Are you ready kid(ney)s? Aye-aye captain!

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Introduction

As of 2018, canine heartworm infection has been diagnosed in all fifty states, with the top 5 hot spots being Mississippi, Louisiana, Arkansas, Texas, and Tennessee, respectively. In Mississippi alone approximately one in ten dogs are heartworm positive[1]. The four clinical stages of heartworm infection are classified based on severity as mild, moderate, severe and caval syndrome. In mild heartworm disease, the patient can be asymptomatic or have a mild cough. With moderate heartworm disease, the patient can have a cough, exercise intolerance and abnormal lung sounds. In severe heartworm disease, the patient can have a cough, exercise intolerance, dyspnea, a heart murmur, harsh lung sounds, syncope, asities and even death. The most immediate life-threatening clinical presentation of heartworm disease is caval syndrome. Caval syndrome is characterized by a large worm burden that results in sudden onset of severe lethargy, weakness, anorexia, hemoglobinemia, hemoglobinuria, respiratory distress, arrhythmias and sudden death[1,2]. The mainstay of therapy for caval syndrome is surgical extraction of the heartworms but managing the sequalae from such a large number of worms may not be successful, sometimes leading to the death of the patient.

History and Presentation

Spongebob, an approximately 3-year-old male mix breed dog, presented to MSU-CVM Emergency Service on November 25, 2018 for suspected caval syndrome. Spongebob originally presented to his regular veterinarian on October 9, 2018 after being rescued by his current owners and was then initially diagnosed as heartworm positive with radiographic evidence of cardiac and pulmonary vasculature enlargement. A complete blood count preformed then revealed an eosinophilia and mild anemia and chemistry values were within normal limits. At

that time, Spongebob was started on oral heartworm prevention and doxycycline (300 mg) and the plan was to start melarsomine treatment in December.

Over the next month and a half, Spongebob did have a cough that was noted daily but was otherwise apparently healthy and happy until November 23, 2018, when he presented again to his regular veterinarian for coughing and gagging that suddenly started that morning. It was reported that Spongebob now had an arrhythmia with radiographic evidence of severe right heart enlargement and moderate to severe pulmonary congestion. An automated complete blood count revelated a moderate thrombocytopenia of 56 K/ul L (160-650) and a hematocrit of 42.5%. He was also reported to have hematuria. Spongebob was prescribed cephalexin, benazepril, maropitant and furosemide. Spongebob then presented again the next day, November 24, 2018, for severe lethargy, inappetence, diarrhea and vomiting throughout the night. On presentation, Spongebob was nonambulatory, depressed but responsive, his heart rate was 140 beats per minute with a right sided grade III/VI murmur and poor peripheral pulses, he was tachypneic with a respiratory rate of 80 breaths per minute, and a visible jugular pulse was noted. A presumptive diagnosis of caval syndrome was made. Spongebob was started on maintenance intravenous fluids and it was recommended to start sildenafil 1-3 mg/kg in preparation for referral to PetMed Emergency Center for supportive overnight care until Spongebob could be transported to MSU-CVM for further diagnostics.

On presentation to PetMed Emergency Center Spongebob was found to be hemoglobinuric and hypotensive (60 mmHg) with a moderate amount of ascites in all 4 quadrants and was noted to be serosanguinous on abdominocentesis. He had a PCV of 32%, normal PT, abnormal PTT of 119 sec (10.0-20.0), severe azotemia with a BUN of 112.9 mg/dl (8-24) and creatinine of 3.8 mg/dl (0.5-1.4), mild hyperalbuminemia of 4.6 g/dl (2.5-3.9), and a

hyperbilirubinemia of 4.8 mg/dl (0.2-0.6). He was stabilized and supported overnight with sildenafil 1 mg/kg, intravenous fluids, a dobutamine CRI, dexamethasone SP 0.13 mg/kg, spironolactone 0.8 mg/kg, and was continued on doxycycline, maropitant, and pantoprazole. On the morning of November 25, 2018, Spongebob's PCV decreased from 32% to 28% and he was transported to MSU-CVM.

