Review

Ocular Dirofilariasis of the Eyelid: A Case Report and Systematic Review of the Literature

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Ocular Dirofilariasis of the Eyelid: A Case Report and Systematic Review of the Literature

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Abstract

Background/Objectives: To present a case report of eyelid dirofilariasis and conduct a systematic review of the corresponding literature. **Methods**: A 79-year-old patient presented with a painless mass in the left upper eyelid of 2 months duration, which was complicated during the latter period by two episodes of recurrent periorbital edema extending to the left cheek. The ophthalmic examination did not reveal any other ocular or adnexal pathology. On MRI images, the lesion was depicted as a slightly heterogeneous solid mass with unclear borders and heterogeneous enhancement. **Results**: A complete surgical excision of the lesion was performed, as the possibility of malignancy could not be ruled out. The histopathological examination revealed visible cross-sections of a nematode helminth, further identified as Dirofilaria repens based on its specific microscopic morphological characteristics, which ultimately established the diagnosis of dirofilariasis. A review of the respective literature, including 117 published cases, is provided attempting to summarize the clinical and diagnostic characteristics of the ocular cases of dirofilariasis affecting in specific, the eyelids. **Conclusions**: Ocular dirofilariasis should be included in the differential diagnosis of every eyelid subcutaneous tumor-like nodule or cyst of unknown etiology. An in-depth familiarization with its particularities is required in any sense, especially in the forthcoming years, when the endemic regions of Dirofilaria will expand, encompassing previously unaffected geographical areas.

Keywords: *Dirofilaria repens*; parasitosis; ocular dirofilariasis; palpebral mass; eyelid lesion

1. Introduction

Human dirofilariasis, albeit a rare helminthic zoonotic infection in total, represents nowadays an increasingly reported worldwide entity. This anthropozoonosis is endemic in many countries with mild, moist, semitropical or tropical climate conditions, such as the Mediterranean coast, Southern and Eastern Europe, Minor and Central Asia, North and South America, while it has also been associated with travelers' infections [1,2]. Nevertheless, global warming (especially warm summers), linked with the continuing outspread of competent vectors in northern latitudes, along with global mobility of people, are to blame for an ongoing spread of *Dirofilaria* infections in previously pure zones, such as Europe [3].

The responsible pathogen is a nematode classified in the genus *Dilofilaria* being transmitted to humans (the *accidental* or *final host*) via more than 70 different genera of mosquito vectors (*intermediate hosts*) [4] from other multiple definitive or natural hosts (reservoirs), mainly domesticated (dogs, cats) and secondly wild animals [2] (***Figure 1***). Out of the 40 species of *Dirofilaria*, only six are liable for

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human disease: *D. repens*, *D. immitis*, *D. tenuis*, *D. ursi*, *D. striata* , and *D. spectans* [5]. *D. repens* and *D. immitis* are the two most predominant, with *D. repens* being reported in the majority of cases from Europe and Greece in specific [6]. Despite that *Dirofilaria* species infections have been diagnosticated in various anatomical sites, ocular and periorbital localization remains one of the most frequent in general [2,6]. Due to the non-specific, polymorphic, and sometimes confusing clinical appearance, as a rule, the correct diagnosis is settled retrospectively through histopathological examination, except possibly in cases where a protruding worm is noticed during clinical evaluation [7].

