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Human Dirofilariasis: An Emerging Zoonotic Infection with Diagnostic and Surgical Challenges - A Narrative Review

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ABSTRACT

Dirofilariasis is an infectious disease spread via vectors, mainly caused by D. immitis and D. repens, and which affects both dogs and humans globally. Clinicians are generally unaware of this condition, especially in non-endemic areas, leading to inappropriate drug prescriptions and delayed diagnosis and treatment. Dirofilariasis is increasingly reported in some European countries, Asia, and the Americas due to climate change, increasing numbers of mosquitoes, and greater pet mobility. This review discusses the life cycles of dirofilariasis, its diagnostic challenges, its surgical treatment, and the reasons why pharmacologic treatments are rarely needed when addressing dirofilariasis. The central point in this essay is that human dirofilariasis is underdiagnosed, often overlooked, and easily curable once diagnosed.

Keywords: *Dirofilariasis, Surgical treatment, zoonotic infections*

INTRODUCTION

In temperate, subtropical, and tropical parts of the world, Dirofilariasis the disease caused by Dirofilaria spp., especially Dirofilaria immitis and Dirofilaria repens in dogs occurs commonly in dogs and cats and infrequently in people. Dirofilariasis is still a significant veterinary and public health problem in endemic places, despite the availability of very effective, safe, and easy preventative medications for the disease's treatment over the past thirty years [1]. Dirofilariasis is the term for the infection that this genus causes in humans. It is a zoonotic infection that affects people all around the world. Of the forty species of Dirofilaria, six are known to infect humans: Dirofilaria immitis, repens, striata, tenuis, ursi, and spectans. The species that infect humans differ depending on where they live. A vertebrate species serves as the definitive host for the worm's life cycle, while an arthropod serve as an intermediate host and vector [2].

METHODS

This narrative review was performed regarding the human cases of dirofilariasis. The search of the PubMed and Google Scholar databases until February 2026 was done using combinations of the following keywords: "human dirofilariasis," "Dirofilaria immitis," "Dirofilaria repens," "pulmonary dirofilariasis," "subcutaneous dirofilariasis," and "ocular dirofilariasis." Also, the references of all included papers were manually screened. There were no limitations on publication dates; however, preference was given to those written in

English since 2010. In addition, conference proceedings and preprint articles were not taken into account.

ETIOLOGY AND LIFE CYCLE

Etiology- The genus Dirofilaria represents filarial nematodes belonging to the family Onchocercidae [3]. They are vector-borne worms that parasitize mammals in the form of carnivores as definitive hosts including dogs, cats, foxes, and wild life. Although there are around 40 species of the genus, only a few of them represent zoonoses. Among them, three species including D. immitis, D. repens, and D. tenuis, are the common causative agents for human infections. There are sporadic cases reported from human infections caused by D. striata and D. ursi-like species [3], [4]. Human dirofilariasis has been categorized into two types based on their locations; pulmonary dirofilariasis, mainly caused by D. immitis, and subcutaneous or ocular dirofilariasis, mainly caused by D. repens and D. tenuis [3], [5].

Life Cycle- Dirofilaria immitis life cycle involves a definitive host, commonly a canid animal like the dog, as well as an intermediate host that includes mosquitoes belonging to the genera Aedes, Culex, Anopheles, and Mansonia [5]. A mosquito becomes infected after taking a blood meal from an infected dog and ingesting microfilariae (L1). The microfilariae cross the stomach lining in the mosquito and move to the Malphigian tubules and become first-stage larvae (L1). After around 10-20 days, two molts occur resulting in the development from L2 to L3 stage larvae. Third-stage larvae then move to the proboscis of the mosquito and can subsequently infect another host through its bite [4], [5].

As the dog gets bitten by the infected mosquito, L3 larvae get introduced into the skin of the dog. The development from L3 larvae to L4 larvae happens after about 7 to 14 days, followed by migration from the subcutaneous tissues to the abdomen region of the dog, where larvae will pass to the thoracic cavity by penetrating the diaphragm. After about 45 to 60 days, larvae become L5 larvae and finally reach the pulmonary arteries and right ventricle of the heart. The length of the adult female is between 230-310 mm, and its width is 350 micrometers; while the length of the adult male is between 120-190 mm, and its width is 300 micrometers. The life span of the adult is about 5 to 10 years [4].

