

HUMAN PULMONARY DIROFILARIASIS: A REVIEW

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SUMMARY

The authors presented a detailed summary of the geographical distribution, clinical and pathological aspects of human pulmonary dirofilariasis. Although benign, this zoonosis, of which *Dirofilaria immitis* is the major etiological agent, represents a medical problem since it produces symptoms which may be confused with neoplasia and thus may subject patients to unnecessary thoracic surgery. Of 229 cases cited in the literature, only 17 were reported in Brazil, despite the existence of highly favorable conditions for the transmission of this infection in man. Thus it may well be that this parasitic infection remains underdiagnosed. Finally, the importance of a differential diagnosis between dirofilariasis and pulmonary neoplasia is emphasized in cases where there is a solitary subpleural nodule ("coin lesion") present. In addition, the development and improvement of modern immunological diagnostic techniques are essential to distinguish this benign disease from other pathological conditions and thus avoid unnecessary surgery. These techniques may reveal the true prevalence of this parasitic infection in our environment.

KEYWORDS: Human pulmonary dirofilariasis; Epidemiology; *Dirofilaria immitis*; *Dirofilaria repens*; Brazil.

INTRODUCTION

Dirofilariasis is a zoonosis caused by different etiological agents that induces clinical subcutaneous or pulmonary disorders in man^{15, 41, 47, 83}. Human pulmonary dirofilariasis is caused mainly by immature worms of *Dirofilaria immitis* (Leidy, 1856) Railliet & Henry, 1911^{2, 9, 32, 59, 93} and occasionally by *Dirofilaria repens* Railliet & Henry, 1911^{81, 82, 85}. Nevertheless, *D. repens* has been referred to as a frequent cause of subcutaneous lesions in man^{20, 23, 34, 35, 100} and less commonly, ocular lesions^{23, 24, 87}.

The first case of human pulmonary dirofilariasis

was reported in a child from Rio de Janeiro, Brazil, in 1887⁶⁷. However, this infection was not diagnosed in the United States until the 1940's and has since been considered as an emergent zoonosis⁹⁵.

In the majority of human cases, *D. immitis* is most often found in the lungs, but has also been observed at other sites including the cardiovascular system^{62, 104}, subcutaneous tissue^{64, 65, 79}, ocular region^{36, 70}, abdominal cavity¹⁰³, bladder⁷⁷, and breast⁶⁹.

LIFE CYCLE

Dirofilaria immitis has a sylvatic life cycle that

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involves wolves, foxes and cats; however, dogs are believed to be the most important host ^{20, 22}.

This zoonosis is usually transmitted by blood-sucking mosquitoes of the genera *Culex*, *Aedes*, *Anopheles*, *Mansonia* and *Psorophora* when they feed on dogs infected by *D. immitis*. Microfilariae develop within the insect and after 10-16 days become mature ⁹³. When the insect feeds again these infecting forms are transmitted to their definitive hosts and are able to develop. In the definitive hosts, the microfilariae (L3) migrate to the subcutaneous or subserous tissues, and moult twice during the subsequent months. After the fifth moulting, the juvenile forms reach the heart via the venous circulation. Within the natural hosts the minimum prepatent period is 6 months ^{1, 90, 106}.

The insect vector can also bite people and in this case the evolution occurs in a different way from that in the definitive host. Man seems to be an accidental host, since the parasite is not able to find the necessary conditions for survival and sexual maturation. The immature worms die in the heart (right ventricle) and are carried to the lungs through the pulmonary artery. They remain in the lungs attached to the minor vessels and produce symptoms of pulmonary embolism ⁹⁹.

GEOGRAPHICAL DISTRIBUTION

D. immitis has a wide geographic distribution. It occurs in tropical, subtropical and some temperate areas ⁵⁴.

Cases of human dirofilariasis have been reported in several countries throughout the world, including Italy, Spain, France, Greece, Egypt, Israel, the former USSR, United States, Canada, Australia, Japan, Malaysia, Sri Lanka, Senegal, Argentina and Brazil ^{23, 29, 44, 49}.

Tables 1 and 2 show the number of human cases reported in the literature (total = 229 cases) separated by country. The 17 reported Brazilian cases are subdivided according to State ^{12, 48, 51, 57, 71, 76, 99, 105, 110, 111}.

The majority of human cases have been reported in the United States (Table 1). In this country, CIFERRI ²⁷ observed that the geographic distribution of human pulmonary dirofilariasis was similar to that of canine dirofilariasis. Recently, a similar observation was made in Spain ^{6, 89}.

The profile of dirofilariasis in Italy is different from that found in the United States, in that the subcu-

TABLE 1
Geographic distribution of human pulmonary dirofilariasis.