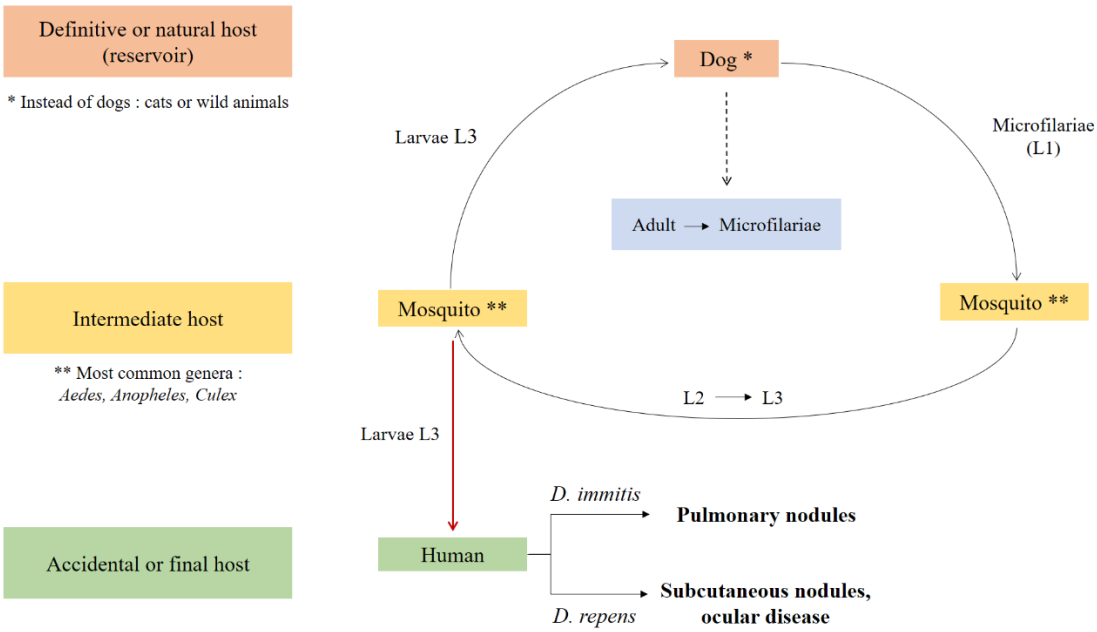

Figure 1. Graphical representation of Dirofilaria spp life cycle.

In this article, we report a case of eyelid dirofilariasis, which presented without any specific history, posing a diagnostic dilemma. The existing bibliography, relevant to this condition, is not particularly extensive and, in fact, it consists of scattered and heterogeneous data. Therefore, we herein also provide a thoroughly updated review on the subject. To the best of our knowledge, this is the first attempt in the literature to gather data from all reported clinical cases of eyelid dirofilariasis.

1.1. Case Report

A 79-year-old male patient presented with a painless mass in his left upper eyelid of 2 months duration (***Figure 2 a-b***). The patient reported that during the latter period he had experienced two episodes of periorbital edema extending to the cheek. By the time of consultation, the patient was already receiving systemic antibiotic (azithromycin, 250mg/day) and corticosteroid (methylprednisolone, 16mg/day) treatment, prescribed a week earlier by another physician. The clinical examination revealed a palpable mass, firm in consistency, without any fluctuance, tenderness or signs of bite on its surface. The overlying skin had no findings, whereas no other ocular pathology was observed.

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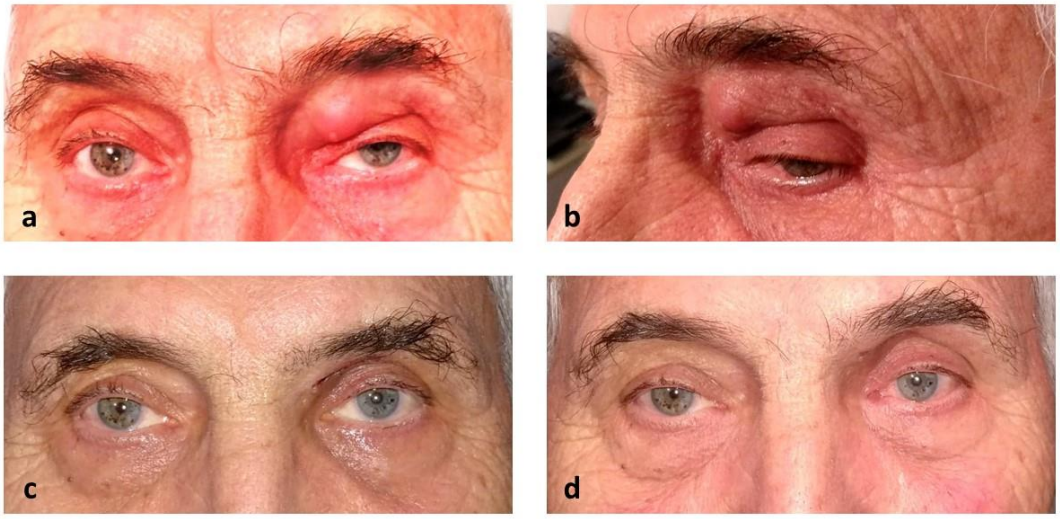

