

## A case of human *Dirofilaria repens* in Rome, Italy: A clinical and radiological challenge

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### Abstract

Human subcutaneous dirofilariasis caused by *Dirofilaria repens* is a vector-borne zoonotic disease mostly transmitted from dogs to humans through a mosquito's blood meal. Heartworm replication is amplified by the climate change, the increase of the range of suitable vectors, the facilitation of pet travel and the high rate of undiagnosed dirofilariasis in dogs. We describe a case of a young Romanian woman, resident in Rome for 18 years, that came to our attention for the appearance for five months of a subcutaneous nodule in the left arm. The patient reported that she first felt an insect bite, after which she noticed the onset of an erythematous and itchy wheal in the same skin area, turned into a subcutaneous nodule within a few weeks. The ultrasound examination showed a hypochoic subcutaneous formation of 1,2 cm in diameter, containing a ribbon-like structure made up of hyperechoic parallel double lines, reminiscent of a worm. Based on this suspicion, we opted for the surgical radicalization of the lesion. The histological examination confirmed the radiological hypothesis of a worm-like foreign body morphologically compatible with *Dirofilaria repens*. Our experience shows how a clinical nonspecific skin nodular lesion may conceal an unexpected and unsettling diagnosis of subcutaneous *Dirofilaria repens*.

### Case report

In February 2021, a 43-year-old woman born in Romania and living in Rome for 18 years, came to our Institute for the appearance since October 2019 of a painless subcutaneous nodule on her left arm. At the

time the patient worked as a cleaner in two families who owned dogs. The patient remembered that this lesion was preceded by an insect bite of few weeks earlier. The sting was immediately followed by a large swelling with an erythematous border and localized itching which lasted 5-7 days. After few weeks the inflammatory reaction turned into an asymptomatic nodular lesion of about 1 cm, unchanged over a year and a half, firm on the underlying tissues and consistent on palpation. The skin overlying the nodule was normal as well as the lymph node stations.

Under the clinically palpable swelling of the left arm, in the context of the subcutis, soft tissue ultrasound performed with 14 MHz linear probe highlighted an oval formation of 1.2×1 cm. It contained fluids and a serpiginous tubular structure characterized by hyperechoic parallel walls and anechoic centre. No movement was detectable as well as vascular signals with Colour Doppler ultrasound. Based on clinical non-specificity and radiological suspicion, an excisional skin biopsy was performed in our hospital that macroscopically showed a 1 cm grey-whitish mass. Microscopic examination was found to be decisive for the diagnosis because it revealed the presence of a nematode. Its body cross sections had tubular structures inside and were surrounded by an inflammatory granulation tissue composed by eosinophils, lymphocytes and foreign body giant cells. Moreover, the worm was equipped with a multi-layered cuticle showing fine transverse striations and prominent longitudinal ridges, typical of adult *Dirofilaria repens*. Laboratory findings were normal, with slight and non-significant white and red blood cells reductions. Surgery was definitive as the lesion was completely excised and no further treatments had been taken into account. The patient was later referred to a parasitology centre in order to rule out microfilaremia.

### Discussion

The mosquito-carried nematodes causing zoonosis with the greatest impact on public health are *Dirofilaria repens* and *Dirofilaria immitis*.<sup>1</sup> The idea of the existence of two species of *Dirofilaria* involved in canine filarial infections dates back to Ercolani in 1874, who deduced that when no worms were found in the heart of microfilaremic dogs, they were present in the subcutis or in other body sites.<sup>2</sup> In fact *Dirofilaria immitis*, having a cardiac tropism, provokes a severe disease in dogs

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(heartworm disease) and rarely affects humans. Differently *Dirofilaria repens* triggers a clinically silent subcutaneous infection in dogs, nevertheless representing the main agent of human dirofilariasis in the Old World.<sup>1</sup> Dogs, followed by cats, foxes, wolves and coyotes are the main reservoirs of these filaroid helminths. *D. repens* adult worms usually lie hidden in the subcutaneous tissues of these hosts. Microfilariae enter the bloodstream and are swallowed by mosquitoes during their blood meal. These intermediate hosts belong all to the family *Culicidae* (*Aedimorphus*, *Anopheles*, *Armigeres*, *Ochlerotatus*, *Stegomyia*, *Culex*, *Coquillettia* and *Mansonia*).<sup>3</sup>

