Parasitology Research
https://doi.org/10.1007/s00436-021-07309-2

HELMINTHOLOGY - REVIEW

Confirmed cases of human *Onchocerca lupi* infection: a systematic review of an emerging threat

Ali Asghari[1] · Ghazaaleh Adhami[2] · Seyyed Ali Shariatzadeh[3,4,5] · Bahareh Kordi[6] · Davood Anvari[7,8] · Morteza Shams[9,10] · Hamidreza Majidiani[9] · Mohammad Mahdi Darvishi[11]

Received: 12 May 2021 / Accepted: 31 August 2021

Abstract

Diverse *Onchocerca* species are present mostly parasitizing ungulates, with the exception of *Onchocerca volvulus* (*O. volvulus*) in humans and *O. lupi* in canids and cats. The human cases due to the *O. lupi* have been more highlighted during last years. So, the present review was performed to determine the detailed characteristics of confirmed human *O. lupi* case reports documented worldwide. Hence, a systematic search was done using English international databases (Scopus, PubMed, Web of Science, Embase, ProQuest, and Google Scholar). Totally, 14 confirmed human cases were documented during the last decade, mostly from the USA and Turkey with 7 and 3 cases, respectively. Most cases (7 individuals) were male with the age range of 22-month-old to 54-year-old. The parasite was frequently isolated from the right eye (5 cases), followed by the left eye (4 cases), cervical spinal canal (3 cases), scalp, and right forearm (one case each). Molecular identification of the isolated agent was the preferred way of diagnosis in most cases (9 records). In conclusion, human *O. lupi* cases have been more highlighted in recent years, whether due to the improved diagnostics and/or host-switching phenomenon, and both veterinarians and healthcare authorities should be alerted.

Keywords Onchocerciasis · *Onchocerca lupi* · Human cases

Introduction

The Onchocercidae family of nematodes (Filarioidea, Spirurida) hosts diverse parasitic species of humans as well as animals (Anderson 2000). The motile first-stage larvae (L1),

Section Editor: Sabine Specht

✉ Morteza Shams
Shamsimorteza55@gmail.com

✉ Hamidreza Majidiani
H.majidiani@modares.ac.ir;
Hamidreza.Majidiani@gmail.com

1 Department of Medical Parasitology and Mycology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

2 Department of Veterinary Pathobiology, Faculty of Veterinary Medicine, Islamic Azad University of Sanandaj, Sanandaj, Iran

3 Department of Parasitology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

4 Toxoplasmosis Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

5 Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

6 Department of Pathobiology, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran

7 Department of Parasitology, Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

8 School of Medicine, Iranshahr University of Medical Sciences, Iranshahr, Iran

9 Zoonotic Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran

10 Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran

11 Pathobiology Department, Shahmirzad School of Veterinary Medicine, Semnan University, Semnan, Iran

Published online: 14 September 2021

known as microfilariae, present in the vertebrate definitive hosts are sucked up by arthropod vectors as intermediate hosts, where they further develop into the infective third-stage larvae (L3) (Orihel and Eberhard 1998; Otranto and Deplazes 2019). The adult worms inhabit a wide array of biological tissues within host's body, such as the blood vessels, lymphatic ducts, body cavities, and/or connective tissues (Otranto et al. 2013a). The roundworms of the genus *Onchocerca* (27 species) release microfilariae in tissue spaces of the skin rather than in peripheral bloodstream, being taken up by simuliid (genus *Simulium*) or ceratopogonid (genus *Culicoides*) insect vectors (Anderson 2000; Bosch et al. 2016). *Onchocerca* spp. are relatively harmless to domestic animals, with lesions being mostly limited to inflammation of joints and musculature as well as lameness in ungulates (Deplazes et al. 2012). In humans, *Onchocerca volvulus* (*O. volvulus*), the causative agent of river blindness, represents a major threat to the public health mainly in tropical Africa, affecting about 37 million people worldwide (WHO 2014). Nevertheless, human *Onchocerca* infections may, also, have a zoonotic origin. Previously, various *Onchocerca* spp. were identified as the agents of zoonoses in humans, comprising *O. gutturosa* (Orihel and Eberhard 1998) and *O. cervicalis* (Burr Jr et al. 1998) as cattle and horse parasites, respectively, with ocular localizations in humans, as well as *O. jakutensis* (Koehsler et al. 2007) and *O. dewittei japonica* (Uni et al. 2010) as European deer and wild boar parasites, respectively, found in human subcutaneous tissues.

The only *Onchocerca* species known to infect canids and felids is *O. lupi* (Grácio et al. 2015). This enigmatic helminth was originally described in periocular tissues of a wolf (*Canis lupus cubanensis*) in the Caucasian Republic of Georgia about 53 years ago (Rodonaja 1967). The parasite remained unrecognized for decades until 2001, when the morphology of adults and microfilariae was thoroughly revealed, demonstrating exclusive features within the genus. Further, genetic characterization studies using 5Sr DNA spacer sequences, also, suggested that the parasite possesses unique molecular patterns (Egyed et al. 2001). It is presumed that *O. lupi* has early diverged from other *Onchocerca* spp. in the evolution process as a primitive species, according to Egyed et al. (2002). Later in 2008, *O. lupi* was shown to be involved as the causative agent of canine ocular onchocerciasis, with acute or chronic ocular manifestations such as lacrimation, ocular discharge, photophobia, exophthalmia, conjunctivitis as well as nodule formation on nictitans, sclera, conjunctiva, and the eyelids (Dantas-Torres and Otranto 2020b; Sréter and Széll 2008). Three years later, the parasite was isolated and described for the first time in felids (two domestic cats) in the USA, adding more to the complicated biological behavior of this species (Labelle et al. 2011). The first zoonotic attributes of *O. lupi* were documented in the context of three human investigations in Turkey between 2011 and 2013 (Ilhan et al. 2013a; Otranto et al. 2012b; Otranto et al. 2011). Further in 2013, Mutafchiev et al. (2013) re-described this species on the basis of scanning electron microscopy, microscopy of periocular histopathological sections, and molecular confirmation. So far, no direct finding of *O. lupi* biological vector has been documented around the world, and only *Simulium tribulatum* in California has been found to harbor parasite DNA, suggesting possible involvement in transmission (Hassan et al. 2015).

