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REVIEW

Feline heartworm disease: a 'Rubik's-cube-like' diagnostic and therapeutic challenge

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Abstract Feline heartworm disease presents a unique diagnostic, therapeutic, and preventive challenge for veterinarians. Due to the elusive clinical nature and peculiar physiopathology of heartworm infection in cats, a multistep diagnostic process is mandatory. Clinical signs may be absent or atypical. At the present time there is no single ante mortem diagnostic test that can reach a high level of sensitivity for feline heartworm infection. The most efficient approach for the diagnosis of feline heartworm disease is based upon a synergic association of several tests: thoracic radiography and serum antibody tests for rising index of suspicion, and echocardiography and serum antigen tests for confirming the infection. Other tests should be considered of secondary importance, even if they can help to support the diagnosis. Treatment of feline heartworm disease is typically based on clinical signs, as adulticidal therapy is associated with a high rate of complications and cats frequently self-cure. Chemoprophylaxis, knowledge of the biology of the parasite, and a high index of suspicion seem to be the most important tools for combating feline heartworm disease.

Introduction

Dirofilaria immitis, a filarial nematode, is the causative agent of heartworm disease in dogs and

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Abbreviations

BAL	bronchoalveolar lavage
D. immitis	*Dirofilaria immitis*
D. repens	*Dirofilaria repens*
HARD	heartworm-associated respiratory disease
HDU	Heartworm Development Unit
WSP	*Wolbachia* surface protein

wild canids (wolves, foxes, coyotes), cats (and wild felids), and ferrets.[1] The dog is the final host and the natural reservoir of the parasite that is vector-borne transmitted by more than 70 different species of culicid mosquitoes, mainly from the genera *Culex, Aedes and Anopheles*.[2] Human beings and other mammals (wild mustelids, monkeys, marine mammals, and rodents) are seldom accidentally affected.[1,2]

Dirofilaria immitis infection has been reported worldwide in warm climates from USA, Brazil, Argentina Caribbean, Venezuela, Italy, Portugal, Spain, Romania, Bulgaria, Hungary, Japan, Korea, Australia, The Philippines, Malaysia, Tahiti, Papua New Guinea, and China. Prevalence is variable and depends on the canine population, the presence of mosquito vectors, and the climate.[1] In temperate latitudes, the seasonality of heartworm-transmission is influenced by the amount of accumulated heat in the environment during the incubation of the larvae in the mosquito. The climate must be sufficiently warm to allow for the presence of mosquitoes, and the development of larval stages in the insects. The parasite is actually spreading into new countries due to the increasing number of infected animals traveling from endemic areas, the introduction of new species of mosquitoes able to act as vectors, climate change caused by global warming, and the development of human activity in new areas.[3] A mosquito's optimal temperature ranges from 25 to 27 °C. The prevalence of mosquito and heartworm larva infection rates is determined by rainfall and humidity. Research into larval development in a range of mosquito hosts has suggested that infected mosquitoes are unlikely to survive for more than 30 days in the wild, and that the lowest temperature threshold for larval development is 14 °C.[4]

A predictive model has been developed to predict the seasonality and geographical distribution of heartworm infections by using units called Heartworm Development Units (HDU). One HDU consists of a mean daily temperature of 1 °C above the threshold of 14 °C. The model is based on the knowledge that development ceases below 14 °C and 130 HDUs are required for the development of infective larvae, and the assumption that infected mosquitoes survive for a maximum of 30 days. Mosquitoes should therefore be exposed to 130 HDUs within a 30-day period.[5] However, care has to be taken about these data. Man-made environmental changes, such as the formation of 'heat islands' due to urban environments, and changes in natural climatic conditions have increased the heartworm infection potential by creating microenvironments that support the development of heartworm larvae in mosquito vectors during colder months, thereby lengthening the transmission season.[6,7] The complete life cycle of *D. immitis* is shown in Table 1 and Figure 1.

Cats are considered to be susceptible but resistant hosts to the infection, and some differences may be observed when compared to dogs. In dogs, the majority of infective larvae (75%) mature into adults that can live for 5—7 years. In cats, most juvenile worms die shortly after arriving in the pulmonary arteries, initiating an inflammatory response; 25% of cats are naturally resistant to the infestation.[2,8] In a small percentage of cats, a few worms become mature adults that can live for 2—4 years.[2,8] In cats experimentally infected with 100 L3 larvae, 3—10 adult worms may develop in 75% of the cats.[2,8] These L3 larvae molt to L4 and L5 stages, with some loss along the way, but there is a very high worm mortality rate of the L5 as they reach the lungs 3—4 months after infection. In dogs, microfilariae are detectable between 7 and 9 months after infection, while few cats have patent heartworm infections 7—9 months after infection. However, microfilaremia occurs in 20% of cats with mature male and female heartworms, and is transient. Adult worms survive for 2—4 years in cats, compared with 5—7 years in dogs.[2,8] Another indication that the cat is an imperfect host for heartworms is that aberrant migration occurs more frequently in cats than in dogs, involving body cavities, systemic arteries and the central nervous system.[2] Most heartworm infections in cats are comparatively light and consist of less than six adult worms.[2,8]

Although severe infections are sometimes observed, usually only one or two worms are present, and approximately one-third of these consist of worms of the same sex.[2] No sex predilection based on host antibody seropositivity has been observed in naturally exposed cats, nor a preference by vector mosquitoes for either sex.[2]

Table 1 Life cycle of *Dirofilaria immitis* in the definitive host (dog).

