Review article

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HUMAN OCULAR DIROFILARIOSIS: CLINICAL AND EPIDEMIOLOGICAL FEATURES

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Dirofilarioses are zoonoses caused by filaria of the genus Dirofilaria, the parasites of domestic and wild animals. People are just random carriers of this parasite. In Europe, human dirofilariosis is caused by two species: Dirofilaria repens (D. repens, also known as a species of The Old World), usually with the superficial localization of infection, and D. immitis, which is present throughout the world, and causes, beside superficial, visceral dirofilariosis. So far, based on the data from reference literature, it can be observed that in Serbia about 34 cases of human dirofilariosis have been diagnosed and published. It is assumed that the prevalence of this parasitosis is significantly higher as our country is an endemic area for dirofilariosis in dogs and the region where species of mosquitoes, which are transitory hosts and vectors of Dirofilaria spp., are present.

The clinical picture of dirofilariosis depends on the type and location of the parasite in the human body. In our country, patients diagnosed with dirofilariosis had subcutaneous or subconjunctival infection in the majority of cases. Ocular dirofilariosis may affect the orbit and the periorbital region, the skin of the eyelids, the conjunctiva, the Tenon membrane, a retrobulbar space or has an intrabulbar localization. These patients may have a severe disability, and surgery alone can be complicated due to localization. The aim of this review is to highlight the importance of this unexpected important zoonoses, with special emphasis on the importance within the ophthalmic practice. *Acta Medica Medianae 2014;53(1):80-84.*

Key words: *ocular dirofilariosis, D. repens, D. immitis*

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Introduction

In Serbia, about 34 cases of human dirofilariosis have been reported, usually with subcutaneous and subconjunctival localization (1-5). It is assumed that a large number of cases have remained undiagnosed or have not been published, due to the fact that after extensive systematic research it has been found that: 1) Vojvodina, the northern part of the country, is a hyperendemic zone for *Dirofilaria repens* (*D. repens*) and an endemic for *D. immitis* infections in dogs (6,7); 2) the southern part of Serbia, formerly a hyperendemic zone for *D. repens* infections in dogs, is now endemic for this filariosis (2,8) and 3) the determined seroreactivity to *Dirofilaria* antigens in humans in different parts of our country ranges from 5.3 to 27.1% (9).

The literature described that cases of human dirofilariosis were mainly registered from the area of Belgrade (which is located along the the major rivers, Danube and Sava) and Voj-vodina (Zrenjanin, Sombor, Pančevo, Vršac). In addition, the observed sporadic cases are from the towns of Varvarian, Šabac, Pirot, Jagodina, Zaječar. All identified *Dirofilaria* in these patients belonged to type *D. repens* (1-5). In the recent years, in the laboratories of the Department of Parasitology, Public Health Institute, five cases of human *D. repens* dirofilariosis were diagnosed (4 subcutaneous and 1 subconjunctival) in patients from Vranje, Leskovac and Niš (3-5).

The aim of this review was to highlight the importance of this unexpected important zoonoses, with special emphasis on the ocular forms of infection.

Morphology, life cycle and epidemiological characteristics of *Dirofilaria spp.*

According to the classification of the genus *Dirofilaria*, there are more than 40 described species, but only a few of them cause human infections: *D. immitis, D. tenuis, D. repens, D. inermis* and *D. ursi.*

The life cycle of *Dirofilaria* as with other filaria is conducted through five developmental forms in the final and transitional host (1-3,10,11). The adult female *Dirofilaria* brings thousands of live larvae (microfilariae) of the first stage, which are present in the blood of the host organism and which the transient host, hematophagous insect (mostly mosquitoes of the genus *Aedes*, *Anopheles* and *Culex*), introduces in its body during the blood-meal. Into the body of mosquito, larva develops to the third stage (infective form) and migrates from the abdomen through the chest to the salivary glands, allowing transmission to an another carrier, animals or humans (7,12-14). Definitive host of *Dirofilaria* are dogs, cats, wolves, coyotes, foxes and other animals. Man becomes infected in the same way. In the course of human infection, *Dirofilaria* can be developed to the stage 4 or 5, or in the course of this helminthosis may be developed immature adult forms of nematodes in the various tissues and organs (7,15).

The body of *D. repens* is of whitish color, cylindrical and elongated, with the tapered ends. The cuticle has clearly visible longitudinal and lateral stripe. The front end of the body is round. The tail is dull and slightly bent ventrally. The male has a body length of 5-8 cm, the maximum thickness of the body is 320 μm. The length of the female can be 10-17 cm, and its maximum thickness is up to 550 μm. The female is vivipare and lays live larvaes (microfilariae), which are blown through the bloodstream throughout the body. The length of microfilariae, according to various authors, is different and ranges within the boundaries of the 300–360 μm and more. Their thickness can range from 6-8 μm (15,16).

