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D. IMMITIS-A 3-MONTH DISEASE CYCLE: PREVENTION AND TESTING

INTRODUCTION

By common definition, Dirofilaria immitis is discussed as having a 6-month life cycle (infection of host through development and sexual maturity). It is assumed that clinical disease does not develop until the parasite is a 6-month-old adult is incorrect.

The initial arrival of immature L5 in the small pulmonary vessels of the lungs is associated with an intense eosinophilic pulmonary reaction and radiographic signs may be present in this 3-6 month post-infection period. This 3-month disease cycle precedes the production of microfilaria and circulating antigen by 2-3 months. Because of the difference in the host immune reaction, and mortality of the immature L5 worms, the clinical signs, diagnosis, and effects of prophylaxis are different in the dog vs the cat with heartworm infection.

LIFE CYCLE

Adult females (27 cm long) and males (17 cm long) normally reside in the pulmonary arteries and right ventricles without causing major occlusion of blood supply. Microfilariae (315 µm long and 6-7 µm wide) are discharged into the blood stream and survive 1-3 years. The number of circulating microfilaria in dogs is increased in warm ambient temperature, after eating, and late at night. The microfilariae are ingested by a mosquito during feeding. The infective larvae (L1) migrate to the stomach and then the mouthparts (L3) during development. The rate of development can be as short as 8 days at 30°C or as long as 28 days at 18°C. After a mosquito acquires the microfilaria (L1), adequate exposure to warm temperatures must occur during the relatively short life span (1 month) of many of the mosquito vectors. The infective larvae are deposited on the skin of an animal when the mosquito feeds again and the L3 enters through the bite wound. A maximum of 10-12 L3 can be transmitted by a single mosquito.

The L3 stages molt to L4 and L5 (adults) and migrate to the pulmonary arteries arriving as L5 (1-2 cm in length) approximately 90-100 days after infection. These small L5 are distributed mainly to the caudal distal pulmonary arteries, and over the next 2-3 months, develop to sexually mature adults and migrate back toward the right ventricle. If both sexes are present, microfilaria are produced 6-7 months after L3 exposure and can be detected in the blood in the dog, rarely in the cat. The common detection methods for adult antigen are positive typically about 6-7 months after infection. High enough quantities of the glycoprotein to be detected are only associated with fully mature adult female heartworms.

D. IMMITIS - HEARTWORM OR LUNGWORM

Adult heartworms can live 3-5 years in the dog and 1½-2 years in the cat. Although an endarteritis is produced, emboiliation and total vascular occlusion are rare when the worms are alive. The severity of the pathology is influenced by the number of parasites but pulmonary vascular disease is also exacerbated by the shear stress of high blood flow associated with exercise. Severe pathology can be induced by low worm burdens in athletic dogs. The classically described cor pulmonale syndrome is only induced in dogs with an exercise pattern forcing right ventricular hypertrophy from increased cardiac outputs and increased pulmonary vascular resistance. In endemic areas, the average worm burden in the dog is about 15 worms and in the cat 3-1 worms. High worm burdens can be found in dogs with minimal cardiac changes if the dog is sedentary. Thus the majority of dogs and almost all cats with heartworms have no significant clinical disease associated with pulmonary hypertension or heart failure. The death of worms, either spontaneous or induced, is associated with severe pulmonary parenchymal disease. The majority of the clinical signs and most of the life-threatening aspects of heartworm disease are pulmonary function related.

INITIATION OF DISEASE-3 MONTHS AFTER INITIAL INFECTION

With the arrival of L5 as 1.5 cm worms in the right and left caudal arteries, small vessel disease and lung parenchymal pathology are initial insults. As would be expected of any foreign body of this size, the parasite is ejected out the pulmonary outflow tract and most are deposited in the right and left caudal pulmonary arteries. Consequently, initial damage associated with the 3-6 month post infection period is most noted in these arteries and caudal lung lobes. The host response to the infection during this initial insult is inflammatory and eosinophils can be detected in the alveolar space and interstitium.

In dogs, the majority of L5 which arrive in the lungs will survive and develop into adult heartworms. In cats, there is a high mortality rate of the initial L5 worms. Some cats will have all of the L5 will die during the next months and have no adults at 6-7 months post infection.