During last decade, there have been accumulated evidences of human *O. lupi* infection as an emerging zoonotic threat (Dantas-Torres and Otranto 2020b). The parasite may be capable to complete its life cycle in humans, and at least in some cases, gravid worms were isolated. As well ocular and nervous tissue involvement is prominent, causing pain/irritation in eyes as well as cervical spinal nodules leading to headache and neck stiffness. All of these emphasize the medical significance of *O. lupi* infection in humans (Grácio et al. 2015). Thus, the objective of this systematic review was to elevate the current knowledge on the poorly known *O. lupi* infection in humans.

Methods

This systematic review was accomplished on the basis of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al. 2010).

Information sources and search

The systematic searching process was accomplished without time limitation until 5th November 2020. All case-report and/or case-series articles on the presence/identification of *O. lupi* roundworm in humans were gathered via major English databases (Scopus, PubMed, Web of Science, Embase, ProQuest, and Google Scholar), using specified search terms, including "*Onchocerca lupi*", "infection", "Human cases", and "Case-report", using AND and/or OR Boolean operators. Also, cross-sectional studies on potential animal hosts within the explored time period were included for better appraisal of the epidemiology of *O. lupi* human cases, using the following keywords: "*Onchocerca lupi*", "Prevalence", "Epidemiology", "Morphological diagnosis", "Molecular identification", and "Carnivores".

Eligibility criteria, study selection, and data collection

Only papers with accessible full-texts were included for further analysis. Also, in case of any contradiction in the study inclusion and/or data extraction steps, discussion and consensus were used to reach a final decision. The systematic search and extraction procedures were completely performed by a group of expert researchers, then double-checked by other colleagues. The following data were extracted from included articles: reference, sex, age, country, year of report, parasitized organ, signs/symptoms, previous contact with animals and/or insect bite, diagnostic methods, and treatment/outcome. For animal studies, first author's name, year of study, continent, country, animals host, diagnostic method, total number of examined animals, number of positive records, gender, and age were considered for data extraction.

Meta-analysis

This section was only done for the statistical estimation of the pooled prevalence of *O. lupi* infection in potential animal hosts, as previously mentioned (Ghasemi et al. 2020). For all included studies, point estimates and their respective 95% confidence intervals (CIs) of weighted prevalence were calculated. Heterogeneity among these studies or variation in study outcomes was visualized by drawing forest plots, calculated by I^2 and Cochrane's Q tests. The subgroup analysis was performed based on year, country, sample type, symptoms, and diagnostic methods. The presence of publication bias was estimated by using Egger's regression test. P value less than 0.05 was considered as statistically significant. All analytical functions were applied by STATA/S.E. software version 12.0 (StataCorp, College Station, TX 77,845, USA).

Results

Since 2011, a total number of 14 confirmed cases of human *O. lupi* infection were documented in six countries around the world, including the USA (7 cases) (Biswas and Yassin 2013; Cantey et al. 2016; Chen et al. 2015; Dudley et al. 2015; Eberhard et al. 2013), Turkey (3 cases) (Ilhan, et al. 2013b; Otranto et al. 2012a; Otranto et al. 2011), as well as Norway (Sandell et al. 2020), Tunisia (Otranto et al. 2012a), Germany (Bergua et al. 2015), and Iran (Mowlavi et al. 2014) (one case per country). Among all cases, 7 individuals were male, and 5 individuals were female, while in two case reports from Tunisia and Germany, the sex of the examined subjects was not exactly mentioned. The age range of the *O. lupi* patients was from 22-month-old (in USA) to 54-year-old (in Norway). The parasite was mostly isolated from the right eye (5 cases), followed by left eye (4 cases), cervical spinal canal (3 cases), scalp, and right forearm (one case each). Among nine eye cases, pain and irritation (6 cases), as well as involvement of the superior and medial rectus muscles (3 cases), were mostly reported. Of note, eye multi-nodule involvement was only reported in the Iranian case report, documented by Mowlavi et al. in 2014 (Mowlavi et al. 2014). In three cases involving the spinal canal, C2 to C4 vertebral regions were the most preferred sites of infection, all of them being reported from the USA. In 9 out of 14 cases, there were no reports on previous contact with animals and/or insect bite exposure. Additionally, 4 cases never traveled abroad or to other areas of their country, 4 cases had only abroad travel history, 5 cases had traveled to some areas in their country, and one case report mentioned nothing. Also, in six cases ivermectin and/or doxycycline had been administered for treatment, while surgical removal of worms was the preferred therapy. Finally, in most case reports (9 records), molecular characterization of the isolated parasite was performed. The detailed characteristics of each case report study are provided in Table 1. Animal cross-sectional studies (6 records) (Colella et al. 2018a; Maia et al. 2015; Miró et al. 2016; Otranto et al. 2013c; Otranto et al. 2012c; Roe et al. 2020) were mostly done in Portugal (3 records) and Greece (2 records), with dogs as the most investigated animal species, while single studies were done on coyotes and cats. The pooled prevalence of *O. lupi* in carnivorous hosts was calculated as 6.43% (95% CI: 2.87–11.28%), with significantly higher prevalence in dogs with 9.49% (95% CI: 4.51–16.05%) ($Q = 32.4$, df $= 59$, $I^2 = 98.9\%$, $P < 0.0001$) (Supplementary Fig. 1 and Supplementary Table 1 and 2). Moreover, Publication bias was checked by Egger's regression test, showing that it may not have a substantial impact on total prevalence estimate (Egger's bias: 2.2, $P = 0.255$) (Supplementary Fig. 2).

