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Feline heartworm disease: a clinical review

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Feline heartworm disease is caused by the filarial nematode *Dirofilaria immitis*, and is transmitted by mosquitoes in heartworm-endemic areas worldwide. While dogs are the definitive hosts for this parasite, cats can also be infected, and the overall prevalence in cats is between 5% and 10% of that in dogs in any given area. The spectrum of feline presentations varies from asymptomatic infections to chronic respiratory signs, sometimes accompanied by chronic vomiting to acute death with no premonitory signs. Ante-mortem diagnosis can be challenging and relies on a combination of tests, including antigen and antibody serology, thoracic radiography and echocardiography. As treatment with heartworm adulticidal drugs can be life-threatening and heartworm infection in cats is often self-limiting, infected cats are frequently managed with supportive treatment (corticosteroids, bronchodilators, and anti-emetics). Surgical removal of filariae using extraction devices may be considered in some acute cases where immediate curative treatment is necessary, but filarial breakage during the procedure may result in an acute fatal shock-like reaction. Necropsy findings are mainly pulmonary and include muscular hypertrophy of the pulmonary arteries and arterioles on histopathology. A number of safe and effective macrocytic lactone drugs are available for prophylaxis in cats. These drugs can kill a range of larval and adult life-cycle stage heartworms, which may be advantageous in cases of owner compliance failure or when heartworm infection status is undetermined at the time prophylaxis is commenced. An index of suspicion for feline heartworm disease is warranted in unprotected cats with respiratory signs, and perhaps chronic vomiting, in areas where canine heartworm disease is endemic. Many cats, once diagnosed and with appropriate supportive care and monitoring, will resolve their infection and be free of clinical signs.

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Heartworm (*Dirofilaria immitis*) infection is an increasingly diagnosed entity in feline practice due to heightened awareness of the disease in cats and improved diagnostic methods. Clinically affected cats may present at veterinary clinics with a wide range of clinical signs, such as chronic coughing, laboured breathing and vomiting and some infected cats die suddenly without any premonitory signs (Dillon 1998b, Atkins et al 2000). However, many cats are subclinically infected (Dillon 1998a, Atkins et al 2000) and infection tends to be self-limiting (Atkins et al 1996). Feline heartworm disease is clinically challenging on a number of different levels. Diagnostic confirmation usually requires a combination of tests (Atkins 1999) and treatment is most often limited to symptomatic therapy as curative medical and surgical treatments place the feline patient at significant risk (McIntosh Bright and Daniel 1999, Brown et al 1999b). Safe and effective prophylactic drugs which kill a number of life-cycle stages are readily available. The following clinical review will present what is currently known of the life-cycle, prevalence, pathophysiology, clinical signs, the acute death syndrome, diagnosis, treatment, necropsy findings and prophylaxis for feline heartworm disease.

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Life-cycle of *D immitis*

Dogs are the usual definitive hosts for *D immitis* but the life-cycle may also be completed in cats. Mosquitoes act as the intermediate host in both canine and feline infections. Cats are less easily infected with heartworms than dogs (Atkins et al 1996); there are fewer filariae in feline infections (usually six or less filariae); and the lifespan of the filariae is only about half the length of that in dogs (2–3 years compared with 5–7 years) (Brown et al 1999a). Microfilarial counts in experimentally infected and naturally infected cats are usually very low and transient, seldom lasting more than 1–2 months, probably due to the immune response of the host (McCall et al 1994). The cat does not serve well as a definitive host because of the low and erratic microfilaraemias detected (Lok and Knight 1998). The average prepatent period is 7–8 months, 1–2 months longer than that in dogs (McCall et al 1994). Aberrant migration of fourth-stage larvae (L_4) occurs more frequently in cats than in dogs and ectopic heartworms have been found in the body cavities and central nervous systems of infected cats (Atkins et al 1996).