→ A female mosquito bites an infected dog with circulating microfilariae ingesting them (L1 larvae).
→ Microfilariae develop within the mosquito. The rate of development depends on the environment temperature: at 26 °C the molt to the L2 stage takes about 10 days, and to L3 about 13 days after ingestion. Larval development stops below 14 °C.
→ About 17 days after ingestion, the L3 larvae migrate to the mosquito's head and mouthparts.
→ *Dirofilaria immitis* infective larvae (L3) are then transmitted from one animal to another when the mosquito feeds on the new host: infective L3 larvae leave the mouthparts and are deposited on the skin.

The larvae then penetrate through the wound left by the mosquito's mouthparts.

→ The L3 larvae continue to develop in the subcutaneous tissues of the host, migrating to the abdomen and thorax as they molt to L4 and L5 stages.
The molt to L4 occurs from 3 to 12 days after infection.
→ Juvenile worms are usually called L5 larvae; but as they do not undergo subsequent molts, they should be more properly considered immature or juvenile worms.
→ Juvenile worms mature into an adult stage over several months.

They are carried in the bloodstream from the peripheral veins, to and through the heart, reaching the caudal pulmonary arteries from 75 to 90 days after infection.
By day 100, immature worms are about 3 cm long.

→ Worms become sexually mature at about 120 days after infection. They then start mating and releasing microfilariae.

The prevalence of feline heartworm infection is not well known because ante mortem diagnosis is difficult, but it is generally considered to be 5—20% of the canine counterpart population in the same area.[2,9] Host preference by some of the most abundant vectors may favor the dog, and contribute to the lower prevalence of infection in cats. However, *Culex* spp. and *Aedes albopictus* mosquitoes, the most common species in many urban areas, feed on both cats and dogs without any preference.[2]

Pathogenesis

The clinical importance of heartworm disease in cats is amplified because even a small number of parasites are potentially life threatening. Although in the pulmonary arteries the alive adult worms cause a local arteritis, some cats do not show clinical signs.[10,11] When the symptoms are obvious, they usually develop during two main phases of the infestation:

(1) Arrival of immature worms in the pulmonary arterial vessels

The first phase coincides with the arrival of immature adult worms, 3—4 months old, in the pulmonary arteries and arterioles. The early signs are caused by an acute vascular and parenchymal inflammatory reaction to the arriving worms, and the subsequent death of most of them. This first phase is often misdiagnosed as asthma or allergic bronchitis, but is actually part of a syndrome known as Heartworm-Associated Respiratory Disease (HARD).[10—12]

Clinical signs associated with this acute phase decline or disappear as the worms mature, but the histopathological lesions are still evident in those cats where the infestation aborts.[13—16]

The following may be observed: bronchiolar lesions; partial obstruction of some primary bronchi, with almost complete obstruction of the lumen by epithelial cells with mucus containing cellular debris, eosinophils, neutrophils, granulocytes and macrophages; hyperactivity of goblet cells; interstitial lung disease and signs of hyperplasia and hypertrophy of the muscular layer. The most characteristic histological alterations are represented by medial and small pulmonary artery hypertrophy, as a result of the mechanical action of the parasites on the endothelium.[15]

Once the pulmonary infection is established, live heartworms seem to be able to suppress immune function and modulate vascular tree responses, resulting in an anti-inflammatory effect that minimizes clinical signs in infected cats. This allows many cats to bear the infection without

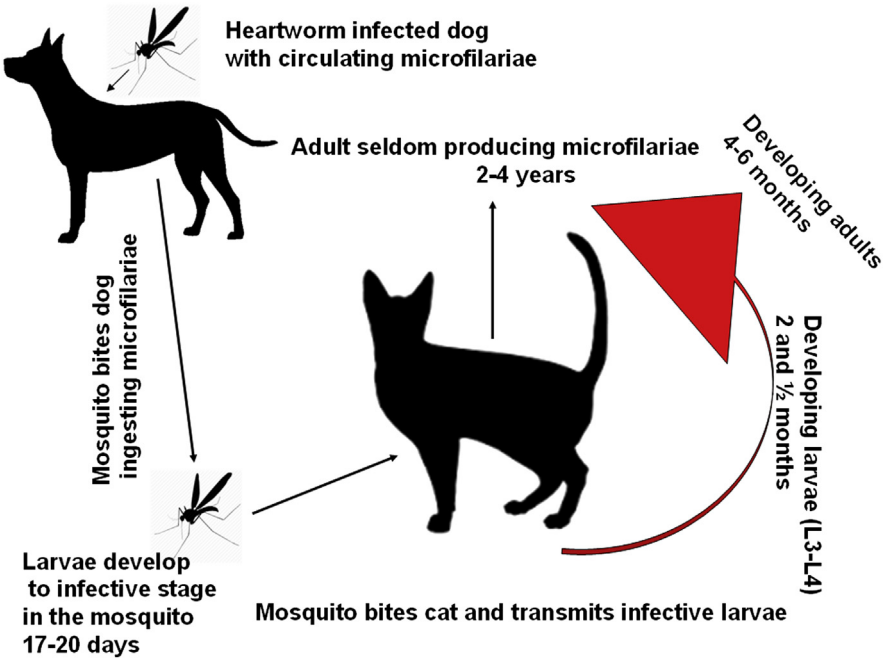

Figure 1 Life cycle of *Dirofilaria immitis* in cats. Microfilariae production (patency) occurs at 5—7 months after infection.