On presentation to MSU-CVM Spongebob was sternally recumbent, quiet, alert, and responsive. He had a temperature of 99ºF, a pulse of 103 beats per minute, and was tachypneic with a respiratory rate of 80 breaths per minute. Femoral pulses were strong and synchronous bilaterally. His mucous membranes were moist, pink and mildly icteric with a CRT of < 2 seconds. He had a grade III/VI left systolic murmur and a grade II/VI right systolic murmur. His abdomen was soft and non-painful on palpation and hemoglobinuria was noted. SpongeBob presented with a patent intravenous catheter in his right cephalic vein and a nonpatent intravenous catheter in his left saphenous vein, which was removed. Thoracic FAST scan revealed a bundle of heartworms bouncing between the right atrium and right ventricle through the tricuspid valve. No pleural or pericardial fluid was noted. Abdominal FAST scan revealed a scant amount of abdominal free fluid. Initial blood work performed revealed that Spongebob had a mild acidosis, mild to moderate anemia of 22.9% (34-60), moderate thrombocytopenia of 64 K/ul L (manual count; 160-650), severe azotemia with a BUN of 185 mg/dl (8-24) and creatinine of 6.57 mg/dl (0.5-1.4), moderate hyperbilirubinemia of 2.3 mg/dl (0.2-0.6) and severe hyperphosphatemia of 11.6 mg/dl (2.5-5). Thoracic radiographs revealed the classic bulge in the region of the main pulmonary artery and enlarged and tortuous pulmonary arteries. The echocardiogram revealed a large bundle of worms within the right atrium and ventricle and pulmonic valve insufficiency presumptively due to pulmonary hypertension. A pulmonary

pressure could not be obtained due to the large worm burden. Due to the large presence of heartworms in the right atrium and ventricle, Spobgebob's worsening anemia from 42% to 22% in two days and severe azotemia, the decision was made to move immediately to manual surgical extraction of the heartworms at the time of presentation.

Pathophysiology

Caval syndrome is characterized by a large worm burden that results in sudden onset of severe lethargy, weakness, anorexia, hemoglobinemia, hemoglobinuria, respiratory distress, arrhythmias and sudden death. Caval syndrome only occurs in about 20% of dogs with heartworm disease. Seventy-five to 90% of dogs with caval syndrome are intact male, larger, hound type breeds[7,9,10]. The life-threatening clinical signs associated with caval syndrome such as the sudden onset of severe lethargy, weakness, anorexia, hemoglobinemia, hemoglobinuria, respiratory distress, and arrhythmias are due to the abnormal distribution of heartworms within the right side of the heart[1,2,10]. While the specific reason for atypical heartworm distribution is still unknown, many theories have been presented. One of the most plausible theories is the retrograde movement of the heartworms from the main pulmonary artery, where they sexually mature, to the right ventricle. This migration is most likely due to an acute worsening of pulmonary hypertension and decrease in cardiac output[2,7,10]. The thought for the increasing pulmonary hypertension is mechanical worm trauma and stimulation of the hosts' immune system damage the vessel intima ultimately leading to progressive endarteritis, villous endothelial proliferation and perivascular cuffing with inflammatory cells[8,10]. Once in the right ventricle, the heartworms are thought to entangle with the tricuspid valve. Complications from tricuspid valve regurgitation and subsequent right heart failure are observed[8].