Inside them microfilariae migrate from the midgut to the Malpighian tubules and melt into the second (L2) and third (L3) infective larval stage. During L3 stage they make their way to the proboscis where they nest and wait to be transmitted with a new sting to the next host.<sup>4</sup>

Humans represent an accidental host in which the parasite doesn't reach the adult stage and gets stuck in immature form generating subcutaneous nodules. Less frequently than skin, the worm can reach also the eyes and other organs, as lungs. In literature the prevalence of *D. repens* appears to be closely related to male gender, people having guard dogs, older age and outdoor lifestyle, all factors implying a higher exposure to mosquito bites.<sup>5</sup>

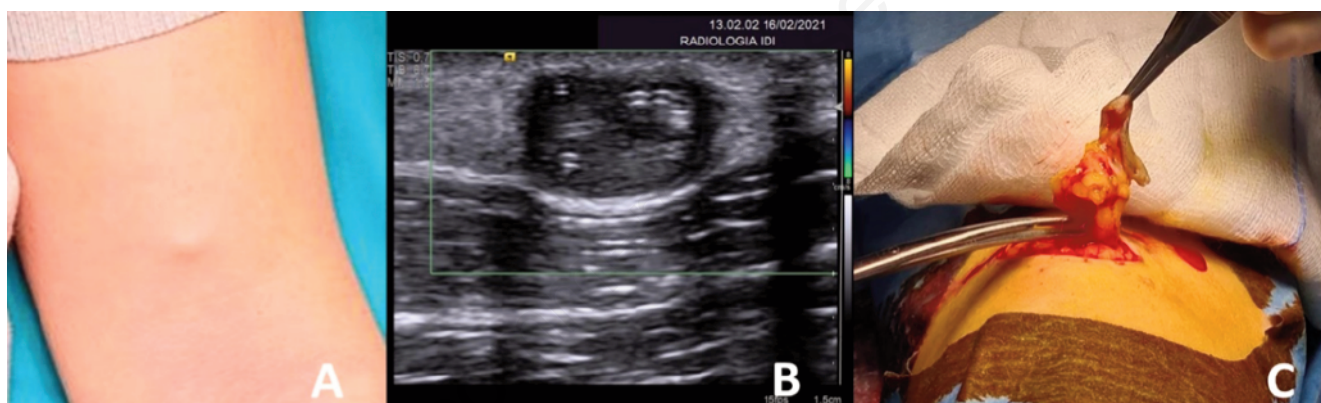
*D. repens* started to spread during the first decade of the new millennium from southern to central and northern Europe, becoming an emerging pathogen. The highest incidence of human cases has been

detected in the Mediterranean countries such as Italy, Southern France and Greece and in the last two decades in some eastern European countries like Ukraine, Russian Federation and Belarus.<sup>6-8</sup> The most recent data indicate that *D. repens* is endemic in all our peninsula and major islands, Sicily and Sardinia, with a prevalence ranging between 1.5-12%<sup>9,10</sup> and that dogs are often co-infected with other filarioids, such as *Acanthocheilonema reconditum* and *D. immitis*.<sup>11</sup> Unfortunately, many human cases are not reported and the comprehensive framework of the distribution of human dirofilariasis remains still unknown.

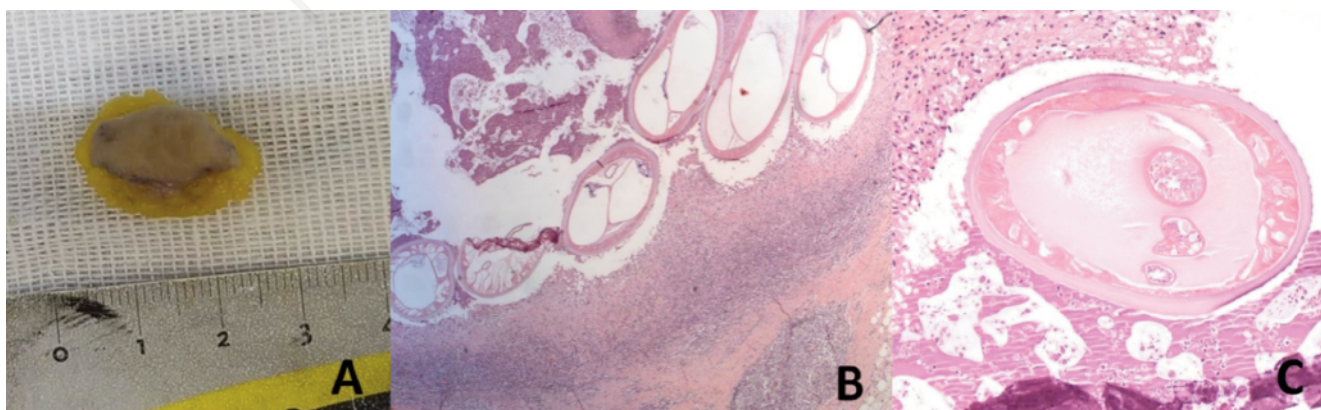
The most extensive case study of this zoonosis reported worldwide by a single study group was conducted in Italy, concerning sixty new cases of human dirofilariasis occurred in our peninsula between 1990 and 1999. The nodules appeared singularly and, in 49 Italian cases out of 60, randomly in the subcutis especially of head,