D. immitis is a parasite whose body is white, of cylindrical and elongated shape, round at the front end, wrapped in a smooth non-segmented cuticle. The corners of the mouth are without lips, surrounded by 6 small and weakly expressed papillae. The male has a length of 12-20 cm and a thickness of 700-900 um. His rear end is thinner and curled into a spiral. In this section, there are the side little tail fins. The female has a length of 25-31 cm and a body thickness of 1-1,4 mm. Her rear end is conical in shape. The vulva is located at the front end of the body at the level of the esophagus. The female lays live larvaes (vivipare), which are blown through the bloodstream throughout the body and can be detected by direct microscopic examination of fresh blood smears (15,16).

Diagnostically, these two species are present in Europe. We can differentiate them on the basis of morphological and morphometric characteristics and the cuticle (*D. immitis* has a smooth cuticle, while the cuticle of *D. repens* is wrinkled) (15,16).

In the course of infection in the definitive host, the diagnosis can be set on the basis of morphological and morphometric characteristics of the microfilariae, which is not the case with human infection, as in humans, as a no final hosts, *Dirofilaria* species rarely reaches sexual maturity, and also microfilariae can be expected only in case of infection of *Dirofilaria* of both sexes. In case of human dirofilariosis, there are only few cases with detected microfilariae in the blood of the infected (17,18).

The prevalence of human dirofilariosis is correlated with the prevalence of dirofilariosis in dogs, the presence of the vectors (mosquito) and the activity of the people, which determines the exposure to the vectors. The prevention involves suppression of infected animals and the intermediate hosts. It has been discussed that it is difficult to talk about the prevalence of these infections in humans and animals, with the assumption that a large number of asymptomatic cases have never been diagnosed, or diagnosed but not published. The current epidemiological situation indicates that in the last ten years there have been several reports about human dirofilariosis (19). Most of the new cases were discovered in the Mediterranean countries, also in Ukraine and Russia. However, there are isolated cases or short series of cases in the Balkan states, as well as in the central and northern Europe (20-22).

The most frequent challenger of human dirofilariosis is *D. repens*. Infection is the most superficial, occurs in the majority of cases in the upper half of the body, especially on the head, and the ocular area, as well as on the upper limbs.

Clinical features and diagnosis of human dirofilariosis

The clinical picture of dirofilariosis depends on the type and location of the parasite in the human body. In most patients with a visceral, pulmonary form, dirofilariosis is caused by the *D. immitis*, and the infection was asymptomatic approximately in 52-62% of cases. Infections by *D. repens* in most cases are in the form of subcutaneous nodules or have subconjunctival localization. Benign nodules of subcutaneous tissue can mimic skin tumors (3,10,11,13).

Patients from our country, who had been diagnosed with dirofilariosis, had the infection localized subcutaneously or subconjunctivaly in the majority of cases. Only in two cases the parasite was localized in the epididymis (1-5).

The diagnosis was possible on the basis of anamnesis, eosinophilia in the blood and sputum within pulmonary dirofilariosis, the histopathological analysis of a biopsy material, based on the morphological and morphometric characteristics of the extirpated helminth, if the parasite was not significantly damaged. Lately, the methods of molecular biology (PCR) have been used, allowing the identification of species in the presence of minimal amounts of nematodes, as well as the presence of significant damage to the parasite. However, the amplification assays involves the

extraction of the parasite, and the biopsy as an invasive method (23-25). The serological tests for the detection of specific antibodies can be administered as a non-invasive diagnostic procedure. In addition to diagnosis, the serological tests are important for epidemiological studies of human dirofilariosis, especially in the endemic regions and hyper-endemic ones. The disadvantage is reflected in the fact that there are no commercial tests for the diagnosis of human dirofilariosis. There are only experimental–home made serological tests.

As additional diagnostic procedures in human dirofilariosis, radio-imaging, tomography, ultrasonography, magnetic resonance and scanners may be used (26,27).

Human ocular dirofilariosis

Clinically, ocular dirofilariosis can affect the orbit and periorbital region, the skin of the eyelids, the conjunctiva, the Tenon membrane, a retrobulbar space or have intrabulbar localization. These patients may have a severe disability, and the surgery alone can be complicated due to localization (28-33). The differential diagnosis should definitely consider parasitism with ocular localization caused by *Dirofilaria spp*.

