DATES OF TREATMENT

June 13th, 2022; June 27th, 2022

PATIENT SIGNALMENT

Feline; Domestic Short-Hair; M/N; 14.5 years old

PATIENT HISTORY

Moe presented to an emergency hospital with a two-day history of labored breathing. At presentation, he was tachypneic (80 RPM), and had increased bronchovesicular sounds, however, no heart murmur was appreciated upon auscultation. He was normotensive with a systemic blood pressure (BP) of 125 mmHg systolic. A thoracic Focused Assessment with Sonography in Trauma (TFAST) scan was performed that showed subjective left atrial enlargement (LAE). A baseline CBC and serum chemistry panel showed him to be mildly azotemic and mildly hypokalemic [BUN 57.8 mg/dL, reference (ref.) range 15.0-32.0 mg/dL; Crea 1.5 mg/dL, ref. range 0.8-1.8 mg/dL; potassium (K) 3.1 mmol/L, ref. range 3.4-5.3 mmol/L]. A UA and T4 were recommended but were declined. A feline N-terminal pro brain natriuretic peptide (NT-proBNP) point-of-care assay test was also performed, and results were abnormal. It was recommended to hospitalize Moe for suspected congestive heart failure (CHF).

Thoracic radiographs (CXR) were obtained that showed a moderate interstitial coalescing to alveolar pattern throughout the lungs, and scant pleural effusion consistent with CHF. He was treated with a furosemide CRI in hospital at 1 mg/kg/hr (5mg/hr - based on weight of 5 kg) as well as pimobendan 0.25 mg/kg (1.25 mg) PO q 12 hr and clopidogrel 3.75 mg/kg (18.75 mg) PO q 24 hr. He was placed on O2 support and hospitalized overnight (O2 concentration unknown).

As his respiratory rate (RR) improved overnight, he was transitioned to oral furosemide 2 mg/kg (10 mg) PO q 12 hr, and his supplemental O2 was weaned down to room air. Moe was sent home on his current doses of furosemide, pimobendan and clopidogrel, and a cardiology consultation was recommended for further evaluation.

COMPLETE PATIENT STATUS UPON PRESENTATION

Upon PE, Moe was bright, alert, and responsive. He weighed 5.3 kg, and his vitals were as follows: temp 100.6 F; heart rate 196 BPM; RR 32 RPM; mucous membranes were pink; capillary refill time < 2 seconds.

Upon cardiac auscultation, the Applicant appreciated a grade II/VI sternal systolic heart murmur, with strong femoral pulses and an irregular rhythm with associated pulse deficits. No transient heart sounds were present. During respiratory auscultation, he had diffusely increased lung sounds without crackles, and mild hyperpnea.

PROBLEM LIST

The problem list included the following: a grade II/VI sternal systolic heart murmur; hyperpnea; arrhythmia; pulse deficits; history of CHF and azotemia.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis (DDX) included the following: hypertrophic cardiomyopathy (HCM) [rule out (R/O) primary HCM versus (vs) secondary to systemic hypertension vs secondary to hyperthyroidism]; R/O hypertrophic obstructive vs dilated vs restrictive vs nonspecific cardiomyopathy; left-sided congestive heart failure (L-CHF) (pulmonary edema and pleural effusion); early azotemia [R/O primary chronic kidney disease

(CKD)]; atrial premature complexes (APCs) (secondary to LAE); ventricular premature complexes (VPCs) (R/O CHF vs increased sympathetic tone vs myocardial hypoxia).

INITIAL ASSESSMENT OF PROGNOSIS

Moe's prognosis was poor; cats diagnosed with CHF have a typical survival rate of several months, dependent on the patient's response to therapy and concurrent diseases.

INITIAL DIAGNOSTICS AND RESULTS

A Doppler BP was obtained by the Applicant that was high normal in a clinical setting (150 mmHg systolic). To further evaluate his arrhythmia, the Applicant obtained a 50 mm/sec ECG, and identified an underlying sinus rhythm with frequent single APCs and VPCs. The Applicant performed measurements on the aforementioned ECG strips: Mean electrical axis (MEA) +45; P-R interval 80 milliseconds (ms); Q-T interval 180 ms; P wave amplitude 0.1 millivolts (mV); P wave duration 40 ms; QRS duration 20 ms; R wave amplitude 0.9 mV; T wave amplitude -0.1 mV.