Figure 2. Clinical photographs showing our case of dirofilariasis–related left eyelid lesion upon presentation (a & b), 1 week (c), and 1 month postoperatively (d).

On further examination, MRI scan showed a slightly heterogeneous solid mass (hypo- to iso-intense in T1 and T2, respectively), with slightly irregular borders and heterogeneous enhancement with gadolinium (***Figure 3 a-b***). The radiologist's report could not exclude the possibility of malignancy. Therefore, an excisional biopsy of the mass under local anesthesia was decided, which was performed 3 days later. Regarding the surgical procedure, the mass was approached through a medial sub-brow incision, and part of the overlying skin was removed. Intraoperatively, during the exploration, there were signs of adjacent tissues' infiltration and induration. The excision of the mass was complete (excision in toto) with the excision margins reaching the periosteum. Special care was taken to preserve and avoid any damage to the levator palpebrae superioris muscle. The tissue sample was marked and sent for histopathologic evaluation.

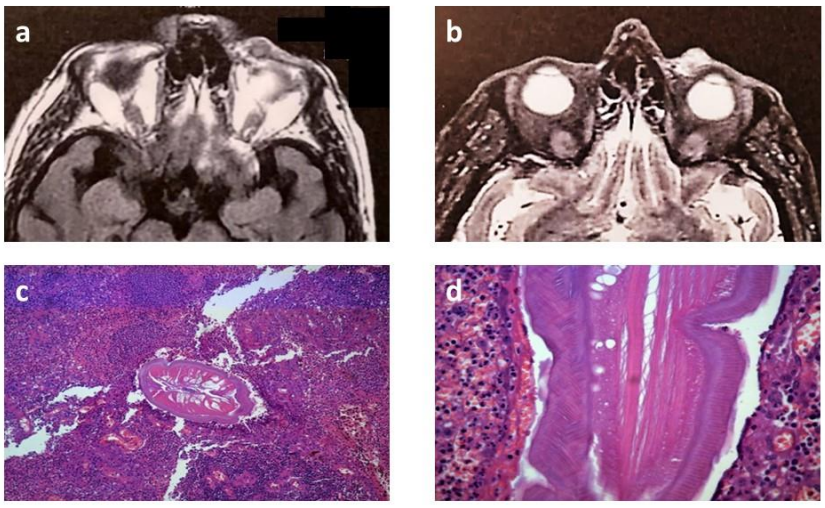

Figure 3. T1 (a) and T2 (b) MRI scans depicting the lesion in the left upper eyelid, and histopathological findings after H&E stain (c, d).

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The pathology laboratory received a tissue sample of a spindle-shaped skin section measuring 1,9*1,2 cm with subcutaneous tissue thickness of 0.9 cm. For the most part, histological examination revealed growth of inflammatory granulation tissue in cutis, subcutaneous fat, and orbicularis oculi muscle with abundant inflammatory infiltrates by lymphocytes, plasma cells, and numerous neutrophils, abscessation, and bleeding sites. In one spot, there were visible cross-sections of a nematode helminth, further identified as *Dilofilaria repens* based on its specific microscopic morphological characteristics (***Figure 3 c-d***).

Postoperative edema subsided completely after 1 week. There were no visible signs of inflammation, and the wound healing of the surgical incision was uneventful (***Figure 2 c-d***). No recurrences or other complications were seen during a 2-year follow-up.

