A Worm Welcome for Bella

Canine Heartworm Disease

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Introduction

The canine heartworm, *Dirofilaria immitis,* affects a variety of species including dogs, cats, ferrets, and wildlife such as foxes, coyotes, and wild felids. *Dirofilaria immitis* is a nematode that is introduced into biting vector flies by ingestion of a blood meal containing microfilariae[2]. Wild canids, unprotected domestic dog populations, and changes in preventative and treatment drug options, all aid in the prevalence of heartworm disease. Heartworm infections are reported in all 50 states and is endemic in southern United States[8]. Within the United States, thirteen species of mosquitoes have been shown to be infected with *D. immitis* larvae. Species of mosquitoes infected include *Aedes, Anopheles, Culex,* and *Psorophora*[2].

The mosquito is the required vector and intermediate host of the heartworm life cycle. The mosquito bites an animal with microfilaria and becomes infected. Within the mosquito, the microfilaria must develop into larval stage 1 (L1) and molt from L1 to L3. In temperatures around 80.6 F, relative humidity of 80%, and a time frame of 10-14 days, larvae within the mosquito will reach L3 (the infective stage)[1]. When the infected mosquito bites another dog, it will deposit the L3 larvae onto the dog's skin. The larvae enter the dog's skin through the mosquito bite and travel into subcutaneous tissue and eventually enter the circulatory system. Immature adults reach pulmonary vasculature by 90 to 120 days. A mature adult heartworm is present as early as 120 days and can have circulating microfilaria by 7 to 9 months[1].

Consequences of heartworm disease include main pulmonary artery enlargement, pulmonary lobar arteries enlargement, right ventricle enlargement, pulmonary damage, hepatomegaly, and ascites. An enlarged main pulmonary artery can lead to pulmonary hypertension[9]. Canines should be tested annually for heartworm infection. Treatment of

heartworm disease includes a macrocyclic lactone, tetracycline, and melarsomine injections. The only FDA approved drug used to kill adult heartworms is melarsomine as a 3-injection protocol[6].

History and Presentation

Bella is a 5-year-old, female spayed yellow Labrador Retriever that presented to Reelfoot Animal Hospital on May 15th, 2020 for episodes of hindlimb paresis and seizure like activity for the past month. Bella had episodes of seizure like activity mainly when she would get excited. The owner described that she was still conscious, and the event would last 10-15 seconds. Bella tested heartworm positive at another veterinary clinic years prior, however, she was never treated or kept on heartworm prevention.

On physical examination, Bella was bright and alert. She weighed 79.1 lbs and was a body condition score of 6/9. She had a temperature of 104.6 F. Her ears, eyes, nose, and throat were clean and clear and within normal limits. On cardiothoracic auscultation, an irregular heart rhythm with pulse deficits was discovered. She had a right systolic grade 4/6 heart murmur with asynchronous femoral pulses. Her lungs auscultated within normal limits with no wheezes or crackles. Based off history and physical exam, it was evident Bella was having syncopal episodes, not seizures.

Diagnostic Approach

A three-view radiographic study was performed. On the ventrodorsal view, the main pulmonary artery was significantly enlarged as well as the right atrium. A complete blood count revealed a mild reticulocytosis and mild thrombocytopenia. Serum biochemistry was within

normal limits. Bella was sent home on Furosemide (1.4 mg/kg PO Q12H), Enalapril (0.8 mg/kg PO Q12H), and Pimobendan (0.3 mg/kg PO Q12H).

Seven days later, Bella presented for anorexia, vomiting, and diarrhea. Clinical signs began after starting medications. Bella weighed 76.3 lbs and had a temperature of 102.7 F. An ultrasound of her heart was performed to look for any masses located in or around the heart. No masses were detectable on ultrasound. An electrocardiogram was performed and showed a dropped p-wave with every QRST complex. She was also tachycardic with a heart rate of 160 beats per minute. Furosemide, Enalapril, and Pimobendan were discontinued and Bella was started on Propranolol (0.1 mg/kg PO TID). She was referred to Nashville Veterinary Specialists at this time.

On June 1st, 2020 Bella presented to Nashville Veterinary Specialists Emergency Department. She was lethargic, anorexic, and still having episodes of syncope. She was having 8-10 syncopal episodes daily. She continued to have diarrhea and vomiting. She weighed 77.0 lbs, 101.1 F rectal temperature, heart rate of 115 beats per minute, and respiratory rate of 45 breaths per minute. Her capillary refill time was 2-3 seconds and mucus membranes were pale-pink and tacky. Cardiothoracic auscultation revealed normal rate, rhythm, and normal bronchovesicular sounds. No murmur was auscultated, and femoral pulses were fair and synchronous. Her blood pressure was 126 mmHg systolic with a sinus tachycardia present on electrocardiogram.