To evaluate the efficacy of Moe's current doses of CHF medications, the Applicant acquired three view CXR. In reviewing the images, the Applicant identified a bronchointerstitial pattern consistent with residual cardiogenic pulmonary edema, with no evidence of pleural effusion. The Applicant calculated a Vertebral Heart Score (VHS) of 9.5 (ref range 6.7-8.1), and identified the bronchi, pulmonary arteries, pulmonary veins, the caudal vena cava, and the aorta on the lateral projections.

As Moe had previous mild azotemia and hypokalemia prior to initiating diuresis, monitoring his kidney values and electrolytes at minimum would be imperative to management of his disease. A limited blood panel consisting of BUN, Crea and K was obtained to evaluate

tolerance to his current doses of furosemide, and he was found to be progressively azotemic (BUN 75 mg/dL, ref. range 9.0-29.0 mg/dL; Crea 2.0 mg/dL, ref. range 0.4-1.5 mg/dL). K was within normal limits (WNL).

The Applicant assisted with an echocardiogram, and identified moderate left ventricular (LV) concentric hypertrophy [interventricular septum (IVS) in diastole (IVSd) 6.8 mm; LV posterior wall in diastole (LVPWd) 7.8 mm], moderate to severe LAE [left atrium to aorta ratio (LA/Ao) 2.2], with normal systolic function [fractional shortening (FS) 41%)], trace mitral regurgitation (MR) on color flow (CF) Doppler, and no evidence of LV outflow tract (LVOT) obstruction (LVOT velocity 1.2 m/s). The Applicant also identified a trace amount of pericardial effusion (PCE) suspected to be secondary to L-CHF, and spontaneous echo contrast (SEC) with low velocity flow in the left auricular appendage due to aggregated red blood cells.

DISCUSSION OF CASE MANAGEMENT AND OUTCOME

Though a serum T4 was still needed to R/O hyperthyroidism as a potential contributing factor, it was suspected that Moe had primary (genetic) HCM. Due to his residual pulmonary edema and PCE, it was recommended to cautiously increase his furosemide to 2.36 mg/kg (12.5 mg) PO q 12 hr. His owners were educated to monitor for signs of worsening azotemia which include inappetence, lethargy, vomiting, and diarrhea. No changes were made to his pimobendan or clopidogrel doses. His owners were also educated about Moe's risk of potential clot formation due to the observed SEC. They were told to watch out for signs of a potential aortic thromboembolism (ATE), including vocalization with pain or loss of function in his legs, and to return to the Applicant's facility immediately should he exhibit any of these signs.

Moe returned June 27th for a two-week recheck after increasing his diuretic. The Applicant appreciated a grade II/VI sternal heart murmur, with an irregular rhythm and strong

femoral pulses with occasional pulse deficits. He continued to have increased lung sounds without crackles present. The Applicant acquired CXR to evaluate the efficacy of the increased diuretic. The radiology report indicated improved pulmonary vasculature in comparison to the previous films, with unchanged generalized cardiomegaly, and no evidence of cardiogenic pulmonary edema. A TFAST scan was performed that revealed no evidence of current pericardial effusion, indicating controlled CHF as a result of the increased diuretic.

A serum chemistry panel and T4 level was sent out to a reference laboratory to monitor Moe's tolerance of medications, as well as to evaluate for hyperthyroidism as a potential contributing factor to Moe's diagnosis. Results showed stable azotemia and a normal T4 [BUN 65 mg/dL, ref. range 14.0-36 mg/dL; Crea 2.4 mg/dL, ref. range 0.6-2.4 mg/dL; T4 1.8 microgram (µ)/dL, ref. range 0.8-4.0 µ/dL]. Due to both hyperthyroidism and systemic hypertension having been previously R/O as contributing factors to Moe's disease, primary HCM was his diagnosis.

As his CHF appeared to be under control on his current medications, no adjustments were made. The owners were instructed to continue to monitor for signs of worsening azotemia or acute renal failure, recurrent CHF, as well as signs of an ATE. A cardiac recheck was recommended in three to four months unless he develops clinical signs. No recheck was scheduled as of date of submission.

