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Dirofilariasis of eyelid and orbit (clinic, diagnosis, treatment)

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Background: *Human dirofilariasis is a larval helminthiasis, and there has been an increase in its incidence in recent years, possibly due to global warmth, urbanization, and increased numbers of stray animals and their migration between settlements.*
Purpose: *To review the clinical features of ocular dirofilariasis in patients treated for the disease at the Filatov Institute of Eye Diseases and Tissue Therapy over 2006-2022.*
Material and Methods: *Medical records of 58 patients treated for dirofilariasis at the Filatov institute in 2006-2022 were retrospectively reviewed. Of these patients, 13 (22.4%) were males and 45 (77.6%) were females, and mean age was 48.8 ± 15.2 years. They underwent a routine eye examination. In addition, they underwent an ocular and orbital ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). The disease was treated by worm extraction surgery in all patients. The worm was verified at Parasitological Laboratory, and the capsule formed around the parasite was examined at Pathomorphology Laboratory of the institute. Statistics 7 software (StatSoft, Tulsa, OK) was used for statistical analysis. Data are presented as mean plus or minus standard deviation. Student t test was used for data comparison. The level of significance $p \leq 0.05$ was assumed.*
Results: *Patients treated were most commonly from the city of Odesa and Odesa region (25.9% or 15 patients). Odesa-region patients most commonly were from Izmail and Bilhorod Dnistrovskyi districts. The worm was more commonly located in the orbital tissue (53 of 58 patients or 91.4%) than in the eyelids (5 patients or 8.6%). All patients complained of skin redness and swollen eyelids. With further migration of the worm deep into the orbital tissue, 15 patients (28.3%) developed exophthalmos of not more than 2-3 mm and 15 patients (28.3%) developed diplopia. The study showed evidence of D. repens infection by parasitological methods of diagnosis in all the 58 study patients, with a mature female found in 44 patients (75.9%), mature female remnants in 11 patients (19.0%), an immature female in 2 patients (3.4%), and a male in one patient (1.8%). The worms were elongated, less than or equal to 1.0-mm thick and 2.2-15 mm in length.*
Conclusion: *First, worm extraction surgery is an essential treatment for ocular dirofilariasis (irrespective whether the worm is located in the eyelid, orbit or eye) and must be accompanied by disinfectant, anti-inflammatory and antihistamine therapy, both topical (eyedrops and ointments) and oral. Second, an ultrasound of the orbital tissue and eyelids may become a gold standard (along with CT and MRI) for the differential diagnosis of dirofilariasis.*

Keywords:
ocular dirofilariasis, incidence, clinical features, treatment

Introduction

Human dirofilariasis is a parasitic eye disease, and belongs to larval helminthiases. The Dirofilaria genus includes species such as *dirofilaria (D.) repens* and *D. immitis* (parasites of dogs and cats), *D. ursi* (a parasite of brown bears and Amur tigers), *D. tenius* (a parasite of raccoons), *D. lutrae and D. spectans* (parasites of Brazilian and North American otters), and *D. Striata* (a parasite of wildcats).

The microfilariae of *D. repens* and *D. immitis* cause most cases of human dirofilariasis, and are 290-320 µm long and 5-7 µm wide.

The microfilariae commonly do not reach full maturity in the human body, and the clinical picture of the disease is determined by the migration of immature helminths through human tissues or internal organs.

The microfilariae are accidentally transmitted from animals (most commonly, canids and felines) to other animals or humans by Culex and Aedes mosquitoes (Fig. 1), intermediate end hosts for the parasite. Other sanguivorous insects (ticks, fleas, louses and horseflies) play a role in the natural circulation of Dirofilaria. The Dirofilaria completes a full development cycle in the animal body, a dead end host for the Dirofilaria. Because coupling of female Dirofilaria and birth of microfilariae do not take place in a human body, the latter is considered to be a biological dead end for the parasite. Therefore, humans cannot be a source of infection with Dirofilaria species. Most larvae do not survive after being transferred to the human body [1,2,3,4].