A 4DX Plus test was positive for Dirofilaria and below detectable limits for Lyme, Anaplasma, and Ehrlichia. Serum biochemistry revealed mildly increased BUN and mild hyperphosphatemia. Radiographs and echocardiogram revealed severe pulmonary hypertension, tricuspid valve dysplasia, and right sided-congestive heart failure causing pleural effusion and

ascites. The echocardiogram also revealed a normal LA/AO of 0.74. She had a severely enlarged right atria, severe right ventricular dilation, tricuspid valve dysplasia with severe regurgitation and severely elevated pulmonary arterial systolic pressure estimate. Her main pulmonary artery and pulmonary branches were diffusely dilated with mild pleural effusion and ascites present. At her visit, Bella received IV fluids, Furosemide (2 mg/kg IV) and Sildenafil (1 mg/kg PO Q8H).

Pathophysiology

Adult heartworms wreak havoc on the cardiopulmonary system. The severity of lesions to the pulmonary arteries, lungs, and heart is associated to the worm burden number, exercise routine, and length of infection[2]. Adult heartworms can cause pulmonary parenchymal inflammation and arterial obstruction[6]. Death of adult worms can cause thromboemboli, arterial obstruction, and vasoconstriction within the pulmonary vasculature[2]. The pulmonary arteries often become thickened, dilated, and tortuous which causes decreased oxygen transport to the rest of the body. Vasoconstriction by vascular endothelial cells leads to pulmonary hypertension and decreased cardiac output[2]. Hypoxia and syncope are most often exacerbated with exercise or excitement. Pulmonary thromboemboli and pulmonary consolidation are also other factors that initiate hypoxia and syncopal episodes[2].

Serious side effects of heartworm disease include right sided heart failure, eosinophilic pneumonitis, eosinophilic granulomatosis, glomerulonephritis, and caval syndrome. Right sided heart failure can occur due to increased pulmonary pressure causing right ventricle, atrial dilation, and wall thickening. Eosinophilic pneumonitis is an inflammatory reaction to the killing of microfilariae within the pulmonary microcirculation[2]. Eosinophilic granulomatosis can also occur from trapped microfilariae, neutrophils, and eosinophils forming granulomas in the lungs. Dead heartworms cause damage to vasculature, restrict pulmonary blood flow, and cause an

increase in coagulation. Overall, focal pulmonary parenchymal lesions are more common than generalized lesions within the lungs of heartworm positive patients. Glomerulonephritis is also a sequelae of heartworm disease and is caused by antigen-antibody complexes that are deposited into the kidney causing damage to the glomeruli[2]. Caval syndrome is a life-threatening event that occurs due to the adult heartworms obstructing blood flow through the tricuspid valve or adult heartworms backing up into the right ventricle, right atria, and entering the vena cava. Surgery must be performed to extract the heartworms[1].

To determine disease severity, a complete blood count (CBC), serum chemistry, urinalysis, thoracic and abdominal radiographs should be performed. Additional tests include an electrocardiogram and echocardiogram. On CBC, most often a nonregenerative anemia, eosinophilia, basophilia, and thrombocytopenia will occur. A serum chemistry may reveal azotemia which only occurs in 5% of patients, and elevated liver enzymes can occur due to heart failure. Proteinuria and hemoglobinuria may be present on urinalysis due to glomerulonephritis[2]. Radiographs offer a great method for evaluating disease progession. On radiographs, a “reverse D” shape of the cardiac silhouette is often present. This is indicative of main pulmonary enlargement paired with right atrial and ventricular hypertrophy. The right caudal lobar artery is often enlarged and torturous as well[9]. Patients in heart failure may have hepatomegaly, splenomegaly, pleural effusion, and ascites[2]. Echocardiography can help further evaluate right heart enlargement and can sometimes show worms in the pulmonary artery. Electrocardiography is not typically useful in heartworm disease. Arrhythmias are rare except in heart failure or caval syndrome patients[2].

Prevention, Treatment, and Management

Prevention of canine heartworm disease includes macrocyclic lactones. They work by killing the L3 and L4 larvae within the host and all tissue stages in the last 30 days. To test for heartworm infection, a blood antigen test screens for the presence of uterine glycoprotein located within adult female heartworm. Therefore, a positive antigen test reveals the patient has been infected at least 6-7 months prior to presentation. If a dog is positive on antigen test, repeat another antigen test and do a direct blood smear to check for microfilaria. Adult heartworms typically live 5-7.5 years and microfilaria can live 1-2.5 years[2].

