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FELINE HEARTWORM DISEASE: WHAT'S NEW?

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Though recognized since 1921¹, heartworm infection (HWI) in the cat has received increasing interest over the last decade. Reasons for this are multiple, with an increasing diagnostic armamentarium, an increasingly aware and demanding public, and the development of safe, effective, and broad-spectrum preventative drugs. With this comes the responsibility of understanding the pathogenesis, clinical signs, diagnostic process, treatment, and most importantly, preventing HWI in cats.

Etiology

The domestic cat, though an atypical host, can be parasitized by *Dirofilaria immitis* (HW) with resultant heartworm disease (HWD). The clinical manifestations of the disease are different and more severe in this species, but the infection rate is only 5-20% of that of the dog.¹ Experimental infection of the cat is more difficult than in the dog; <25% of L3 reach adulthood. This resistance is also reflected in natural infections, in which feline heartworm burdens are usually less than 6, and typically only 1-3 worms.¹ Other indications of the cat's inherent resistance to this parasite are a shortened period of worm patency, high frequency of amicrofilaremia or low microfilaria counts, and shortened life span of adult heartworms (2-3 years).² Additionally, while some species of mosquito may feed on cats, most prefer the dog and, for a cat to become infected, the mosquito must first have fed on a dog. Nevertheless, studies have shown a prevalence as high as 10-14% in shelter cats^{1,1a} and a study performed at NCSU revealed HWD in 9% of cats presented with cardiorespiratory signs.³ Furthermore, antibody testing showed 26% of 100 of these cats to have been exposed to HW.³ Similar to dogs, some studies have shown the male to be at higher risk for HWI than the female. Aberrant worm migration appears to be a greater problem in cats than in dogs.

Pathogenesis

The pathological, clinicopathological, and clinical response to infection with *D. immitis* in cats is not well understood. The pulmonary arterial response to adult heartworms is more severe than that of the dog, although pulmonary hypertension has infrequently been reported. Dillon demonstrated pulmonary enlargement within one week of transplantation of adults, suggesting an intense host-parasite interaction.⁴ A severe myointimal and eosinophilic response produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly hypertension.⁵ Because the feline pulmonary artery tree is smaller than that of the dog and has less collateral circulation, embolization, even with small numbers of worms, produces disastrous results with infarction and even death. Although uncommon, cor pulmonale and right heart failure can be associated with chronic feline HWD and is manifested by pleural effusion (hydro- or chylothorax) and/or ascites. The lung per se also is insulted by HWI, with eosinophilic infiltrates in the lung parenchyma (pneumonitis), pulmonary vasculature, and air spaces. The pulmonary vessels may leak plasma producing pulmonary edema, which has been considered by some to represent acute respiratory distress syndrome (ARDS). If the cat survives this initial insult, type II cells proliferate, replacing

damaged type I cells, potentially impairing O₂ diffusion.⁴ The end result is diminished pulmonary function, hypoxemia, dyspnea, and cough.

Acute or sudden death is typically associated with worm death and fulminant pulmonary failure, possibly associated with pulmonary embolism. Recent research suggests, however, an immune-mediated reaction to HW antigens in the feline shock organ (lung).^a Fatal respiratory failure probably results when HW antigen is released, producing bronchiolar and bronchial constriction, pulmonary congestion, superficial pulmonary hemorrhage, and periarterial hemorrhage.^a

“HARD”. It has been known since 1996 that cats exposed to heartworms but which reject maturation develop radiographic lesions.¹³ Recently, studies of both natural and experimental infections have confirmed this finding.^{4a,4b} In natural infections, pulmonary arterial lesions (myointimal proliferation and thrombotic obliteration) have been demonstrated in HW-free, antibody-positive cats^{4a} and airway, pulmonary artery and pulmonary interstitial lesions have been demonstrated in cats heavily, experimentally-infected cats in which pharmacological abortion of the infection at the early L₅ stage was performed.^{4b} This combination of data from experimental and natural infections indicates that when cats abort infections at the early L₅ stage, radiographic and histological changes develop in the lungs, likely producing the most commonly recognized signs in cats, cough, dyspnea and wheezing. The American Heartworm Society has utilized this information in a campaign for heartworm awareness, labeling it “HARD” or “**H**earthworm-**A**ssociated **R**espiratory **D**isease”.^b The fact that larvae that never fully mature can cause disease is important to our understanding of this syndrome. We do not know if the resultant pathology is persistent whether it can result in fatality, and if it explains signs later in the disease course. It also causes confusion as to the exact terminology for HWI as a cat may fall outside the standard concept of “exposed and uninfected” as opposed to “infected”. This has led me to invoke a new term for the HWI infection in cats that is aborted at the young L₅ stage: “Pulmonary Larval *Dirofilariasis*” meaning a HW larval infection that produces disease without full larval maturation.

