



Human Oral Dirofilariasis: A Case Report and Comprehensive Literature Review

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Abstract

Many case reports indicate that human oral dirofilariasis is rare and has presented the case as a diagnostic challenge to dentists and oral surgeons due to similarity in clinical presentation with tumors. However, an in-depth review of the literature resulted in finding more than 80 cases of oral dirofilariasis reported throughout the world. There is a lack of awareness among dentists and oral surgeons about the rapidly spreading zoonotic infection. This paper presents a case report of a 25-year-old male patient diagnosed with dirofilariasis in his right buccal subcutaneous nodule. Besides the case report, the paper also presents the parasitic infection process, factors contributing to the spread of the infection, common clinical symptoms, diagnostic methods, treatment options and ways to control the infection. The paper brings about various knowledge gaps that need in-depth study. The primary objective of this work is to spread awareness among dentists and oral surgeons about the rapidly spreading zoonosis and highlight the need for a coordinated effort to control the infection.

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Keywords

Oral Dirofilariasis; Cheek; *D. Repens*

Introduction

Human oral dirofilariasis is zoonotic filariasis caused by infection with several species of worms belonging to the genus *Dirofilaria*. There are more than 40 recognized species of *Dirofilaria* with *Dirofilaria repens* was frequently reported to be the cause of oral dirofilariasis in humans [1]. The definitive hosts of these parasites are mainly carnivorous, especially canines and felines, with mosquitoes being the vectors carrying the infection to humans [2,3]. *Dirofilaria* is mainly transmitted to humans via bites of *Anopheles*, *Aedes*, *Ochlerotatus*, *Culex*, *Culiseta* and *Coquillettidia* genera mosquitoes [3-5]. While humans are considered accidental hosts, the infection does leave local inflammation, nodule and granuloma formation in the oral region [6]. Most often, these infections begin as asymptomatic and are often misunderstood as cancer nodules [7-9]. Unless the parasite becomes visible to the naked eye, the oral surgeons or clinicians are unlikely to suspect the parasitic nature of the nodule [10]. It must be kept in mind that human cases of oral dirofilariasis are most probably underreported because many of them remain undiagnosed or unpublished. Lack of reliable, inexpensive and rapid diagnostic tools, limited understanding of parasitic biology, along with limited awareness of symptoms caused by the infection make diagnosis difficult for oral surgeons [11]. This leaves clinicians to go for a differential diagnoses approach. One of the biggest problems with the differential diagnosis approach is the health care cost for the patient [12]. reported that the average cost incurred by a patient due to differential diagnosis of dirofilariasis in the US is upwards of 80,000\$ back in 2005 [12]. The experience of the authors had been that there is a tendency among some patients to procrastinate treatments owing to socio-economic challenges when a definitive diagnosis is not done immediately. This approach leads to dirofilariasis infection detected many months after initial infection [13]. In other cases, the patients are subjected to severe psychological problems when the diagnosis is not clear as they are likely to link the nodule to cancer. Third, in some cases, when not diagnosed properly in a timely manner the parasite can migrate causing confusion for dentists and clinicians leading to therapeutic challenges [14].

The earlier reviews were both more comprehensive and focused on dirofilariasis on the whole which includes other dirofilariasis species or review of the maxillofacial dirofilariasis cases [3]. Chaudhry, et al., reported in the literature without highlighting the knowledge gaps, diagnostic procedures, or guidelines needed for dentists or oral surgeons to make a necessary diagnosis. In addition to case report, this paper attempts to shed light on causes, clinical presentations, diagnostic tools and treatment plans currently available to oral

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surgeons/clinicians to count dirofilariasis as one of the possible diagnoses to augment disease control efforts in humans, thus reducing public health concerns. The review also brings out the knowledge gaps wherever needed [15].