Most commonly, humans become infected with helminths when performing agricultural activities or having outdoor recreation in areas with mosquito colonies

Fig. 1. An Anopheles mosquito

(e.g., at surface-water bodies) during an insect's activity period from May to September. An increase in the incidence of human dirofilariasis has been reported in recent years, possibly due to climate change (global warmth), urbanization, and increased numbers of stray animals and their migration between settlements. Dirofilariasis is prevalent in the Central Asia, Armenia, Georgia, Azerbaijan, Kazakhstan, Ukraine and Russia. There have been reports on dirofilariasis the North America, Brazil, India, Sri Lanka, Japan, Korea, Vietnam, Malaysia, Australia, Africa, and Europe (Italy, Spain, France, Greece and Hungary). Iran and Greece are believed to be countries with an especially high incidence of dirofilariasis [1-26].

A Portuguese medical doctor, Amato Lusitano, was the first to describe ocular dirofilariasis in the 18th century, and to remove the parasite from the girl's eye. Subsequently, similar cases of dirofilariasis were described in Italy and France. A.P. Vladychensky was the first in Russia to report a case of dirofilariasis in Ekaterynodar in 1915; he extracted a worm from the tumor located between the internal wall of the orbit and the globe. Systematic research of these parasites in the Soviet union and some other countries began in 1930, with a report by academician K.I. Skryabin, the founder of the helminthological school, and his pupils A.Ya. Althausen and E.S. Shulman, describing another case of ocular dirofilariasis, with worm extraction from the deep inferior eyelid compartment in a 27-year-old female resident of Kharkiv, Ukraine [2]. According to Tarello, by 2002, 298, 131, 75 and 69 cases of human dirofilariasis were reported in Italy, Sri Lanka and France, respectively. According to Guskov and colleagues, 110 cases of human dirofilariasis were reported in Russia from 1915 to 1995. In 2005, Murashko and colleagues described a case of dirofilariasis in the right eye in a resident of Belarus [2].

The pathogen has an incubation period of several months to years, with the period depending on the individual's immune reactivity and helminth growth [5]. The helminth grows to the maximum size approximately half a year after gaining entrance to the human host. Most commonly, the parasite is found in the skin or mucous membrane, with an enclosing connective tissue capsule formed around the parasite. Several days after a mosquito bite, a small dense itching mass develops at the bite site. It gradually grows to become as large or larger than 4 cm in diameter, the skin above it becomes red and swollen, itching increases in severity and local pain may develop. The worm can migrate at a speed of 30 cm a day. Therefore, the disease is characterized by periods of remission and recurrence. With the parasite migrating from one point to another, it commonly leaves no trace at the former site, a dense nodule develops at the new site, and a sensation of "movement" under the skin develops. An abscess may develop at the location of the parasite and rupture on the surface if poked, digitally manipulated or accidentally lanced. Dirofilariasis may also cause symptoms like headache, weakness, nausea and fever, which disappear after the extraction of the parasite [3, 8, 13, 14].

Almost half of the reported cases of dirofilariasis are those of ocular dirofilariasis, with the parasite localized subcutaneously under the lid skin, subconjunctivally, intraocularly or in the orbital tissue [1, 5, 7, 9-14,16-18, 21-24].

We noted that there has been some increase in the incidence of ocular dirofilariasis in Ukraine in recent years. Therefore, **the purpose** of this study was to review the clinical features of ocular dirofilariasis in patients treated for the disease at the Filatov institute in 2006-2022.

Material and Methods

Medical records of 58 patients treated for dirofilariasis at the Filatov institute during 2006 to 2022 were retrospectively reviewed. Of these patients, 13 (22.4%) were males and 45 (77.6%) were females. Patient age ranged from 18 to 76 years, and mean age was 48.8 ± 15.2 years.

They underwent a routine eye examination which included a detailed physical examination of the eyelids, conjunctiva, and orbit; visual acuity assessment, tonometry, visual field examination, biomicroscopy, and ophthalmoscopy. In addition, they underwent an ocular and orbital ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). Exophthalmos measurements were performed and eye position and motility were assessed if the lesion was located in the orbit.

All patients were treated surgically. If the mass was located in the orbit, a transpalpebral orbitotomy with the removal of the dense mass was performed, and a worm was found after incising the mass.

The worm was verified at Parasitological Laboratory, and the capsule formed around the parasite was examined at Pathomorphology Laboratory of the institute.

Informed consent for diagnosis, treatment, surgery, anesthesia and data use in research was obtained. The principles of the Declaration of Helsinki and the European Convention on Human Rights were complied with.

Statistics 7 software (StatSoft, Tulsa, OK) was used for statistical analysis. Data are presented as mean plus or minus standard deviation. Student t test was used for

data comparison. The level of significance $p \leq 0.05$ was assumed.