Prevalence

D immitis infections in cats have been reported in many areas of the world – from Brazil, Venezuela, Italy, Japan, Australia, The Philippines, Malaysia, Tahiti, Papua New Guinea, China, Sierra Leone, Armenia, Canada and from 29 of 50 states in the USA (Ryan and Newcomb 1995). Evidence from both published reports and personal communications suggests that, despite a relatively steady prevalence rate of canine heartworm disease in the USA over the past 10 years, the number of infected cats being diagnosed has increased. This apparent increase may reflect an increase in both veterinary and owner awareness and surveillance of cats (Brown and Thomas 1998).

The distribution of feline *D immitis* infection parallels that in dogs with an overall prevalence in cats of between 5% and 10% of that in dogs in any given area (Ryan and Newcomb 1995). It has been suggested that the lack of a consistent ratio between the prevalence of heartworm infection in dogs and cats in the same area reflects the willingness of the local species of mosquitoes in the area to feed on both dogs and cats (Dillon 1999). The true prevalence of heartworm infection in cats may be understated due to their greater tendency to either spontaneously eliminate the parasite or die from the infection (Atkins et al 1996).

Pathophysiology of feline heartworm disease

Feline infection can occur at any age and immunosuppression is not a prerequisite for infection (Atkins et al 1996). Indoor and outdoor cats are equally represented (Dillon 1998a). Male cats were thought to have a higher prevalence of infection than female cats (Dillon 1998a), but a relatively large retrospective study disputes this point (Atkins et al 2000). Acute lung injury is a major contributing factor to the initiation of clinical signs. It is hypothesised that the arrival of fifth-stage larvae in the lungs and the death of the adult are the most likely stages of the life-cycle to be associated with clinical signs. After an initial host response, the signs may abate and become subclinical. In chronic cases, perivascular reaction and evidence of thrombus formation with recanalisation are noted (Dillon 1998a).

D immitis has evolved an array of specific molecular strategies to evade host immune attack. Marked differences in the surface properties of the third and fourth larval stages may delay potentially destructive immune responses to these stages in the host (Grieve 1990). Clinical and laboratory investigations have suggested that the acellular nature of the *D immitis* cuticle and its thrombo-resistant surface properties allow the parasite to circumvent the host's immune response and improve long-term survival (Kadipasaoglu et al 1993).

There is evidence that Wolbachia, an endosymbiontic bacterium present in *D immitis*, may play a role in the immunopathogenesis of heartworm disease (Kramer 2004, Simon et al 2007). Heartworm-infected cats can be exposed to Wolbachia when larvae, or adult worms, are killed; when Wolbachia are released with microfilariae from the uterus of the females; and possibly through the excretory system of both male and female worms (Kozek 2005). One recent study demonstrated a strong IgG response against the surface protein of Wolbachia in heartworm-infected cats, leading to the suggestion that bacteria could play an important role also in the inflammatory reactions which characterise the heartworm infection in cats (Morchón et al 2004).

Clinical signs

Clinical presentations of feline heartworm disease vary widely in severity and include acute death, chronic coughing or intermittent dyspnoea, and asymptomatic infections (Dillon 1998a). In one study of 50 cases, asymptomatic infections were diagnosed incidentally in 28% of cats (Atkins et al 2000). Cats infected with immature worms, or as few as one adult worm may show clinical signs (Snyder et al 2000). At presentation, clinical signs are most commonly related to the respiratory tract, with dyspnoea and coughing most often observed. Vomiting is a relatively common finding, reported in about a quarter to a third of cases (Dillon 1998b, Atkins et al 2000), but the pathogenesis of this is unknown. Neurological signs, including syncope, collapse, blindness and vestibular signs, may also occur (Dillon 1998b, Atkins et al 2000), probably in association with aberrant larval migration through the brain. The initial host response of diffuse pulmonary infiltrate and resultant clinical signs occurs most frequently about 4–7 months after infection and is usually followed by a subclinical stage. However, the subsequent death of adult heartworms may cause additional severe signs, such as acute collapse and death (Dillon 1998b).

