Review

HUMAN DIROFILARIASIS

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ABSTRACT

Human infections with zoonotic filariae are frequently observed throughout the world. Filarial worms of the genus dirofilaria are well known nematodes of carnivorous mammals and can be found in Asia and Africa as well as in the United States and in Europe. Human dirofilariasis is an infection caused by filarial nematodes of the genus dirofilaria. Man is only occasionally infected. The parasite's life cycle involves uptake of microfilariae from the peripheral blood circulation of infected dogs or cats by mosquitos (Anopheles, Culex, Aedes). Dirofilariasis is transmitted by haematophagous arthropods to man, in whom the nematodes usually die before reaching sexual maturity. Identification of dirofilariae from tissue sections is difficult, but knowledge of the parasite's geographic distribution and patients travel history may be helpful.

KEY WORDS

filarial infection, dirofilariasis-parasitology, Dirofilaria repens, subcutaneous nodules

Human dirofilariasis is an infection caused by filarial nematodes of the genus dirofilaria usually transmitted by mosquitoes from carnivorous mammals to humans. There are two different forms of clinical manifestation. Man is occasionally infected, the disease manifest itself either as subcutaneous nodules or as pulmonary coin lesions (15,11).

Pulmonary dirofilariasis is usually caused by *Dirofilaria immitis* (dog heartworm), a common parasite of carnivorous mammals (cats, dogs, foxes and wolves). It is distributed throughtout almost all tropical and subtropical countries. The adult male worm measures 120-250 mm, the female worm 220-310 mm in length, both are 1 mm in diameter. Microfilariae (first stage larvae) measure 220 - 330 μm by 5-6 μm.

In humans, parasites normally die at the inoculation site in the subcutaneous tissue before reaching sexual maturity, resulting in a granulomatous reaction. In a few cases they reach the right heart ventricle where they die and get passively transported to the lung. The embolization of pulmonary arteries leads to subpleural pulmonary infarction with a granulomatous reaction (11,14,16). Infected persons are asymptomatic in about 50%. In some cases patients show cinical symptoms such as cough and chest pain. Furthermore symptoms as hemoptysis, malaise, myalgia, chills and sometimes fever may be found (1,14). Pulmonary dirofilariasis is often discovered incidentally

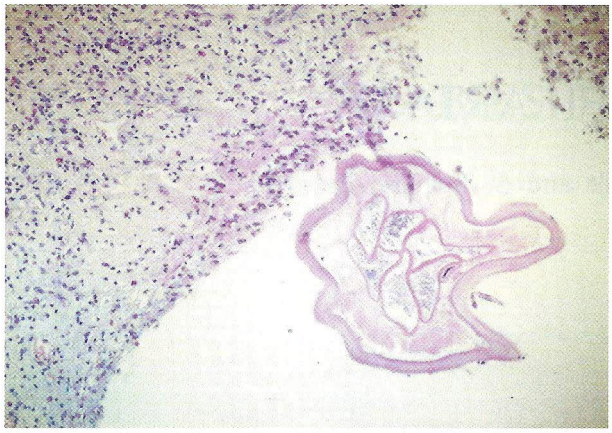

Figure 1. Cross section of Dirofilaria repens surrounded by an inflammatory infiltrate, showing a multilayered cuticle, a well developed musculature and internal organs.

on routine chest radiography. Diagnosis is sometimes difficult since radiological findings only consist of single pulmonary nodules and may resemble pulmonary neoplasms (benign, carcinoma, metastasis), tuberculosis, fungal infections and hamartoma. In many cases only surgical exploration with excisional lung biopsy leads to the correct diagnosis (1,14).

The second manifestation of human dirofilariasis is subcutaneous dirofilariasis, caused by *Dirofilaria repens* and *Dirofilaria tenuis*. *Dirofilaria tenuis* is known as a parasite of the raccoon (procyon lotor).

Dirofilaria repens whose principal reservoirs are cats and dogs (canis familiaris, felis domestica) measures 13 cm in length by 0.5 mm in diameter. It is distributed throughtout Europe, Africa, and Asia. In Europe the parasite is found especially in the mediterranean countries (10,15) (Table 2). Human infections with Dirofilaria repens have been reported from Italy (7,13), Greece, Spain and other mediterranean countries.

Clinical symptoms comprise migratory erythematous swellings, subcutaneous nodules due to granulomatous reaction in the subcutaneous tissue (9) and pruritus caused by migration of the worm through subcutaneous tissue. Subcutaneous nodules may appear anywhere on the body and have been found on the head, neck, arms, legs, trunk, scrotum, and penis. Even conjunctival and orbital infections have been described (2,6,11).

Identification from histological sections is sometimes difficult but the location of the nodule in the subcutaneous tissue, the diameter of the worm in section, the presence of a multilayered cuticle with fine longitudinal ridges on the external layer and lateral cords, a well developed musculature and the typical arrangement of internal organs may lead to the correct diagnosis. Figure 1.