Results

Patients treated for dirofilariasis at the Filatov institute over 2006 to 2022 were most commonly from the city of Odesa and Odesa region (25.9% or 15 patients), followed by Poltava and Khmelnytskyi regions (8.6% or 5 patients each), Donetsk, Zaporizhzhia and Cherkasy regions (6.9% or 4 patients each), and Kyiv and Kirovohrad regions (5.2% or 3 patients each). Each of the rest regions was represented by one or two patients. Of note that, Odesa-region patients most commonly were from Izmail and Bilhorod Dnistrovskyi districts.

Figure 3 shows annual numbers of patients seeking examination and treatment for dirofilariasis at the institute over 2006-2022.

Female patients outnumbered male patients almost four to one, and significantly ($p < 0.05$). In addition, most commonly, patients were aged 41-60 years (29 patients or 50.0%) (Table 1). Moreover, the worm was more commonly located in the orbital tissue (53 patients or 91.4%) than in the eyelids (5 patients or 8.6%), but no dirofilaria lesions were found in the conjunctiva or ocular media. All patients complained of skin redness and swollen eyelids (Table 2).

Of the five patients with Dirofilaria found in the eyelid (the upper eyelid in all cases with eyelid lesions), all complained of a dense, itchy mass, and three noted a sensation of a foreign body moving in the eyelid. Of the 45 patients with Dirofilaria found in the orbital tissue, 10 initially noted a dense mass with skin reddeness above it and itching deep in the eyelid or in the periorbital region (most commonly, at the temple or lateral nasal wall). Usually in 2-3 weeks, the mass was noted to disappear, the eyelid became swollen, and a dense nodule developed in the superior interior compartment of the orbit. With further migration of the worm deep into the orbital tissue, 15 patients (28.3%) developed exophthalmos of not more than 2-3 mm and 15 patients (28.3%) developed diplopia.

In all the patients, visual acuity corresponded to the refractive error and age-related changes. Patients with Dirofilaria found in the orbit underwent CT or MRI. Commonly, heterogeneous newly formed tissue, with a density of 45 to 60 Hounsfield units (HU), was found in the superior interior compartment of the orbit, and was intimately associated with the medial rectus muscle or located at the trochlear nerve. A worm was clearly detected in the newly formed tissue in 8 patients (13.8%).

An ultrasound of the orbital tissue and eyelids was performed for diagnostic evaluation in 30 patients, and a

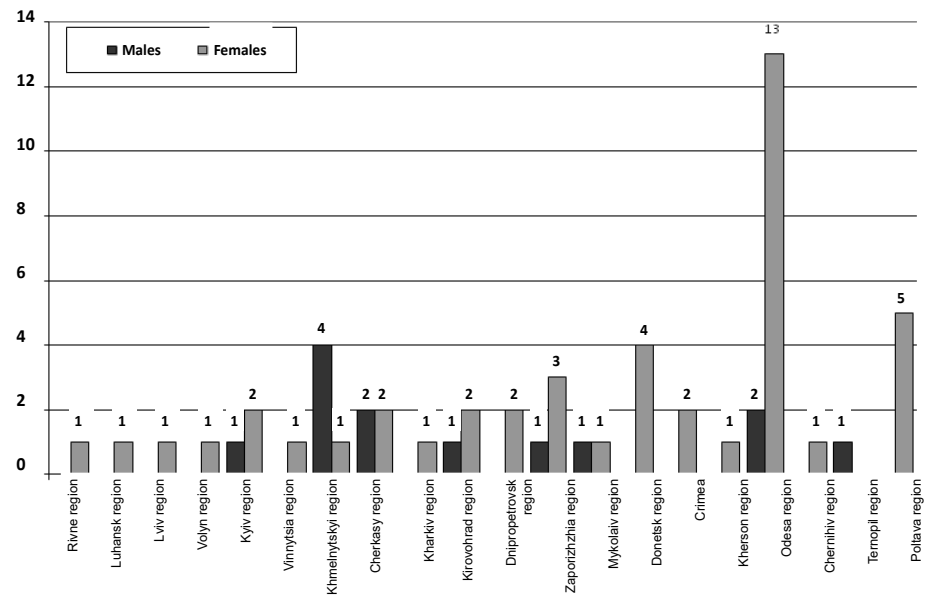

Fig. 2. Incidence of dirofilariasis in different regions of Ukraine as assessed by numbers of presentations to the institute in 2006-2022