Discussion

The filarial worms of the genus *Onchocerca* have a worldwide distribution, with ungulates as the main host species (Sréter and Széll 2008). Interestingly, the human cases of onchocerciasis have been increasingly documented around the world, highlighting the zoonotic potential of some *Onchocerca* species (Cambra-Pellejà et al. 2020). About half a century ago, *O. lupi* was described as a new species in a Russian wolf (Rodonaja 1967); however, its significance was gained only during the last two decades. At present, canine ocular onchocerciasis and, more recently and remarkably, the emerging cases in humans are two important concerns regarding *O. lupi* infections (Grácio et al. 2015). Therefore, the present systematic review was done to highlight the current knowledge on confirmed human case reports of this important zoonosis and to address the gaps for future directions.

Previously published review by Grácio et al. (2015) provided a historical look at the description of *O. lupi* in both animals (wolf, dog, cat) and human cases, from the origin

Table 1 Detailed characteristics of the confirmed human cases of *O. lupi* worldwide

No	Reference	Sex, age, country, year of report	Parasitized organ	Signs/symptoms	Previous contact with animals and/or insect bite	Travel history	Diagnostic methods	Treatment and outcome
1	Otranto et al	F/18/Turkey/2011	Left eye	Subconjunctival mass on the superonasal quadrant of bulbar conjunctiva/Initially, a 6-day history of painless redness/28 days after the first visit, pain and a tiny mass were evident	She had a painful fly-bite history on her left upper lid about 30 days before onset of symptoms	Never traveled abroad or to other areas of Turkey	Morphologic identification, Molecular characterization using *cox1* and 12S rDNA genes	Worm removal/The patient's eye was normal 5 months after the last visit
2	Otranto et al	M/26/Turkey/2012	Right eye	Irritation and itchiness/Growing redness nasally to the right eye for 2 weeks/5 × 5 mm swelling and a conjunctiva mass in the nasal conjunctiva region	No history of insect bites was reported	Never traveled abroad except to Antalya (Turkey)	Explorative surgery, morpho-anatomical features, histological examination, molecular identification using *cox1* and 12S rDNA genes	Worm removal and patient recovery
3	Otranto et al	Child?/8/Tunisia/2012 (redescribed)	Right eye	Fastidious pain of the right eye for 4 weeks/Presence of subconjunctival mass	No history of insect bites was reported	Never traveled abroad or to other areas	Explorative surgery, morpho-anatomical features, histological examination	Worm removal and patient recovery
4	Eberhard et al	F/22-month-old/USA/2013	Cervical spinal canal	Extradural mass extending from C2 to C4/Neck pain and stiffness/Limitation of neck's range of motion/Moderate to severe compression of the cord	Exposed to sheep, horses and dogs	Born in New Mexico, while later her family migrated to Northern Arizona	MRI, laminectomy, a small biopsy, histopathological examination	Laminectomy, primarily ivermectin (150 μg/kg, every 3 months until 5 years), doxycycline was not warranted

Table 1 (continued)

No	Reference	Sex, age, country, year of report	Parasitized organ	Signs/symptoms	Previous contact with animals and/or insect bite	Travel history	Diagnostic methods	Treatment and outcome
5	Ilhan et al	M/28/Turkey/2013	Right eye	Painless, immobile mass measuring approximately 10×12 mm in size/The mass also extended posteriorly through the orbital septum, near the superior rectus muscle/Small lid edema and conjunctival hyperemia around mass	There was no evidence of an insect bite nor was there a history of an animal attack	Never traveled abroad or to other areas	MRI, surgical excision, histopathologic examination, PCR amplification using *cox1* and *nad5* genes	Worm removal/The patient's eye was normal 10 months after the last visit
6	Biswas and Yassin	M/19/USA/2013	Right eye	Subconjunctival nodule in the medial aspect/Irritation and watering of the right eye, without any visual loss	He has never had any pets such as dogs and cats	Recent trip to New Delhi (India) and Siwa (an oasis in western Egypt)	Morphologically, histopathological examination, hematologic and serologic evidences	Ivermectin (100 mg/kg) once without recurrence during a two-year follow-up
7	Mowlavi et al	M/20/Iran/2014	Left eye	Suffering from a yellowish conjunctival nodule during last 12 months/mild conjunctival hyperemia/normal intraocular pressure and eye movement Also, there were two more nodules in the belly of medical rectus muscle	The patient did not recall any fly bites on his face	No recent history of travel to other cities or abroad	CBC, ESR, C-reactive protein, ACE and tuberculosis skin tests (differential diagnosis for sarcoidosis and tuberculosis), explorative surgery, morphological examination, PCR assay using 12S rDNA gene	Cryotherapy (for nodule remnants) and mitomycin C 0.04% followed by irrigation with 100 ml balanced salt solution, dexamethasone to soothe urticaria, improvement

Table 1 (continued)