Differential diagnosis comprises inflammatory diseases, granulomatous diseases, as well as benign and malignant tumors. Also infections with other nematodes must be considered (*Dracunculus medinensis, Wuchereria bancrofti, Loa loa, Onchocerca volvulus, Brugia malayi, Mansonella*). (Table 1).

There are about 30 species of dirofilarial worms which parasitises various mammals (Table 2). The vector of dirofilariae are mosquitos (arthropods) of the genera Culex, Aedes and Anopheles. Lice, flies and ticks are possibly also vectors.

LIFE CYCLE

During their development dirofilarial worms undergo four molts before they reach sexual maturity and become adult worms. Their larval stages are called first, second, third and fourth stage larvae (Tab.3). First stage larvae are called microfilariae. They are released from female worms and are deposited in

Table 1. Differential diagnosis of subcutaneus nodules.

DIFFERENTIAL DIAGNOSIS OF SUBCUTANEUS NODULES	
inflammatory diseases	pyoderma (abscess, carbuncle)
granulomatous diseases	sarcoidosis, granuloma anulare
tumors	lipoma, fibrolipoma, neurofibroma cutaneous metastasis, lymphoma
lymphadenopathy	leukemia, metastasis, lymphadenoma
nematode infections	Dracunculus medinensis, Wuchereria bancrofti, Loa loa, Onchocerca volvulus, Brugia malayi, Mansonella

Table 2. Geographical distribution of the most important dirofilarial worms.

GEOGRAPHICAL DISTRIBUTION OF THE MOST IMPORTANT DIROFILARIAL WORMS		
D. immitis	(dog, cat, fox, bear)	worldwide
D. repens	(dog, cat, fox)	Europe, Africa, Asia
D. tenuis	(raccoon)	North America
D. ursi	(bear)	North America, Japan, Russia
D. striata	(wild felines)	North and South America

the peripheral blood stream. There they can be found for several months. Microfilariae pass to the intermediate host by ingestion while the insect feeds (blood meal). In the intermediate host, which are mosquitos (arthropods) of the genera Culex, Aedes and Anopheles, larvae molt two times to reach the infective stage. When the mosquito partakes of another blood meal, 3rd stage larvae gain entrance to the definitive host (usually cats and dogs) where they undergo two more molts to reach sexual maturity and become young adults (8,15). Sometimes they are transmitted by chance to humans.

Since man is a "dead end host" and provides an unsuitable environment, dirofilarial worms are not able to undergo their full stages of development and usually die before reaching sexual maturity.

The time between infection and detection of the nodule depends on the species maturation time (11). In case of pulmonary dirofilariasis, adult worms appear in the host's heart particularly in the right ventricle and pulmonary arteries after about 8 to 9 months. The development of *Dirofilaria repens* in primates to adolescent or mature stages takes from about 6 months to a few years (4,11).

There are some reports where gravid worms have been described. All those patients had a defective immunologic system in common. To our knowledge, microfilariaemia has been found only once in a patient with systemic lupus erythematosus, who had taken high doses of cortisone (3,4,11,12).

A phenomenon which can be found in the host's peripheral blood stream is the so-called microfilarial periodicity. It means a certain degree of periodicity where a maximum number of microfilariae can be found in the peripheral blood. It enhances the chances of the microfilariae for ingestion by the insect vector. Microfilarial periodicity seems to depend on physiological changes due to the 24 hour rhythm of the host such as: body temperature, oxygen pressure, carbon dioxid tension or body acidity (8).

TREATMENT

Surgical removal in many cases is diagnosis and treatment at the same time. Additional treatment with diethylcarbamazine in a dose of 3 x 2mg/kg daily over 4 weeks starting with 50 mg/day may be applied. Contraindications are epilepsy and renal insufficiency.

Table 3. Life cycle of dirofilarial worms.

HOST	MOLTS	DEVELOPEMENT
Host cats and dogs	1 st stage larva = Microfilariae	adult worm microfilaria in blood stream
↓ Intermediate host haematophagous arthropods: Culex, Aedes, Anopheles	 2 nd stage larva 3 rd stage larva	**removed from blood stream by arthropods** 2 molts achieving infective stage
↓ Host cats dogs ↓ Man dead end host	 4th stage larva mature worm	**introduced through skin** 2 molts maturing to adult worm

CONCLUSIONS

Human dirofilariasis may be acquired in most mediterranean countries.

Migratory skin nodules or singular pulmonary nodules may be the only signs of a possible infection with dirofilarial worms. Identification of dirofilarial worms from tissue sections is difficult; knowledge of the parasite's geographic distribution and the patient's travel history may be helpful. Growing tourism to foreign countries may lead to an increasing number of dirofilarial infections in regions where the disease is not autochthonous.

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