Canine Dilated Cardiomyopathy:

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Class of 2020

Clinicopathologic Conference

October 11, 2019

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Introduction

Dilated cardiomyopathy (DCM) is a common acquired heart disease of large breed dogs and is classified as primary (genetic/idiopathic) or secondary in nature. DCM is characterized as a functional abnormality in the myocardium, caused by primary systolic dysfunction with secondary eccentric dilation, typically affecting the left ventricle and atria, although right sided dilation in association with atrial fibrillation has been reported[1]. This ultimately culminates in cardiac dilation and systolic dysfunction, often with arrhythmias, with disease progression leading to decreased cardiac output and eventual congestive heart failure. It typically affects large breed dogs, with males (63%) being more common than females. The median age at diagnosis is 6.5 years, with ages ranging from 4.7-8.5 years.[7] An exception to this median age range is a juvenile form which occurs in Portuguese Water Dogs and Toy Manchester Terriers, often developing before 1 year of age.[1] Most patients do not show any clinical signs until late in the disease process. Treatment depends on the etiology of the disease but generally consists of management of congestive heart failure and any arrhythmias should they arise. Prognosis is dependent on the underlying cause, but a worse prognosis is associated with age of onset, pleural effusion, pulmonary edema, ascites, and atrial fibrillation.[10]

Etiologies of dilated cardiomyopathy are thought to be due to a variety of myocardial insults such as infectious, nutritional, metabolic, toxic, and genetic, although most are considered idiopathic. Surveys taken in North America compared to Europe showed differences in incidence of certain breeds which may suggest an environmental component but is more likely due to genetic influences based on breed popularity in certain regions.[1] In boxers, DCM has been associated with a homozygous deletional mutation in the gene striatin; however, other genetic causes have not yet been identified.[5] When dilated cardiomyopathy arises in atypical

breeds, external factors such as infectious agents and nutritional imbalances should be examined. Nutritional imbalances are rarer in dogs than cats, but taurine and L-carnitine deficiencies have been implicated in Cocker Spaniels and may be familial in Golden Retrievers.[1] Diets composed of lamb meal and rice as well as boutique grain-free diets have been implicated in large breed dogs with taurine deficient dilated cardiomyopathy. Taurine supplementation in dogs with nutritional cardiomyopathy has been shown to improve clinical signs and echocardiographic measurements within 3-6 months.[4]

History and presentation

Tyson was a 4 year old, intact male boxer that presented to MSU-CVM emergency service on June 24, 2019 for what his owners described as a fast heart rate, cool extremities, weakness, and lethargy of four days' duration. His diet at presentation was a grain-free boutique diet. Further history on Tyson revealed he came from a line of inbred boxers, with both of his parents dying suddenly at approximately 6-7 years of age in the absence of clinical signs. No history of medical illness was reported by his owners other than chronically elevated liver enzymes.

Upon presentation, Tyson was depressed and non-ambulatory. Physical exam revealed tachycardia and muffled heart sounds. His pulses were non-synchronous, his breathing was stertorous, and he was mildly dyspneic. His extremities were cool to the touch. His mucous membranes were pale pink and his capillary refill time was 3-4 seconds, indicating inadequate perfusion. Abdominal FAST scan revealed a large amount of peritoneal effusion. A thoracic FAST scan revealed a subjectively severely enlarged heart that was minimally contracting. A 6-lead EKG was placed revealing atrial fibrillation. A diltiazem bolus was given to reduce his

heart rate to an acceptable range. Diltiazem is a calcium channel blocker used for atrial fibrillation and slows AV node conduction while prolonging refractory time.

He was then placed on a dobutamine CRI and given furosemide. Dobutamine is a beta-1 agonist which increases contractility while also causing peripheral vasodilation to reduce afterload. Furosemide is a loop diuretic used for treatment of congestive heart failure causing diuresis. Shortly after initiation of the dobutamine CRI, Tyson was able to lift his head for the first time since initial presentation and was much brighter and more alert. Pimobendan and clopidogrel were started just prior to being transferred to the internal medicine service. Pimobendan is an oral positive ionotrope used to increase contractility. Clopidogrel (Plavix®) is a platelet aggregation inhibitor used to prevent the chances of having a pulmonary thromboembolism in his procoagulative state.