No	Reference	Sex, age, country, year of report	Parasitized organ	Signs/symptoms	Previous contact with animals and/or insect bite	Travel history	Diagnostic methods	Treatment and outcome
8	Dudley et al	F/5/USA/2015	Cervical spinal canal	The girl with trisomy 21 presented with 2 months of neck pain, without neurological findings on examination or cutaneous abnormality/spinal onchocercoma or a dural-based mass from C2 to C4 causing spinal cord compression	No contact with animals (except two healthy dogs in her family) or insect bite exposures	She has not traveled outside the USA but frequently visited Navajo Lake (New Mexico)	MRI, radiography, histopathological examination	Surgical excision, ivermectin single dose every 3 months and doxycycline for 6 weeks/improvement
9	Bergua et al	?/28/Germany/2015	Right eye	Painful localized swelling of the bulbar conjunctiva supratemporally of the eye since 2 months ago, accompanied by severe episcleral and conjunctival hyperemia/lack of response to steroids	No history of insect bite or animal contact was reported by patient	Traveling to Mediterranean cities of Turkey (3 years before) and Tunisia (2 years before)	Slit-lamp examination, Surgical excision, 12S rDNA PCR amplification	Antibiotic therapy with tobramycin cefuroxime, along with anti-inflammatory therapy
10	Cantey et al	F/10/USA/2016	Scalp	A minimally tender, erythematous swollen area on the right posterior-parietal scalp since 2 months ago/The mass was progressively enlarging	She had been bitten on the head by a flying insect while boating	The patient had traveled only to New Mexico (Navajo Lake) and Colorado 2 years earlier	Morphological and molecular identification	The patient remained asymptomatic after worm removal, without antiparasitic therapy
11	Cantey et al	F/50/USA/2016	Right forearm	Rubbery, non-tender, non-erythematous, and non-pruritic subcutaneous nodule on the dorsal aspect of her forearm	Insect bite was reported on her right arm extending from shoulder to wrist	She had traveled to Jamaica (a Caribbean Island nation) during May and June 2013	Histopathological examination and PCR analysis	Single dose Ivermectin (for microfilariae) and 6 weeks of doxycycline (for adults), improvement

Table 1 (continued)

No	Reference	Sex, age, country, year of report	Parasitized organ	Signs/symptoms	Previous contact with animals and/or insect bite	Travel history	Diagnostic methods	Treatment and outcome
12	Cantey et al	M / 10 / USA / 2016	Left eye	Progressive left upper eyelid drooping, periorbital edema, and conjunctival injection beginning 2 weeks earlier/1.5 cm mass in the superior rectus muscle, compressing the globe, with a thick capsule and a necrotic-appearing center	A pet dog that had conjunctivitis and an eye lesion of unknown etiology had lived in the home prior to diagnosis	Fishing in a fresh water lake near his home A car trip in 2012 summer from Texas to South Dakota	MRI, orbitotomy and operational surgery, PCR identification	The patient received one dose of ivermectin and a 6-week course of doxycycline, improvement
13	Chen et al	M/13/USA/2016	Cervical spinal canal	Had over a week of worsening left-sided neck pain/Bacterial meningitis was suspected and treated/A month later symptoms recurred and MRI showed an intradural, extramedullary mass within the upper cervical spinal canal/abscess formation	Not mentioned	A resident in Northeastern Arizona. Travel history not mentioned	CT, MRI, CSF analysis, Histopathological examination	After first surgery, oral Doxycycline (100 mg) twice a day for 6 weeks was administered Following second surgery, a 6-week doxycycline and oral ivermectin (9 mg, every 3 months) was administered
14	Sandell et al	M/54/Norway/2020	Left eye	Painful red eye was initially evident after a visit to Turkey/a mobile, elevated subconjunctival mass superonasally/a white thread-like structure was protruded from the lesion	Not mentioned	A Norwegian resident with Turkish nationality; The patient had been visiting his family on frequent occasions	Surgical excision, morphological, and PCR analysis	Topical steroids in tapering doses, Symptoms were gradually resolved

(1967) before the parasite was more widely recognized until 2015, whereas an in-depth exploration of updated, confirmed human case reports was provided in the present study. Accordingly, fourteen cases from six countries within the Holarctic region, particularly from Europe, had reported the occurrence of human infections. Probably, the first described human case originated from the Crimean Peninsula, where ocular infection by an *Onchocerca* sp. occurred in 1965, 2 years before the official discovery of *O. lupi* in wolf (Azarova et al. 1965). Since then, six additional suspected human cases were documented in Greece (Vakalis and Himonas 1997), USA (Burr Jr et al. 1998), Albania (Pampiglione et al. 2001), Hungary (Sallo et al. 2005), and Tunisia (Ziadi et al. 2005) from 1997 until 2005. Six years after Ziadi et al. study in Tunisia, finally, the first human case was molecularly confirmed somewhere in Turkey during 2011 as a subconjunctival painful mass, where canine onchocerciasis had never been documented (Otranto et al. 2011). *Onchocerca lupi* infections in humans are highly abundant, comparable to other *Onchocerca* spp., including *O. dewittei japonica* (Uni et al. 2015), *O. jakutensis* (Wesołowska et al. 2020), *O. gutturosa* (Takaoka et al. 1996), and *O. cervicalis*. In general, various potential hosts could be attributed to onchocerciasis, leading to species diversification phenomenon (Cambra-Pellejà et al. 2020). The primitive species of *Onchocerca* were emerged in Africa and current species possibly diverged through two evolutionary hypotheses, namely co-speciation with a particular host or host switching (Chabaud and Bain 1994). For instance, host switching may have caused *O. ochengi* (the cattle parasite) to be settled and evolved to novel species like *O. volvulus* in humans over a long period of time (Bain 1981; Cambra-Pellejà et al. 2020). Some researchers believe that domestication of animals may have played a significant role in the occurrence of host switching (Hussein et al. 1988). Maybe, *O. lupi* is undergoing such evolutionary change, since the parasite's life cycle could be completed in humans, rendering the establishment of a zoonotic onchocerciasis.