As the worms increase in size and grow back up the pulmonary arteries towards the heart, the surface arterial lesions become more evident. The periarteritis allows additional leakage and inflammation will extend into the lung parenchyma. At the distal capillary bed level, even the alveolar septa will develop edema and injury of the capillary beds. These lesions are significantly worse associated with dead and dying worms. High flow at critical times of early lesions will promote fibrosis rather than normal repair. Demonstration of heartworm antigen in interstitial areas distal to the physical presence of heartworms emphasize that the inflammatory response is throughout the pulmonary parenchyma. The microvascular lesions are severe when worms are alive, but become exaggerated associated with worm death. Type 1 pneumocytes are disrupted from the endothelial cells, leaving many of the alveolar sacs as denuded airways. Although more severe in lobes where heartworms are dying, similar lesions can be demonstrated in other lobes. The author has produced similar histologic lesions with cell free extracts of adult heartworms. The resultant lung injury is typical of Adult Respiratory Distress Syndrome (ARDS). During these critical times of natural or induced worm death, the lung develops severe periarteritis, interstitial edema, and acute inflammatory interstitial disease. The ciliated bronchial columnar epithelium can also be damaged and undergoes necrosis.
LUNG RESPONSE IN THE DOG

After initial endothelial damage and alveolar injury, the body will either attempt to repair the lesion with normal cellular structures or repair by scarring and fibrosis. The shear forces on endothelial cells during high flow and increased permeability contribute to increased capillary bed damage, alveolar flooding, and resulting fibrosis. All of which contribute to decreased areas of gas exchange and promote the fibrosis which further increase pulmonary vascular resistance. Unfortunately, the microvascular disease cannot be radiographically evaluated and only in dogs where the disease is extreme or the exercise pattern of the dog has exacerbated the right-sided heart strain, will the typical pattern of cor pulmonale be demonstrated. The microvascular lesion of fibrosis of pulmonary capillary bed would appear to be irreversible. Chronic disease is influenced by the blood flow through the lungs and number of heartworms dying over time.

LUNG RESPONSE TO EARLY INJURY-CAT VS DOG
Response of the Cat Lung to Adult Heartworm

If the course of a D immitis infection is evaluated chronologically, the changing nature of the disease is evident. As the parasite first arrives in the lungs as early as 90 days after being infected by a mosquito, the lung responses with intense inflammation and "asthma- like" symptoms may develop. The cat has specialized macrophages (Pulmonary Intravascular Macrophages- PIMs) in the capillary beds of the lung that are not present in the dog. After the mature parasite develops, the clinical signs may be intermittent or absent. The parasite seems to be able to suppress the macrophage function in the lung. The cat will have classic radiographic and histologic findings of feline heartworms, but may not show clinical signs. After the adult parasite develops, the pulmonary parenchymal changes and even enlarged caudal pulmonary arteries on VD radiographs may decrease. However, at the time of worm death, the suppression of macrophage function is decreased and the lungs become extremely inflamed and the specialized macrophages may become important in the intense reaction. The result is a non-functioning lung and an acute respiratory distress syndrome. Although this reaction can occur as the result of even a single worm burden, spontaneous death of cats from heartworm infection is uncommon compared to clinical disease associated with the early 3-6 month disease. Usually severe dyspnea associated with heartworm disease and especially that which results in death is the consequence of an adult heartworm dying. After the removal of dead heartworms, there may be continued inflammatory lung disease in some cats.

Response of the Cat to the Early Infection

The disease associated with feline heartworm infection is a moving target, with the pathology, and resulting clinical signs, dependent on the stage of the life cycle involved. Early arrival of L5 results in classic asthma-like radiographic and clinical signs. In cats during this early part of the infection, coughing and dyspnea can be intermittent. A peripheral eosinophilia may or may not be present. Typically, the cytology of BAL reveals an eosinophilic reaction. The radiographic pattern can be dynamic and right-sided cardiac changes are not present. The inflammatory pattern in the lung parenchyma is peribronchial but may be severe enough to be a diffuse alveolar pattern. Pulmonary arterial patterns may be normal although if the periarterial inflammation is severe, the right and/or caudal pulmonary arteries may appear enlarged. Often, the inflammatory lung pattern is severe enough that the pulmonary arteries cannot be visualized.