apparent disease, until the mature worms start to die, which begins the second phase of the clinical expression.[10—12]

(2) Death of adult heartworms

Dying heartworms result in pulmonary inflammation and thromboembolism, which often lead to severe acute lung injury. This reaction in cats can occur even in single worm infections as that worm dies. Eosinophilic pneumonitis is the most commonly reported parenchymal lesion, and is caused by immune-mediated destruction of microfilariae within the pulmonary vessels and consecutive inflammatory reaction. Less frequently reported is a form of pulmonary eosinophilic granulomatosis, which develops when microfilariae trapped within the lungs are surrounded by neutrophils and eosinophils, leading to granuloma formation.[14,15] Once the adult worm dies, the down regulation of the immune systems ceases and the most severe forms appear. The fragmented worms cause a dramatic inflammatory and thromboembolic response, which can cause sudden or acute death in up to 20% of cats.[10,11,17] In surviving cats, hyperplasia of Type II alveolar cells replace the normal Type I, which may cause permanent respiratory dysfunction and chronic respiratory disease, even in absence of worms.[14,15]

Because heartworm infections in cats usually have a small number of worms and are of relatively short duration, these lesions are localized and ordinarily fail to cause sufficient obstruction to produce relevant pulmonary hypertension. Consequently, right ventricular hypertrophy and right heart failure are less common in heartworm-infected cats than in dogs. Even when narrowing of a lumen is compounded by worm-induced thrombosis, the bronchopulmonary collateral circulation is usually adequate enough to prevent infarction of the lung.[14,15]

Heartworm infection may also lead to glomerulonephritis and proteinuria secondary to antigen—antibody complex formation, and cats infected with mature adult heartworms are at risk of developing proteinuria relatively soon after infection.[18]

Heartworms can also produce disease by means of aberrant migration into tissues such as the brain, spinal cord, eye, liver or skin. The resulting lesions depend on the site of migration.[10,11]

Most of the recent interest in heartworm immunology and pathophysiology has been on the role of *Wolbachia*. *Wolbachia*, an endosymbiont of some filarioid nematodes, is an intracellular gram-negative bacterium belonging to the order Rickettsiales[19] that certainly plays a role in the pathogenesis of canine and feline heartworm infection, although the precise role is unclear.[20]

Antibodies against *Wolbachia* surface protein (WSP) have been detected in naturally infected dogs and cats. In experimentally infected cats,

anti-WSP antibodies remain high after antibodies to *D. immitis* have waned.[21]

The treatment of experimentally infected cats with ivermectin against the L3–L4 larvae increases anti-WSP titers even further, suggesting that death of the worms releases *Wolbachia* organisms and stimulates a strong host immune response.[21] It is well known that treatment with doxycycline and ivermectin prior to melarsomine administration reduces the severity of lung pathology in heartworm-infected dogs.[20] However, in naturally infected cats and dogs, there are no clear differences in lung pathology between animals with circulating anti-WSP antibodies or detectable WSP antigens in their lungs and those that do not have detectable levels of WSP antigen or anti-WSP antibody.[21]

Clinical signs

The clinical signs of heartworm disease are different in the cat when compared with the dog. Many cats bear the infection well, without any evident clinical signs, or with only transient symptoms.[10,11,22] In 50 naturally infected cats, diagnosis was an incidental finding in $<25\%$ of them.[23] Cats infected with immature worms or as few as one adult worm may show either chronic or, more frequently, acute clinical signs consisting of predominantly respiratory or gastrointestinal (emesis), or occasionally neurological (blindness and vestibular signs).[10,11,22] Signs of chronic respiratory disease such as persistent dyspnea, tachypnea, intermittent coughing, and increased respiratory effort are most common. Anorexia and weight loss occur in some cats.[10,11,22] Intermittent vomiting unrelated to eating is frequently reported, but the pathogenesis of this is unknown.[22] A systolic heart murmur may be present in cats when worms reside in the right atrioventricular junction and interfere with tricuspid valvular function. Other abnormalities, such as ascites, hydrothorax, chylothorax, pneumothorax, ataxia, seizures (associated with aberrant migratory worms), and syncope have been reported, but are uncommon.[10,11,22] In a multicenter study, it was reported that 24% of the cats with heartworm disease presented with vomiting, 41% with respiratory signs, and 29% had both vomiting and respiratory signs.[24]

