Dirofilaria immitis and D. repens in dog and cat and human infections

Editors
Claudio Genchi, Laura Rinaldi, Giuseppe Cringoli

Reprinted in the IVIS website with the permission of the Editors
Pathogenesis of *Dirofilaria* spp. infections

Giulio Grandi, Tatjana Živičnjak, Relja Beck
Introduction

*Dirofilaria* spp., helminths belonging to Dirofilariaidae superfamily, are able to cause a wide range of diseases. The best known and studied is heartworm disease, common in dogs and cats in areas where *Dirofilaria immitis* is widespread. Other species of *Dirofilaria*, like *D. repens*, are less important from a pathogenic point of view, but their differentiation from *D. immitis* is a fundamental diagnostic task. The zoonotic risks related to each species is also extremely important.

Pathogenesis of heartworm disease (*D. immitis*)

*D. immitis* infection is characterised by several different clinical pictures, caused both by adults and first stage larvae (microfilariae). However, the pathophysiology of heartworm disease is mainly due to the presence of adult worms in the pulmonary arteries. The primary lesions occur in the pulmonary arteries and lung parenchyma and are mostly attributable to the intravascular adult parasites. They cause pulmonary hypertension that, if not treated, progresses inevitably to congestive heart failure. Other syndromes are related to the disturbance of blood flow due to the location of heartworms in the right atrium at the level of tricuspidal valve.

This event causes massive haemolysis and related haemoglobinuria, responsible for the vena caval syndrome (liver failure disease) (Ishihara et al., 1978; Kitagawa et al., 1986). Microfilariae play a relatively minor pathogenic role but may cause clinically significant pneumonitis and glomerulonephritis.

Some individuals develop a hypersensitivity to microfilariae. Occasionally, aberrant migration results in parasites becoming trapped in ectopic locations like the anterior chamber of the eye (Weiner et al., 1980) or systemic arteries (Liu et al., 1966; Slonka et al., 1977). Data regarding immunopathogenesis and in particular the role of cytokines, mediators as well as cellular components of the immunity in the development of heartworm-related lesions have been recently revised (Grandi et al., 2005). Although the spectrum of pathologies related to heartworm infection is broad, the most important clinical manifestation in dogs is congestive heart failure (cor pulmonale).

Congestive heart failure (CHF, syn.: cor pulmonale)

Heartworms are primary agents of vascular disease, rather than the cause of simple obstruction and/or blood flow disturbances. Intimal proliferation occurs in arteries occupied by living worms and embolic worm fragments trigger thrombosis, both of which may completely obstruct segments of the pulmonary arteries (Adcock, 1961). These effects, both leading to pulmonary hypertension, are strongly correlated to worm burden, in turn related to the degree of their distribution through lung parenchyma (Knight, 1980).

The juvenile adult heartworms are only about 2.5 cm long when they reach the systemic venous circulation. They passively embolize the pulmonary arteries and are disbursed in propor-
tion to the lobar blood flow. Generally, the larger right caudal lobar artery accumulates more worms than the left (Atwell and Rezakhani, 1986). Contact between the parasite and the intima of the pulmonary arteries is an important, if not essential, initial step in the development of the endovascular lesions.

The earliest lesions are limited to the small peripheral branches where the worms first come to rest. As the parasite grows, lesions occur in more proximal segments. Intimal thickening and narrowing of the vessel lumen in small peripheral branches of the pulmonary arteries are the major cause of obstructed blood flow and pulmonary hypertension. The intimal proliferation is caused by migration of medial smooth muscle cells through the internal elastic laminae (Munnel et al., 1980; Patterson and Luginbuhl, 1963; Schaub et al., 1981).

The pathogenesis of the arteritis caused by heartworms remains a matter of speculation. Disruption of endothelial cell junction and denuding of the intimal surface are characteristics of the first lesions that occur only after a few days of presence of worms. Physical trauma, metabolic and immune-mediated cytotoxicity induced by the parasite (Keith et al., 1983a), as well as other less likely mechanisms (Schaub and Rawlings, 1980) have been considered. Several facts seem to be more consistent with mechanical trauma as the initiating event rather than cytotoxicity or induction of host immune responses. The evidence suggests that injury to the endothelium occurs immediately upon arrival of the parasite, too soon for the components of an immune response to fall in place without prior sensitisation.