Case Report

In 2015, a 25-year-old man, poultry farm worker from Mandya, South India presented with a swelling on the right buccal mucosa (Fig.1). The swelling was intermittent in nature and the patient gave a history of multiple episodes of enlargement of the right side of the face for 3 months. No systemic symptoms like fever/weight loss were observed during this time. Extraoral examination revealed a diffuse swelling in the right side of the face causing mild facial asymmetry. The swelling was firm in consistency and the overlying skin appeared to be normal. Intra orally, an oval shaped nodular swelling measuring 1 × 1 cm, was noticed in the buccal mucosa. The nodular lesion was firm in consistency, mobile and slightly tender. The patient was treated with Amoxicillin without symptomatic relief. Extra-oral radiographs did not show any bone lesion. Chest X-rays showed no abnormality. Ultrasound of right cheek region showed a well-defined hypo echoic lesion measuring 2.0 x 1.0 x 1.8 cm noted in the right cheek subcutaneous plane. No internal vascularity was found within the nodule. It also showed linear echogenic strands with movements. It was reported as a lesion in the right cheek subcutaneous plane-a possible parasitic infestation. FNAC was performed with a wide bore needle in different planes and a live worm was aspirated from the nodule measuring about 8-10 cm. The live worm was sent to microbiology department for identification of the parasite in 70% ethanol solution. Later the lesion was excised under local anesthesia with blunt and sharp dissection of the nodule in the submucosal plane (Fig. 2). The specimen was fixed in a 10% buffered formalin solution and embedded completely in paraffin wax. Later the parasite was sent to veterinary hospital and the species was identified. Patient was prescribed albendazole, an anti-helminthic drug for five days as the live worm confirmed the presence of a parasite in the buccal mucosa [16].

A thorough microbiological examination revealed a thick laminated cuticle with external longitudinal ridges and the presence of a well-developed circumferential musculature interrupted by two lateral cords was identified in relation to the retrieved specimen which was characteristic features of *Dirofilaria* species. Microbiological exam revealed the actual length of the worm to be around 10.5 +/- 0.1 cm with a thickness of 0.35 cm pointing to an adult worm. Cuticle was found to be 20 µm thick. This was followed by the cutting and staining of the multiple 0.5 cm thick sections of the worm with hematoxylin and eosin. The live worm was a female worm giving us a suspicion if there were any larvae (microfilaria) present somewhere else in the body, but we had no confirmation about the presence of a male worm. Modified

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Knott Test, as prescribed by Genchi, et al. [17], was done to confirm the presence of microfilaria. Meanwhile, the patient was prescribed Albendazole and Ivermectin for a week. For this specimen the sediment was poured on two slides and Leishman and Giemsa differential staining techniques were used, respectively, to stain the two slides (Fig. 3). The stained slides showed the presence of non-sheathed microfilaria. Furthermore, Conventional Polymerase Chain Reaction (CPCR) conducted on worm confirmed the species as *D. Repens*. Patient was prescribed diethyl carbamazine for another week to kill the other microfilaria present. Patient was called for regular follow up to two years and was asymptomatic.



Figure 1: Clinical presentation of the swelling in the right buccal mucosa.

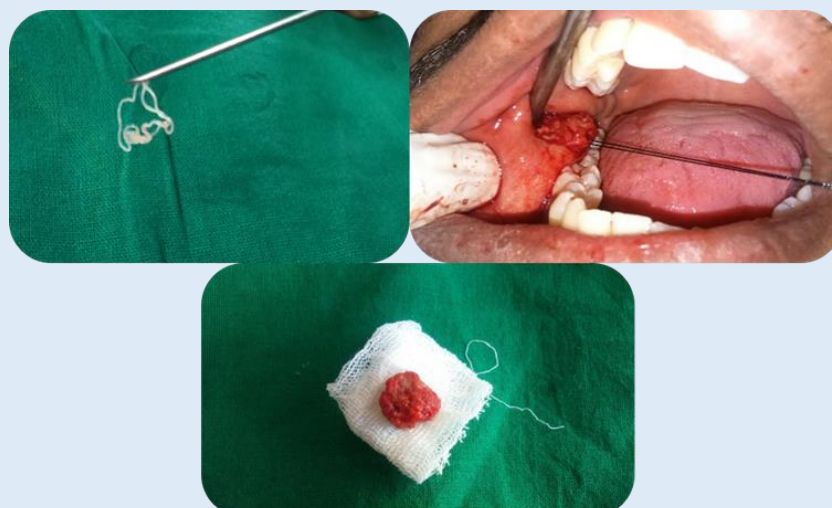


Figure 2: Showing live parasite from FNAC (Top left), subcutaneous nodule on the right buccal mucosa (Top right) and excised lesion (Bottom).