Table 1. Age and gender distribution for patients with dirofilariasis

Gender	Patient age, n (%)							Total
	Younger than 20 years	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years	
Males	-	2 (3.5)	3 (5.2)	2 (3.5)	2 (3.5)	2 (3.5)	2 (3.5)	13(22.4)
Females	1	5 (8.6)	4 (6.9)	16 27.5)	9 (15.5)	6 (10.3)	4 (6.8)	45(77.6)
Total	1 (1.7)	7 (12.1)	7 (12.1)	18(31.0)	11(19.0)	8 (13.8)	6 (10.3)	58(100.0)

Note: n, number of patients.

Fig.3. Annual numbers of patients seeking examination and treatment for dirofilariasis at the institute in 2006-2022

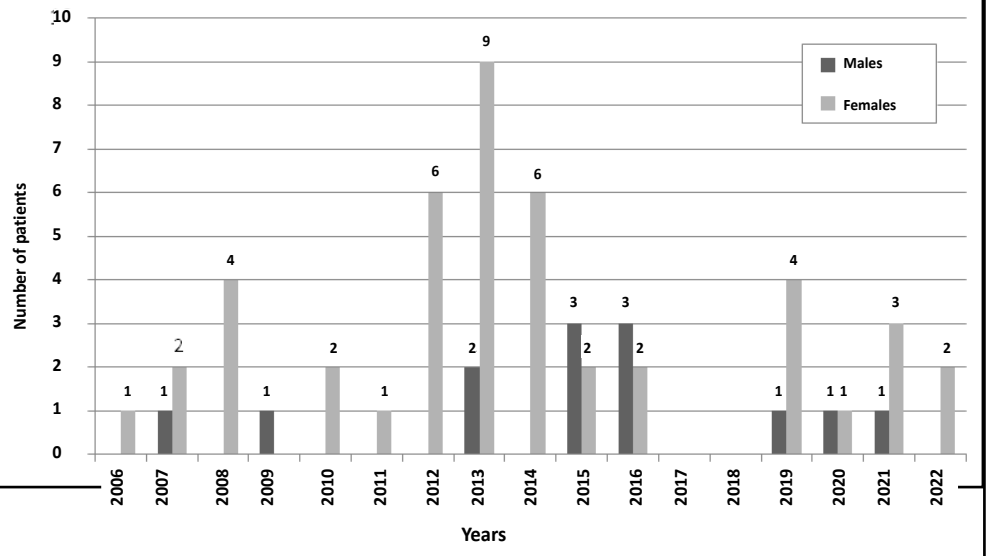

Table 2. Complaints of patients with dirofilaria larva found in the eyelids or orbit

Complaints	Location of dirofilaria larva	
	Eyelids (n = 5) n (%)	Orbit (n = 53) n (%)
Eyelid skin redness	5 (100.0%)	53 (100.0%)
Swollen eyelids	5 (100.0%)	53 (100.0%)
Itching	5 (100.0%)	22 (41.5%)
Dense mass	5 (100.0%)	30 (56.6%)
Foreign body sensation	3 (60.0%)	8 (15.1%)
Mobile mass	3 (60.0%)	8 (15.1%)
Migration of mass or worm	3 (60.0%)	10 (18.9%)
Bulging eye	-	15 (28.3%)
Loss of upward and inward eye movements	-	53 (100.0%)
Loss of reposition	-	15 (28.3%)
Diplopia	-	15 (28.3%)

Note: n, number of patients.

worm was clearly detected in the newly formed tissue with clear margins (i.e., a capsule) in all these patients. Because worms in the newly formed tissue were detected more readily with ultrasound scanning than with CT or MRI, the former method can be recommended as a must item for the diagnostic assessment of a dirofilariasis infection suspect.

The pathohistological examination of the capsule enclosing the worm found the connective tissue with inflammatory lesions and lymphoid infiltration with eosinophiliain all patients, and fungal mycelium in 3 patients. All patients were found to have a blood eosinophil count of 6% to 12%.

The current study showed evidence of *D. repens* infection by parasitological methods of diagnosis in all the 58 study patients, with a mature female *D. repens* found in 44 patients (75.9%), mature female *D. repens* remnants in 11 patients (19.0%), an immature female *D. repens* in 2 patients (3.4%), and a male *D. repens* in one patient (1.8%). The worms were elongated, less than or equal to 1.0-mm thick and 2.2-15 mm in length (Fig. 4).