Acute death syndrome in feline heartworm disease

Acute death has been widely reported in asymptomatic cats infected with heartworms (Dillon 1984, Holmes 1993, Dillon 1995, Ralston et al 1998, Evans et al 2000), but the pathogenesis of the syndrome has yet to be elucidated. Acute collapse may occur with or without previous clinical signs and may be caused by only one worm (Dillon 1998b). This is a much more common clinical presentation in feline heartworm disease than in canine heartworm disease (Ralston et al 1998). In an Australian report, 21 of 45 heartworm-infected cats (47%) exhibited acute death either at home or upon arrival at the veterinary clinic (Evans et al 2000). This may overestimate the percentage of heartworm-infected cats that present with the acute death syndrome, as acute death is more readily diagnosed and recalled than other presentations of feline heartworm disease.

Acute death in heartworm-infected cats has been attributed to circulatory collapse and respiratory failure from acute pulmonary arterial infarction (Dillon 1984), specifically acute pulmonary thromboembolism as a result of spontaneous death of adult heartworms (Dvorak 2000). However, in the acute death syndrome, filariae are not always found embolising the main pulmonary arteries (Dillon 1998a) and radioisotope studies have demonstrated that lung lobes are rarely ischaemic (Dillon 1999). It has been suggested that pulmonary hypertension may also play a role, but it is rarely present in affected cats, at least based on secondary signs such as right-sided heart failure and congestive heart failure (Lok and Knight 1998).

Extraction procedures performed in cats, complicated by the accidental dissection of worms, have resulted in an acute shock-like reaction and death. It is hypothesised that the damage to the heartworm cuticle causes the sudden release of large amounts of heartworm antigen (Ag) resulting in acute systemic anaphylaxis (Brown et al 1999b). Interestingly, in an experimental model of acute systemic anaphylaxis using *D immitis*-sensitised cats challenged with intravenous heartworm Ag, a similar acute shock-like reaction was reported, and was characterised by dyspnoea, hypoxaemia and systemic hypotension and haemoconcentration (Litster and Atwell 2006). The same model demonstrated that the amount of exposed internal filarial Ag may influence the severity of the response to challenge (Litster et al 2007).

Diagnosis

A thorough diagnostic approach using a combination of tests is necessary in the diagnosis of feline heartworm disease because of the low worm burdens and light Ag load (Atkins 1999). Table 1 describes the interpretation of clinical tests used in the diagnosis of feline heartworm disease.

Serology available for the diagnosis of feline heartworm infection includes serum Ag and serum antibody (Ab) tests. In the serum Ag test, an enzyme-linked immunosorbent assay (ELISA) detects a protein found primarily in the reproductive tract of the female worm. This test may lack sensitivity due to low worm numbers and the possibility of infection solely with male worms and so it is not recommended as a screening test for feline heartworm infections. However, the rate of false-positive results with Ag serology is low, so that a positive result generally indicates a current infection. ELISA Ab tests are available commercially as screening tests for cats when there is an index of suspicion for heartworm infection. The specificity of Ab tests

Table 1. Interpretation of heartworm diagnostic tests/procedures in the cat (after Nelson et al 2007)*

Test	Description	Result	Interpretation	Limitations
Antibody test	Detects serum antibodies to heartworm larvae as early as 8 weeks post-transmission by mosquito	Negative Positive†	Lower index of suspicion Increasing index of suspicion – confirms that cat is at risk	Antibodies confirm infection with heartworm larvae, but do not confirm disease causality.
Antigen test	Detects antigen from adult female filariae or dying male or female filariae	Negative‡ Positive§	Lower index of suspicion Confirms presence of heartworms	Immature or male-only worm infections are rarely detected.
Thoracic radiography	Detects enlargement of pulmonary arteries, pulmonary parenchymal inflammation and oedema (the latter only in ARDS-like syndrome)	Normal Signs consistent with feline heartworm disease	Lower index of suspicion Enlarged arteries greatly increases risk of suspicion	Radiographic signs subjective and affected by clinical interpretation.
Echocardiography	Detects adult filariae in the pulmonary arteries, right ventricle, right atrium or caudal vena cava	No filaria seen Filaria/e seen	No change to index of suspicion Confirms presence of heartworms	Ultrasonographer experience with heartworm detection appears to influence accuracy rate.