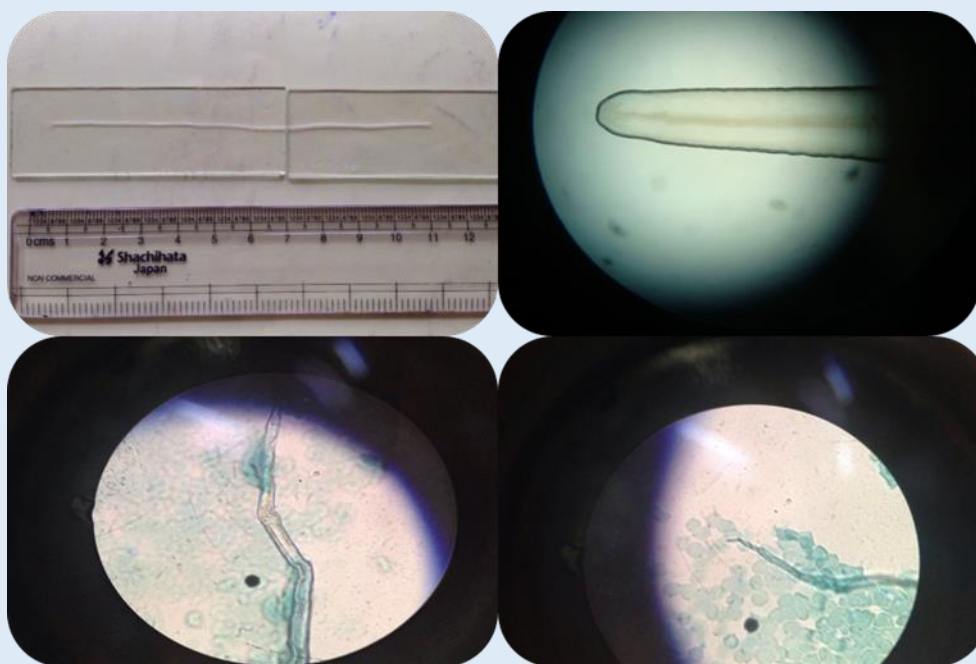


Figure 3: Adult female parasite dirofilaria (Top left), microscopic cross section (Top right), Knott Test-Microscopic blood Picture of microfilaria (bottom pictures).

Literature Review Methodology

The review of all the oral dirofilariasis cases shown in was done on papers collected from PUBMED, Science direct, google scholar and Wiley. In some cases, the non-English articles cited by articles in English were also collected, translated into English using google translate, to confirm the authenticity of the data presented in the English article. The oral dirofilariasis cases reported in non-English articles by Pampiglione, et al., were cited as it is without obtaining the original articles [16,18,19].

Pathophysiology of Parasitic Infection

Fig. 4 shows the life cycle of *D. Repens*. It comprises of a definitive host and a vector that can infect numerous mammalian species like domestic and wild feline and canine groups which act as reservoirs [3]. *D. Repens* worms are present in the subcutaneous and intramuscular connective tissues of canines and felines. After mating *D. Repens*, being ovoviviparous, releases microfilaria into the blood of canine and less so in feline which is picked up by the mosquito during its blood meal. The vectors are females of various mosquito species of the Culicidae family (genera: *Culex*, *Aedes*, *Ochlerotatus*, *Anopheles*, *Armigeres*, *Coquilettidia* and *Mansonia*) that are able to transmit dirofilariae [19-21]. In the mosquito which is the

intermediate host, the microfilaria lodges in the Malpighian tubules where microfilaria (L1) molt into second (L2) and third (L3) larval stages [22]. It is important to recognize that the percentage of microfilaria taken during blood meal that complete their development into infective L3 larva can vary between 0 and 100%. The infective L3 migrate to the proboscis of the mosquito until it is transmitted to the next definitive host [3]. When the bloodsucking mosquito feeds on dogs, cats, humans, the infective larvae L3 penetrate into the hosts. It must be recognized that transmission of infective larvae to mammalian hosts is an ineffective process with only 55% chance of transmission [12]. Once the infective larva is deposited in dogs and cats, the mature adult worm is formed in the mammalian host when the L3 migrate to the subcutaneous tissue and undergo two additional molts (from L3 to L4 and to pre-adult worms). These pre-adult worms further develop into adult worms and produce more microfilaria in the blood stream [22]. However, in humans, the vector lodges the L3 larva in the subcutaneous and intramuscular tissue of various regions in the body. This larva grows into adult male or female worm. While many articles in the literature report that humans are accidental host and these worms don't reach sexual maturity, there were many cases where microfilaremia observed in the humans [23,24] including in the case we reported in this paper. Only one study has reported the presence of two live worms-both male and female worms [25]. Interestingly, in this case, no microfilaria was seen in peripheral blood. No predisposing factors are known to explain why in some cases microfilaria develop in the blood stream. It is still not clear how a single adult female worm found in human infection cases developed microfilaremia without a male worm found and further study needed to know more about the same [3,22,26].

