonary edema; however, recheck bloodwork showed a severely worsening azotemia. Due to poor prognosis and limited improvement of signs, humane euthanasia was elected on the fourth day of treatment.

Case Outcome:

Post-mortem examination confirmed the diagnosis of CHF with ruptured CT. Pulmonary edema and hemosiderosis were diffuse. Multiple CT were ruptured, with acute severe left atrial dilation, chronic severe mitral and tricuspid endocardiosis, pulmonary and aortic valvular dysplasia, and subaortic fibrous stenosis. Myocyte disarray, fibrosis, endothelial fibroelastosis and steatosis were also noted on cardiac histopathologic review. Other chronic conditions that are associated with advanced age in dogs were also present on necropsy, including chronic renal and prostatic disease.

Gizmo's case is one of classic acute onset of clinical signs of CHF following rupture of multiple CT. Congenital valve abnormalities may have initiated a degenerative heart condition that caused a nodular thickening of the valve margins, impairing valve closure. The remodeling and tissue scarring weakened the CT, which fatigued and ruptured. A sudden inadequacy of valve closure resulted, and acute decompensation ensued. Gizmo's valvular disease was classified as Stage C since he was euthanized prior to determination of refractory disease. Although not thoroughly studied, CT rupture has been anecdotally associated with poor outcomes despite aggressive treatment.[4,17]

REFERENCES

1. Aoki T, Fujii Y, Sunahara H, et al. Morphological Investigations of the Anterior Leaflet and its Chordae Tendineae in Canine Mitral Valves. Intern J Appl Res Vet Med 2015; 13:159-163.
2. Leroux AA, Moonen ML, Pierard LA, et al. Animal Models of Mitral Regurgitation Induced by Mitral Valve Chordae Tendineae Rupture. J Heart Valve Dis 2012; 21:416-423.
3. Sargent J, Connolly DJ, Watts V, et al. Assessment of mitral regurgitation in dogs: comparison of results of echocardiography with magnetic resonance imaging. J Small Anim Pract 2015; 56:641-650.
4. Serres F, Chetboul V, Tissier R, et al. Chordae tendineae Rupture in Dogs with Dengenerative Mitral Valve Disease: Prevalence, Survival, and Prognostic Factors (114 Cases, 2001-2006). J Vet Intern Med 2007; 21:258-264.
5. Abbott JA. Acquired Valvular Disease. In: Tilley L. Manual of canine and feline cardiology. 4th ed. St Louis: Elsevier Saunders, 2008; 110-138.
6. Diana A, Guglielmini C, Pivetta M, et al. Radiographic features of cardiogenic pulmonary edema in dogs with mitral regurgitation: 61 cases (1998-2007). J Am Vet Med Assoc 2009; 235:1058-1063.
7. Gunning G and Murphy BP. Characterisation of the fatigue life, dynamic creep and modes of damage accumulation within mitral valve chordae tendineae. Acta Biomater 2015; 24:193-200.
8. Sedransk KL, Grande-AllenKJ, and Vesely I. Failure Mechanics of Mitral Valve Chordae Tendineae. J Heart Valve Dis 2002; 11:644-650.

9. Atkins C, Bonagura J, Ettinger S, et al. Guidelines for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease. J Vet Intern Med 2009; 23:1142-1150.
10. Gompf, RE. The History and Physical Examination. In: Tilley L. Manual of canine and feline cardiology. 4th ed. St Louis: Elsevier Saunders, 2008; 2-23.
11. Shaw DH and Ihle SL. Cardiovascular Diseases. In: Small Animal Internal Medicine. Ames: Blackwell Publishing, 2006; 137-201.
12. Ware WA. Cardiovascular System Disorders. In: Nelson RW and Couto CG. Small Animal Internal Medicine. 5th ed. St Louis: Elsevier Mosby, 2014; 1-73, 115-129.
13. Jacobs GJ, Calvet, MG, Mahaffey MB and Hall DG. Echocardiographic Detection of Flail Left Atrioventricular Valve Cusp From Ruptured Chordae Tendineae in 4 Dogs. J Vet Intern Med 1995; 9:341-346.
14. Dillon AR, Dell'Italia LJ, Tillson M, et al. Left ventricular remodeling in preclinical experimental mitral regurgitation of dogs. J Vet Cardiol 2012; 14:73-92.
15. Poteet BA. Radiology of the Heart. In: Tilley L. Manual of canine and feline cardiology. 4th ed. St Louis: Elsevier Saunders, 2008; 24-48.
16. Van Vleet JF and Ferrans VJ. Cardiovascular System. In: McGavin MD and Zachary JF. Pathologic Basis of Veterinary Disease, 4th ed. St. Louis: Mosby Elsevier, 2007; 559-611.