CASE DISCUSSION

Primary HCM is the most common cardiac disease in cats. It is characterized by concentric hypertrophy (thickening inward) of the myocardium, most commonly affecting the left ventricle. The word *primary* in this context indicates that the hypertrophy is due to an inherent problem in the myocardium (Kienle & Kittleson, 1998), and not secondary to other

contributing factors such as systemic hypertension or hyperthyroidism. Though the underlying etiology of HCM is unknown, a genetic basis has been considered likely (Durham, 2017).

Familial inheritance of HCM has been found in several predilected breeds, including Maine Coon, Ragdoll, Persian, British Shorthair, American Shorthair, Norwegian Forest Cat, and Sphynx (Luis Fuentes et al., 2010), and cats with heritable disease can often develop left ventricular hypertrophy (LVH) as early as four months of age (Abbott, 2000). In Maine Coons and Ragdolls in particular, a myosin-binding protein C gene mutation was identified, allowing for genetic screening available via a commercial assay (Tilley & Sleeper, 2016). Primary HCM is the most common acquired disease found in feline patients and can also be seen in canines on rare occasion. Though the average age of onset for cats is between 5.5 to 6.5 years old (Tilley & Sleeper, 2016), it can be diagnosed as young as a few months old, or in a geriatric patient. While it is becoming more commonplace for patients to seek cardiac screenings, more often a diagnosis is obtained once a patient has developed a heart murmur, gallop sound, arrhythmia, or displays clinical signs of their disease.

When obtaining a history, many affected cats are seemingly healthy (Luis Fuentes et al., 2010) and a murmur or gallop sound is an incidental finding. When a patient does present in CHF, frequent clinical symptoms include tachypnea, dyspnea, lethargy, inappetence, or inability to use the limbs/lameness. Less common symptoms can include collapse/syncope, or coughing. Sometimes CHF is preceded by an inciting event such as: anesthesia/surgery, recent fluid administration, or recent steroid administration (Tilley & Sleeper, 2016).

Upon PE, patients often present with a systolic murmur best heard at the sternal or left parasternal border, though a dynamic (functional) component may also be present. A heart murmur is the sound of turbulent blood flow in the cardiac system, often the cause of structural

heart murmurs in HCM is secondary to either mitral regurgitation (MR), outflow tract obstruction, or a combination of both (Kienle & Kittleson, 1998). Subjectively, heart murmurs can be described as ranging from soft to moderate in intensity (grade I-IV/VI), with murmur intensity not directly correlating to the disease severity. A gallop sound may be present in diastole (R/O S_3 vs S_4 vs a summation of S_3 and S_4) but, given the rapid heart rates of cats in clinic, it is almost impossible to differentiate between and diagnostically unnecessary (Tilley & Sleeper, 2016).

Arrhythmias in feline patients with HCM are most often secondary to cardiac structural changes and a diagnostic ECG should be obtained to evaluate the underlying cause of the arrhythmia. APCs and VPCs are impulses that arise from ectopic foci in the atria and ventricles respectively (Tilley, 1992). In cats, APCs often occur secondary to LAE. If the APCs and VPCs are hemodynamically insignificant, they do not warrant antiarrhythmic therapy (Tilley & Sleeper, 2016). Another common ECG abnormality with HCM patients is an intraventricular conduction defect called a left anterior fascicular block. As Moe's ECG only showed occasional single APCs and VPCs, no treatment was warranted at that time, though future monitoring was advised.

An echocardiogram is essential for definitive diagnosis of HCM in feline patients. Hypertrophy in cats can display a wide array of varying morphologies. Diffuse or focal hypertrophy may be noted in the LV free wall, IVS, and/or the papillary muscles (Durham, 2017). Due to the various patterns of hypertrophy, it is recommended a diagnosis only be made after several two-dimensional (2D) images are obtained in diastole for confirmation (especially in cases of regional/segmented hypertrophy) (Tilley & Sleeper, 2016). HCM is a disease of diastolic dysfunction while systolic function is generally not impaired in HCM (and is often

hyperdynamic). Diastolic dysfunction is the result of the following: impaired myocardial relaxation, restriction to the LV filling, and increased LV filling pressures (Boon, 2011). Evaluation of Doppler transmitral inflow patterns may help evaluate for diastolic dysfunction (Durham, 2017). A ratio of the left atrium to aortic root size (LA/Ao) is used to measure left atrial dilation, as the aorta maintains a fixed relationship with the other chambers (Boon, 2011). Patients with observable SEC or a mature thrombus on echocardiogram are at higher risk for a potential ATE. Moe had severe LAE with an LA/Ao of 2.2 and SEC present making him at risk for an ATE. Other potential echocardiographic findings can include a dynamic obstruction of the LVOT caused by systolic anterior motion (SAM) of the mitral valve. Also, if a patient is found to have areas of increased echogenicity within the papillary muscles or subendocardial areas, it is thought to be a marker of chronic myocardial ischemia and subsequent fibrosis (Ware, 2007).