Fig. 5 shows various factors influencing the rate of infection in a given ecological region. These factors are: (i) number of pets infected with dirofilariae and (ii) climatic and environmental factors that determine the dirofilaria species larval development in mosquitos iii) Vectorial capability [3,27,28]. As far as number of pets infected in the geographical area is dependent on number of pets in the area and pet management such as proper diagnosis, application of proper chemotherapy and sterilization procedures [3]. The other reason for a possible infection is the geographical region to which the pets are exposed. Transportation of pets to and from endemic areas are more likely to increase the scope of infection to non-endemic regions [27].

Climatic and environmental factors are expected to play a significant role in increasing dirofilariasis infection by altering the survival rates of parasite and vector [22,28,29]. Poor sanitation and drainage systems can lead to increased growth of vector species [30,31]. Additionally, it was experimentally shown that the larval development to infective L3 in the mosquito is temperature dependent and takes about 8-13 days at 27-30 °C, 10-12 days at 24-26 °C, 16-20 days at 22 °C and this increases to 28 days at 18 °C [32]. Below 14 °C, the development of the larva is arrested although it can be restarted when the temperature goes above this threshold [33]. This also means summer temperatures are enough to foster the development of dirofilaria even in non-endemic colder climatic regions. Based on the study

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done on mosquitos from Corsica Island, there is a 10 time increase in infection rate of dirofilaria between the month of April and August [34]. While the timing may vary depending upon the geographical area, there is an increased risk due to climate change. In addition to the larvae development, a rapid geographical expansion of some invasive mosquitoes and/or the increase in their density, such as what happened in northeastern Europe, was also attributed to climate change [26,35]. With the abundance of mosquitoes, increased infective and lifetime of mosquitos, increased concentration of vector capable of transmitting infective larvae can lead to enhanced rate of infection. A mathematical model by Gutiérrez-Jara, et al., showed that there is likelihood of >300% increase in case incidence between 2027 and 2037 when the vector population remains active for 9 months of a year [28]. A possibility of significant increase in case incidence in coming years warrants not only educating veterinarians, oral surgeons, dermatologists and physicians about the zoonotic importance of filarial nematodes but to have an integrated approach and coordination of activity between clinicians and the veterinary service.