Recently, a symbiotic bacterium, *Wolbachia*, has been found within filarid parasites and their microfilariae.^{4c} This bacterium is essential for filarial reproduction and well-being. It has been hypothesized that antigens from these bacteria are proinflammatory, contributing to the HWD, particularly upon the death of the adult HW and that, possibly, treatment of bacteria with tetracycline might be a strategy in the treatment adult *dirofilariasis*.^{4d} Currently, there are no data to support this interesting hypothesis.

Clinical Signs

Cats with HWI may be asymptomatic and, when present, clinical manifestations may be either peracute/acute or chronic.^{3,4,6-8} Acute or peracute presentation is usually due to worm death, embolization or aberrant migration and signs variably include salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death.

More commonly, the onset of signs is less acute (chronic form). Reported historical findings in chronic feline HWD include anorexia, weight loss, lethargy, exercise intolerance, signs of right heart failure (pleural effusion; rare), cough, dyspnea, and vomiting. We have found dyspnea and cough to be a relatively consistent findings and, when present, should cause suspicion of HWD in endemic areas.⁸

In a report of 50 natural cases of feline HWI seen at North Carolina State University, presenting signs were most commonly related to the respiratory system (32 cats; 64%), with dyspnea (24 cats; 48%) being most often noted, followed by cough (19 cats; 38%), and wheezing.⁸ Vomiting was reported in 17 (38%) cats and was noted frequently in 8 (16%). Five (10%) heartworm-infected cats were reported to have exhibited vomiting without concurrent respiratory signs and vomiting was a presenting sign in 7 (14%). Neurological signs (including collapse or syncope, which were described in 5 [10%]) were reported in 7 (14%) cats. Five (10%) of the cats were dead at the time of presentation. Murmurs were infrequently noted in cats that did not have concurrent heart disease, independent of heartworm infection. Heart failure was present in 1 cat but this cat had concurrent hypertrophic cardiomyopathy. Heartworm infection was considered to be an incidental finding in 14 (28%) of the cats in this study.

Physical examination is often unrewarding although a murmur, gallop, and/or diminished or adventitious lung sounds may be audible. In addition, cats may be thin and/or dyspneic. If heart failure is present, jugular venous distension, dyspnea, and rarely ascites are typically detected.

Diagnosis

The diagnosis of HWI/HWD in cats poses a unique and problematic set of issues.⁴ First, the clinical signs are often quite different from those seen in the dog. In addition, the overall incidence in cats is low, so suspicion is lessened; eosinophilia is transient or absent; electrocardiographic findings are minimal; and most cats are amicrofilaremic.

Immunodiagnostic methods are also imperfect in cats because of the low worm burdens (1-7, mean = 3)¹ and hence, antigenic load. In a recent study, ELISA antigen tests were positive on sera from 36-93% of 31 cats harboring 1-7 female HW, with sensitivity increasing as female worm burden increased.⁹ Cats with male worm(s) were not detected as positive. Therefore, false negative tests occur frequently, depending on test used, maturity and gender of worms, and worm burden. All tests were, however, virtually 100% specific. It is important to realize that infection with signs may be present prior to the presence of detectable antigen (from gravid adult females); McCall reports that, in natural infections, the antigen test detects less than 50% of cases.¹⁰ Snyder and colleagues present differing results from cats natural infections in which blood was obtained as long as 2 hours post-euthanasia. In this study the antigen test was found to be more sensitive than previous reports (74%).¹¹ Recently an antigen test "for cats" (IDEXX's SNAP^R Feline Heartworm Antigen Test) has been marketed. This is an adaptation of the canine test with a reported increase in sensitivity of 15% over conventional antigen tests.

Though not specific for **mature** infections, heartworm antibody tests are of use in the detection of **exposure** to (and partial development of) heartworms. These tests are, therefore, useful to determine cats at risk for HWI and to determine the potential for HWI in antigen-negative cats, in which HWI is a consideration. This author uses a negative antibody test to "rule out" HWI in cats with HWD-compatible signs. It must, nevertheless, be kept in mind that 14% of cats with a proven natural infection were shown to be the antibody-negative.⁸ This "false-negative" number reached 50% in smaller study of 10 cats.^{1a} Furthermore, although infrequent (2%), cats may be antibody-negative and antigen-positive, leading some to suggest that the 2 tests be run in tandem when HWI is suspected.^{11a} Nevertheless, for routine screening, the antibody test is preferred. There is now an "in clinic" feline heartworm antibody test available (HESKATM SOLO STEPTM FH).