2. Discussion

2.1. Synopsis of Dilofiraria's Life Cycle

As mentioned above, dirofilariasis is spread to humans through mosquito bites. Those vectors harbor larvae obtained from animal reservoirs and allow them to mature through the L2 and L3 stages. *Dirofilaria* nematodes are deposited in humans as third-stage filarial larvae (L3) of their life cycle, every time a female mosquito-carrier takes a blood meal (***Figure 1***). In human tissues, the larvae give birth to reproductively inactive adult worms, and thus no microfilaremia is detected [1,2], which signifies that the life cycle is incomplete, fully justifying the term "accidental hosts" for infected humans (biological dead end). Nonetheless, Sergiev et al. reported a case of a patient in whom microfilaremia (L1 stage) and reproductively active parasites were present, questioning our previous knowledge [8]. As a rule, worms of species *D. immitis* migrate to the pulmonary circulation and form pulmonary nodules, whereas *D. repens* worms are responsible for subcutaneous nodules, including the ocular region [9]. However, cases of subcutaneous eyelid disease linked with *D. immitis* have interestingly been reported as well [10].

2.2. Ocular dirofilariasis and Involved Tissues

In humans, cases of ocular dirofilariasis represent approximately one-third of the total reported incidents [11]. Regarding the involvement of ocular tissues, even though the subconjunctival area constitutes the prevailing site [12], *Dirofilaria* nematodes have also been isolated from lesions found in the eyelids subcutaneously, below the Tenon's layer [13], in the orbital zones, intraocularly (in the anterior chamber or in the vitreous body) [14,15], in the retrobulbar region [16] or, lastly, in the lacrimal glands [17]. Recently, Gupta et al. reported on a case of ocular dirofilariasis leading to extensive chorioretinal damage and presented clinically as diffuse unilateral subacute neuroretinitis [18].

2.3. Eyelid Dirofilariasis

2.3.1. Literature Review - Methodology

Bibliographically, there are numerous reports of ocular dirofilariasis concerning the eyelid. We, herein, provide an up-to-date review of the literature relating to published cases. PubMed, Cochrane Library, and Web of Science databases were searched using a predefined search algorithm ***(Supplemental Appendix 1)*** for papers reporting human cases of eyelid dirofilariasis. Any relevant article written in English, German, or Greek was included, without limitations regarding study type or patient characteristics. Papers written in other languages were also included if an English abstract provided sufficient information to identify the parasite as *Dirofilaria* and the location of the lesion as palpebral. Records with no full-text available (e.g., conference papers) were excluded if the information provided in the abstract was not adequate. The end date of the search period was April 1st, 2024. The results were checked meticulously in order to include only cases of purely palpebral location of the lesions and exclude those that imitated such a clinical appearance. Aside from this, we

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also detected all the eligible cases which were mentioned as references in the results from our prior search, as well, in other reviews relevant to dirofilariasis.

For each of the registered reports, we extracted information on: first author's name, year of publication; number of total reported cases and those of eyelid disease; region and country of origin; relevant travel history; demographic characteristics of patients (sex, age); lesion localization; nematode species and sex; molecular confirmation of the diagnosis; presenting symptoms and signs; selected treatment; final outcome and/or recurrences.

2.3.2. Literature review - Results

The literature search revealed 117 published cases of eyelid dirofilariasis [10,11,14,15,19–99]. A flow chart of the article selection process is presented in ***Supplemental Figure 1***. Case characteristics are summarized in ***Table 1***, while all cases are presented in full detail in ***Supplemental Table 1***.

Table 1. Summary of case characteristics.