Acute death may occur with or without previous clinical signs, and with infections by as few as one worm.[10] Acute collapse is a much more common clinical presentation in feline heartworm disease than in canine heartworm disease.[10] In a case series report, 21 out of 45 cases of feline heartworm disease (47%) exhibited acute death.[25] The most widely accepted hypothesis was that an acute anaphylactic reaction, precipitated by the death of the parasite, was the underlying cause.[26] Lister et al. demonstrated that the physical form of heartworm antigen used for IV challenge in *D. immitis*-sensitized cats is an important factor for determining the characteristics of the after-challenge reaction, and the amount of exposed internal filarial antigen presented to the feline immune system may influence the severity of the response to challenge.[26]

Caval syndrome is associated with heartworm displacement from the pulmonary arteries into the right ventricle, right atrium, and/or venae cavae, which often results in moderate-to-severe tricuspid regurgitation.[27] Concurrent moderate-to-severe pulmonary hypertension exacerbates the hemodynamic effects of tricuspid regurgitation, and results in right-sided heart failure and reduced right ventricular output.[27] The syndrome rarely occurs in cats because infections are usually light; however, even one or two worms may cause caval syndrome, with the same symptomatology found in dogs (dyspnea, weakness, onset of a right-sided systolic murmur, jugular vein distension and pulsation, anemia, hemoglobinuria, hepatic and renal dysfunction, disseminated intravascular coagulation, as well as both forward and backward heart failure).[27]

Diagnosis

Due to the elusive clinical nature and peculiar physiopathology of heartworm infection in cats, a multistep diagnostic process is mandatory. At the present time there is no single ante mortem diagnostic test that can reach high levels of sensitivity for feline heartworm infection, especially considering the unique adult- and premature-stage-associated syndromes. The most efficient approach to the diagnosis of feline heartworm disease is based upon a synergic association of four main tests: thoracic radiography and serum antibody tests for rising index of suspicion, and echocardiography and serum antigen tests for confirming the infection. Other tests should be considered of secondary importance, even if they can help support the diagnosis.

It is of paramount importance to consider that the above tests can only be evaluated using necropsy, and that detection of adults is the gold standard; therefore, no information on their

diagnostic performances in case of immature infection, such as HARD, are available.

Complete blood count

In cats, no significant changes in erythrocyte, platelet and leukocyte concentrations are strictly associated with heartworm infection, except from absolute peripheral eosinophilia, which is reported as starting approximately 70 days after infection in experimental conditions.[16] Despite this experimental finding, absolute eosinophilia cannot be considered as a good marker of heartworm disease as the percentage of naturally infected cats showing eosinophilia is unknown. Moreover, eosinophilia in cats is not a specific alteration but a common finding secondary to several parasitic and allergic diseases.

Blood test for microfilariae

Microfilaremia is rarely observed in feline filarial infections and cannot be used as a sensitive test for diagnosis of *D. immitis* infection. Microfilariae can be detected from 7 to 9 months after infection, in case of infection with both living adult males and females, it can only persist for 1—2 months due to the immune response of the feline host.[11] Even using special techniques for concentration of microfilariae (Knott's test or millipore filter) microfilaremia is detected in <20% of cats harboring adult heartworms.[11] The low sensitivity of blood tests for microfilariae in cats is related to the difficulty of *D. immitis* to establish a patent infection in the feline host, due to the mainly single adult or single sex infection and reduced lifespan of both adults and larvae.[13] The specificity of microfilariae for diagnosis of heartworm infection is considered to be 100%, nevertheless in Europe, Africa and Asia, cats can be infected by other filarids that are able to cause microfilaremia, including *Dirofilaria repens* (*D. repens*) or *Brugia phangi*.[28] Particular care has to be taken to correctly identify microfilariae in blood by means of their morphological and morphometric distinctive features through special staining, such as acid phosphatase, delafield hematoxylin or by PCR (Fig. 2).[29—31]

Blood test for adult antigens

Tests detecting adult heartworm antigens are still considered to be the 'gold standard' for the diagnosis of heartworm disease, thanks to their ability to provide a definitive proof of infection. Detectable antigenaemia develops at about 5.5—8 months after infection.[11,16] Antigenic tests detect the antigens from mature females and, therefore, they have a very high specificity for mature infections, around 96—99%, but sensitivity can be as low as 50%.[32—34] In naturally infected cats,