Several factors may be involved in *O. lupi* transmission to humans, including the prevalence of the infectious agent in the potential animal hosts (Takaoka et al. 2005). Very few cross-sectional animal studies (6 records) were done, mostly examined dogs in Portugal and Greece. Due to the low number of studies and lack of adequate studies on other potential hosts (cats, coyotes, etc.), we could not clearly deduce the true weighted prevalence of the parasite. Based on the investigations on dogs, a pooled prevalence of 9.49% was calculated; however, more epidemiological studies are indeed required to reach a rational conclusion. All European animal infections have been found in countries located at the Mediterranean Basin (Portugal, Spain, and Greece), which inevitably provide a favorable milieu for likely simuliid vectors of *O. lupi*. Hence, future studies should focus on this area to escalate our knowledge on the epidemiology and transmission dynamics of this zoonotic threat. In the USA, coyotes have been nominated as possible reservoirs of *O. lupi* in the Southern borders, particularly in Arizona state with highest prevalence in coyotes from Navajo county (35.4%) (Roe et al. 2020). Additionally, deforestation and urbanization on the on hand, and climate change on the other hand have all favored the increased contact between animal hosts and humans (Uni et al. 2015). This highlights the importance of a travel history to those areas favoring parasite transmission. Based on our results, four cases had abroad travel history, including two cases previously visited New Delhi (India)/Siwa (Egypt) (Biswas and Yassin 2013) and Jamaica (Cantey et al. 2016) both from USA, a German patient with a travel history to Mediterranean cities of Turkey and Tunisia (Bergua et al. 2015), and the most recent case being a Turkish man inhabiting Norway visiting his family in Turkey on frequent occasions (Sandell et al. 2020). Turkey and Tunisia are known as possible endemic areas for *O. lupi*, while there are paucity of data regarding India, Egypt, and Jamaica, which should be considered for future researches. It is also noteworthy that five cases had a travel history to areas within their country (Cantey et al. 2016; Dudley et al. 2015; Eberhard et al. 2013; Otranto et al. 2012a); most of them were USA patients previously visited and/or inhabited New Mexico and Navajo Lake in the Southwestern USA. This is consistent with the infected dogs having a travel history to New Mexico, rescued dogs from other Southwestern states and infected coyotes in Navajo country (Otranto et al. 2015; Roe et al. 2020). Accordingly, this territory is a probable hotspot for parasite circulation between different hosts and zoonotic evidences of *O. lupi* infection in the USA may exist within possibly infected animal hosts and blackflies in this area, which deserves further excavation. More recently, two additional human cases were confirmed to be infected with *O. lupi* in the USA using duplex real-time polymerase chain reaction (PCR) assay; these patients had visited Utah and New Mexico previously (de Almeida et al. 2020). Albeit, this paper was out of the scope of the systematic search criteria, and no additional information was reported, hence it was not mentioned in the list of the included papers.

Notably, the geographical distribution of vector mosquitoes is another important factor in parasite transmission. The exact vector of *O. lupi* is yet to be elucidated and only few studies have shown the potential of simuliid blackflies as a vector for this filarial nematode. In this context, Hassan et al. (2015) found six out of 213 black flies (*S. tribulatum*) in California infected with the parasite using a *cox1*-based nested-PCR assay (Hassan et al. 2015). This species is substantially abundant and widespread in North American territories, generally feeding on large mammals and only rarely humans (Adler and McCreadie 2019). As well, Latrofa al. (2018) examined 152 blackflies and mosquitoes/midges using a quantitative real-time PCR based on partial *cox1* gene and found that 8 experimentally infected specimens may have a role in parasite transmission, including 6 *Simulium* sp., 1 *S. ornatum* and 1 *S. erythrocephalum* (Latrofa al. 2018). Still, such molecular tests could not discriminate the viable/non-viable parasites and/or infective and immature larvae; hence, they fail to validate the actually competent vectors. Favorable ecological habitats for such gnats are including rocks, mud, and aquatic vegetation along with running water streams. The activity time of blackflies is mostly in the midday as well as the late afternoon (Currie and Adler 2007). Otranto et al. (2013b) showed that the highest aggregation of *O. lupi* microfilariae in skin of definitive hosts is in afternoon, which is consistent with the blackfly activity (Otranto et al. 2013b). This is a so-called circadian rhythm which orchestrates the parasite-vector interplay and warrants parasite transmission and survival (Carvalho Cabral et al. 2019). Another possible risk factor would be the international transportation of infected dogs, posing a major health threat, particularly for humans, in non-endemic regions (Colella et al. 2018a). In such areas, the parasite has displayed durable lifespan from 3 to 8 years (Hodžić et al. 2018; Verocai et al. 2016). Altogether, most human cases of *O. lupi* infection have been reported from USA and Europe, without any records from Sub-Saharan Africa, Latin America, and large parts of Asia, in spite of the fact that multiple blackfly species are endemic to these areas, some of which are known as potent vectors for *Onchocerca* spp (Grácio et al. 2015).

The spectrum of clinical consequences of *O. lupi* infection in recorded human cases were from a growing redness nasally to the eye or a subconjunctival mass frequently reported in adults, to spinal cord compression and neck movement limitation due to the cervical spinal canal involvement in under 5-year-old children. Characteristic ocular lesions due to *O. lupi* in confirmed cases were mostly itching, irritation, or blurred vision, whereas more severe signs may include eyelid drooping, conjunctival hyperemia, and ocular pain. According to our results, pain and irritation were reported in 6 out of 9 ocular cases, followed by the rectus muscle (superior and medial) involvement in three cases. It is noteworthy that all previous suspected human cases (1965–2005) had, also, reported ocular involvement such as the presence of filarioids in eye muscle tendon (Azarova et al. 1965) or anterior chamber (Burr Jr et al. 1998), rendering eyes as the most preferred organ in human cases. The unusual tropism of this nematode to the central nervous system (CNS) in some patients and lack of adequate therapeutics implicate hospitalization and explorative surgical operations to remove nodule-dwelling parasites (Dudley et al. 2015; Eberhard et al. 2013). The diversity of parasitized body parts in cases from the USA (spinal, ocular, scalp, and forearm lesions) in contrast to cases from other countries (ocular lesions) is an interesting finding in our study, and the underlying reason remains obscure (Dantas-Torres and Otranto 2020a). Curiously, a travel history to endemic areas and/or outdoor affairs beside river/lakes such as fishing and camping has been reported in most cases from the USA.