Thoracic radiographs have been suggested as a screening test for HWI in cats. However, Schafer and Barry showed that the most sensitive radiographic criterion (left caudal pulmonary artery greater than 1.6 times the 9th rib at the ninth intercostal space) was only detected 53% of

cases.¹² Furthermore, even though most cats with clinical signs have some radiographic abnormality, the findings are often not specific to HWD. In addition, a study by Selcer, et al. demonstrated that radiographic findings were often transient and that radiographic abnormalities were found in cats which ultimately resisted maturation of HW and were negative on post-mortem (ie "false positive").¹³ Radiographic findings include enlarged caudal pulmonary arteries, often with ill-defined margins, pulmonary parenchymal changes include focal or diffuse infiltrates (interstitial, broncho-interstitial, or even alveolar), perivascular density, and occasionally, atelectasis. Pulmonary hyperinflation may also be evident. Pulmonary angiography has also been utilized to demonstrate radioluscent linear intravascular "foreign bodies", as well as enlarged, tortuous, and blunted pulmonary arteries with loss of normal patterns of arborization.

Echocardiography, in our experience, is more sensitive in cats than in dogs.^{3,14} Typically, a "double-lined echodensity" is evident in the main pulmonary artery, one of its' branches, the right ventricle, or occasionally at the right atrioventricular junction. We found HW echocardiographically in 78% of 9 naturally occurring cases³ as did Selcer in 16 experimentally-infected cats.¹³ It is important to realize that heartworms most often inhabit the main pulmonary artery or its branches, which require some expertise and an index of suspicion from the sonographer. Heartworm infection can be missed by ultrasound when worms are immature (hence, smaller) or when they have died and compacted into the more distal pulmonary arteries.

Prevention

The question arises as to whether heartworm prophylaxis is warranted for cats because they are not the natural host and because the incidence is low. Necropsy studies of feline HWI in the Southeast have yielded a prevalence of 2.5 to 14% with a median of 7%.¹ When considering the question of institution of prophylaxis, it is worth considering that this prevalence approximates, or even exceeds that of FeLV and FIV infections in comparable populations.¹⁵ A 1998 nationwide antibody survey of over 2000 largely asymptomatic cats revealed an exposure prevalence of nearly 12%.¹⁶ While outdoor cats are at greater risk for HWI¹⁶, it is noteworthy that, based on owners' information, nearly one-third of cats diagnosed with HWD at NCSU were housed solely indoors.⁸ Lastly, the consequences of feline HWD are potentially dire, with no clear therapeutic solutions. Therefore, I advocate preventative therapy in cats in endemic areas. There are now three drugs with FDA approval and which are marketed for use in cats. Ivermectin is provided in a chewable formulation, milbemycin as a flavored tablet and selamectin, a broad-spectrum parasiticide, comes in a topical formulation. Additionally, a new broad-spectrum, topical preventive (moxidectin and imdacloprid) is being used in Australia and Canada and is pending approval in this country. The spectrum, as well as the formulation of these products varies, and hence the clients' individual needs are easily met in most cases (Table 1). The risk of an adverse reaction to dying microfilariae is small because of the microfilarial "slow-kill" property of most macrolide preventatives (with milbemycin being the exception) and because most cats are amicrofilaremic or have low microfilarial burdens. Nevertheless, precaution should be taken (i.e., in-clinic or home-observed administration after first macrolide dose) in known microfilaremic cats.

Treatment

The use of arsenical-adulticides is problematic. Thiacetarsamide, if available, poses risks even in normal cats. Turner and colleagues reported death due to pulmonary edema and respiratory failure in 3 of 14 normal cats given of thiacetarsamide (2.2 mg/kg twice over 24 hours).¹⁷ Dillon could not confirm this acute pulmonary reaction in 12 normal cats receiving thiacetarsamide, but 1

cat did die after the final injection.¹⁸ More importantly, a significant, though unquantified, percentage of cats with HWI develop pulmonary thromboembolism after adulticidal therapy.^{4,6,7} This occurs several days to a week after therapy and is often fatal. In 50 cats with HWI, seen at North Carolina State University, 11 received thiacetarsamide. There was no significant difference in survival between those receiving thiacetarsamide and those receiving symptomatic therapy.⁸

