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Title: International dog travelling and risk for zoonotic *Onchocerca lupi*

Running Title: Introduction of zoonotic *Onchocerca lupi*

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Summary

Onchocerca lupi is a recently recognized threat for the health of animals and humans in European, American, African and Middle Eastern countries. We describe a case of imported *O. lupi* infection in Italy and report the lifespan of this parasite in a non-endemic area, to advocate increased awareness of the veterinary community for this zoonotic parasitosis.

Keywords: *Onchocerca lupi*; PETS; Travel medicine; Zoonoses; Animal travelling.

Main text

Limited scientific knowledge of helminths affecting human and animal eyes challenge their diagnosis and treatment (Otranto and Eberhard, 2011). Among these parasites, *Onchocerca lupi* is a zoonotic nematode localising to the ocular and adnexal tissues of dogs, which act as reservoir hosts (Otranto et al., 2013; Colella et al., 2018). A recent increase in *O. lupi* infection has been reported from dogs, cats, and humans living in European (Romania, Hungary, Greece, Switzerland and Portugal), American (U.S. and Canada), Middle Eastern Asian (Iran), and Northern African (Tunisia) countries (Gracío et al., 2015). Adult worms cause from mild ocular lesions to blindness, but the majority of infected dogs do not display overt clinical signs (Otranto et al., 2013). *Onchocerca lupi* has been in the limelight for its zoonotic potential (Otranto et al., 2011) and the severe consequences upon the infections of children in the U.S. (Eberhard et al., 2013; Dudley et al., 2015). The nonspecific tropism of this nematode for the CNS and the absence of resolute pharmacological treatments entail hospitalization and invasive surgery for the removal of the parasite-embedding nodules in humans (Eberhard et al., 2013; Dudley et al., 2015). The challenging diagnosis and

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the lack of information on the species acting as vector, delay the establishment of surveillance and control strategies of *O. lupi*. Here, we describe a case of imported *O. lupi* infection in Italy and provide information on the lifespan of this parasite in a non-endemic area, to raise veterinary community's awareness.

In 2013 a female mixed breed dog was adopted in Italy from southern Portugal, an area classified as endemic for canine onchocercosis (Otranto et al., 2013). The dog was referred to a practitioner in Italy for ocular discomfort and subjected to an ultrasound examination (US) of both eyes and adnexal tissues (Franchini et al., 2013). Hyper-echogenic structures were noticed in the eyes of the dog and those on the anterior sclera removed via an exploratory surgery with the aid of US guidance (Franchini et al., 2014). The dog recovered without complication and lived in Italy without further travelling abroad. The nodules were examined under a light stereomicroscope, revealing the presence of adult *O. lupi* nematodes (Mutafchiev et al., 2013). Skin samples were collected by using a disposable punch ($\approx 0.4 \times 0.5$ cm) from the interocular and interscapular regions of the dog, soaked in 0.9% saline solution for 12h at room temperature, and recovered microfilariae morphologically identified as *O. lupi* (Otranto et al., 2013). Genomic DNA from the nodules and from the microfilariae was extracted using a commercial kit (DNeasy Blood & TissueKit, Qiagen, Germany) and molecularly processed for amplification and sequencing of the partial cytochrome oxidase subunit 1 (*cox1*) gene, following procedures described elsewhere (Otranto et al., 2013). Nucleotide sequences obtained from adults and skin DNA displayed 100% identity with those of *O. lupi* from Portugal (GenBank accession no EF521410). In October 2017, the dog died from acute pancreatitis and was necropsied. Non-encapsulated adult eyeworms were promptly recognized upon the enucleated ocular globe (Figure 1), and morphologically identified as *O. lupi* adult nematodes. Skin samples were collected by biopsy (≈ 0.5 cm) from the ears, nose, interocular and interscapular regions, which were analysed by molecular means (as described above). Genomic DNA extracted from these parasites and skin biopsies of the dog was amplified and were 100% identical to sequence from samples collected from the same animal in 2013 (GenBank accession no EF521410). All study procedures on the dog were performed after receiving the owner's informed consent.

International *O. lupi*-infected dog transportation poses a threat for the introduction of this zoonosis in non-endemic areas and for the clinical consequences on human health. This nematode displays a very long lifespan ranging from 3 (Verocai et al., 2016) to 8 years (Hodžić et al., 2017) in non-endemic countries. Similarly, *Onchocerca volvulus* can live in human nodules for approximately 15 years (<https://www.cdc.gov/dpdx/onchocerciasis/index.html>). In this study *O. lupi* displayed a survival time of 4 years coupled with positivity of skin samples from several anatomical sites, which stands for the presence of microfilariae in the dog's dermal tissues. This is paramount considering that *O. lupi* can live for a long time and its offspring can be available to a vector species, even in non-endemic areas where the infection could potentially establish. However, the risk for the introduction of *O. lupi* with travelling dogs cannot be assessed in the absence of information about the presence of the vector(s) in a given area (Verocai et al., 2016; Hodžić et al., 2017). Attempted treatments included various combination and dosages of melarsomine, ivermectin, topical and systemic antibiotics (Otranto et al., 2015), and oxfendazole, though studies proving

the efficacy of these compounds are lacking (Colella et al., 2018). Likewise, surgical treatment did not prove successful in curing canine onchocercosis, which is in line with previous reports of recurrent disease in dogs relocating from endemic regions (Verocai et al., 2016; Hodžić et al., 2017). While recognizing the efforts of non-profit organizations dealing with pet's adoption/relocation, an increased awareness of the veterinary community to promptly diagnose canine onchocercosis is fundamental to limit the introduction of *O. lupi* with international transportation of animals from disease-endemic areas. Advocacy for a stronger commitment should be also implemented by policy makers in Europe and U.S. to tackle the threat of this neglected pathogen by making canine onchocercosis a reportable disease. For instance, the California Department of Food and Agriculture has recently included onchocercosis by *O. lupi* in the disease priority list by reporting the diagnosis within 7 days from time of identification (<http://publichealth.lacounty.gov/vet/docs/2016LACountyAnimalReportableDiseaseList.pdf>).

Refined intervention strategies should consider the application of surveillance and proper treatment of *O. lupi* infected dogs to avoid the introduction and/or spread of this life-threatening parasitic nematode.

Conflict of interest statement

We declare that we have no conflict of interest.

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127 **Figure Legend**

128 Figure 1. *Onchocerca lupi* adult nematodes in the retrobulbar of the enucleated globe of the imported dog.

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