The traditional detection method for *Onchocerca* spp. has been morphological examinations, comprising the morphometric of outer cuticle crests, body thickness and the shape of the anterior end, and the presence and shape of inner cuticle striae (Grácio et al. 2015). In case of *O. lupi*, a thick and multilayered cuticle with eminent annular ridges on the external surface and internally located typical transverse striae are the distinctive features (Otranto et al. 2011). Morphological analysis is much easier to perform than other costly (molecular) and/or time-consuming (histopathological) techniques. Nevertheless, several diagnostic challenges make conventional morphological diagnosis difficult, including (i) isolation of larval/immature worms such as the case of isolated larva from the anterior chamber of a resident in OR, USA (Eberhard et al. 2012), (ii) difficulty in isolation of intact worms in most cases, and (iii) erroneous identification of the parasite as other zoonotic filarial nematodes, such as *Dirofilaria immitis* detection in a Tunisian child (Ziadi et al. 2005). In order to overcome such obstacles, molecular tools are highly recommended. Reportedly, 9 out of 14 papers utilized molecular assays for species identification of the isolated worms, mostly through amplification of *O. lupi*–specific cytochrome c oxidase 1 (*cox1*), NADH dehydrogenase subunit 5 (*nad5*), and 12S ribosomal RNA (rRNA) gene sequences. Nevertheless, only 4 out of 9 molecular studies provided the phylogenetic analysis of the isolated parasite in comparison with other animal and human isolates. In this sense, 12S rRNA gene was the most preferred sequence, showing that the isolated parasites clustered with at least *O. lupi* of canids from Portugal (Accession Number: GU365879). In other case reports that did not use molecular techniques, species identification was done through histopathological examination of the worm sections. Imaging techniques are, also, non-invasive methods of diagnosis especially for enhanced analysis of the developed mass and its anatomical location (Eberhard et al. 2013). In total, a combination of parasitological, histopathological, and, more significantly, molecular tools are highly recommended for improved diagnosis of *O. lupi* infection (Verocai et al. 2018).

Only in two infant cases reported by Eberhard et al. (2013) (22-month-old) and Dudley et al. (2015) (5-year-old), gravid female worms having microfilariae in their uterus were harvested, while in other studies nematodes were non-gravid (9 cases) or nothing was mentioned (3 cases). Possibly, mature immune responses against the parasites in adult cases may hamper worm development, such as the case of human toxocariasis (Ma et al. 2018). Surgical removal of nematodes is still the most efficient therapy in *O. lupi* human cases. Nevertheless, ivermectin and/or doxycycline were also administered in six cases reported here to heal the affected patients. Ivermectin was known for its ability to kill microfilariae of *O. volvulus* (Basáñez et al. 2008), while doxycycline makes *O. volvulus* females sterile via elimination of *Wolbachia* endosymbionts, implicated in parasite survival and reproduction (Hoerauf et al. 2008). Hence, they are also applied to *O. lupi* human cases. No dosage information was represented in three out of six case reports (Cantey et al. 2016; Dudley et al. 2015), while two cases were healed by only ivermectin administration, as 100 mg/kg once (Biswas and Yassin 2013) or 150 µg/kg/dose every 3 months for 5 years (Eberhard et al. 2013). When applicable, doxycycline was administered for a 6-week interval. An interesting finding was derived from Chen et al. study, where authors remarked that doxycycline alone may not completely eliminate the parasitic infection and oral ivermectin (9 mg) every 3 months is necessary for an absolute cure (Chen et al. 2015). Alternative less common therapeutic options were topical steroids, anti-inflammatory, and antibiotic agents along with cryotherapy; all were applied to ocular infections. Of note, intravenous corticosteroid therapy (dexamethasone) was, also, applied for the Iranian case suffering from a generalized, itching urticarial rash as well as eosinophil and IgE upsurge (Mazzotti reaction) (Mowlavi et al. 2014; Simonsen et al. 2013).

Concluding remarks

The increasing emergence of the enigmatic filarial nematode, *O. lupi*, in humans worldwide, whether due to the improved diagnostics and/or gradual host switching of the parasite, is in the limelight for potential zoonotic capacity. As well, this nematode could reproduce and complete its life cycle within human hosts, involving ocular and nervous tissues. In confirmed human cases, ocular damage was the most frequent clinical manifestation of *O. lupi* infection, whereas the most severe cases suffered from spinal cord involvement with neck pain and stiffness. Molecular identification with subsequent phylogenetic analysis must accompany with traditional diagnosis to enhance our knowledge on the true epidemiology of the parasite. The age range of affected patients, the spectrum of clinical disease, and the as-yet-unknown vector hosts demonstrate that many aspects of *O. lupi* infection are still open to question. Animal infections were mostly detected in Mediterranean countries (Portugal, Greece and Spain); hence, physician in these areas must be informed of the threat of *O. lupi* in humans. As well, most human cases were reported from the USA, particularly in those people that had visited New Mexico, representing diverse organ involvement never seen in other countries. These issues implicate a special attention to USA, mostly Southwestern states, in future studies. Finally, an urgent need is required to clarify the epidemiological status and distribution of *O. lupi* in potential hosts and vectors in many areas of the world, including Asia, Sub-Saharan Africa, and Latin America.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00436-021-07309-2.