Human beings are considered accidental hosts, which are often referred to as “dead-end” hosts. In case an infected mosquito introduces L3 larvae in a human host, the larvae will migrate following a migration path like that found in dogs. The difference is that human beings will not allow for full development of the larvae. Instead, the larvae will arrest their development, die early, and get trapped in small pulmonary arteries, resulting in infarction and granulomatous inflammation leading to the formation of solitary “coin lesions” in chest radiography [3], [4], [5].

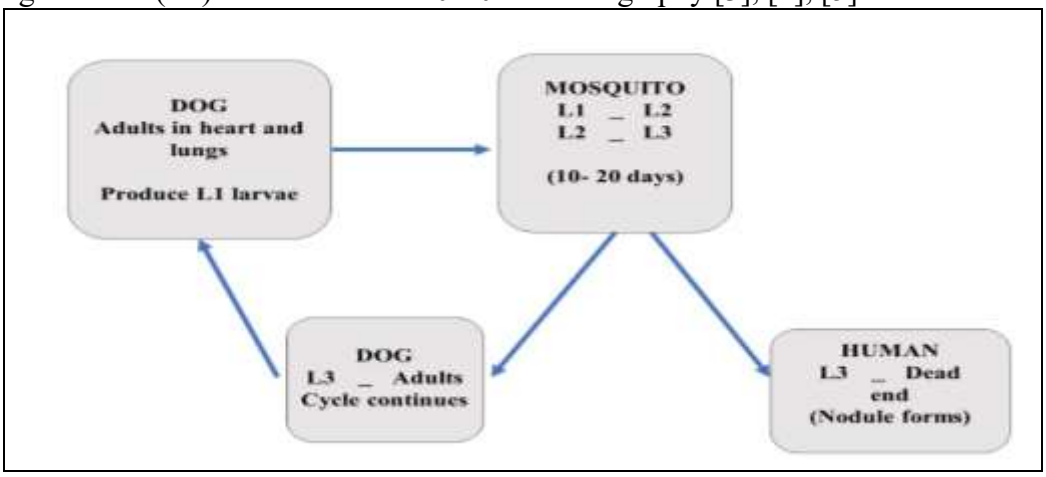

Figure 1: Life Cycle of Dirofilaria immitis

The adult worms occupy the pulmonary artery and right ventricle of the definitive host (the dog). The female worm produces L1 microfilariae which enter the bloodstream. A mosquito feeds on the blood and takes in the microfilariae, which take 10-20 days to progress from L2 stages to L3 infective larvae. The infected mosquito deposits L3 larvae in the next host where they develop into adults in the case of dogs. In humans (an accidental host), the larvae do not develop and die, causing pulmonary or subcutaneous nodules.

EPIDEMIOLOGY

While some illnesses exhibit geographic predominance, cutaneous infections and infestations are common. An increased risk of acquiring these infestations may result from immigration, international trade and travel, climate change, and the rise in pet ownership [6]. Dogs and other animals are frequently infected with the parasitic worm Dirofilaria. Dirofilariasis, a very rare human ailment, is spread via mosquito bites. Pulmonary(heartworm) and subcutaneous lesions are present in most cases of human dirofilariasis. Dirofilaria repens is a vector-borne zoonotic disease that causes subcutaneous dirofilariasis in humans [3]. There are about 40 different species of Dirofilaria known to exist, with Dirofilaria repens and Dirofilaria immitis being the most prevalent species that infect humans [7]. Human dirofilariosis's geographic distribution during the 2000–2019 time period, as determined by the examined case reports [5].

CLINICAL PRESENTATIONS

The clinical indications generated by immature helminth migration in human tissues or internal organs evolve slowly and over time. Dirofilariasis is distinguished by the sensation of a living "worm" moving and crawling within a seal, tumor, or subcutaneous node. Dirofilariasis symptoms may include headache, nausea, weakness, and soreness near the helminth, as well as radiation along nerve trunks. Clinical symptoms are determined by the location of the helminth [8].

literature	Country	Gender	age	Presenting complaints	Main diagnosis	investigations	treatment
[9]	Slovakia	Female	66	Chest pain, cough, asphyxia, purulent sputum	Dirofilaria immitis Pulmonary dirofilarisis	Chest x-ray, CT, Histopathological analysis	a wedge surgical resection of the nodule was performed.
[7]	Austria	Female (Bosnian origin)	64	Erythema, creeping sensations in her right eye and eyelid, mild eczema of right eyelid	subcutaneous dirofilariosis	Physical examination, and a high-frequency ultrasound examination of the orbital and ocular tissues, Eosinophil counts and serum IgE levels	Surgical removal of the worm under local anesthesia
[10]	Italy	Female	62	persistent redness, pain, and discomfort in the eyes, together with itching and a foreign body feeling in the right eye	D. repens ocular dirofilariasis	Slit lamp biomicroscopic examination, fundus examination revealed nothing abnormal.	urgent surgical excision to avoid further migration