The surgical procedure resulted in worm extraction in all patients. Anti-inflammatory and antitoxic therapy facilitated relief of inflammatory response in adjacent tissues and enabled complete recovery from the infection without ophthalmic complications in all study patients. Below is presented an example case of orbital and palpebral dirofilariasis.

Example case

A 31-year-old female patient (medical record No. 690091) presented to the institute on June 30, 2022, with a two-day history of swollen left eyelids, dense tissue of the middle one-third upper eyelid, a reddened skin area above the left eye, and an enlarged left submaxillary lymph node. She cannot refer the disease to any special cause.

On examination at presentation, there was marked lid edema, a reddened area of the upper lid skin, dense tissue of the middle one-third upper eyelid, and total ptosis. On examination with the help of a lid retractor, the conjunctiva was hyperemic, ocular media clear, and fundus unremarkable. There was no exophthalmos or motility restriction. Visual acuity was 1.0. The left submaxillary lymph node was enlarged. Body temperature was 36.6 °C.

On July 7, 2022, orbital and paranasal sinus CT scans were obtained with a 160-slice CT scanner (Aquilion Prime 160, Toshiba, Japan) and showed no bone tissue destruction. In addition, although eye globes, optic nerves and retrobulbar space were unremarkable, left upper and lower eyelid fat regions and left periorbital fat regions were thickened and dense (Fig. 5). The patient

was urgently admitted to the ocular oncology department with a diagnosis of a phlegmon developing in the upper eyelid and orbit. A stye abscess was suspected. The patient was prescribed anti-inflammatory and antitoxic therapy including parabulbar and intramuscular antibiotics. The next day, the edema subsided, eyelid density decreased, and the left palpebral fissure widened 5.0 mm.

On examination on July 4, 2022, there was marked improvement in the state of the eyelids, and dense tissue was more clearly seen in the superior interior compartment of the orbit, and was mobile with respect to the surrounding tissues. Because a suspicion for dirofilariasis arose, the patient had an ultrasound of the orbital tissue and eyelids. There was sonographic evidence of an oval-shaped and elongated (2.8-mm thick and 8.5 x 4.5 long) structure, possibly a capsule, in the medial third of the superior interior compartment of the orbit (Fig. 6). We noted linear elements (possibly, dirofilaria larva) as wide as 0.4 mm inside the capsule. In this connection, the patient was offered to have surgery, and accepted the offer.

At the day of surgery, the worm migrated under the skin of the upper lid (Fig. 7).

Discussion

Previous reports have noted that dirofilariasis was most common in the south of Ukraine, and our current study (of the patients treated for the disease at the Filatov institute during 2006 to 2022) demonstrated that there was an increase, both in the number of Ukrainian regions with patients with, and in the incidence of the disease.

During 2006 to 2022, most commonly, our patients with dirofilariasis were from the city of Odesa and Odesa region (15 of 58 patients).

According to reports by the Odesa Region Branch of the State Veterinary Medicine Service of Ukraine, dirofilariasis cases have been registered in the region since 1969. In addition, according to the 2021 annual report, the annual incidence of the disease in the region has increased over the past five years, but, unfortunately, no clarification of the percentage amount was given [3].

With regard to the number of patients seeking care for dirofilariasis at the Filatov institute over 2006-2022, the city of Odesa and Odesa region (15 patients) was followed by Poltava and Khmelnytskyi regions (5 patients each), Donetsk, Zaporizhzhia and Cherkasy regions (4 patients each), and Kyiv and Kirovohrad regions (3 patients each). Each of the rest regions was represented by one or two patients.