Three Month Disease Cycle-Diagnostic And Preventative Considerations

With the initiation of pulmonary disease at 3 months after the infection, pathology and clinical signs may be present 3 months before antigen or microfilaria would be present in the blood and 3 months before heartworms could be visualized echocardiographically. Thus, dogs and cats with lesions during this early phase are "heartworm negative" by the typically applied screening tests used in practice. Although the radiographic and histopathologic lesions are present during the early phases (months 3-6 post L3 infection) in the dog, rarely are dogs presented for clinical signs during this time frame. However, because of the intense reaction of the cat lung to the arrival of these 1-2cm L5 at 3 months and/or the reaction of the lung to the higher mortality of these early young adults, clinical signs are frequently noted during this stage of the infection.

Some cats will develop these early lesions and become antibody positive, but over time (3-6 months) the young adult parasites in the distal pulmonary arteries all die. Although this form of heartworm infection could be considered as "self-curing," lesions were induced, clinical signs may have develop, and long term consequences of this infection are unknown. The alveolar and bronchial changes associated with this early form of the disease will clinically and radiographically mimic "feline asthma." Cats will develop an eosinophilic BAL cytology, radiographic bronchial lesions without pulmonary arterial changes, and clinical signs of coughing and/or dyspnea will respond to typical corticosteroid therapies. Cats that are heartworm antibody positive have been successfully infected with the L3 which have molted to the L4 and L5, typically (depending on the test methods) lived 2 ½ to 3 months, and may or may not have gone on to arrive in the distal pulmonary arteries as L5.

In a study of cats presented to practicing veterinarians with a history of coughing and/or dyspnea, 42% were heartworm antibody positive. When cats with radiographic lesions and/or positive serology were examined over a 3-month time frame, the changes demonstrated that this infection is dynamic and a diagnostic challenge. Discordant serologic results between test methods can occur because each identifies a different antibody during the initial phases of the infection.

Consideration in Dogs

With the understanding that dogs also have heartworm lesions associated with this 3-6 month post infection period, the concept of a "reach back effect" should be revisited. Monthly preventives administered to dogs 3-4 months after infection will be heartworm negative when these medications are administered for a 1-year period. However, based on histopathologic and serology studies, this should not be considered as a successful "preventative" in the typical manner used with owners. Veterinarians assure owners that if a monthly preventative is administered, any exposure initiated in the previous month will not be successful in developing in the heart and lungs. However, to suggest that a preventative has a reach back effect 3 or 4 months would be inaccurate and incorrect; because at this point, these small young adults (L5) are typically already in the distal pulmonary
arteries inducing damage at that time. As noted in the experimental studies, initiation of preventative medications 3-4 months post L3 even allow some of these worms to develop long enough to produce antigen before they die.

Dogs that are antigen and microfilaria negative can have 3-6 month old young adults at the time of initiation of monthly preventative medication. As noted in the cat, death of the immature heartworms is associated with increased pulmonary damage. Preventative medications which accelerate the death of immature heartworms is also associated with an increased inflammatory arterial and pulmonary damage during the time of worm death. However, elimination of these immature worms is preferred to allowing the worms to continue to develop, increasing their size and mass, inducing damage over the next several years, and then as a significantly larger worm burden dying and creating significantly more damage.

Heartworm Adulticides: Rapid Kill vs Slow Kill-The Complications

Although the clinical signs of heartworm disease have been documented, the exact pathogenesis of the disease is multifactorial. As complicated as the disease process is when heartworms are alive, the dramatic changes associated with the death of heartworms, either spontaneously or induced, are clear indications of the dramatic host vs parasite reaction.

REACTION OF HOST TO HEARTWORM DEATH

Based on experimental transplantation of dead heartworms or administration of extracts of homogenated worms, the death of heartworms is associated with severe pulmonary edema and loss of alveolar Type I cells and even ciliated epithelium lining the bronchi. The acute necrosis was noted to be more severe in dogs than in cats. Pulmonary capillaries were often obstructed by plugs of platelets and eosinophils. No increase in PIM phagocytosis was noted in cats with dead heartworms. Type II cell hyperplasia, showing evidence of the repair of lung injury, was more common in cats than in dogs. Based on lung scans and histopathology, infarction of the lung associated with dead heartworms was occasionally observed in dogs but was rare in cats. The death of heartworms results in severe capillary bed fragility, loss blood into the alveolar space, and causes the type of lung injury associated with adult respiratory distress syndrome (ARDS) in humans. The acute lung injury from dying heartworms is not a direct toxic effect of the worm by-products, occurs in dogs and cats with no prior exposure to D. immittis, and is related to the worm mass and rate of worm death.