Table 01: Comparison of different published cases

The commonest presentations include subcutaneous, pulmonary and ocular dirofilariasis. Simón et al's [5] systematic review on human dirofilariosis identified 71 anatomical sites with nodular lesions/worms, with the most common places being the subconjunctiva (92 instances), lung (76 cases), and eyelid (39 cases) (Figure 7). A statistical examination of anatomical sites and patient age found a strong correlation between genital sites and younger patients (<1-9 and 10-19 years of age) ($p<0.05$) [5].

DIAGNOSTIC CHALLENGES

A typical technique for identifying circulating microfilariae is microscopic analysis of blood smears, which is easy to use and reasonably priced. It depends on recognising the worms' morphological characteristics. Certain morphological characteristics are looked at in order to distinguish between the species. However, when there are few microfilariae in peripheral blood samples or when the parasite burden is low, this method may have limited sensitivity [11]. In order to identify microfilariae in blood samples, the Knott's test is essential. Red blood cells are lysed for this test, and the material is centrifuged to concentrate microfilariae, which are then inspected under a microscope [12]. However, modifications to Knott's test have been suggested to improve sensitivity and accuracy, such as adding extra phases to boost microflorae recovery or using alternatives [13].

Only extremely specialised labs are permitted to use amplification testing. Since formalin impairs inhibiting DNA polymerase, samples stored in formalin typically extirpated samples for histopathological analyses are transported and preserved in formalin cannot be studied using this technology. Both necessitate the prior use of intrusive methods to eradicate the worms; nevertheless, surgical removal poses a unique challenge in cases of lung infection [14].

Different issues arise when D. repens is identified and diagnosed in humans. While the majority of pulmonary nodules are unintentionally discovered by thoracic radiography, subcutaneous nodules are typically discovered by the patient. Surgery is typically advised because subcutaneous and pulmonary nodules can raise suspicions of malignant tumours and other pathological disorders (tuberculosis, fungal infection [15]. Facts regarding the prevalence of dirofilarioses produced by either D. repens or D. immitis species are unreliable due to the lack of diagnostic methods for determining dirofilaria, which causes human infection [14].

Due to the similarities in morphological characteristics between species and the disruption of normal anatomy caused by the host tissue response, histological identification of worms in nodules removed by surgery may provide challenges. Molecular biological methods could be used as substitutes. However, both cutting-edge DNA analysis and conventional morphology have limitations as dirofilariasis diagnosis methods. Helmint must be in the adult form, remain intact during the extirpation, and not be severely damaged by the parasitological investigations to assess morphological and morphometrical parameters [14].

Serology may be a better option than invasive diagnosis for therapeutic and epidemiological research, because it eliminates the need for surgical intervention and allows for the detection of concealed infections. Serology does have certain drawbacks, though. Firstly, it is impossible to determine the precise level of the test's positive and negative predictive value; these tests are still in the experimental stage and are not yet commercially available. Higher seroincidence in individuals exposed to mosquitoes possible vectors in endemic areas are an issue. Prior to immunodiagnosis, this should always be taken into account [14].

Traditional diagnostic methods for dirofilariasis face intrinsic difficulties notwithstanding their effectiveness.

Particularly in cases of mild infections or illnesses with low microfilarial densities, microscopic procedures like the Knott's test and blood smear examination may not be sensitive enough to identify low levels of microfilariae, resulting in false-negative results. Similar to this, cross-reactivity with antibodies against related parasites can impact serological assays, such as enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assay (IFA), potentially leading to false-positive results and misdiagnosis. Particularly in the early stages or when mature worms are not yet present in measurable quantities, radiographic imaging methods like chest X-rays and ultrasonography may not always give definitive proof of dirofilariasis. Furthermore, despite being the gold standard for diagnosis, necropsy with histopathological examination may not always be possible due to the practicality and dependability of conventional dirofilariasis diagnostic techniques, ultimately enabling prompt and appropriate management of affected individuals [13].