Furthermore, the disappearance of endothelial cells occurs without evidence of degeneration and is followed by an aggressive build-up of cells and structural elements. This suggests that cells have been dislodged rather than destroyed in situ. Macrophages, granulocytes, and platelets are attracted to the site of endothelial damage and adhere to the exposed subendothelium. Shortly after their arrival, vascular smooth muscle cells migrate into the intima and a very active process of myointimal proliferation produces rapid growth of the lesions. The integrity of the endothelium covering the intraluminal villous-rugose growths is restored and thrombosis is not a feature at this stage of the disease (Munnel et al., 1980; Schaub et al., 1981). The prominence of platelets in the acute lesions and their documented ability to stimulate growth of the vascular smooth muscle, through the release of platelet-derived growth factors (PDGFs) (Ross, 1986), are hypothesized to be a likely mechanism for triggering and sustaining the growth of these lesions (Schaub and Rawlings, 1980; Schaub et al., 1981). The circumferential lesions of the peripheral distributing arteries transcend into more discontinuous rugose ridges in the larger elastic branches (Keith et al., 1983b).

In cross section, these ridges have a villous appearance and are considered pathognomonic for heartworm infection. Although the lesions thicken the wall of these large elastic vessels and produce a rough texture on the intimal surface, they do not obstruct blood flow by narrowing the lumen. On the contrary, the large distributing arteries actually dilate as pulmonary hypertension becomes increasingly severe.
Pulmonary blood flow is impeded primarily by the reduction in cross-sectional area of the arterial vascular bed, caused by obliterative endarteritis of small peripheral branches. Recently, in heartworm infected dogs it has been demonstrated that there are markedly increased plasma level of endothelin-1, a mediator that induces acute vasoconstriction and chronic vascular remodeling. It is probable that both these events contribute in turn to the development of pulmonary hypertension (Uchide and Saida, 2005). Thrombosis and thromboembolism may further compromise the pulmonary circulation.

As worms accumulate, lesions also develop in the large distributing arteries, which dilate and become stiffer as pulmonary blood pressure rises. The decreased distension of the large vessels significantly increases cardiac work by coupling the right ventricle directly to the high vascular resistance in the obstructed peripheral vasculature.

Right ventricular hypertrophy is a compensatory response to the increased pressure load. As heartworm infection impedes flow in an increasing number of branches, the pulmonary vascular reserve diminishes. For a time, normal pulmonary blood pressure is preserved at rest and rises only modestly during exercise as patent arteries reach full distension. Eventually, the pulmonary arterial tree is restricted to the point that it assumes the characteristics of a system of rigid tubes and pulmonary vascular resistance becomes fixed. This occurs about the time pulmonary blood pressure becomes elevated at rest (Knight, 1977). At this stage, pressure rises in direct proportion to further increase in flow. Consequently, the more severe the disease and active the patient, the more cardiac work must be performed. In advanced cases of heartworm disease, low-output congestive heart failure develops as a result of the right ventricle’s inability to generate and sustain the high perfusion pressures required to move blood through the lung. At a molecular level, in the myocardium of heartworm infected dogs it has been observed a decrease of extracellular collagen matrix; this event can contribute to the dilatation of the ventricle, thereby markedly affecting the systolic and diastolic functions of the heart (Wang et al., 2005). Frequently, dogs at this stage experience syncope when attempting to suddenly increase cardiac output. Right-sided congestive heart failure (R-CHF) with ascites, hepatomegaly, and cachexia is a late sequela and may be precipitated by an acute episode of pulmonary thromboembolism.