ARDS - Acute Respiratory Distress Syndrome.
*In the cat, a combination of tests is used to determine the likelihood that clinical heartworm disease is present.
†A positive antibody test indicates the cat has been infected but does not mean that the life-cycle has been completed to the stage of adult filariae present in the heart. Serum antibody levels probably remain elevated for weeks or months after clearance.
‡Antigen tests are not sensitive enough to consider a negative as indicative of absence of heartworms.
§It is possible that a cat could clear the infection and circulating Ag would remain detectable for weeks after clearance. A negative antibody test indicates the cat is either not infected or was infected less than approximately 50–60 days ago.

may be compromised because they detect exposure to migrating heartworm larvae and will also be positive in cats with previous heartworm infections (Snyder et al 2000). False-negative Ab test results were previously considered rare, but in two independently conducted studies, 14% of infected cats had negative Ab test results (Atkins et al 1998, Genchi et al 1998). Another more recent study reported that more than 20% of Ag-positive heartworm-infected cats were Ab-negative (Kalkstein et al 2000). Combining the results of serum Ag and Ab tests achieves higher sensitivity and specificity than by using either test alone (Snyder et al 2000). Sensitivities of up to 100% and specificities of up to 99.4% were reported in a study by Snyder et al (2000) when Ag and Ab tests were used in combination, compared to a maximum sensitivity of 89.5% and specificity of 92.9% when serum Ag or Ab tests were used alone. In Table 2 the diagnostic performance of heartworm Ag and Ab tests reported in a recent US study involving 380 cats is given (Berdoulay et al 2004).

Thoracic radiography is a valuable tool for diagnosis and case monitoring in feline heartworm disease (Ackerman 1987). Radiographic changes associated with feline heartworm disease include enlargement, blunting and tortuosity of the peripheral pulmonary arteries, especially on the right side in the dorsoventral (DV) or ventrodorsal (VD) view; cardiomegaly and right ventricular enlargement; and patchy focal or diffuse pulmonary parenchymal changes (Holmes et al 1992). A mean ratio of greater than 1.6 for the width of the right pulmonary artery (at the caudal border with rib 9) to the width of rib 9 in the DV or VD view has been reported in association with feline heartworm disease (Schafer and

Table 2. Diagnostic performance of heartworm Ag and Ab tests in 380 cats (after Berdoulay et al 2004)

Serological test	% Sensitivity	% Specificity	True positives	False positives	True negatives	False negatives
IDEXX Snap Ag	79.3	98.0	23	7	344	6
SA Scientific CHAT Ag	79.3	99.7*	23	1	350	6
Synbiotics DiroCHEK Ag	86.2	99.1	25	3	348	4
Synbiotics Witness Ab‡	62.1	98.6	18	5	346	11
Antech Diagnostics Ab	72.4	80.9†	21	67	284	8

*SA Scientific CHAT Ag specificity was significantly higher when compared to IDEXX Snap Ag ($P = 0.031$).
†Antech Diagnostics Ab specificity was significantly lower when compared to the other tests ($P = 0.001$).
‡This test was no longer available at the time of publication of this article.

Berry 1995, Litster et al 2005). Objective measurement of radiographic heart size in heartworm-infected cats showed that mean heart size on lateral radiographs was significantly larger than the reference value for vertebral heart score. There was also a significant positive correlation between mean diameter of the caudal vena cava and heart size on lateral radiographs of infected cats (Litster et al 2005). Alterations to structures visible on thoracic radiographs may occur less consistently in feline heartworm disease than in canine heartworm disease and the absence of radiographic abnormalities does not exclude a diagnosis of heartworm disease in cats (Schafer and Berry 1995).