Locality	Number of cases	Reference
Rio de Janeiro	01	Magalhães, 1887
Unknown	01	Leonardi et al., 1977*
São Paulo	01	Schneider et al., 1986
Rio de Janeiro	03	Madi et al., 1990
São Paulo	01	Saad et al., 1991
São Paulo	09	Barbas Filho et al., 1992
São Paulo	01	Amato Neto et al., 1993
Total	17	

* Patient living in Brazil but diagnosed in the USA.

taneous form, caused by *D. repens*, appears to be more common ^{84, 88}. The 1st case of human dirofilariasis caused by *D. repens* was reported in 1984; this infection seems to be rare. Italian authors suggested that the lung lesions were due to the presence of *D. repens* ^{38, 81, 85, 88}.

PREVALENCE IN DOGS

Guerreiro et al. ⁴⁶ investigated dirofilariasis in 28,000 dogs distributed in eight countries (France, Italy, Spain, Portugal, Argentina, Colombia, Mexico and Brazil). Diagnosis was made either by identifying microfilariae in the blood or using an enzyme-linked immunosorbent assay (ELISA). In all of these countries, dogs were found with circulating microfilariae. The prevalence of infection based on ELISA was somewhat higher. In Brazil, for instance, 253 (8.5%) of 2985 dogs were found to be positive for circulating microfilariae, while 77 (9.3%) of 825 dogs tested were serologically positive.

There are few reports regarding the occurrence of canine dirofilariasis in Brazil. In the States of Rio de

TABLE 2
Human cases of pulmonary dirofilariasis in Brazil

Country	Number of cases
USA	133
Japan	49
Australia	17
Brasil	17
Spain	10
France	01
Colombia	01
Unknown	01
Total	229

Janeiro, São Paulo, Pernambuco, Maranhão, Espírito Santo, Santa Catarina and Rio Grande do Sul, the prevalence ranges from 9% (São Paulo) to 25% (Espírito Santo) ^{7, 19, 25, 54, 58, 60}. However, in other States the prevalence is not known ⁵.

It was observed that the prevalence of canine dirofilariasis in Rio de Janeiro and São Paulo, was higher in the littoral region ^{58, 60}. LARSSON ⁶⁰ reported an increase in sero-prevalence in São Paulo from 0.5% in 1978 to 9% in 1990 ^{60, 61}.

Since the national territory is very large, with an extensive sea-coast, it might be expected that the canine dirofilariasis in the other littoral States would show identical rates to those observed in the researched areas.

PATHOLOGICAL AND CLINICAL ASPECTS

Patients suffering from pulmonary dirofilariasis are frequently asymptomatic. Nevertheless, they sometimes develop chest pain, coughing, hemoptysis, shivering, fever, dyspnea, fatigue, syncope or weight loss ^{8, 17, 30, 39, 53}.

In the radiological image, the pulmonary lesion usually is round in shape, known as "coin lesion" ^{14, 18, 32, 38, 55, 68, 93, 112}.

D. immitis worms found in the nodules are normally immature. In a single case investigators observed the presence of microfilariae in an adult female ¹⁶.

Pulmonary infarcts, which are typically round and located in the subpleural area with a granulomatous reaction, often appear as self-limiting processes ⁹⁴. A single nodule is usually found in the peripheral portion of the lung, randomly located among the lobes ²⁶. Occasionally two nodules can be observed in a single patient ^{11, 20, 27}.

Upon anatomopathological examination the pulmonary lesions appear macroscopically as circumscribed yellow-greyish nodules 1 to 3 cm diameter, surrounded by normal pulmonary parenchyma ^{20, 95}. Microscopically, there is a central necrotic area surrounded by a narrow, granulomatous region formed by epithelial cells, plasmocytes, lymphocytes and eventually giant-cells. The lesion is peripherally delimited by fibrous tissue. The pulmonary parenchyma surrounding the lesion contains scattered lymphocytes, macro-

phages and eosinophils ^{20, 33}. AKAOGI et al. ⁴ described the presence of atypical cells in these lesions, which are related to epithelial regeneration in the presence of the parasite.

A single immature *D. immitis* is usually found necrosed and calcified in the lumen of a small artery and encircled by necrotic tissue. The worm and the associated intense, fibroblastic proliferation completely obstruct the arterial lumen ^{20, 40}. The lesion contains a central area of coagulation necrosis surrounded by a zone of fibrosis, which is not compatible with the embolic etiology of the lesion. To explain this observation it has been suggested that the worms release a toxic substance ^{20, 31}.

Although this lesion is not usually a health threat, it is medically important because it can often be misdiagnosed radiologically as a primary or metastatic pulmonary tumor. For proper diagnosis, surgery of the thorax may be necessary to obtain a pulmonary biopsy ⁹⁴. Because atypical cells occur in the filarial lesion, a careless examination of a single pulmonary nodule can suggest malignancy, leading to an incorrect diagnosis of malignant tumor. Therefore, whenever a pulmonary lesion suggests dirofilariasis either through X-ray or cytological analysis, serological tests should be indicated ⁴.

DIAGNOSIS

Direct or indirect methods can be used for the laboratory diagnosis of canine dirofilariasis. The circulating microfilariae can be seen directly by light microscopy. Serological tests provide an indirect method of diagnosis.