**D. immitis infection in the cat**

The general pulmonary pathology in the cat is similar to the one observed in dog. Muscular hypertrophy, villous endarteritis, and cellular infiltrates of the adventitia are typically more severe in the caudal pulmonary arteries (Dillon, 1998). A characteristic feature of the reaction in felines in response to heartworm infection is the development of severe muscular hypertrophy in the smaller arteries (McCall et al., 1994). The host’s response to the parasite is intense and the role of inflammation is very important, being platelet factors release less important in the cat rather
than in the dog (Furlanello et al., 1998). The cause of the acute and often fatal crisis in the cat is lung injury resulting in respiratory distress. Frequently this event is associated with the death of as little as one adult heartworm. The lung can become acutely edematous and respiratory failure, instead of heart failure, becomes the life threatening event. Being pulmonary hypertension an occasional event, right sided heart failure and severe cor pulmonale is uncommon in feline heartworm infection (Dillon, 1998; Genchi et al., 1995).

**D. repens infection**

Much less is known about the pathogenesis of *D. repens* infection, which usually is characterized by the occurrence of painless subcutaneous nodules in which adult parasites reside (Bredal et al., 1998). The localization of adult worms can vary, and recently it has been reported also the presence of a female of *D. repens* in the conjunctiva of a dog (Hermosilla et al., 2006). This asymptomatic pattern of infection, which seems to be the most common, transforms the discovery of *D. repens* infection in an accidental finding. This occurs mainly in dogs (and cats) that are showing other symptoms or diseases, not related to the presence of these nematodes in the subcutaneous tissues. Indeed, the majority of infected animals do not present any clinical sign, notwithstanding the occurrence of persistent microfilaremia, therefore making it difficult to assess the pathogenicity of *D. repens* (Soulsby, 1982).

Some authors classified the rare clinical manifestations observed in association with the presence of *D. repens* into two clinical syndromes (Scarzi, 1995). The first one is characterized by a nodular multifocal dermatitis, mainly localized in facial region (Scott and Vaughn, 1987), the second instead is characterized by the presence of several pruriginous papulae; this one is considered similar to sarcoptic mange (Halliwell and Gorman, 1989), although the clinical experience of one of us (Tatjana Živičnjak) suggests that pruritus rarely occurs in *D. repens* microfilaremic dogs. The most frequent reports, however, are of dermatological signs (generalized dermatitis, localized alopecia, scratching and rubbing) associated with the presence of adults and microfilariae in the skin (Lee Gross et al., 1992; Kamalu, 1986; Mandelli and Mantovani, 1966; Scarzi, 1995; Živičnjak et al., 2006).

It has been suggested that the pathology may be significant in cases of massive infection (Kamalu, 1991; Mandelli and Mantovani, 1966; Mantovani, 1965; Restani et al., 1962). In the few cases found to be massively infected with adult worms and with simultaneously high microfilaremia, gross and histopathological changes have been reported in many organs, like spleen, liver, kidneys, lungs, heart and brain (Kamalu, 1991; Mandelli and Mantovani, 1966, Restani et al., 1962). The nature of these lesions suggests combined mechanical and immunopathological effects elicited by both micro- and macro-filariae (Mantovani, 1965), also if it is not possible to determine what underlying mechanisms may be involved, also due to the lack of experimental infection with reproduction of these clinical signs. Nothing is
currently known about the potential ability of microfilariae to cause hypersensitivity and inflammatory reactions at the cutaneous level, although this is likely one of the major mechanisms involved. Furthermore, it has been suggested that *D. repens*-related dermatitis is a conditioned pathology, that requires the presence of other infectious agents or stress (Bonvicini, 1910; Beaufils and Martin-Granel, 1987; Cazelles and Montagner, 1995). Single case reports of acute liver failure in the cat (Schwan et al., 2000) and cutaneous hyperpigmentation in a dog have been attributed to *D. repens* infection (Kamalu, 1991).

Conclusions

The pathogenesis of *D. immitis* is well known, while that of *D. repens* is still far from being understood, also if in the last years this parasite has been suspected to be not as harmless as usually considered. However, both parasites are important agents of zoonosis, in particular *D. repens*, and veterinarians play an essential role in protecting humans from infection. For this reason, it is essential that clinical signs are recognized, correct diagnosis is made and efficient treatment and prophylaxis are guaranteed not only to safeguard the health and well-being of our pets, but also that of our clients, neighbours and ourselves.

References