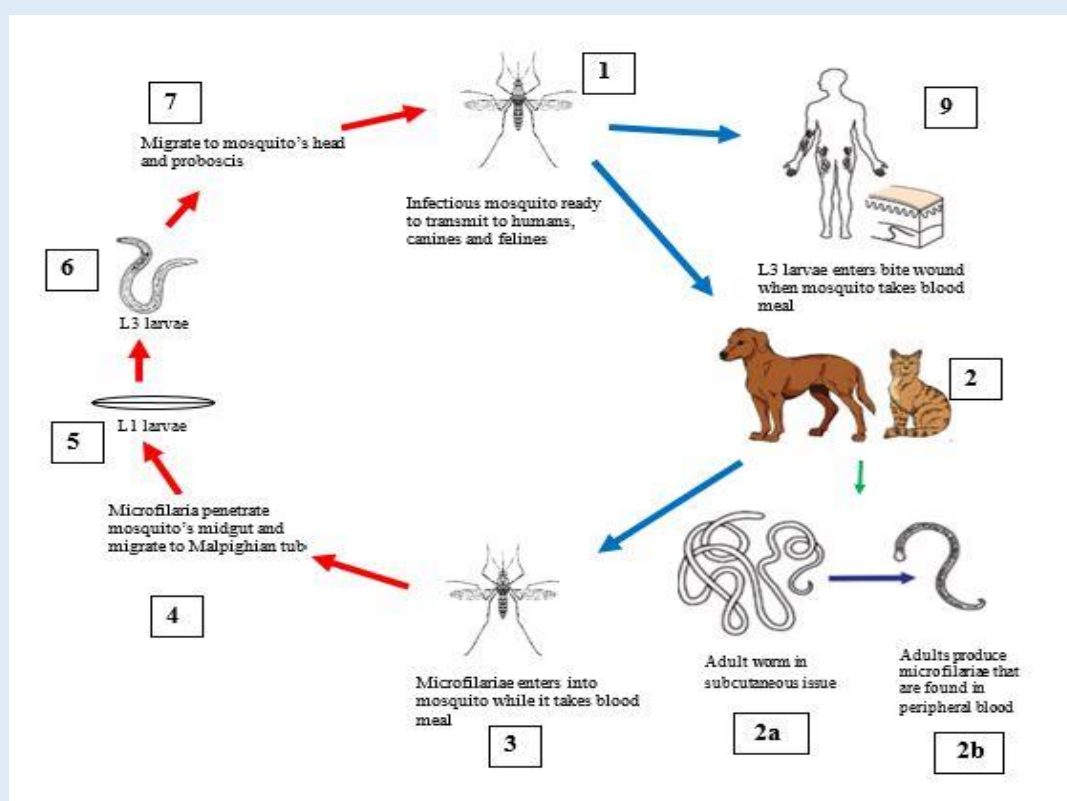


Figure 4: Life cycle of *D. Repens* Adapted from CDC website [36].

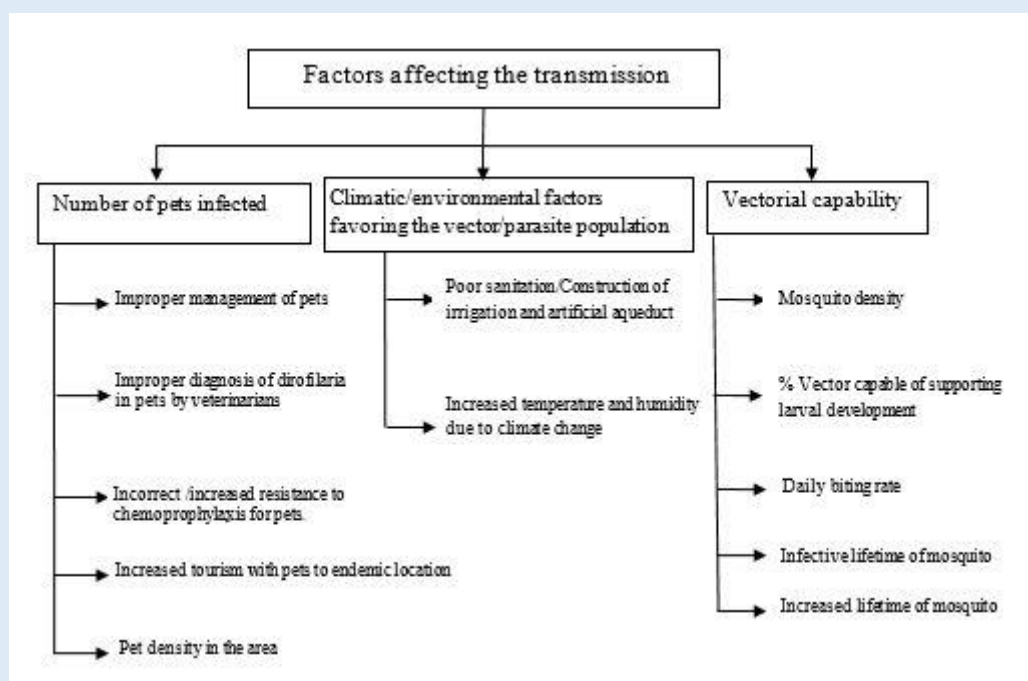


Figure 5: Factors affecting of transmission rate [3,22,27,32].

Clinical Presentations

Dirofilariasis infection in the oral region can manifest as an inflammatory reaction in surrounding tissues and may have various clinical presentations depending on the site of infestation. After the bite of an infective mosquito, a stronger reaction with erythema, swelling, granuloma formation and pruritus have been reported [6,25,37]. This reaction usually occurs closer to mosquito bite [16]. The subsequent formation of the nodule in which the nematode remains trapped by the defensive reaction of the host is an essential feature, typical of the parasitosis and of which it may prove to be the sole clinical manifestation. The nodules are usually 1 to 2 cm in diameter, well encapsulated by a rim of fibrous tissue of variable thickness and they move through soft tissues until blocked by the host's defense mechanism [1]. The nodules are often accompanied by swelling, erythematous and itchiness, sometimes painful and rarely by fever [18].