One of the most common and life-threatening complications of caval syndrome is the intravascular hemolysis caused by the mechanical destruction of the red cells as they are forced around a large number of heartworms[7,11]. There is also evidence to suggest that in dogs with caval syndrome there are alterations in serum free and esterified cholesterol concentrations and lecithin acyltransferase activity. This leads to red cell membrane instability and thus increased fragility of the red cells[7,10]. The resultant intravascular hemolysis leads to hemoglobinemia, then hemoglobinuria and subsequently an acute kidney injury. Normally, when small numbers of red cells are destroyed in the vasculature the free hemoglobin is bound by the plasma protein haptoglobin and the hemoglobin:haptoglobin complexes are cleared by macrophages in the liver and spleen. Consequently, when there is severe intravascular hemolysis the large amount of free hemoglobin saturates the protective haptoglobin binding system and glomerular filtration of the free hemoglobin becomes the major way which hemoglobin is removed from circulation. Glomerular filtration is a very efficient way for free hemoglobin removal with a half-life of plasma clearance being less than one hour, but this exposes the kidneys to large quantities of free hemoglobin. When the kidneys are forced to process excess amounts of hemoglobin they oxidize ferrous hemoglobin (Fe^{2+}) to ferric hemoglobin (Fe^{3+}) and large quantities accumulate in the kidney. Free heme is also released which promotes the heme-related cellular damage pathway in tubular epithelial cells[4,5]. This all results in hemoglobin and iron deposition in the tubular lumen, epithelial cells and denaturation of cellular DNA[4,5,6]. On necropsy, kidneys from dogs with caval syndrome frequently demonstrate tubular necrosis, tubular heme casts and hemosiderosis[7].

Treatment and Management

The mainstay of therapy for caval syndrome is accomplished by manual extraction of the heartworms in the right atrium. However, even with the appropriate treatment the prognosis for

caval syndrome is guarded to poor and mortality rate is often 30-40%[7]. Manual extraction of heartworms can be performed under light sedation, with chemical restraint or general anesthesia based on how stable the patient is. The right lateral neck is clipped and cleaned in a sterile fashion and the skin is incised over the jugular vein. The jugular vein is isolated using blunt dissection and a venotomy is performed. Then most commonly long alligator forceps are passed through the vein and advanced with caution in to the heart. However, there are numerous rigid or flexible forceps or endoscopic baskets that can be implemented. Echocardiographic or fluoroscopic guidance can be used to assist with advancement of the forceps and visualization of the forceps to ensure they are in the proper location. Once the tip of the forcep is visualized in the right atrium the jaws are opened, advanced slightly, then the jaws are shut, and the forceps are fully removed with heartworms in tow. This process is repeated several times until there are multiple unsuccessful attempts or only few heartworms are visualized on echocardiogram. The jugular vein is ligated, and the skin is closed in routine fashion. Manual heartworm extraction can result in maceration of the worms which causes a massive antigen release that leads to pulmonary vasoconstriction. If maceration occurs, it is recommended to add in an anti-inflammatory dose of parenteral glucocorticoid and heparin[7,10].

During and following manual heartworm extraction the patient should be maintained on intravenous fluids. Fluid administration helps to improve cardiac output, help prevent hemoglobin nephropathy and anuria, and reverse any lactic acidosis from decreased tissue perfusion due to decreased cardiac output[7,10,11]. If a patient survives manual heartworm extraction they need to be monitored closely for complications such as pulmonary thromboembolism from the macerated worms, anemia, anuria and acute renal failure. Each complication is typically treated as they arise. If a patient survives manual heartworm extraction

without complication, then the patient should continue the American Heartworm Society's recommended heartworm treatment protocol[2,7,10].

If a patient develops anuric or oliguric acute kidney injury and efforts made towards urine production fail two treatment options are hemodialysis or peritoneal dialysis. The gold standard of treatment is hemodialysis, in which blood is passed through straw-like semipermeable membranes that are bathed in dialysate, and uremic solutes are removed by diffusion across the semipermeable membrane. Hemodialysis for veterinary patients is only available a select locations across the country and is very expensive. The second-best, more readily available treatment option is, peritoneal dialysis. Peritoneal dialysis uses the same principle as hemodialysis, but the peritoneum is employed as the semipermeable membrane across which fluids and uremic toxins are exchanged. During peritoneal dialysis, the dialysate is infused into the peritoneal cavity through a sterilely placed indwelling abdominal catheter, allowed to sit for a period of time to permit equilibration of water, toxins, electrolytes and other small molecules through diffusion and osmosis. The dialysate is then drained and discarded, carrying the uremic toxins and water with it. This process is repeated as needed until the bloodwork reveals that uremia is controlled. While peritoneal dialysis sounds great it is not without numerous but manageable complications. The most common complications are catheter occlusion with dialysate retention, subcutaneous leakage of dialysate, electrolyte disturbances, hypoalbuminemia and bacterial peritonitis[3].