Once a patient is diagnosed with HCM, additional testing should be performed to R/O any potential reversible cause. This includes systemic hypertension and hyperthyroidism. As Moe's BP in both the emergency setting and during his initial cardiac evaluation were WNL, systemic hypertension was ruled out as a contributing factor. During his recheck examination, T4 was found to be within a normal range, ruling out hyperthyroidism.

In an emergency setting, a cat with dyspnea may not be able to tolerate diagnostics or treatments and taking a step-by-step approach may be necessary. An NT-ProBNP point-of-care test can help differentiate whether a dyspneic patient is in respiratory distress due to cardiac disease or primary respiratory disease. A brief TFAST scan can show subjective LAE, as in Moe's case, and can identify pleural effusion.

Taking an initial set of CXR can play a pivotal role in differential diagnosis in patients

with a cough, respiratory distress, and tachypnea (Luis Fuentes et al., 2010). In HCM, common radiographic findings can range from a normal cardiac size, to mild-to-moderate LVE and LAE on lateral projections. Pulmonary edema may present itself with variable degrees of mixed interstitial and alveolar infiltrates, or a diffuse edema may be present. Perihilar edema is less common (Owens & Biery, 1999). Pleural effusion is also common in both acute and chronic cases, and at times can be very large, obscuring the cardiac silhouette (Luis Fuentes et al., 2010). In these cases, often a VD projection is required to aid in better visualization. CXR can also aid in evaluating the efficacy of a patient's current medication regimen.

Treatment for feline patients in CHF is generally aimed at decreasing LA and pulmonary venous pressure (Kienle & Kittleson, 1998), as well as aiming to prevent a thromboembolic event. Furosemide, a loop diuretic, is initiated for treatment of pulmonary edema. In a hospital setting it can be given IV, IM, SQ, or a CRI. Once the patient shows clinical improvement they can be transitioned to oral furosemide. Though controversy has surrounded the administration of pimobendan in cats with HCM and CHF, the potential pharmacodynamic benefits include preload reduction, positive lusitropy, and positive inotropic effects (Tilley & Sleeper, 2016). Lastly, the addition of clopidogrel, a platelet inhibitor, is beneficial in reducing the occurrence of thromboembolic disease (Durham, 2017). Aspirin is rarely used as a monotherapy antithrombotic medication anymore but is still occasionally used in combination with clopidogrel.

It is important to obtain blood work to evaluate renal function, and thereby assess the patient's ability to tolerate diuresis as CKD is one of the most common geriatric diseases in cats (Cohn, 2020). Initially, Moe's BUN was elevated with a normal Crea and, though further

diagnostics would be required to evaluate for complete International Renal Interest Society (IRIS) staging (Cohn, 2020), he potentially could have been considered at risk. Due to the reabsorption of urea from the renal tubule in states of low blood flow such as heart failure, the increase of BUN (but not Crea) prior to initiating CHF treatment may also indicate the increase to be secondary to failure (Cohn, 2020) and not prerenal azotemia. In patients with both CHF and underlying potential azotemia, the use of diuretics can have adverse effects on kidney function and overly aggressive diuresis with excessive dehydration should be avoided. Strategies should be used to reduce the total daily dose of diuretic, and potential use of a positive inotropic drug such as pimobendan to help increase cardiac output and kidney perfusion (Pouchelon et al., 2015). Serial monitoring of kidney values and electrolytes (at minimum) should be monitored closely to evaluate tolerance to medications, with an emphasis on the owners monitoring for signs of progression of azotemia (anorexia, weight loss, halitosis, lethargy, vomiting) (Cohn, 2020).

Ultimately, feline HCM patients who present in CHF have a poor prognosis, with a median survival of 3-18 months on average (Durham, 2017). As this disease is progressive, further complications may include development of an ATE, acute kidney injury/failure, syncope, worsening arrhythmias, end-stage HCM, and sudden death.

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