It is difficult to assess dirofilariasis incidence in different regions of Ukraine on the basis of the literature, because the literature is scant on reports about this subject. Zhuravliov and colleagues (2008) [9] reported that according to the reports by sanitary and epidemiological administrations, 300 cases of human *D. repens dirofilariasis* were registered in Ukraine during 1996-2004. In addition, *D. repens* was extracted from the eye in 27 patients; from the eyelids in 12 patients; from the eyebrow, nose and sternum, in one patient each; from the forehead, head, frontal bone, and forearm, in three patients each; etc. Moreover, 16 cases of

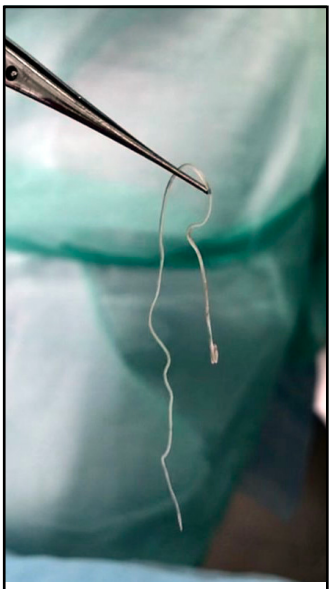

Fig. 4. The longest of the extracted worms of dirofilaria

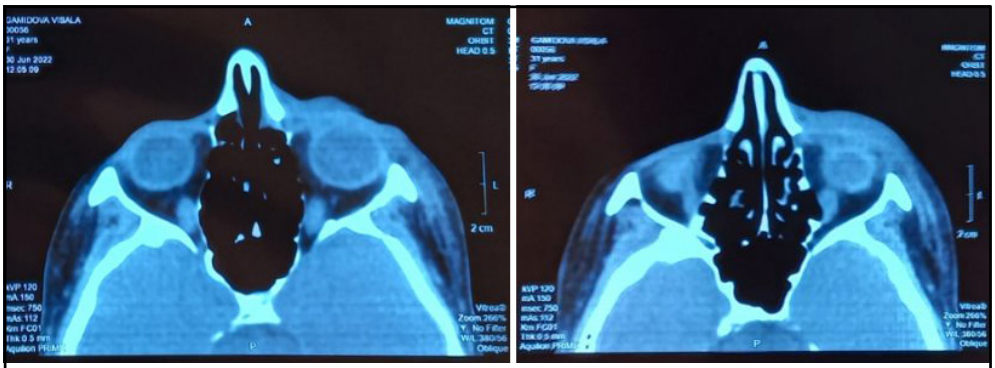

Fig. 5. Orbital computed tomography images showing dense left upper and lower eyelid fat region and left periorbital fat region

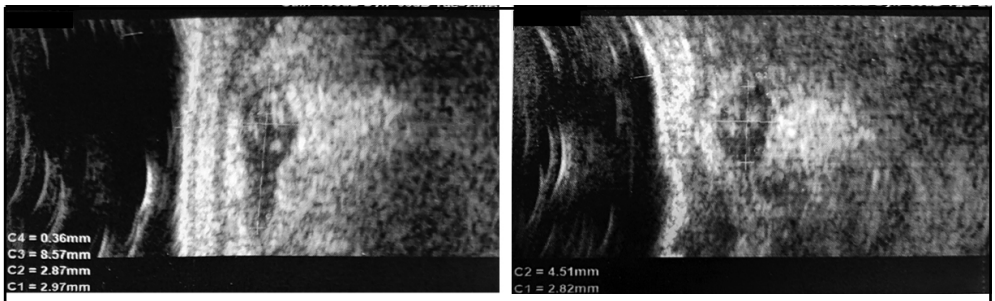

Fig. 6. Ultrasound scans showing the presence of dirofilaria larva enclosed a capsule in the superior interior compartment of the left orbit

Fig. 7. Photograph of a patient with dirofilaria migrated under the skin of the upper eyelid. The dirofilaria larva was surgically extracted along with a capsule (Fig. 8). The postoperative period was unremarkable.

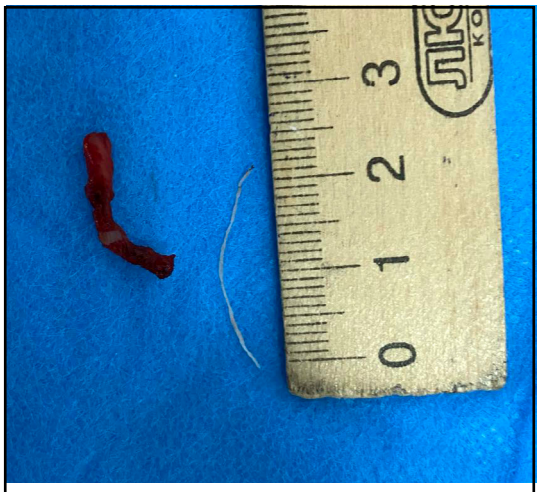

Fig 8. Capsule (a) of the extracted dirofilaria larva (b)

D. repens dirofilariasis were registered in Kharkiv region during the four years before 2008, with the incidence being approximately the same in the city of Kharkiv and in the districts of Kharkiv region [9]. We noted that only one individual from that region sought care for dirofilariasis at the Filatov institute during 2006-2022.