limbs and chest wall; instead, the minority affected the epididymis, spermatic cord, omentum, lung, breast, and conjunctiva. The clinical diagnosis was invariably fallacious, and it ranged from epidermoid and hematic cyst, abscess, probable onchocerciasis and appendicitis (in the cases involving the omentum), to suspected cancer (in those affecting breast and lungs).<sup>12</sup>

In fact, the nematode is both able to remain at the injection site, as reported by some patients who develop the lump in the same skin area where they had felt a painful sting weeks or months before, and to migrate subcutaneously in several parts of the body. The heartworm often presents with mild and unrecognized symptoms, less frequently with larva migrans-like symptoms, such as irritation and itching. In case of nematode's migration, after several weeks and months from the entrance in human host, *D. repens* can stop its path and



**Figure 1.** *Dirofilariasis* appears clinically as (A) a subcutaneous nodule of the left arm, at ultrasound as (B) an oval formation of 1.2x1 cm containing fluids and a serpiginous tubular structure. Based on clinical non-specificity and radiological suspicion of a foreign body a 2x1 cm excisional skin biopsy was performed (C).



**Figure 2.** At cut surface a 1 cm grey white mass was detected (A). Haematoxylin/Eosin-stained section showed cross section of a nematode, surrounded by an inflammatory granulation tissue composed by eosinophils, lymphocytes and foreign body giant cells. The multi-layered cuticle of the worm showed fine transverse striations and prominent longitudinal ridges as adult *Dirofilaria repens* (H/E 2,5x) (B). Nematode at higher magnification (H/E 10x) (C).

form a lump of about 1 cm in various locations, including the entire body surface subcutis, which is the preferred one, but also the lymph nodes, abdominal cavity, lungs, muscles and dura mater.<sup>5</sup> The easiest mistake doctors can make is ignoring it, considering it a benign growth, and consequently not treating it. This conduct is responsible for the survival of the nematode in humans for up to a year and a half, when larvae die. The most decisive element for the diagnosis of *D. repens* is the grooving of its cuticle with longitudinal ridges, of which other humans infecting filariae are lacking, with the exception of *Dirofilaria* sp. “hongkongensis”<sup>13</sup> and *Dirofilaria ursi*, not yet present in Italy.<sup>14</sup> Our species diagnosis is based on the pathological examination that highlighted this specific morphological feature. To be precise, diagnostic gold standard is represented by molecular tools such as PCR, for which refrigerated or frozen helminth is needed.<sup>15</sup> Since our Institute is not a centre specialized in infectious diseases, we didn’t have the chance to perform it. *D. repens* doesn’t cause severe symptoms in humans, therefore it doesn’t require any other treatment except surgical radicalizing one. In our case, during the surgery, it was not possible to see the worm, as it was totally encapsulated in a fibrous cap, factor which positively influenced the outcome of the operation and its effectiveness. The dual therapy based on albendazole and doxycycline appears to be useful in cases where the worm is still in the migratory phase, promoting the formation of a fixed nodule that can be removed more easily.<sup>16</sup> In our case, since it had been a single fixed nodule for a year and a half, there was no need to prescribe medical treatments.

## Conclusions

Both *D. immitis* and *D. repens* are endemic in the Old World, but the difference lies in the frequent lack of clinical symptoms of suspicion in *D. repens* that

makes its effective monitoring more difficult.<sup>17</sup> Knowledge of this heartworm in the scientific community can concretely improve its detection and ensure a faster treatment. We hope the reported human cases and the expansion of areas of endemicity will encourage major vigilance and interest in human dirofilariasis, both in clinicians and researchers, adopting effective preventive measures.

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