The oral dirofilariasis manifests as swelling in cheek, lip, buccal mucosa regions, oral cavity and tongue [15]. Table 1 shows the list of oral dirofilariasis cases reported in the literature. The maximum cases were found on cheek (58% of cases) and followed by buccal mucosa (19% of cases). This is not unexpected as cheek is one of the exposed parts for mosquito to bite. Clinical diagnosis of dirofilariasis is usually done on a differential diagnosis basis with the initial diagnosis being cyst, adenoma, malignancy, hematoma, lipoma, abscess and a wide range of differentials except dirofilariasis [38]. It was suggested that a nodule appears approximately

after a period of approximately 2-12 months from the penetration of the parasite, although much longer periods cannot be ruled out since it is often impossible to recall the moment when infection took place [1]. In most of the cases a single worm subadult/adult worm was found within the nodule. Occasionally, these worms develop to a mature adult, fertilizes and releases microfilaria into bloodstream [22,24]. While it is generally considered that human hosts are unsuitable for completion of the *D. repens* life cycle [39], the detection of microfilaria suggests sexual maturity of worms. However, per knowledge of the author, as of date there is only one study that has reported the presence of both male and female worms in the same case with no manifestation of microfilaria [25].

In some cases, the worm within the nodule was reported to migrate throughout various parts of the body causing diagnostic difficulty to clinicians. One such example was reported by Hennocq et al. where the nematode migrates to various parts of the body of patient in a span of few days in what is called as creeping dermatitis [14]. The paper also notes that the nematode migrated 6 cm over a span of 24 hours. Similarly, Antolova also reported movement of the parasite throughout the body [23]. While this is a problem to clinician, the stress suffered by the patient during the time elapsed between the discovery of the nodule and the identification of the parasites, or when migrating or emerging worms are detected should not be underestimated. Furthermore, if the nematode is not removed, it is presumed that it will die and degenerate. Granuloma formation often follows, with "calcification or abscess production and subsequent expulsion of the organism within the surrounding purulence" [40]. Therefore, it is vital for the physician or oral surgeon to consider creeping dermatitis in their clinical presentation and diagnosis.

The review of the literature, as summarized in Table 1, shows that oral dirofilariasis was observed on patients of all age group from <1 year to 80 years with about 75% of reported cases fall in the age group of 20-59. Also, there is no big difference in prevalence of cases between genders (48% for female versus 52% for male) (Fig. 6). One possible explanation for higher case incidence in the age group for 20-59 years can be attributed to larger amount of time spent in outdoor activities or the discrepancies might merely be caused by the small size of our study population and the possibility of missed cases due to the lack of a central reporting system. The reporting of cases can be fixed by improving the working relationship among oral surgeons, physicians, dermatologists with histopathologists and parasitologists [41]. Additionally, Best Known Practices (BKP) from other countries such as creating central reporting system, educating all the stake holders, together with digital documentation of reference laboratory data of every confirmed case can increase the pre-surgery clinical diagnosis [41].

Except for the cases from USA, all other cases where worm type was identified were found to be caused by *D. Repens*. The cases from USA were found to have *D. tenuis*. The data in Figure

6 also reflects that India (22%) has topped the list followed by Sri Lanka (20%) and Italy (~12%), in the reported number of cases which could be credited to one or more of the following: wide range of climatic conditions, huge population density, large rural population, lack of personal hygiene, reduced availability of preventive health-care facilities, abundance of stray animals and vectors, reduced education, awareness among masses and reduced veterinary facilities [15].