Case Outcome

A total of 125 heartworms were manually removed from the right atrium. A pulmonary pressure check following heartworm removal revealed severe pulmonary hypertension of 108 mmHg. Spongebob also received a whole blood transfusion during and after the procedure. A

urinary catheter was placed and Spongebob was maintained in an oxygen cage overnight in the ICU where his oxygen level, ECG, urine production, and abdominal ascites were all monitored. Sildenafil 2 mg/kg, doxycycline 10 mg/kg, dexamethasone sodium phosphate 0.13 mg/kg, maropitant 1 mg/kg, and spironolactone 1.6 mg/kg were continued as previously prescribed. He was also started on cefazolin 22mg/kg, and methadone 0.1mg/kg. Overnight he became anuric, producing 0.1 ml/kg/hr, which did not respond to multiple doses of furosemide; then a furosemide CRI was started at 1 mg/kg/hr. That morning, November 26, 2018, renal values were re-measured and were severely elevated. His BUN was 370 mg/dl (8-24) and creatinine was 9.06 mg/dl (0.5-1.4) (on presentation BUN was 185 mg/dl (8-24) and creatinine was 6.57 mg/dl (0.5-1.4)), and he was also severely hyperphosphatemic at 19.1 mg/dl (2.5-5). Spongebob was monitored throughout the day and remained anuric, continuing to produce on average less than 0.1mg/kg/hr of urine so a CRI of diltiazem at 0.16 mg/kg/hr was added. Spongebob still remained anuric and his respiratory effort increased, he developed pulmonary edema and his ascites progressed from moderate to severe, so crystalloid fluids were discontinued. Due to his declining condition it was discussed with the owners that his prognosis was grave and that he required hemodialysis as his best chance to recover renal function, but the closest facility was Auburn University. The owners requested to give Spongebob one more evening to respond to medical management while they discussed their options.

The next day, November 27, 2018 the owners decided not to take Spongebob to Auburn for hemodialysis and asked if we had any additional options available at MSU. Peritoneal dialysis was then discussed as a less successful option for dialysis that could be performed at MSU and discussed the aforementioned complications. Ultimately, the owners elected to attempt peritoneal dialysis. Prior to dialysis an abdominal ultrasound was performed, which showed

hyperechoic and heterogeneous kidneys with normal blood flow bilaterally. Recheck renal values showed a severe but slightly improving BUN of 260 mg/dl (8-24) (previous BUN 370 mg/dl), a worsening creatinine of 11.06 mg/dl (0.5-1.4) (previous creatinine 9.06 mg/dl) and a severe but slightly improving hyperphosphatemia at 17.6 mg/dl (2.5-5) (previous phosphorus of 19.1 mg/dl (2.5-5)). His hematocrit was also remaining stable at 28%. The evening of November 27, 2018 a peritoneal dialysis catheter was placed under light sedation and a local block and peritoneal dialysis was started. The owners had declined the recommended surgical placement of the of the peritoneal dialysis catheter. Spongebob was continuously monitored and remained oxygen dependent throughout the procedure and was maintained on flow-by oxygen. After each dialysis treatment blood was drawn for an iSTAT or NOVA to monitor his electrolytes. After his second treatment, Spongebob's respiratory effort had greatly increased so he was placed back in the oxygen cage and allowed to rest. At that time Spongebob also began having episodes of regurgitation.