Data on melarsomine in experimental (transplanted) HWI in cats are limited and contradictory. Although there is an abstract report in which 1 injection (2.5 mg/kg; ½ the recommended canine dosage) of melarsomine was used in experimentally-infected cats without treatment related mortality, the worm burdens after treatment were not significantly different than those found in untreated control cats.¹⁹ Diarrhea and heart murmurs were frequently noted in treated cats. A second abstract report, using either the standard canine protocol (2.5 mg/kg twice over 24 hours) or the “split-dosage” (1 injection, followed by 2 injections, 24 hours apart, in 1 month), gave more favorable results.²⁰ The standard treatment and split-dosage regimens resulted in 79% and 86% reduction in worm burdens, respectively and there were no adverse reactions. Although promising, these unpublished data need to be interpreted with caution as the transplanted worms were young (<8 months-old and more susceptible), the cats may not have had time to develop antibodies to HW antigens, thereby reducing the risk of anaphylaxis, and the control cats experienced a 53% worm mortality (average worm burden was reduced by 53% by the act of transplantation). Additionally, the clinical experience in naturally-infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk, lack of clear benefit, and the short life expectancy of heartworms in this species, this author does not advocate adulticidal therapy in cats. Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboemboli. The mortality seen in the only published case series was, unfortunately, unacceptable (2 of 5 cats).²¹ This procedure holds promise for the future, however.

Cats with HWI should be placed on a monthly preventative and short-term corticosteroid therapy (prednisone at 1-2 mg/kg q48h-tid) used to manage respiratory signs. If signs recur, alternate day steroid therapy (at the lowest dosage that controls signs) can be continued indefinitely. For respiratory emergencies, oxygen, corticosteroids (dexamethasone at 1 mg/kg IV or IM or prednisolone sodium succinate at 50-100 mg IV/cat) and bronchodilators (aminophylline at 6.6 mg/kg IM q12h, theophylline sustained release at 10 mg/kg PO or terbutaline at 0.01 mg/kg SC) may be employed. Bronchodilators have logic, based on the ability of agents, such as the xanthines (aminophylline and theophylline), to improve function of fatigued respiratory muscles. In addition, the finding of hyperinflation of lung fields may indicate bronchoconstriction, a condition for which bronchodilation would be indicated. Nevertheless, this author does not routinely utilize bronchodilators in feline HWD.

Recently, doxycycline (10 mg/kg/day for 30 days) has been used to clear *Wolbachia* from a heartworm-infected dog with proteinuria and antibodies against *Wolbachia*, in hopes of reducing proinflammatory mediators (e.g. interleukin 8), prior to adulticidal therapy.^{21a} While logical, there are no published studies to indicate that the use of doxycycline in should become routine practice in the management of HWI.

The use of aspirin has been questioned as vascular changes associated with HWI consume platelets, increasing their turnover rate and effectually diminishing the antithrombotic effects of the drug. Conventional doses of aspirin did not prevent angiographically-detected vascular lesions.²² Dosages of aspirin necessary to produce even limited histological benefit approached the toxic range. However, because therapeutic options are limited; because at conventional doses (80 mg PO q72h), aspirin is generally harmless, inexpensive, and convenient; and because the quoted studies

were based on relatively insensitive estimates of platelet function and pulmonary arterial disease (thereby possibly missing subtle benefits), the author continues to advocate aspirin for cats with HWI. Aspirin is **not** prescribed with concurrent corticosteroid therapy.

Since the vast majority of cats are amicrofilaremic, microfilaricidal therapy is unnecessary in this species. Management of other signs of HWD in cats is largely symptomatic.

Prognosis

In the aforementioned study of 50 cats with natural heartworm infection, at least 12 cats died of causes other than heartworm disease. Seven of these and 2 living cats were considered to have survived heartworm disease (lived ≥ 1000 days).⁸ The median survival for all heartworm-infected, cats living beyond the day of diagnosis, was 1460 days (4 years; range 2-4015 days), while the median survival of all cats (n=48 with adequate follow-up) was 540 days (1.5 years; range 0-4015 days). Survival of 11 cats treated with sodium caparsolate (mean 1669 days) was not significantly different from that of the 30 managed without adulticide (mean 1107 days). Likewise, youth (≤ 3 years of age), presence of dyspnea, cough, ELISA-positivity for heartworm antigen, presence of echocardiographically-identifiably worms, or gender of the cat did not appear to affect survival.⁸ The effect of HWI on survival has been compared to that of other cardiovascular diseases.²³ Overall, the prognosis for HWI in cats is comparable to that of hypertrophic cardiomyopathy, the most benign of primary feline heart diseases.

References

Available upon request.

Table 1. Comparisons of macrolides currently in use in cats for heartworm prevention.

Ivermectin	+	+				chewable tablet flavored tablet topical topical
Milbemycin	+	+	+			
Selamectin	+	+	+	+	+	
Imidacloprid/Moxidectin	+	+	+	+	+	