Sixty five cases of D. repens dirofilariasis were registered in Dnopropetrovsk region during 2014-2018, with the annual number of cases reported ranging between 10 and 20 [13,15]. Only two individuals from that region sought care for orbital dirofilariasis at the Filatov institute during 2006-2022.

Golubovska [3] noted that the infection caused by *D. repens* is the only helminthiasis transmissible to humans in Ukraine, but it cannot be ruled out that Ukrainian individuals may be infected by *D. immitis* outside the country.

In the US, D. immitis affects men twice as women, whereas *D. repens* affects women more often (55.0%) than men [14].

In Russia, the age of individuals affected with dirofilariasis ranged from 3 to 75 years, with 64.4% of them being females [8].

We also noted that, in Ukraine, female patients affected with dirofilariasis outnumbered male patients affected with dirofilariasis almost four to one, and significantly ($p < 0.05$), and, most commonly, patients were aged 41-60 years (29 patients or 50.0%). It is likely that our findings could be different if our study sample included also individuals affected with *D. immitis,* but, actually, none of the patients was found to be affected by this species. Associated clinical symptoms were in agreement with those described in previous literature [1-26].

The differential diagnosis of dirofilariasis is difficult, especially when the pathogen has a retrobulbar location. Data from history collection, eye examination, blood eosinophil count and special imaging procedures like ultrasound, CT and MRI are important in diagnostic assessment. It is noteworthy that, only one imaging modality (an ultrasound), but not such expensive ones as CT and/or MRI, should be used for the initial differential diagnosis of ocular dirofilariasis, because we found that an ultrasound, compared to CT or MRI, allowed for a more frequent suspicion of the presence of a worm in the newly formed orbital tissue and eyelids. Nowadays, auxiliary laboratory techniques (assays for parasite antigen detection in blood) are available for differential diagnostic purposes. These include enzyme immunoassay for the detection of somatic antigen of dirofilaria, polymerase chain reaction (PCR) for the detection of DNA of particular dirofilaria species or cuticular antigens of other dirofilaria species, and immunoblot analysis for the detection of antigens of adult species and larvae [10]. Our patients, however, did not have these studies.

Dirofilariasis in humans and in animals is resistant to conservative treatment. The treatment should be targeted at killing adult parasites that may be located in the caverns of the right ventricle and auricle, lung arteries, subcutaneous fat, and microfilaria circulating in the bloodstream of an infected human or animal. Arsenic drugs are commonly used for killing adult worms [2].

Ivermectin (Stromectol) and diethyl carbamazine citrate (DEC or hertrazan) are used against D. immitis infection both in humans and in animals. In addition, the treatment should be aimed at decreasing the severity of the intoxication caused by (1) side effects of chemotherapy used for killing adult worms and larvae and (2) products of worm disintegration [2,10]. Given that usually there is only one individual immature parasite and no microfilaria is born in man, we, like others [2,3,9,10], believe that treatment with antihelmintic drugs (piperazine adipate, decaris (Levamisol), Vermox (Mebendazole), Mintezol (Thiabendazole), etc.) against Dirofilaria is not feasible, since this treatment can lead to serious side effects,

especially on the liver and kidneys. There is an opinion that, to prevent worm migration, a patient should have ditrazin prior to worm extraction surgery [2].

Foreign clinical experience as well as ours [1-26] demonstrates that worm extraction surgery is needed in the treatment for dirofilariasis.

Prevention is important in combating human dirofilariasis, and requires implementing comprehensive state programs aimed at (1) developing diagnostic serological tests, (2) treating patients, and (3) blocking transmission from mosquitoes, fleas and ticks to dogs and cats using repellents and anti-parasitic collars.

Conclusion

First, worm extraction surgery is an essential treatment for ocular dirofilariasis (irrespective whether the worm is located in the eyelid, orbit or eye) and must be accompanied by disinfectant, anti-inflammatory and antihistamine therapy, both topical (eyedrops and ointments) and oral.

Second, an ultrasound of the orbital tissue and eyelids may become a gold standard (along with CT and MRI) for the differential diagnosis of dirofilariasis.

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