Total cases, N	**117**	
Patient age		
Median	39 years	
Mean (±standard deviation)	40.1 (±18) years	
Range	11 months - 77 years	
Patient sex, n (%)		
Female	69	(59)
Male	41	(35)
Not reported	7	(6)
Lesion localization, n (%)		
Upper eyelid	64	(54.7)
Lower eyelid	35	(29.9)
Lateral canthus	1	(0.85)
Medial canthus	1	(0.85)
Not reported	16	(13.7)
Geographic region[ŧ], n (%)		
Eastern Europe	34	(29.1)
Southern Europe	19	(16.2)
Western Europe	11	(9.4)
Central Asia	2	(1.7)
Eastern Asia	2	(1.7)
Western Asia	5	(4.3)
South-eastern Asia	4	(3.4)
Southern Asia	31	(26.5)
Northern America	6	(5.1)
Northern Africa	2	(1.7)
Not reported	1	(0.9)
Reported travel history to an endemic region, n (%)	10	(8.5)
Nematode sex, n (%)		
Female	31	(26.5)
Male	7	(6)
Not reported	79	(67.5)
Nematode species, n (%)		
D. repens	103	(88)
D. immitis	2	(1.7)
D. tenuis	4	(3.4)
D. hongkongensis	1	(0.9)
Not reported	7	(6)

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Molecular confirmation of the diagnosis, n (%)	20	(17.1)

[†]Subdivision according to the United Nations geoscheme. Available from: https://unstats.un.org/unsd/methodology/m49/.

The mean age of the patients was 40.1 years, ranging between 11 months and 77 years, with a slight gender predilection toward females (69/117 cases, 59%). More than half of the reported cases originated from Eastern Europe (29.1%) and Southern Asia (26.5%), with Southern Europe following in the third place (16.2%). In ten cases, a relevant travel history was reported. The upper eyelid was predominantly affected (54.7% of all cases), followed by the lower eyelid (29.9%) and median and lateral canthus (0.85% each), while the localization of the lesion was not specified in 13.7% of the cases. As far as the responsible nematode is concerned, *D. repens* was identified in the vast majority of cases with eyelid dirofilariasis (103/117, 88%), while four cases of *D. tenuis*, two cases of *D. immitis*, and one case of *D. hongkongensis* were also reported. A positive PCR confirmed the diagnosis in 20 patients (17.1%). When nematode sex was specified (38 cases), female parasites were found in a greater proportion (81.6%).

2.3.3. Clinical Appearance

In the vast majority of cases, a solid palpable mass or a subcutaneous nodule of the eyelid is noticed during clinical evaluation. Typically, eyelid dirofilariasis masses are single; multiple simultaneous locations imply multiple separate inoculations [76]. These lesions can be firm in consistency or swollen, with well-defined borders, movable or static, painful or painless, and progressively growing, whereas they are typically accompanied by local signs of inflammation (such as tenderness, redness, hyperemia), itchiness, or sometimes overlying brownish skin discoloration. These signs can yet be completely absent, and then the lesions masquerade clinically as non-inflammatory swelling [69]. In several cases, patients presented with a lesion of threadlike appearance [63,69,70,86,88], indicating with a quick inspection towards the probable subcutaneous presence of a worm, and some of them complained of a sensation of movement under their skin, owing to the motility of the living parasite [43,56,63,86,92].

Before the perception of eyelid symptomatology, patients can refer to having experienced flulike symptoms [65], recurrent episodes of edema [69,85,88], or diffuse migratory erythematous rash [66]. Extreme incidents have also been reported, regarding the emergence of a live motile nematode following the eruption of the eyelid lesion [76,88] or even the far migration of a nematode through the subcutis from the lower left eyelid to the neck, the axilla, the abdominal wall and finally the lower right eyelid [52]. A peculiarity of the case reported herein is the fact that our patient described two past episodes of recurrent periorbital edema extending to the cheek, before consulting our department eventually.