Treatment for heartworm disease includes a macrocyclic lactone, tetracycline, and melarsomine. Macrocyclic lactones aid in killing microfilaria and prevention of new infection while a tetracycline such as Doxycycline, helps in killing an endosymbiont bacterium, *Wolbachia*, that lives within the heartworm[1]. *Wolbachia* is essential in *D. immitis'* fertility and long-term survival. It is now a target of therapy to eliminate the *Wolbachia* population to help aid in killing the adult heartworms[4]. It is also shown that Doxycycline can help reduce pathology of pulmonary parenchyma prior to administration of melarsomine [(1,7)]. One case study showed dogs given Doxycycline had fewer respiratory complications (6.52%) compared to dogs that did not receive Doxycycline (19.4%). Respiratory complications included coughing, dyspnea, and hemoptysis. This was a small case study, but results do suggest including Doxycycline in heartworm treatment protocol[7]. Glucocorticoids such as prednisone can be added to treatment plan to help control inflammation associated with a pulmonary thromboembolism (PTE) [(1,7)].

Melarsomine is the only adulticidal drug approved by the US Food and Drug Administration in conjunction with macrocyclic lactone heartworm preventatives. Melarsomine is the adulticide treatment that kills adult heartworms greater than 4 months of age[1].

After diagnosis of heartworm disease on Day 1, the American Heartworm Society recommends administering a macrocyclic lactone for 60 days and giving oral Doxycycline within the first 30 days. A 3-injection protocol of Melarsomine is initiated. The first melarsomine injection is given on Day 60. After the first injection the dog should be on cage rest and exercise restricted for 30 days. Activity level of the dog is the single most important factor in minimizing cardiopulmonary complications. A second melarsomine injection is given 30 days after the first. The third melarsomine injection is given 24 hours after the second injection[1]. The first shot kills 50% of male heartworms with the second and third injection killing the female adult heartworms. Four weeks after finishing this protocol, a direct blood smear should be performed to check for microfilaria. Six months post-treatment, an antigen test should be performed[3].

Heartworm resistance to macrocyclic lactones is a major concern in veterinarians and pet owners. Due to the long survival time of adult heartworms and damage that occurs to the cardiopulmonary system, it is recommended to treat dogs with adulticide treatment. However, due to client financial restraints, the option of “slow-kill method” is often given. Most often injectable moxidectin or topical moxidectin (macrocyclic lactones) are given year-round along with Doxycycline for the first 30 days with the absence of melarsomine adulticidal therapy. This is a less expensive alternative, however resistance to macrocyclic lactones is a major concern. The major cause of heartworm infection in the United States is poor owner compliance with administering preventative medication[5].

Case Outcome

On June 1st, 2020 Bella was discharged from Nashville Veterinary Specialists after the initial cardio work up. It was recommended that Bella go to her primary veterinarian in one week, recheck renal panel in two weeks, and recheck echo in one month. She was prescribed Doxycycline (5 mg/kg PO Q12H x 30 days), Furosemide (2.0 mg/kg PO Q12H), Enalapril (0.3 mg/kg PO Q12H), Pimobendan (0.3 mg/kg PO Q12H), Spironolactone (2 mg/kg PO Q8H) and Sildenafil (1 mg/kg PO Q8H).

On July 7th, 2020 Bella presented to Nashville Veterinary Specialists Cardiology Department for a recheck. Since her last visit, Bella was doing well and was not having any more syncopal episodes at home. On physical exam, she was tachycardic with a regular rhythm. A grade 4/6 right systolic murmur with strong and synchronous femoral pulses were present. Her recheck echocardiogram revealed significantly decreased tricuspid valve regurgitation, normal systolic pulmonary arterial pressure estimate, and a decrease in right atrial dilation from her previous echo one month prior. Bella's owners were instructed to continue giving Furosemide (2.0 mg/kg PO Q12H), Enalapril (0.3 mg/kg PO Q12H), Pimobendan (0.3 mg/kg PO Q12H), Spironolactone (2 mg/kg PO Q8H), and Sildenafil (1.2 mg/kg PO Q8H) and return in six months for an echocardiogram. Bella is scheduled to receive her first melarsomine injection at Reelfoot Animal Hospital this month.

In severe heartworm disease, administration of glucocorticoids, diuretics, vasodilators, positive inotropes, and IV fluids may be required prior to adulticidal treatment. Adulticidal treatment can still be given after the patient has become stable and healthy enough to receive it, however, irreversible damage has occurred to the cardiopulmonary system[2]. This was evident in Bella's case and goals of drug therapy included decreasing pulmonary hypertension, pleural/abdominal effusion, and overall damage to her heart. After melarsomine treatment, there

is a chance Bella’s heart could show continued improvement and she may be able to discontinue some of her medications in the future.

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