Availability of data and material Any data from this paper would be available upon request from the corresponding author.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

Adler PH, McCreadie JW (2019) Black flies (Simuliidae) medical and veterinary entomology. Elsevier, p 237–259

Anderson RC (2000) Nematode parasites of vertebrates: their development and transmission. Cabi

Azarova N, Miretsky O, Sonin M (1965) The first instance of detection of nematode Onchocerca Diesing, 1841 in a person in the USSR. Meditsinskaya Parazitologiya i Parazitarnye Bolezni 34(2):156–158

Bain O (1981) Le genre Onchocerca: hypothèses sur son évolution et clé dichotomique des espèces. Ann Parasitol Hum Comp 56(5):503–526

Basáñez M-G, Pion SD, Boakes E, Filipe JA, Churcher TS, Boussinesq M (2008) Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. Lancet Infect Dis 8(5):310–322

Bergua A, Hohberger B, Held J, Muntau B, Tannich E, Tappe D (2015) Human case of Onchocerca lupi infection, Germany, august 2014. Eurosurveillance 20(16) https://doi.org/10.2807/1560-7917.ES2015.20.16.21099

Biswas A, Yassin MH (2013) An unexpected cause of eye irritation: a case of zoonotic ocular onchocerciasis. Case reports in infectious diseases 2013

Bosch F, Manzanell R, Mathis A (2016) First description of Onchocerca jakutensis (Nematoda: Filarioidea) in red deer (Cervus elaphus) in Switzerland. International Journal for Parasitology: Parasites and Wildlife 5(2):192–197

Burr WE Jr, Brown MF, Eberhard ML (1998) Zoonotic Onchocerca (Nematoda: Filarioidea) in the cornea of a Colorado resident. Ophthalmology 105(8):1494–1497

Cambra-Pellejà M, Gandasegui J, Balaña-Fouce R, Muñoz J, Martínez-Valladares M (2020) Zoonotic implications of Onchocerca species on human health. Pathogens 9(9):761

Cantey PT et al (2016) The emergence of zoonotic Onchocerca lupi infection in the United States - a case-series. Clin Infect Dis 62(6):778–783. https://doi.org/10.1093/cid/civ983

Carvalho Cabral P, Olivier M, Cermakian N (2019) The complex interplay of parasites, their hosts, and circadian clocks. Front Cell Infect Microbiol 9:425