Echocardiography is a useful adjunctive test in cats in which there is a suspicion of heartworm disease, but Ag test results are negative (DeFrancesco et al 2001). One retrospective study of heartworm-infected cats reported that heartworms were detectable by the use of echocardiography in 17 of 43 cats, most often in the pulmonary arteries, but also in the right ventricle, right atrium, and caudal vena cava. Heartworm infection was diagnosed exclusively by the use of echocardiography in five cats in which the Ag test result was negative (DeFrancesco et al 2001). The sensitivity of echocardiography for the detection of heartworm infections in cats is highly operator-dependent and some experienced investigators have reported up to 100% sensitivity (Genchi et al 1998). It is possible to obtain false-positive results when assessing cats at risk for heartworm using echocardiography, due to occasional presence of linear densities that mimic filariae. These densities are found where the main pulmonary artery branches and their cause is unknown, but they are presumed to be sonic reflections from the pulmonary artery wall (Atwell et al 2001).

Necropsy confirmation of heartworm infection has been used as the standard for determining heartworm status in dogs, but routine necropsies may miss ectopic infections, which are more common in cats. Precardiac infections may also cause clinical signs in cats, but are difficult to confirm on necropsy. However, necropsy is still the method against which the performance of other tests is judged (Snyder et al 2000).

Treatment

Medical treatment

Adulticidal treatment of cats with heartworm infection is associated with significant risk. In addition to the toxicity and reported lack of efficacy of heartworm adulticidal agents, adulticide treatment of heartworm-infected cats results in nearly universal and often fatal pulmonary thromboembolism with necrosis (McIntosh Bright and Daniel 1999). Thiacetarsemide is believed to be a less effective adulticide in cats than in dogs (reported efficacy <70%) and cats are more likely to manifest adverse reactions to this arsenical agent (Turner et al 1989). The safety and efficacy of melarsomine in heartworm-infected cats are being investigated, but preliminary data indicate that its efficacy is only about 36% against adult heartworms in cats. For these reasons and because heartworm infection in cats is often self-limiting, infected cats are frequently managed only with supportive treatment (corticosteroids, bronchodilators, and anti-emetics). Prednisone in diminishing doses is often effective for infected cats with radiographic evidence of lung disease, or infected cats that display clinical signs. An empirical oral regimen is 2 mg/kg body weight/day, declining gradually to 0.5 mg/kg every other day by 2 weeks and then discontinued after an additional

2 weeks. At that time the effects of treatment should be reassessed based on the clinical response and/or thoracic radiography. This treatment may be repeated in cats with recurrent clinical signs (Nelson et al 2007). However, conservative management is not without risk, as the acute death syndrome may occur without premonitory signs and in the presence of only one filaria (McIntosh Bright and Daniel 1999).

Surgical treatment

Surgical removal of heartworms is feasible and effective in symptomatic cats with echocardiographically visible filariae in the right heart and main pulmonary arteries (Brown and Thomas 1998). Transjugular catheterisation and removal of heartworms using rigid or flexible alligator forceps, horsehair brushes, endoscopy grasping forceps or basket-type retrieval catheters have been well described in the literature (Glaus et al 1995, Borgarelli et al 1997, Atwell 1998, McIntosh Bright and Daniel 1999, Brown et al 1999b, Atwell and Litster 2002). Other more invasive surgical techniques including right auricular entry into the heart and main pulmonary arteriotomy have also been developed (Brown et al 1999b). Heartworm extraction often results in rapid and dramatic clinical improvement. However, accidental damage to the heartworms during the extraction procedure can result in shock-like signs and death (Sisson 1998, Brown et al 1999b).