Typically heartworms die and fragment over a period of weeks. After the death of mature adult heartworms, even those which have just died and have been surgically implanted in normal Beagles, the adult worms slowly collapse, lose the rigid appearance, fold over, and lodge in the most distal pulmonary artery. However, embolization and infarction of pulmonary parenchymal change associated with heartworm death. The intensity of the pulmonary parenchymal changes would appear to be directly related to mass of heartworms and somewhat related to rapidity of the breakdown of the physical structure of the worm itself. Increased pulmonary blood flow associated with increased cardiac output causes alveolar flooding and in the dog, pulmonary consolidation and capillary bed fibrosis.

ADULTICIDAL THERAPY-COMPLICATIONS

The most serious complication of heartworm adulticidal therapy is 2-3 weeks after heartworm death. Acute lung injury is compounded by endothelial sloughing, pulmonary vascular obstruction, and intense platelet activation. Dyspnea after adulticide therapy in dogs should be considered an emergency and nasal oxygen and glucocorticoid therapy are required to stabilize damaged lung parenchymal damage. Although the dogs may appear in shock, the cardiac output is usually maintained. Large volumes of intravascular colloids should not be administered and central venous pressure carefully monitored. If significant pulmonary embolization with vascular occlusion has occurred, large volumes of fluids will increase end-diastolic right ventricular pressure resulting in poor perfusion of the right ventricular free-wall and myocardial failure.

Some dogs with severe thromboembolism of major pulmonary arteries may present with significant dyspnea and what appears to be relatively "clear" lung field, which are hypoperfused caudal lung lobes. Most dogs with dying heartworms have significant activation of platelets which cannot be blocked with extremely high doses of aspirin. Thrombocytopenia (<100,000/µl) is common 2-3 weeks after adulticide administration even in asymptomatic heartworm dogs. If platelet counts below 100,000/µl are noted, dogs should be screened for disseminated intravascular coagulation. In the absence of DIC, many dogs will respond to oxygen and glucocorticoid therapy within 24 hours. Because of the fragile nature of the capillary beds of the lungs, complete rest should be maintained. After 24 hours of supplemental oxygen, arterial partial pressures of oxygen below 70 mmHg reflects severe diffuse lung injury and often a poor prognosis. Heparin therapy, administration of warfarin derivatives, and clot lysing agents have not been demonstrated to be clinically effective during the crisis.

Early aggressive intervention with glucocorticoid administration continues to provide the best clinical approach during the post-adulticidal period. Because the initial studies demonstrated that daily administration corticosteroids protected adult worms to thiacetarsamide, increased the myointimal proliferation, and increased the incidence of severe embolism, corticosteroids have been advocated only at the time of thromboembolism. Low dosing of alternate day corticosteroid administration has been advocated to treat the periarteritis in heartworm dogs, and has definite indications in dogs with severe eosinophil pneumonia.

Although the first 3 weeks are critical after adulticide therapy, residual worm fragments in small pulmonary arteries can be demonstrated for up to 6 weeks. Strict exercise restriction and maintaining a low cardiac output is important to facilitate lung repair rather than encourage fibrosis. The reversibility of pathology cannot be predicted based on initial
radiographic pattern. Dogs with significant elevations in pulmonary vascular resistance at presentation have irreversible morphologic changes in the pulmonary beds. In addition, an intense response of the dog to worm death may alter the initial clinical impression that the disease state was mild. Because some of the cardiovascular response to heartworm disease is vasoactive, not mechanical, and removal of the heartworms encourages repair, not fibrosis, most owners report clinical improvement after the successful removal of heartworms.