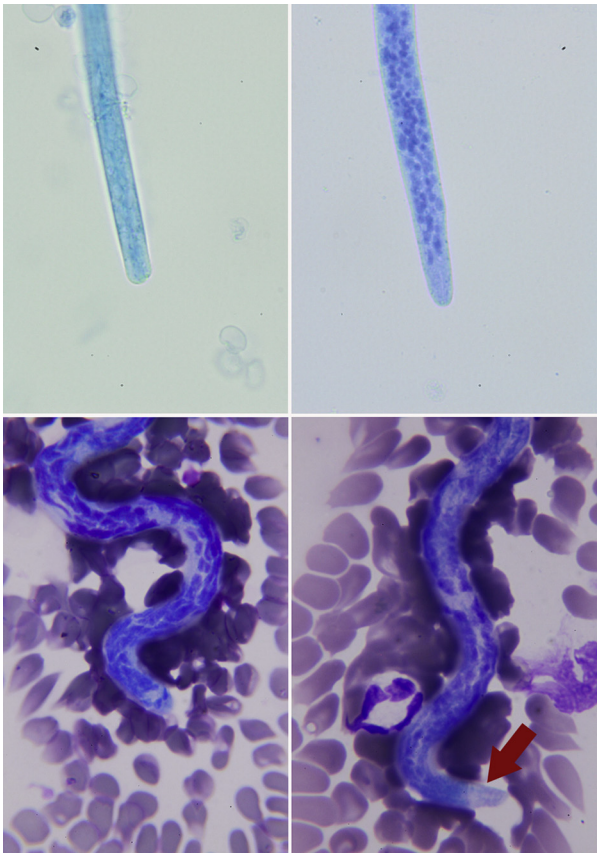

Figure 2 Distinctive morphologic features of *Dirofilaria immitis* and *Dirofilaria repens*. Knott's test, 100× objective (upper images); Blood smear, May-Grunwald Giemsa stain, 20× objective (lower images). Cephalic extremity of *D. repens* has parallel outlines that sharply curves in a blunt angle (upper left), differently *D. immitis* has a gradually tapered and slightly pointed head (upper right). In stained blood smear, nuclei of *D. repens* larvae extend almost to the entire length of the cephalic extremity (lower left) whereas *D. immitis* has a distinctly long cephalic space (arrow) without nuclei in the tapering part of the head (lower right). The mean length of *D. immitis* microfilariae is 302 μm in fresh preparations (Knott's test) or 259 in dry and stained blood smears. Microfilariae of *D. repens* are longer, 369 μm long in fresh preparations and 323 in dry and stained slides. Rear end is usually straight in *D. immitis* and can be straight or hooked in *D. repens*, thus it cannot be considered a reliable morphologic feature, especially in case of mixed infections. In acid phosphatase stain *D. immitis* microfilariae display two spots (excretory and anal pores) while *D. repens* one spot (anal pore).

worm burden is usually very low, a common scenario of only males or single female infections, significantly reducing the sensitivity of antigenic reaction.[11,34] Furthermore, detection of antigens can only confirm the presence of a mature alive parasite, but it has no diagnostic value for pathologies caused by immature stages of the parasites, as in HARD.

Given the low sensitivity, a negative antigenic test cannot therefore be considered sufficient to rule out the infection. The result should be recorded only as positive or 'no antigen detected', but it should not be considered as strictly 'negative'. As in dogs, cases of antigen–antibody complexes interfering with antigen detection are reported. In a study, a heat treatment of the serum at 104 °C for 10 min was used to break down suspect immunocomplexes and release antigens, giving promising results and a significant rise of sensitivity.[35]

Blood test for antibodies to adult heartworm

Due to the variably low sensitivity of antigenic tests and microfilaremia in cats, tests for detection of antibodies can prove useful in the diagnosis of *D. immitis* infection. Antibody testing provides information about previous exposure to *Dirofilaria immits* but not necessarily about current infection. A positive result may represent a concurrent infection with adult worms, a recently cleared infection, an infection caused by premature stages, or the simple exposure to infective stages.[13] Consequently, a positive result is more useful in establishing the risk of exposure to *D. immitis* infective stages and to increase the index of suspicion rather than confirm the infection, and it should be carefully interpreted, taking other relevant clinical information into consideration.

Initial research has reported the sensitivity and specificity of the feline antibody tests to be as high as 98% in cats experimentally infected with adult worms. However, later necropsy surveys of naturally infected cats have shown lower sensitivities, and some single tests have produced >50% false negative results.[32–34] As a consequence, negative antibody results can reduce the index of suspicion, but cannot completely rule out the infection.

It must be taken into account that in cats, antibodies for *D. immitis* are detectable from 2 months after infection; therefore, antibody tests, unlike microfilaremia and antigenic tests, can be positive in cases of premature infections and can be helpful when a suspicion of HARD is present.[13,16]

Bronchoalveolar lavage – transtracheal wash

An increased percentage of eosinophils in bronchoalveolar lavage (BAL) or transtracheal wash (>16–40%) is reported in cats experimentally infected with *D. immitis*, with or without peripheral absolute eosinophilia, and may be noticed starting from 2 to 4 months after the infection.[16] Nevertheless, this finding is not specific for heartworm disease, especially in feline BAL where up to 18% of eosinophils could be considered normal. Moreover, many other causes of increased eosinophils should be ruled out, such as allergic bronchitis, neoplasia and other lung parasites.