Necropsy findings

While a primary aim of necropsy is to locate adult filariae in the heart or pulmonary outflow tract in clinically affected cats where there is an index of suspicion for heartworm disease, most pathological findings in heartworm-infected cats involve the lungs. Affected cats develop villous endarteritis and muscular hypertrophy of the pulmonary arteries and arterioles (Byerly et al 1977, Sisson 1998). One study of pulmonary artery changes in 11 heartworm-infected cats described intimal thickening in the main pulmonary arteries, with the formation of elevated ridges projecting above the surface. Lobar and medium-sized pulmonary arteries were similarly affected, with villous-like structures that protruded into the lumen and partially obliterated affected vessels. Multiple areas of infiltration of eosinophils, lymphocytes, macrophages and plasma cells were observed in the intima and mild multifocal accumulation of macrophages was present in the alveoli of most cats (McCracken and Patton 1993). Medial hypertrophy of the pulmonary arteries is a commonly reported finding (Doi et al 1982, McCracken and Patton 1993, Dillon 1998a, Browne et al 2005), but cats infected with *Toxocara cati* or *Aelurostrongylus abstrusus* may develop similar pulmonary arterial pathology to cats infected with heartworms (Hamilton 1970, Weatherley and Hamilton 1984). In one study, pulmonary arterial hypertrophy and hyperplasia were demonstrated for 2 years after infection with *A abstrusus* and it was suggested that these changes may persist for the entire life of the cat (Hamilton 1966, 1970). Confusingly, pulmonary artery medial hypertrophy and hyperplasia have also been reported in specific pathogen-free cats, with one study reporting the same frequency in both specific pathogen-free and conventional cats, indicating that pulmonary parasitic infection is not a prerequisite for the condition (Rogers et al 1971). Increased muscular thickness of the medial layer of the pulmonary arteries must also be differentiated from vasoconstriction, as both can appear similar microscopically. This is achieved by calculating the area of the media on cross-section in a number of large and small arteries in a section of lung. The resultant figures are compared with reference ranges for normotensive pulmonary arteries and those with moderate and severe pulmonary hypertension (Wagenvoort 1960). In summary, necropsy findings in heartworm-infected cats are almost entirely pulmonary and they vary widely in type and severity. Their interpretation must be approached with caution, especially if conclusions are drawn concerning causation.

Prophylaxis

There are currently four macrocytic lactone drugs registered for feline heartworm prophylaxis – moxidectin (Bayer Advocate Spot-On – imidacloprid 100 g/l plus moxidectin 10 g/l); ivermectin (Merial Heartgard FX Chewables – 165 µg ivermectin); milbemycin oxide (Novartis Milbemax tablets – milbemycin oxide 4 or 16 mg plus praziquantel 10 mg or 40 mg, respectively); and selamectin (Pfizer Revolution Spot-On – selamectin 120 mg/ml) (Companion Animal Parasite Council Guidelines 2007 Products for treatment and prevention of common canine and feline parasites. http://www.capcvet.org/?p=Guidelines_AddendumA&h=0&s=0). These products are a safe and convenient option for cats living in areas where canine heartworm disease is considered endemic and exposure to

infective mosquitoes is possible (Nelson et al 2007). Additionally, depending on the active ingredient, these products protect cats from a variety of common endo- and ectoparasitic infections. Indoor-only housing status is not a reliable method for prevention of infection, as the home environment may not provide an effective barrier to the entry of mosquitoes. One retrospective study reported that 27% of infected cats were kept exclusively indoors (Atkins et al 2000).

Prolonged administration of macrocytic lactone heartworm preventatives has a 'reachback effect', ie, they can kill young larvae, older larvae, immature or young adults, and/or older adult filariae. This is advantageous in cases of owner compliance failure, or when heartworm infection status is unknown at the time that prophylactic treatment is commenced. Efficacy of 95% or more requires dosing for 9–30 months, and older worms are difficult to kill. Of the various macrocytic lactones, ivermectin has the most potent combination of clinical prophylaxis, reachback activity (ability to kill developing larval stages) and adulticidal activity; milbemycin oxime has the least; and selamectin and moxidectin injectable lie somewhere in between. The unique effects of ivermectin are related to the age of the heartworms at the initiation of treatment. The earlier treatment is started, the more stunted and smaller the worms the shorter their survival time (McCall 2005).

Conclusions

Feline heartworm disease remains a significant entity in many areas of the world, and warrants inclusion on the differential diagnosis list for any cat from heartworm-endemic areas presenting with acute or chronic respiratory signs, perhaps accompanied by a history of chronic vomiting, or cats that die acutely without premonitory signs. Exclusively indoor housing status is not necessarily protective and the diagnosis requires commitment from both the cat owner and the attending veterinarian, as a range of tests are required. While heartworm infection can be fatal, most cases are self-limiting and many are asymptomatic. Client education about feline heartworm disease allows cat owners to make informed choices regarding heartworm prophylaxis.

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