**RAPID ADULTICIDAL APPROACH**

The use of melarsamine has provided an effective method of killing adult and immature adult heartworms. Compared to thiacytemarsamide which did not affect immature worms and had poor efficacy on young mature female heartworms, the increased efficacy also increases the risk associated with heartworm death. Because the clinical signs are often not related to heartworm burden, the number of heartworms which are going to insult the lungs cannot be accurately predicted based on the classification system provided with melarsamine. Thus, although an active dog could be classified as severe grade 3, there could be a low worm burden. The alternative is that a class 1 dog with no clinical or radiographic signs which is primary a sedentary dog could have a large worm burden. The death of a large number of worms regardless of the clinical condition of the dog can result in severe complications.

Based on an unknown heartworm burden in client dogs, where monies are not a major concern to the owners, the safest approach to a dog with heartworms is a staged heartworm kill. One injection of melarsamine and then a 1 month rest, followed by 2 injections over 24 hours can result in elimination of approximately 30% of the worm burden initially, 1 month to resolve the pulmonary insult, followed by 2 injections which would eliminate the rest of the worm burden. However, this approach also requires the prolonged restriction of activities during this 2-month period of staged heartworm death. In areas where large heartworm burdens are common, this 3-dose approach is the standard recommended therapy for all heartworm positive dogs.

**SLOW ADULTICIDAL APPROACH**

Based on a series of studies by several investigators, there is a consensus, but not agreement on the efficacy, that administration of the monthly preventative medications over a 1 yr to 18-month treatment will result in a reduction in the number of adult heartworms. With some differences in the experimentations where variables of age of worms, dosing duration, and worm numbers varied, there is evidence to demonstrate that there are long term adulticidal effects associated with dosing of monthly preventatives. The adulticidal effects of monthly preventatives demonstrate efficacy in this descending order: ivermectin with pyrantel pamoate, milbemycin, and selamectin. (Moxidectin Sustained Release administered as a single dose or 3 doses separated by 6 months does not appear to demonstrate a significant adulticidal effect.) Although many of the studies demonstrate a decrease in total worm burdens related to controls, the complete clearance of all the worms in individual dogs (important to clinical medicine) is less defined.

Based on results of studies with ivermectin with pyrantel pamoate, the use of for 16 months (56% effective on 8 month old worms) and for 29 months (95% effective for 7 month old worms) in experimental Beagles, it has been suggested that administration of monthly preventatives is an alternative method of treating clinical heartworm infection. In regards to the adulticidal activity of monthly preventatives, the key question to clinical medicine - "Is this a good thing or a bad thing?"

Understanding that the dogs in the various studies did not demonstrate significant clinical signs associated with the "gradual" worm death, the immediate response would be encouraging even though the total worm mass was not removed in many of these studies. However, experimental studies using purpose breed dogs in confined space for the duration of the experiment would reflect a similar clinical scenario of cage resting a client dog for the 1 ½ to 2 years of worm death and lung injury. Experimental dogs with similar worm burdens, as in these studies, have been administered 2 doses/24 hrs of melarsamine (with 99% efficacy over 3-4 weeks) and have not demonstrated significant clinical signs; but once again the dogs were cage confined.

Acute lung injury is associated with the death of heartworms, regardless of the cause. Increased flow though the disease pulmonary capillary beds can result in fibrosis and extend to hemoptysis and in the extreme, ARDS and death. In the clinical practice of heartworm disease management, it is vital to know when the heartworms die and thus when the lung injury is induced and limited exercise is necessary. In a dog which has no physical activity, this may be a moot question. However, of concern is an active dog in which it is know that even with live worms, the increased cardiac output is associated with increased pulmonary fibrosis and increases in pulmonary vascular resistance. The unanswered question is whether an active dog with worms dying over a gradual period of time will have a greater tendency to develop these lesions as a consequence of the prolonged lung insult. Lung injury is more severe in studies where monthly preventatives were more "effective" at killing 4-month-old L5 adults. Acute consequences of "slow adulticidal" therapy with monthly preventative medications have been anecdotally reported. Clinical trials using unconfined dogs to determine the real risk of adulticidal activity of month preventatives have not been reported.

In active dogs, the use of monthly preventative medications as an adulticide should be used with caution. Owners of dogs receiving such therapy should be advised that any respiratory difficulty should be considered an emergency. Owners should also be advised that this therapy is not as efficacious as the current recommended adulticide melarsamine and a negative antigen test does not equate with successful elimination of all adult heartworms.