SURGICAL MANAGEMENT

Unlike canine species which are generally considered to be the primary hosts for Dirofilaria spp., humans are categorized as "accidental" hosts [16]. The immature microfilariae are usually subjected to annihilation after it has been caught under the radar of the human immune response hence why microfilaria development won't occur. Instead D. immitis, the species of Dirofilaria spp. which infects dogs in humans generally symptom-less in humans and are instead often observed as pulmonary nodules or human pulmonary dirofilariasis [17].In case of D. repens a variant of Dirofilaria although it generally won't develop into adult worms in human hosts, it is weakened immunity that would enable for a parturient female to discharge microfilariae into the blood stream [16].

Due to the "dead-end" nature of humans as hosts, you won't observe a "nest" of these nematodes at discussion, but rather as a solitary juvenile adult as it becomes sequestered in the ocular region as a result of wandering towards its intended migratory path [16]. In ocular cases, patients often report visible helminthic writhing beneath the bulbar conjunctiva or ocular dirofilariasis caused by D. repens [16].This motion or "writhing" is clinically recognized as the "filarial dance sign"[18].Inability of circulating medications to penetrate specific ocular planes due to the lack of vascularization and the blood-ocular barrier, the golden standard is surgical excision typically performed under aseptic precautions and topical anesthesia [18].This is required to address the potential for tissue level inflammation and distress caused to the patient by, the helminth [18].

A female mosquito vector ingests D. immitis microfilariae during hematophagous feeding on an infected definitive reservoir, typically Canis lupus familiaris before facilitating transmission to the final vertebrate host [19].Via venous circulation adult parasites may travel to the host's right ventricle [17].In humans a typical transmission route occurs where following a bite of an infected mosquito, L3 larvae become inoculated [16].However due to the "accidental" nature of the human host, D. immitis, undergo developmental arrest and typically succumb within the right ventricle or pulmonary circulation resulting in the formation of "coin lesions" that are radiographically indistinguishable from bronchogenic carcinoma [17].Given that Human Pulmonary Dirofilariasis (HPD) mimicked primary lung malignancies, operative treatment, specifically VATS wedge resection and lobectomy to form the benign nature of the lesions and rule out the suspicion of pulmonary adenocarcinoma [17].

In a notable case, a 77-year-old Estonian woman was referred to an ophthalmologist. Though they had no history of travelling abroad, patient complained of a painful swelling that occurred prior to the appearance of nodular lesion under the right

lower eyelid. The lesion initially suspected to be a tumor was reclassified as dirofilariasis, following a histopathologic examination. Since there are no standardized diagnostic tools available to diagnose infections due to the D. repens, microscopic examination of the parasite is the golden standard for diagnosis which prevents unnecessary thoracic surgery. In this particular case, that surgical intervention proved sufficient and after the embedded parasite in the case was removed, the clinical manifestations fully subsided [16].

ROLE OF PHARMACOLOGICAL THERAPY

Pharmacological intervention is largely unnecessary due to the incomplete developmental cycle. As humans are non-permissive hosts, the parasite is unable to reach reproductive maturity resulting in a lack of microfilariae [16]. Hence why there is no circulating target for anthelmintic agents such as ivermectin to produce significant therapeutic results which is why for management of this infection requires a surgical solution rather than pharmacotherapy [17].

According to a recent study published in MDPI's Animals, emphasizes that targeting Wolbachia endosymbiont is a significant shift in modern pharmacological framework [19].Filarial nematodes such as the Dirofilaria spp. exhibit mutualistic endosymbiotic dependency on the bacteria [19].Wolbachia are indispensable for developmental success and are pivotal to sustain survival within the host [19].Doxycycline targets the endosymbiont and acts as a proteobactericide, ultimately subjecting the adult macrofilariae to slow-acting lethality and reproductive sterilization [19]. Rapid parasite mortality induces immunogenic response stimulated by the shedding of Wolbachia surface antigens. These antigens activate TLR-2 and TLR-6 leading to acute cytokine production and neutrophil recruitment, exacerbating postoperative morbidity. By implementing a dose regulated regimen clinicians can achieve a protracted antiparasitic effect by administering doxycycline (200mg/day). This strategy prevents hyper inflammatory response associated with abrupt mortality of adult filariae [11].

DIFFERENTIAL DIAGNOSIS

Dirofilariasis can be mistaken for several diseases including tumors or infections, due to the similarities and characteristics of the disease. Consequently, it is crucial to understand the precise difference of this disease in order to diagnose it and to avoid unnecessary interventions [20].