Pathophysiology

The exact etiology of ventricular wall thinning and dilation in dogs with dilated cardiomyopathy is not known but is presumed to be genetic and causes primary pathology of the myocardium.[1] Two different histologic forms of DCM exist. One is the wavy fiber type, in which thin and wavy myocytes are separated by edematous fluid with diffuse subendocardial fibrosis, which occurs most commonly in classical DCM.[7] The second form, being the fatty infiltrative degenerative form, is common in boxers and is more typical of arrhythmogenic right ventricular cardiomyopathy (boxer cardiomyopathy)[8] In this second form, there is fibro-fatty replacement of the myocardium. It is variable as to whether ventricular dilation precedes the development of systolic dysfunction or vice versa.[6] Two stages of this disease process are recognized. The occult stage is the asymptomatic stage and the overt stage begins with the onset of clinical signs. Canine dilated cardiomyopathy primarily affects the left ventricle and leads to

ventricular wall thinning and eccentric dilation but can also be biventricular.[1] As the ventricular walls thin and dilate, they can no longer pump out the blood returning to the heart, leading to decreased perfusion and pulmonary congestion. This in turn activates the renin-angiotensin-aldosterone system (RAAS), which works to expand the plasma volume. RAAS system upregulation leads to increased preload and afterload, contributing to the progression of disease, further stretching and eccentrically dilating the myocytes and eventually leading to left sided congestive heart failure with pulmonary edema.[7] Occasionally, right sided congestive heart failure can arise causing ascites and pleural effusion. Signs of congestive heart failure are manifested as lethargy and collapse, coughing, increased respiratory rate and effort, and ascites.[7]

Atrial fibrillation results as a consequence of the electrical instability of the myocardium. This occurs due to cardiac dilation and decreased oxygen supply, with a simultaneous increased myocardial oxygen demand, which causes ischemic necrosis of the cardiac muscle.[2] Atrial fibrillation is most commonly associated with dilated cardiomyopathy and degenerative mitral valve disease, which leads to electrical and structural remodeling of the atria. This remodeling places them at an increased risk of sustained fibrillation.[3] Dogs diagnosed with atrial fibrillation in conjunction with DCM are at a significantly increased risk of left and right sided congestive heart failure, as opposed to left sided heart failure which is most common in DCM.[2]

Once atrial fibrillation arises, patients may develop multiple pathways within the atria that result in very fast depolarization rates of the atria with a concurrent loss of synchronous contraction of the atria. Most of the fast depolarizations reach the AV node, but some are filtered out, leading to the irregularity of the rhythm. Some of the pulses penetrate the AV node, resulting in alteration of conduction for subsequent impulses, which in turn causes irregular contraction of the atria.[3]

Diagnostic approach and considerations

Radiographs are a standard part of the diagnostic work up and usually left atrial and ventricular enlargement is seen, but generalized cardiomegaly has been reported most commonly in advanced cases with tachyarrhythmias such as atrial fibrillation**.** Echocardiography is the gold standard for diagnosing canine dilated cardiomyopathy. Decreased fractional shortening, decreased ejection fraction, and increased end-systolic volume are characteristic of DCM.[7] Electrocardiogram can be useful to identify any arrhythmias that may be present, which affects prognosis and treatment, although it is generally a poor diagnostic method for diagnosing DCM.[1]

Biomarkers can be used as screening and diagnostic tools, although their efficacy is not yet determined. Atrial natriuretic peptide (ANP) is released in response to increased atrial pressure and stretching. ANP has been shown to be elevated in the occult and overt stages of disease but was determined its sensitivity and specificity is lacking as a reliable screening tool; however, it may be of use in advanced cases to confirm a diagnosis in the presence of other diagnostic aids and clinical signs. Cardiac troponin-I (cTnI) is increased in some cases of DCM in the overt form of disease, but its sensitivity and specificity has been shown to be lacking as well. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are currently the most useful biomarkers used to diagnose DCM in the occult stage of disease. These biomarkers are cleaved from myocytes in response to ventricular dilation, hypertrophy, or increased pressures which occur in congestive heart failure. Doberman Pinschers have been shown to have elevated levels of plasma NT-proBNP up to 1.5 years prior to the onset of clinical signs and development of DCM.[1]