2.3.4. Laboratory Investigation

In human dirofilariasis in general, serological detection of specific antibodies or PCR of blood samples are not incorporated in the diagnostic process, as the microfilariae, which act as primordial triggers of the immune response, cannot typically develop in human hosts in cases of filarial infections [4]. For the same reason, the blood smear is negative for microfilaremia, whereas an increase of serum IgE levels might be rarely present [72]. Eosinophilia bibliographically, is more common in cases owed to *D. immitis* instead of *D. repens*, but regardless of that, it does not represent a consistent finding [100]. The most valuable examination remains until today the histopathological analysis of the biopsy material, which certifies the diagnosis of dirofilariasis and allows additionally the identification of the culpable species based on the morphometric microscopic characteristics of the eradicated nematode. In recent decades, the PCR method has been utilized by pathologists in order to facilitate diagnosis in samples where the helminths are destroyed beyond identification or in samples containing only a small part of the helminth [61,101]. The need for further taxonomic distinguishing of subtypes of the filariae can be met, except for PCR, by DNA and mitochondrial 12S

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ribosomal RNA (12S rRNA) gene sequencing [81]. Interestingly, in a case histopathologically consistent with *D. repens*, 12S rRNA analysis identified the parasite as *D. hongkongensis*, suggesting that several cases could be reclassified upon molecular confirmation of the diagnosis [94].

2.3.5. Imaging Findings

Regarding imaging findings, the literature in question is relatively limited. High-resolution ultrasonography (USG), CT, and MRI scans have been used as part of the diagnostic investigation. In USG, the lesions were hypoechoic (compatible with their cystic nature) [37,68,75,76,85] and, within them, motile, tube-like enfolded structures with parallel echogenic walls (possibly the live worms) were distinguished [68,75]. In other cases [15,66,68,70], a CT scan showed heterogeneous [68] or homogenous [66] well-defined masses or swelling [70] of soft tissue density, with enhanced periphery in one particular occasion [68]. Concerning the MRI findings, the lesions may manifest with cystic characteristics, in shape of an enclosed sac [91], with a center of high signal on T2w images, an encircling capsule of low signal on T1w and T2w images [102] and plausible intermediate signal intensities of tubular shape within the lesion in STIR images, indicating towards the worm [75]. Apart from this data, a rim enhancement of the capsule and parts of the lesion's content may also be revealed on post-contrast fat saturation T1w images due to circumambient inflammation [75,102]. At this point, due to restricted data, knowledge can be drawn from our case report as well, where the MRI revealed a mass of heterogeneous signal intensity and enhancement, with ill-defined edges, displaying an alternative MRI pattern.

2.3.6. Management

Despite that surgical removal of the nematode or excision of the whole lesion is the treatment of choice, it should be performed always after considering the sensitivity of the affected eye's region, the plausible risks or the final cosmetic outcome, choosing a conservative approach if the danger outweighs the profit of the patients [86]. In cases of eyelid localization, surgical excision is usually preferable because it is a definitive cure, and a diagnosis of malignancy cannot be easily ruled out [2]. Irrespective of each case's particularities, efforts must be made to extract intact nematodes or intact nodules encompassing the nematodes, so that an inflammatory or anaphylactic response will not be triggered [1].

Pharmacological therapy with anthelmintic agents is not recommended in instances of human ocular dirofilariasis, as no efficacy has been proven [1,2]; besides microfilaraemia, a prerequisite that could justify such a therapeutic approach, is rarely developed in patients' blood. Notwithstanding the foregoing, some clinicians report having treated their patients either with diethylcarbamazine or ivermectin, supplementary after the surgical removal of the nematode or, instead of that, as sole treatment due to cosmetic reasons [70,76,89], with a good post-surgical response, demonstrating reduced edema.

3. Conclusions

In a nutshell, ocular eyelid dirofilariasis should always be included in the differential diagnosis of a subcutaneous cyst, granuloma, or tumor-like nodule, accompanied or not by episodes of periorbital swelling, especially in countries where *Dirofilaria* cases have been reported. In the years to come, as the endemicity of such cases is about to change radically and embody immune geographical areas, a high index of suspicion and familiarity with the clinical and laboratory manifestations of ocular dirofilariasis is required hereafter in many fields of clinical medicine.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, N.Z. A.D. and A.T.; methodology, A.D., A.K. S.A., G.L. and A.T.; software, G.L., A.K. and A.T.; validation, A.T. and G.L.; formal analysis, A.K., A.T., A.D., S.A. and D.M.;

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