The ocular infection is usually in the form of localized subcutaneous nodule in the eyelid or periorbital region as a benign tumor. The infections of the skin can be presented as the orbital cellulitis (34). It can even imitate the mucoceles of lacrimal sacus (26). The clinical diagnosis in most of these cases was erroneous because of non-consideration of physician-clinicians about the possibility of infection with this parasite. The most frequent localization is subconjunctival or subtenonian space, where diagnosis is easier and more accurate because of the conjunctival transparency and the possibility of direct parasites detecting. In case of parasites migration to the deeper parts of the orbit, diagnosis is made by excisional biopsy, which also represents a complete cure, however, surgery is very complicated (35).

The literature described about 10 cases of the *D. repens* found in the vitreous body, i.e. on the retina, where the most complex ophthalmic interventions were taken to remove it (36).

In most cases, a human ocular dirofilariosis occurs as nonspecific inflammatory reaction, which is resistant to conventional antibiotic and anti-inflammatory therapy. In addition, the possible number of episodes of disease exacerbation can occur until it comes to a definite diagnosis. In the described cases of deeper periocular localization, patients had nonspecific and even unusual symptoms, and were exposed to the harmful effects of various diagnostic procedures (27,37,38). Although the final diagnosis confirmed that these were benign growths, their anatomical location required aggressive surgery to remove them (29,36,38).

The sonography and NMR can contribute to the diagnosis of human ocular dirofilariosis if the localization of the parasite is not subconjunctival or under the Tenon tissue. Few papers have described these diagnostic methods. In one paper, a live worm was shown on ultrasound as actively motile (27). Other authors with the help of high-resolution ultrasound showed a well-defined cyst in the outer part of the upper eyelid with nematodes that followed walls cysts (27, 33,37). Certainly, it should be noted that ultrasonography is a noninvasive technique that allows rapid identification of preoperative nodules with parasite origin. This technique is usually used to diagnose cardiopulmonary dirofilariosis in animals, but is used only sporadically in the diagnosis of human dirofilariosis, which is usually diagnosed postoperatively, after surgical removal of nodules or worm (37-39).

In case of human infection with *D. repens*, after established diagnosis and surgical treatment, the administration of antihelmitics is not justified as there are no microfilariae in the blood of patients.

Conclusion

We can conclude that in our country, as an endemic area of dirofilariosis in dogs, and the region in which there are proven vectors - intermediate hosts of parasites, we can expect an increasing number of human dirofilariosis cases, including ocular forms. In everyday practice, ophthalmologists should consider the possibility of this infection in the differential diagnosis, not only when the parasite is seen beneath the conjunctiva or in the anterior chamber, but if there are repeated inflammatory reactions and swelling of the ocular region, eyelids, and if these changes do not respond to therapy.

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HUMANA OKULARNA DIROFILARIOZA: KLINIČKE I EPIDEMIOLOŠKE KARAKTERISTIKE

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Dirofilarioze su zoonoze izazvane filariama roda *Dirofilaria*. Dirofilarija je parazit domaćih i divljih životinja, ljudi su samo slučajni nosioci ovog parazita. U Evropi humanu dirofilariozu izazivaju dve vrste: *Dirofilaria repens* (*D. repens*, poznata kao vrsta starog sveta), najčešće sa superficijalnom lokalizacijom i *D. immitis*, koja je prisutna u čitavom svetu, izaziva pored superficijalne i visceralnu dirofilariozu. Do danas, na osnovu podataka iz referentne literature, može se istaći da je u Srbiji dijagnostikovano i publikovano oko 34 slučaja humane dirofilarioze. Pretpostavlja se da je prevalencija ove parazitoze značajno viša, jer područje naše zemlje predstavlja endemsku zonu za dirofilarioze pasa i područje sa prisutnim vrstama komaraca koji su prelazni domaćini i vektori dirofilarija.

Klinička slika dirofilarioze zavisi od vrste parazita i lokalizacije u organizmu čoveka. Kod bolesnika iz naše zemlje kod kojih je dijagnostikovana dirofilarioza, lokalizacija infekcije bila je u najvećem broju slučajeva subkutana i subkonjunktivalna. Okularna dirofilarioza zahvata orbitu i periorbitalnu regiju, kožu kapaka, konjunktivu, Tenonovu opnu, retrobulbarni prostor ili ima intrabulbarnu lokalizaciju. Ovi bolesnici mogu imati ozbiljne smetnje, a i sama hirurška intervencija može biti komplikovana zbog lokalizacije. Cilj ovog revijskog rada bio je da ukaže na značaj neočekivano važne zoonoze, sa posebnim osvrtom na značaj u okviru oftalmološke prakse. *Acta Medica Medianae 2014;53(1):80-84.*

Ključne reči: *okularna dirofilarioza, D. repens, D. immitis*