Treatment and Management

Treatment in the overt form of disease in dogs with DCM and congestive heart failure ideally should consist of a positive ionotrope and vasodilator, such as dobutamine or pimobendan, to improve cardiac contractility and reduce afterload.[8] ACE inhibitors are used in the chronic management to blunt the RAAS system and often consist of enalapril or benazepril, with a suggested starting dose of 0.5 mg/kg PO q12h. Diuretics such as furosemide are administered at the lowest possible dose to resolve and control pulmonary edema, pleural effusion, and ascites. Furosemide doses often start at 1-2 mg/kg PO q12h. Any arrhythmias (such as atrial fibrillation) should also be addressed, with the main goal of controlling the heart rate, not necessarily the rhythm. This rate control is often accomplished with diltiazem. Measurement of taurine levels can be considered based on the specifics of the case, with taurine supplementation occurring until normal taurine levels can be confirmed. A normal range for whole blood taurine levels in dogs is 200 - 350 nmol/mL.

Further Case Work-up and Outcome

A minimum database consisting of a CBC, chemistry, and urinalysis was performed to assess Tyson's general health. His CBC was unremarkable. The chemistry panel revealed he was azotemic, hyperphosphatemic, hyponatremic and hypochloremic, and had elevations in his liver enzymes (ALT and ALP). Urinalysis was unremarkable with the exception of a mild amount of blood and crystals in his urine.

A 6-lead EKG was performed upon initial triage revealing a narrow complex tachycardia with a rapid, irregular rhythm and no apparent p waves, indicating atrial fibrillation. Single ventricular premature contractions (VPC's) were noted sporadically during his stay in ICU but were not frequent enough to warrant therapeutic intervention. There is no strict criteria for initiating treatment of VPC's; however, treatment is generally started if there are over 1000

VPC's in a 24 hour period, runs of ventricular tachycardia, or evidence of the R on T phenomenon. Treatment of ventricular arrhythmias is not a benign process, and many ventricular antiarrhythmics have the potential of proarrhythmic effects; therefore, treatment should be instituted at the discretion of the veterinarian based on clinical signs in conjunction with the aforementioned factors. [1]

Diagnostic imaging consisted of thoracic and abdominal radiographs as well as echocardiography, with an IDEXX cardiac consultation completed. Thoracic radiographs revealed a generally enlarged cardiac silhouette, with rounding of the right atrioventricular region and a bulge in the region of the left auricle. His vertebral heart score was above the reference range.

The echocardiogram revealed that both ventricles and atria were severely dilated, with severely reduced contractility. Tyson's fractional shortening was decreased at 18%. Fractional shortening is considered decreased when it is less than 20-25%, and in normal dogs is often between approximately 28-45%.[7] For Tyson, this indicated left ventricular systolic dysfunction. Mild mitral and tricuspid regurgitation was noted and was attributed to annular dilation. Based on the above findings, our suspicion of dilated cardiomyopathy was confirmed. The cardiologist assessment of the diagnostics was severe dilated cardiomyopathy, as a phenotype of arrhythmogenic right ventricular cardiomyopathy based on the breed, with left and right sided congestive heart failure and atrial fibrillation. Recommendations were to resolve the congestion, improve cardiac contractility, and control the heart rate by continuing the therapy he was already receiving (lasix, pimobendan, and diltiazem), as well as measuring taurine levels and beginning taurine supplementation (since he was receiving a boutique grain-free diet).

Whole blood and plasma taurine levels were sent out for assessment of nutritional deficient taurine cardiomyopathy, and taurine supplementation was begun. Whole blood and plasma levels both came back well above the reference range.

A recheck of the fractional shortening was performed to assess his response to cardiac medications. His fractional shortening two days after starting appropriate cardiac medications was unchanged since the previous echocardiogram. After being in the hospital for four days, Tyson began to decompensate. On the fourth day, a NOVA and lactate were performed revealing severe lactic acidosis with a pH of 7.1 and a lactate of 9.7 mmol/L, indicating severe perfusion deficiencies. Tyson's heart rate and perfusion could not be adequately maintained and on the fourth day in-hospital, he became depressed and nonambulatory and went into cardiac arrest. Resuscitation efforts were initiated, but due to his poor to grave prognosis, his owners elected to humanely euthanize him.

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