On November 28, 2018 Spongebob began having seizures and became hyperreactive to noise and light. After his first seizure, he was given a 0.5mg/kg dose of midazolam and responded appropriately, but he became extremely sedate. His respiratory effort continued to increase, and recheck bloodwork revealed a metabolic acidosis. Blood work revealed further progression of azotemia, with a worsening creatinine of 13.23 mg/dl (0.5-1.4) (previous creatinine was 11.06 mg/dl (0.5-1.4)), static BUN of 270 mg/dl (8-24), worsening hyperphosphatemia of 18.2 mg/dl (2.5-5) (previous phosphorus of 17.6 mg/dl (2.5-5)), and a moderate neutrophilia of 38505 /ul (3500-14200). The anemia also had worsened, and his hematocrit decreased from 28% to 21%. He also remained thrombocytopenic at 128 K/ul (160-650), but that was improved from previous which was 64 K/ul (160-650). Cefazolin was

discontinued and cefoxitin was started at 30mg/kg. Mild seizures continued to occur but were treated with 0.1mg/kg dose of midazolam and Spongebob responded appropriately. Spongebob was also started on enoxaparin 0.8mg/kg. Due to his progressive azotemia and persistent anuria, a third dialysis treatment was started. However, upon drainage of the fluid, Spongebob's seizures worsened and multiple doses of midazolam at 0.1 mg/kg were given and a 30mg/kg dose of levetiracetam was given. Spongebob's seizures responded to the medications however; shortly after the seizures, Spongebob began agonal breathing, became hypotensive, his respiration stopped and he passed away.

On necropsy approximately fifty additional worms were identified in the heart (primarily in the right ventricle), there were multiple large thrombi occluding the major pulmonary arteries in both lungs, and severe chronic passive congestion of the liver was noted. The abdominal peritoneal dialysis catheter was patent but was located within the omentum and intermittently blocked with omental fat when suction was applied.

References

1. American Heartworm Society. 2018. Current canine guidelines for the diagnosis, prevention, and management of heartworm (*Dirofilaria immitis*) infection in dogs. American Heartworm Society, Wilmington, DE. http://www.heartwormsociety.org/ . 2018.
2. Bryan, C. “Heartworms in Canine and Feline Patients.” Small Animal Medicine and Surgery I. 2016.
3. Cooper, Rachel L., and Mary Anna Labato. "Peritoneal dialysis in veterinary medicine." Veterinary Clinics: Small Animal Practice. 2011; 41.1:91-113.
4. Deuel, J. W., et al. "Hemoglobinuria-related acute kidney injury is driven by intrarenal oxidative reactions triggering a heme toxicity response." Cell death & disease. 2016; 7.1:e2064.
5. Dukkipati, Ramnath, et al. "Acute kidney injury caused by intravascular hemolysis after mechanical thrombectomy." Nature Reviews Nephrology. 2009; 5.2:112.
6. González, Iván, et al. "Evans syndrome complicated by intratubular hemoglobin cast nephropathy." Case reports in pediatrics 2017. 2017; 5184587
7. Kittleson, Mark D., and Richard D. Kienle. Small Animal Cardiovascular Medicine. 2nd ed., Mosby, 2013.
8. Kitagawa, Hitoshi, et al. "Heartworm Caval Syndrome: Pathophysiology World Small Animal Veterinary Association World Congress Proceedings, 2003."
9. Selby, L. A., R. M. Corwin, and Jr HM Hayes. "Risk factors associated with canine heartworm infection." Journal of the American Veterinary Medical Association. 1980; 176.1:33-35.

10. Strickland, Keith N. "Canine and feline caval syndrome." Clinical techniques in small animal practice. 1998; 13.2:88-95.
11. Venco, L., L. Kramer, and Claudio Genchi. "Heartworm disease in dogs: unusual clinical cases." Veterinary parasitology. 2005; 133.2-3: 207-218.