Chabaud AG, Bain O (1994) The evolutionary expansion of the Spirurida. Int J Parasitol 24(8):1179–1201
Chen T, Moon K, deMello DE, Feiz-Erfan I, Theodore N, Bhardwaj RD (2015) Case report of an epidural cervical Onchocerca lupi infection in a 13-year-old boy. J Neursurg Pediatr 16(2):217–221
Colella V, Lia R, Di Paola G, Cortes H, Cardoso L, Otranto D (2018a) International dog travelling and risk for zoonotic Onchocerca lupi. Transboundary Emer Dis 65(4):1107–1109
Colella V et al. (2018b) Evaluation of oxfendazole in the treatment of zoonotic Onchocerca lupi infection in dogs. PLoS Negl Trop Dis 12(1):e0006218
Currie DC, Adler PH (2007) Global diversity of black flies (Diptera: Simuliidae) in freshwater Freshwater Animal Diversity Assessment. Springer, p 469–475
Dantas-Torres F, Otranto D (2020a) Overview on Dirofilaria immitis in the Americas, with notes on other filarial worms infecting dogs. Vet Parasitol 282:109113
Dantas-Torres F, Otranto D (2020b) Overview on Dirofilaria immitis in the Americas, with notes on other filarial worms infecting dogs. Vet Parasitol:109113
de Almeida M et al (2020) Duplex real-time PCR assay for clinical differentiation of Onchocerca lupi and Onchocerca volvulus. Am J Trop Med Hyg 103(4):1556–1562
Deplazes P, Eckert J, von Samson-Himmelstjerna G, Zahner H (2012) Lehrbuch der Parasitologie für die Tiermedizin. Georg Thieme Verlag
Dudley RW, Smith C, Dishop M, Mirsky D, Handler MH, Rao S (2015) A cervical spine mass caused by Onchocerca lupi. The Lancet 386(10001):1372
Eberhard ML, Sims AC, Bishop HS, Mathison BA, Hoffman RS (2012) Ocular zoonotic Onchocerca infection in a resident of Oregon. Am J Trop Med Hyg 87(6):1073–1075
Eberhard ML et al (2013) Zoonotic Onchocerca lupi infection in a 22-month-old child in Arizona: first report in the United States and a review of the literature. Am J Trop Med Hyg 88(3):601–605
Egyed Z et al (2001) Morphologic and genetic characterization of Onchocerca lupi infecting dogs. Vet Parasitol 102(4):309–319
Egyed Z, Sréter T, Széll Z, Nyirő G, Márialigeti K, Varga I (2002) Molecular phylogenetic analysis of Onchocerca lupi and its Wolbachia endosymbiont. Vet Parasitol 108(2):153–161
Ghasemi E et al (2020) Filarial worms: a systematic review and meta-analysis of diversity in animals from Iran with emphasis on human cases. Parasitology 147(9):909–921
Grácio AJS, Richter J, Komnenou AT, Grácio MA (2015) Onchocerciasis caused by Onchocerca lupi: an emerging zoonotic infection. Systematic Review Parasitol Res 114(7):2401–2413
Hassan HK et al (2015) Isolation of Onchocerca lupi in dogs and black flies, California, USA. Emerg Infect Dis 21(5):789
Hodžić A, Hinney B, König S, Naucke T, Duscher G, Joachim A (2018) A case of ocular infection with Onchocerca lupi in a dog from Germany. Transboundary Emer Dis 65(1):e214–e216
Hoerauf A et al (2008) Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. Med Microbiol Immunol 197(3):295–311
Hussein H, El Mannan AA, El Sinnary K (1988) Onchocerca armillata Railliet and Henry, 1909 andOnchocerca gutturosa (Neumann, 1910) in camels (Camelus dromedarius L.) in the Sudan. Veterinary research communications 12(6):475–480
Ilhan H et al (2013a) Onchocerca lupi infection in Turkey: a unique case of a rare human parasite. Acta Parasitol 58(3):384–388
Ilhan HD et al. (2013b) Onchocerca lupi infection in Turkey: a unique case of a rare human parasite. vol 58, p 384–388
Koehsler M, Soleiman A, Aspöck H, Auer H, Walochnik J (2007) Onchocerca jakutensis filariasis in humans. Emerg Infect Dis 13(11):1749
Labelle AL, Daniels JB, Dix M, Labelle P (2011) Onchocerca lupi causing ocular disease in two cats. Vet Ophthalmol 14:105–110
Latrofa MS, et al. (2018) A real-time PCR tool for the surveillance of zoonotic Onchocerca lupi in dogs, cats and potential vectors. PLoS Negl Trop Dis 12(4):e0006402
Ma G et al (2018) Human toxocariasis. Lancet Infect Dis 18(1):e14–e24
Maia C et al (2015) Onchocerca lupi nematode in cat. Portugal Emerg Infect Dis 21(12):2252
Miró G et al (2016) First detection of Onchocerca lupi infection in dogs in southern Spain. Parasit Vectors 9(1):1–3
Moher D, Liberati A, Tetzlaff J, Altman DG (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8(5):336–341
Mowlavi G, Farzbod F, Kheirkhah A, Mobedi I, Bowman DD, Naddaf SR (2014) Human ocular onchocerciasis caused by Onchocerca lupi (Spirurida, Onchocercidae) in Iran. J Helminthol 88(2):250–255. https://doi.org/10.1017/S0022149X13000060
Mutafchiev Y et al (2013) Redescription of Onchocerca lupi (Spirurida: Onchocercidae) with histopathological observations. Parasit Vectors 6(1):309
Orihel TC, Eberhard ML (1998) Zoonotic filariasis. Clin Microbiol Rev 11(2):366–381
Otranto D, Deplazes P (2019) Zoonotic nematodes of wild carnivores. International Journal for Parasitology: Parasites and Wildlife 9:370–383
Otranto D et al (2011) First evidence of human zoonotic infection by Onchocerca lupi (Spirurida, Onchocercidae). Am J Trop Med Hyg 84(1):55–58
Otranto D et al (2012b) Human ocular filariasis: further evidence on the zoonotic role of Onchocerca lupi. Parasit Vectors 5(1):84
Otranto D, Dantas-Torres F, Papadopoulos E, Petrić D, Ćupina AI, Bain O (2012c) Tracking the vector of Onchocerca lupi in a rural area of Greece. Emerg Infect Dis 18(7):1196
Otranto D et al (2013a) Vector-borne helminths of dogs and humans in Europe. Parasit Vectors 6(1):1–14
Otranto D et al (2015) Canine infections with Onchocerca lupi nematodes, United States, 2011–2014. Emerg Infect Dis 21(5):868
Otranto D et al (2012a) Human ocular filariasis: further evidence on the zoonotic role of Onchocerca lupi. Parasit Vectors 5(1). https://doi.org/10.1186/1756-3305-5-84
Otranto D et al (2013b) Cutaneous distribution and circadian rhythm of Onchocerca lupi microfilariae in dogs. PLoS Negl Trop Dis 7(12):e2585
Otranto D et al (2013c) Zoonotic Onchocerca lupi infection in dogs, Greece and Portugal, 2011–2012. Emerg Infect Dis 19(12):2000
Pampiglione S, Vakalis N, Lyssimachou A, Kouppari G, Orihel T (2001) Subconjunctival zoonotic Onchocerca in an Albanian man. Ann Trop Med Parasitol 95(8):827–832
Rodonaja T (1967) A new species of Nematode, Onchocerca lupi n. sp., from Canis lupus cubanensis. Soobshchenyia Akad Nauk Gruzinskoy SSR 45:715–719
Roe CC et al (2020) Coyotes as reservoirs for Onchocerca lupi, United States, 2015–2018. Emerg Infect Dis 26(12):2989
Sallo F, Eberhard ML, Fok E, Baska F, Hatvani I (2005) Zoonotic intravitreal onchocerca in Hungary. Ophthalmology 112(3):502–504
Sandell T, Skogen AR, Lier T, Pettersen FO (2020) Human ocular Onchocerca lupi infection diagnosed in Norway. International Journal of Travel Medicine and Global Health 8(4):170–173
Simonsen PE, Fischer PU, Hoerauf A, Weil GJ (2013) The filariases manson's tropical diseases: Twenty-Third Edition. Elsevier Ltd, p 737–765
Sréter T, Széll Z (2008) Onchocercosis: a newly recognized disease in dogs. Vet Parasitol 151(1):1–13
Takaoka H et al (1996) Second case of zoonotic Onchocerca infection in a resident of Oita in Japan. Parasite 3(2):179–182

Takaoka H et al (2005) An Onchocerca species of wild boar found in the subcutaneous nodule of a resident of Oita. Japan Parasitol Int 54(1):91–93

Uni S et al (2010) Zoonotic filariasis caused by Onchocerca dewittei japonica in a resident of Hiroshima Prefecture, Honshu. Japan Parasitol Int 59(3):477–480

Uni S et al (2015) New zoonotic cases of Onchocerca dewittei japonica (Nematoda: Onchocercidae) in Honshu. Japan Parasites & Vectors 8(1):1–10

Vakalis N, Himonas C (1997) Human and canine dirofilariasis in Greece. Parassitologia 39(4):389–391

Verocai GG et al (2016) Onchocerca lupi nematodes in dogs exported from the United States into Canada. Emerg Infect Dis 22(8):1477

Verocai GG, Nelson KJ, Callahan RT, Wekesa JW, Hassan HK, Hoberg EP (2018) A cryptic species of Onchocerca (Nematoda: Onchocercidae) in blackflies (Simulium spp.) from southern California, USA. Parasites & vectors 11(1):1–11

Wesołowska M et al (2020) Onchocerca jakutensis ocular infection in Poland: a new vector-borne human health risk? Parasit Vectors 13(1):1–4

WHO (2014) Onchocerciasis. World Health Organization, Regional Office for the Eastern Mediterranean

Ziadi S et al. (2005) La dirofilariose sous-conjonctivale humaine: à propos de deux cas tunisiens. Journal Français d'Ophtalmologie 28(7):773. e1–773. e4