Thoracic radiographs

Thoracic radiography is a valuable tool for diagnosis and case monitoring in feline heartworm disease. The most characteristic radiographic features of heartworm disease in cats, as in dogs, are a subtle enlargement of the main lobar and peripheral pulmonary arteries, characterized by loss of taper, and tortuosity and truncation in the caudal lobar branches.[22] These vascular features are better visualized in the ventrodorsal view, and may be visible only in the right caudal lobar artery where heartworms are mainly found.[22] Enlargement of the main pulmonary artery may occur in heavily infected cats, but is not a reliable marker because most cats do not develop pulmonary hypertension and because the main pulmonary artery is obscured by the cardiac silhouette.[22] Patchy focal or diffuse pulmonary parenchymal change is a common secondary feature.[10] It has been reported that transient clinical signs of respiratory disease are consistently associated with diffuse or focal bronchointerstitial parenchymal patterns or vascular abnormalities on thoracic radiographs.[17] Diffuse patterns are also characteristic of other respiratory diseases in the cat, such as asthma or aelurostrongylosis, and are therefore difficult to distinguish as being strictly related to heartworm infection.[17] The focal patterns in the peripheral areas of the caudal lobes observed in infected cats, however, have appeared to be more typical of heartworm infection (Fig. 3).[17] The cardiac silhouette seldom appears enlarged, with a trend for the cardiac silhouette to increase in size during time and during occurrence of clinical signs.[17,36] The small differences between infected and healthy cats suggests that clinical utility of this finding is extremely limited. Other less frequently associated pulmonary

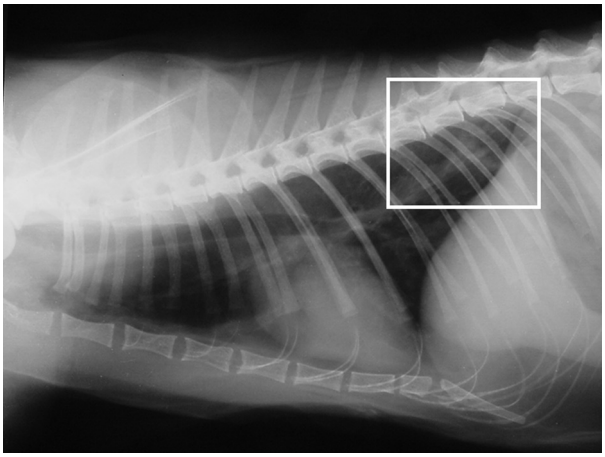

Figure 3 Right lateral thoracic radiograph. Patchy focal interstitial pattern in the peripheral area of the caudal lobe (white square) in a naturally heartworm-infected cat. The cardiac silhouette appears to be normal.

findings include hyperinflation of the lungs with flattening of the diaphragm, consolidated lung lobes, pleural effusion, and pneumothorax.[10,17] In some cases of feline heartworm disease, thoracic radiographs provide no evidence of infection.[17]

Electrocardiography

Heartworm infection does not involve right cardiac chambers. There are no detectable changes in the cardiac electrical axis and arrhythmias are rare. Consequently, electrocardiography cannot provide useful information in infected cats.

Echocardiography

Two-dimensional echocardiography can allows the direct visualization of the parasites in the main pulmonary artery, proximal tract of both its peripheral branches and sometimes in the right atrium, right ventricle and vena cava.[37,38] Adult heartworms are identified as double-lined hyperechoic structures within a cardiac chamber or large vessel. The hyperechoic parallel lines are caused by reflection of the ultrasound waves by the worms' cuticle (Fig. 4, Fig. 5).[39] Sometimes, dead heartworms can be recognized by collapse of the parallel sides of the body wall.[37] An adult heartworm is relatively long compared with the length of the pulmonary arteries in cats. Therefore, there is a better chance in cats than in dogs of finding heartworms extending from peripheral

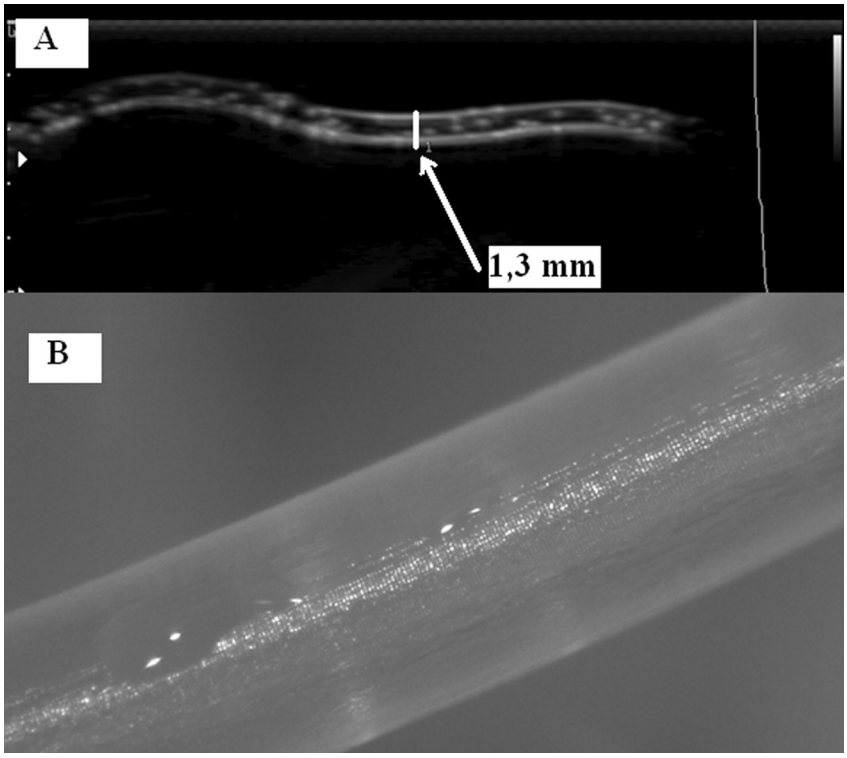

Figure 4 A. Adult heartworms are sonographically identified as double-lined hyperechoic structures with a diameter around 1.3 mm. The hyperechoic parallel lines come from reflection of the ultrasound waves by the worms' cuticle. B. Magnification (stereo microscope) 30× of the body cuticle of an adult heartworm. See the lack of significant longitudinal ridges typical of *D. immitis* compared with the other filarid worms.