In subcutaneous dirofilariasis, long-term ocular swelling may be mistakenly identified as Preseptal cellulitis; however, blood tests, and histopathological analysis can confirm the true diagnosis of dirofilariasis, which is characterized by fragments of the parasite with a cuticle, longitudinal ridges, muscle layer, and body cavity surrounded by dense acute and chronic inflammation in fibroconnective tissue [21]. Also, it is possible to misdiagnose discomfort, pruritus, and a foreign body feeling in the eye as blepharoconjunctivitis. Examination may reveal a vermiform structure with peristaltic motions, and serological testing verifies the existence of antibodies against Dirofilaria spp [22].

Patients with pulmonary dirofilariasis may exhibit symptoms such as fever, coughing, chest pain, haemoptysis, and arthralgias, or they may have an asymptomatic pulmonary lesion in the lobes of their lungs. An oval pulmonary nodular lesion or a single, peripheral, well defined pulmonary opacity in lungs lobe may be seen on an X-ray. This could be mistaken for Tuberculosis. Examining the embolized lung vessel and infarcted tissue can reveal parasite and the diagnosis of Dirofilaria immitis can be confirmed by the observing circular muscle layer, central intestinal tube, pair of reproductive organs (uterus), and smooth laminated chitin-like cuticle without longitudinal ridges [23].

Due to its various clinical manifestations and limited occurrence in humans, dirofilariasis is still a rare but noteworthy illness that presents diagnostic hurdles. Uncommon etiologies, including subcutaneous heartworm infection, should be taken into account, especially in patients with unusual skin lesions or ocular symptoms [22]. Accurate diagnosis of pulmonary dirofilariasis should also be made using imaging and clinical suspicions. Accurate assessment is critical to diagnosis.

CURRRENT CHALLENGES AND LIMITATIONS

Human dirofilariasis poses many diagnostic challenges because of its rarity and vague clinical features. Early detection is therefore still difficult. Sometimes it is misinterpreted as other subcutaneous or pulmonary diseases making identification challenging unless surgical excision is performed. The most challenging issue is the difficulty of early detection and diagnosis, as well as the months long misdiagnosis and treatment of the patient for another illness.

Imaging and diagnostic limitations include dirofilarial infections typically manifesting as subcutaneous nodules or pulmonary coin lesions [15]. When an unusual lesion is observed on ultrasound, fine needle aspiration cytology is required which results in parasite dirofilarial worms together with a large number of neutrophils, eosinophils, and histiocytes. In some cases, due to clinical and radiological diagnostic it is misdiagnosed as breast cancer and radiological tests are insufficient to identify the actual disease [15].

Due to their advanced necrotic stage or their unfavourable orientation for a proper evaluation of the exterior cuticle, worm sections in pulmonary cases are difficult to detect or classify upon histological inspection [4].In some cases lung nodules that are misinterpreted as tuberculosis when they are actually dirofilariasis which presents difficulties in diagnosing unless surgical excision is performed [23].

When individuals from endemic areas exhibit breast enlargement, dirofilariasis should be taken into consideration. Insecticides and bed nets can be used to reduce mosquitoes, and the prevalence of parasitic infections in animal hosts can be decreased [15]. Moreover, doctors' awareness will help with prompt diagnosis, which leads to prompt treatment. When the disease is subcutaneous or pulmonary asymptomatic, better detection and treatment methods are crucial to overcoming the obstacles.

Future Directions

The future research directions should be concentrated on three aspects. Firstly, creating diagnostic methods for detecting nucleic acids from formalin-fixed tissue samples would enable species recognition irrespective of complete morphological analysis. Secondly, increasing clinical awareness among physicians through medical training is of utmost importance, especially in non-endemic countries with imported cases. Thirdly, enhancing surveillance systems for monitoring Dirofilaria species' epidemiology, taking into account climate changes and the corresponding expansion of the geographic range of mosquitoes, would prove essential. Finally, the application of doxycycline against Wolbachia endosymbionts requires additional clinical trials in human populations, although surgery remains the cornerstone of therapy.

CONCLUSION

Human dirofilariasis continues to be an uncommon parasitic infection. The nonspecific symptoms, including subcutaneous nodules, ocular manifestations, or lung coin lesions, are often mistaken for cancer, tuberculosis, or other granulomatous conditions. The diagnosis can only be made after a biopsy with histopathology since serology and molecular techniques are not readily accessible. Treatment with drugs is rarely required as the human host does not allow

the completion of the parasite's life cycle. Nonetheless, the treatment of Wolbachia, which resides in Dirofilaria larvae, with doxycycline could be a viable option in certain instances. Due to the growing prevalence of Dirofilaria across geographical locations owing to global warming and mobility, it is prudent to consider the possibility of dirofilariasis when dealing with patients with mysterious nodules or lung lesions

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