The techniques used in direct methods are those of microfilaria concentration by centrifugation ^{20, 56, 60, 78} or filtration ¹⁰⁹ of blood. Kits for filtration are commercially available (e.g. Difil. Evsco. Buena. N.J.).

Direct parasitological methods assure diagnostic specificity and a quantitative evaluation of microfilaremia. In dogs with circulating microfilariae, existing immunological methods produce results that differ from those of parasitological diagnosis and are less specific. Between 10 to 67% of dogs with a positive serological test for *D. immitis* do not have any detectable circulating microfilaremia ⁸⁰.

RAWLINGS et al. ⁹² documented in dogs four

different types of occult dirofilariasis; 1) pre-patent infection; 2) unisexual infection; 3) infection with adult worms that have been sterilized following treatment; 4) infection with worms that have been sterilized by immune-mediated processes. In such cases, the immunological tests in canine dirofilariasis are valuable for the detection of animals with the occult infection.

Infection caused by *D. immitis* is characterized by periods of occult dirofilariasis. The use of the term amicrofilaremic dirofilariasis must be avoided because the microfilariae may be present although not evident in the blood examined⁴³.

The immunological methods used to demonstrate the presence of antibodies are latex agglutination - LA¹⁰, indirect fluorescent antibody test - IFA, and enzyme-linked immunosorbent assay test - ELISA^{42,45}, which is available commercially in several kits. These tests show better results in the presence of pre-patent infections than in the presence of patent infection²⁰.

Nowadays diagnostic tests for the detection of circulating antigens are preferred, followed by the search for circulating microfilariae. These tests have been used for the diagnosis of occult canine dirofilariasis. Other routinely used methods include latex agglutination and ELISA^{20, 28, 96, 108}.

In contrast to the canine infection, circulating microfilariae do not occur in man and diagnosis is usually made after histopathological analysis.

The typical pulmonary lesion (sole pulmonary nodule) although benign, resembles some other important pathological lesions, such as metastatic malignant tumor neoplasia and transitional cell carcinoma^{41, 52}. Besides dirofilariasis, tuberculosis, fungal infections and hamartomas also present as well defined pulmonary lesions^{21, 91, 101} with nonspecific radiographic and tomographic scans²⁰.

Clinicians have agreed to avoid the adoption of invasive procedures such as needle aspiration or transbronchial biopsy^{8, 30, 39, 50}. Therefore, serological tests are suggested as the initial diagnostic method for *D. immitis* when the epidemiological conditions or symptoms are compatible with dirofilariasis. Commonly used methods are: complement fixation tests²⁷, indirect hemagglutination⁴¹ and ELISA^{37, 41, 72, 73, 75, 98, 102} whose main problem is low specificity. Recently, the detection of specific bands in immunoblots has led to

a higher specificity of the serological methods^{3, 74, 107}.

CONCLUSION

Dirofilariasis is a problem of medical importance because it must be considered in the differential diagnosis of neoplasias and other lesions which often demand surgery of the thorax.

The necessary elements for the maintenance of the life cycle of animal dirofilariasis are found in Brazil. The prevalence of *D. immitis* infection in the canine population is high in many locations where basic sanitation conditions are inadequate, allowing the proliferation of mosquitoes. Consequently, it is likely that this parasitic disease is underdiagnosed in Brazil, and that more cases occur in the country than those previously reported. Clinicians, radiologists, and pathologists must consider the diagnosis of dirofilariasis in patients presenting with a subpleural pulmonary lesion ("coin lesion"). In addition, multiple sections of the nodules must be examined for the localization and histopathological identification of immature worms. The development and application of modern techniques for immunological diagnosis are essential so that this benign disease can be distinguished from serious pathologies, avoiding unnecessary surgeries.

RESUMO

Dirofilariase humana pulmonar: Revisão.

Os autores realizaram minuciosa revisão sobre a distribuição geográfica, a clínica, a patologia e o diagnóstico da dirofilariase pulmonar humana. Esta zoonose, que tem como principal agente etiológico a *Dirofilaria immitis*, é um problema médico porque produz um quadro clínico, embora benigno, que se confunde com neoplasia e, assim interpretado, pode conduzir o paciente à cirurgia do tórax. Dos 229 casos citados na literatura, apenas 17 foram descritos no Brasil, apesar da existência de condições muito favoráveis à transmissão da infecção para o homem, admitindo-se portanto, que é uma parasitose subdiagnosticada. Finalmente, a importância do diagnóstico diferencial entre dirofilariase e neoplasias pulmonares nos casos de presença de nódulo solitário subpleural ("coin lesion") é destacada, além do que o desenvolvimento e aprimoramento de técnicas modernas de diagnóstico imunológico são essenciais para distinguir esta doença benigna de outras patologias mais sérias e evitar cirurgias desnecessárias.

Estas técnicas poderão fornecer a prevalência real da parasitose em nosso meio.

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