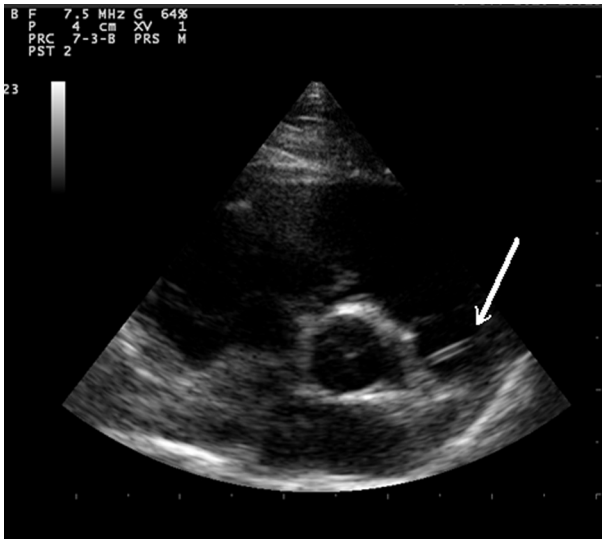

Figure 5 Echocardiography. Right parasternal short-axis view at the base of the heart in a DSH heartworm naturally infected cat. The hyperechoic parallel lines (arrow) show an adult worm in the right ventricular outflow tract.

branches into proximal segments, where they can be visualized.[37,40] The sensitivity of echocardiography for the detection of heartworm infections in cats is highly operator dependent and few investigators have reported sensitivity between 88 and 100%.[37,38,40,41]

To increase the likelihood of echocardiographically detecting heartworms, the pulmonary arteries should be carefully evaluated.[37] It is, however, possible to obtain false-positive results when scanning cats at risk of heartworm infection. False-positive results are thought to be caused by the right ventricular chordae tendineae,[42] or to the occasional presence of linear echoes that mimic adult heartworms into the main pulmonary artery branches, probably due to reflections from the artery wall. Quantification of worm burden is, nevertheless, difficult because the potential serpentine positioning allows echo beams to transect the worm in multiple sites, giving multiple echo images and potentially over or underestimating worm burden.[42]

Even if most of the heartworm-infected cats have histological evidence of pulmonary artery damage, pulmonary hypertension is considered extremely unusual[43]; therefore, echocardiographic signs of right atrial and right ventricular enlargement following pressure overload, as well as the high velocity tricuspid regurgitation on Doppler examination commonly observed in dogs are considered extremely rare in cats.

Treatment

Medical treatment

Medical treatment of feline heartworm disease is typically based on clinical signs, as adulticidal therapy is associated with a high rate of complications, and cats frequently self-cure.[2] If a cat does not show clinical signs and radiographic evidence of pulmonary vascular/interstitial lung disease consistent with the infection, the best choice seems to allow time for a spontaneous self-cure to occur. The disease in these asymptomatic cases has to be periodically monitored at 6—12 month intervals by repeating antibody, antigen testing, thoracic radiography and echocardiography.[44]

Prednisolone administered at 2 mg/kg, tapering down over a 4-week period, is effective medical support for infected cats with radiographic evidence of lung disease, whether or not they appear to be ill. This treatment has to be repeated in cats with recurrent clinical signs.

Cats with severe clinical signs of heartworm disease should be stabilized by administration of intravenous fluids, intravenous corticosteroids, bronchodilators and oxygen supplementation.[44] Diuretics should be absolutely avoided, even if radiographs show severe interstitial or patchy alveolar lung patterns.[44] Aspirin and other non-steroidal anti-inflammatory drugs have failed to produce any benefit and may exacerbate the parenchymal pulmonary disease.[43,44] Once stabilized, treatment can continued, as described above, based on clinical signs.

Adulticide treatment of cats with heartworm disease is associated with significant risk, and is considered to be the last resort for cats in unstable conditions with clinical signs that are not controlled by corticosteroid therapy.[44] There is no experience with melarsomine dihydrochloride at this time; thus, melarsomine treatment is not recommended for use in cats. Few data suggest that melarsomine is toxic to cats at doses as low as 3.5 mg/kg and that its efficacy is about 36% against adult heartworms in cats.[22] Ivermectin at a dose of 24 μg/kg monthly given for 2 years has been reported to reduce worm burdens by 65% as compared with untreated cats. In cats, it is not the worm mass alone that is dangerous but the 'anaphylactic'-type reaction resulting when even a

single worm dies; this will likely also occur when the ivermectin-treated worms die, but the severity of the reaction is unknown.[22]

There is some debate as to whether doxycycline should be administered to heartworm-infected cats to target the *Wolbachia*. Despite evidence in dogs that doxycycline may help to reduce pulmonary pathology prior to adulticidal therapy and may be adulticidal in combination with ivermectin,[20] the benefits for cats, in which adulticide treatment is not advised, have yet to be evaluated. Consequently, doxycycline is not recommended as an adjunctive therapy in cats at this time.[44]

To date, there are no studies that indicate any form of medical adulticidal therapy increases the survival rate of cats harboring adult heartworms.[44] For these reasons and because heartworm infection in cats is often self-limiting, infected cats are managed only with supportive treatment, although conservative management is not without risk, as the acute death syndrome may occur without premonitory signs and in the presence of only one worm.[44]

Surgical treatment

Surgical heartworm removal may be attempted in symptomatic cats when the parasites are echocardiographically visualized in the right heart and main pulmonary arteries. This may be performed with a thin horsehair brush,[45] basket catheters,[46,47,] endoscopic grasping forceps[48] or another intravascular retrieval snare[49] introduced via the right jugular vein into the right cardiac chambers. Surgical extraction of worms can also be attempted via thoracotomy and right atriotomy[50] or ventriculotomy and main pulmonary arteriotomy for removing them from the pulmonary arteries. Care should be taken to remove worms intact, because the frequent accidental damage to worms during extraction can result in acute circulatory collapse and death. This is mainly when parasites are removed via the jugular vein because of the small size of the vessel compared to the worms.[44,47]

Prognosis

The prognosis for heartworm-infected cats should be considered guarded. In two different studies (prospective and retrospective), approximately 80% of the naturally infected cats self-cured, 20% died 8—41 months after diagnosis, often very suddenly.[17,23] The median survival time of cats diagnosed with heartworm disease is 1.5 years, with a better prognosis (4 years) for cats surviving beyond the day of presentation.[23]

Chemoprophylaxis

The best approach to feline heartworm disease is to prevent it by using chemoprophylaxis (the regular monthly administration of preventive drugs that kill the infective larvae in the L3—L4 stage).

Monthly heartworm preventives are a safe and effective option for cats in areas where heartworm infection is considered endemic in dogs, and where exposure to infective mosquitoes is possible. Even the so-called 'indoor' cats may also be considered at risk. When monthly heartworm prevention is chosen, it should be administered within 30 days following the estimated onset of transmission and continued for 30—90 days after that period has ended. Preventives should be started in kittens at 8 weeks of age and be administered to all cats in heartworm-endemic areas during the heartworm-transmission season.

There are currently five macrocyclic lactone drugs registered for feline heartworm prophylaxis, which can be used alone or in combination with other active principles: ivermectin (monthly dose 24 μg/kg) given orally; milbemycin oxime (monthly dose 2.0 mg/kg) given orally; topical moxidectin (monthly dose 1.0 mg/kg); topical selamectin (monthly dose 6 mg/kg); topical eprinomectin (monthly dose 0.48 mg/kg, available in Europe). Additionally, depending on the active ingredient, these products protect cats from a variety of common endoparasitic and ectoparasitic infections (e.g. eprinomectin + praziquantel + S-methoprene + fipronil, Broadline™ Merial). Administering a preventive for a longer time than the supposed transmission period has many advantages. Prolonged year-round administration of macrocyclic lactones heartworm preventatives has many advantages: protection against some other common parasites (fleas, mites), increased compliance, and retroactive efficacy as a safeguard for inadvertently missed doses.[44]

Administration of these drugs in cats is not precluded by antibody or antigen seropositivity. Although testing cats before starting them on heartworm preventives is recommended, it is less useful than doing so in dogs.[44] This apparent contradiction reflects the differences in testing methods and test performance in the two hosts. Pretesting (screening) dogs is limited to documenting either heartworm antigenemia or circulating microfilariae, both of which are specific indicators of adult worm infection. Many, if not

most, cats that are antibody positive have only been transiently infected to the 4th larval stage. Evidence of exposure of a cat to at least 4th stage larvae confirms the potential risk of developing HARD and giving more justification for recommending preventives.[44]

Conclusions

Feline heartworm disease presents a unique diagnostic and therapeutic challenge to veterinarians. The prevalence of *D. immitis* varies widely among different areas, which affects the perceived importance of the disease to both veterinary practitioners and clients. Despite the variations in prevalence, the consequences of heartworm infection in cats are serious and often fatal. Chemoprophylaxis appears to be the most powerful instrument for saving life in cats. Given the difficulties of knowing the exact transmission period in every area, a year-round chemoprophylaxis of all dogs and cats in heartworm-endemic areas is advised. Many drugs are available for heartworm chemoprophylaxis; most of them are effective against other endoparasites and ectoparasites too. When used properly, all products that are specifically formulated for companion animals are safe and effective. Considering that diagnosis is difficult and no safe therapy is known, lack of compliance is the greatest barrier to effective prevention. Knowledge of heartworm biology and diagnostic protocols, together with a high index of suspicion and an open and effective client education have a key role for facing this complex parasitic disease in cats.

Conflicts of interest

None.

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