Country	Year	Age/Sex	Site	Worm Type	Citation
Austria	2000	59/M	Cheek	D.Repens	[42]
Austria	2009	52/M	Cheek	D.Repens	[43]
Brazil	2015	65/F	Buccal mucosa	D.Repens	[44]
Bulgaria	2018	37/M	Buccal mucosa	D.Repens	[45]
China	2003	42/F	Buccal mucosa	D.Repens	[46]
France	2014	52/F	Cheek	D.Repens	[47]
France	2019	40/F	Cheek	D.Repens	[14]
France	1982	42/M	Cheek	D.Repens	[48]
France	1999	66/M	Cheek	D.Repens	[49]
France	2007	35/M	Cheek	D.Repens	[50]
France	1983	19/M	Cheek	D.Repens	[16]
France	1987	47/M	Cheek	D.Repens	[16]
France	1993	29/M	Cheek	D.Repens	[16]
France	1993	56/M	Cheek	D.Repens	[16]
Greece	2009	46/F	Cheek	D.Repens	[51]
Greece	1996	26/F	Cheek	D.Repens	[52]
Greece	1990	48/F	Cheek	D.Repens	[53]
Georgia	1983	28/F	Tongue	D.Repens	[18]
Hungary	2008	62/M	Cheek	D.Repens	[42]
India	1999	39/F	Lip	D.Repens	[54]
India	2010	45/M	Cheek	D.Repens	[55]
India	2013	28/M	Cheek	D.Repens	[25]
India	2013	30/M	Cheek	D.Repens	[56]
India	2013	54/F	Buccal mucosa	D.Repens	[57]
India	2013	27/F	Cheek	D.Repens	[13]
India	2015	32/M	Buccal vestibule	D.Repens	[8]
India	2014	32/M	Cheek	NR	[58]
India	2020	58/F	Buccal mucosa	D.Repens	[37]
India	2018	37/F	Buccal vestibule	D.Repens	[59]

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India	2015	32/M	Buccal mucosa	D.Repens	[6]
India	2014	19/F	Buccal mucosa	D.Repens	[60]
India	2011	45/F	Cheek	D.Repens	[61]
India	2011	39/F	Parotid	D.Repens	[61]
India	2011	40/M	Cheek	D.Repens	[62]
India	2012	54/F	Cheek	D.Repens	[63]
India	2019	26/M	Retromolar	NR	[15]
India	2015	25/M	Buccal mucosa	D.Repens	
Italy	2001	4/M	Cheek	D.Repens	[1]
Italy	1999	27/F	Cheek	D.Repens	[19]
Italy	1993	53/M	Lip	D.Repens	[64]
Italy	1864	20/M	Lip	D.Repens	
Italy	1937	18/M	Cheek	D.Repens	[16]
Italy	1967	71/M	Cheek	D.Repens	
Italy	1967	54/F	Cheek	D.Repens	
Italy	1987	25/M	Mandibular	D.Repens	
Italy	1988	37/F	Cheek	D.Repens	
Italy	2021	20/M	Cheek	D.Repens	[65]
Iran	2002	34/M	Cheek	D.Repens	[66]
Russia	2006	32/F	Cheek	D.Repens	[67]
Russia	2010	30/F	Parotid	D.Repens	
Russia	2003	23/F	Oral cavity	D.Repens	[68]
Russia	2003	43/F	Cheek	D.Repens	[68]
Russia	1997	55/F	Lip	D.Repens	[7] ,[19]
		31/M	Cheek	D.Repens	
Russia	1997	18/F	Cheek	D.Repens	[69],[19]
		33/F	Cheek	D.Repens	
		35/F	Soft palate	D.Repens	
Serbia	2017	45/M	Buccal Mucosa	D.Repens	[70]
Serbia	2021	48/M	Cheek	D.Repens	[71]
Sri Lanka	1997	0.8/F	Cheek	D.Repens	
		3/M	Cheek	D.Repens	[72]
		28/M	Cheek	D.Repens	
Sri Lanka	2003	26/F	Buccal mucosa	D.Repens	[9]
Sri Lanka	2003	04/F	Buccal mucosa	D.Repens	
Sri Lanka	2003	80/F	Buccal mucosa	D.Repens	
Sri Lanka	2003	52/F	Buccal mucosa	NR	
Sri Lanka	2003	28/F	Buccal sulcus	D.Repens	

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Sri Lanka	2003	40/F	Buccal mucosa	NR	
Sri Lanka	2003	53/M	Lip	NR	
Sri Lanka	1999	65/F	Cheek	D.Repens	[73]
Sri Lanka	1999	45/M	Cheek	D.Repens	
Sri Lanka	1999	80/F	Cheek	D.Repens	[74]
Sri Lanka	2015	21/M	Cheek	D.Repens	[75]
Sri Lanka	2015	57/F	Cheek	D.Repens	
Sri Lanka	2013	0.9/M	Cheek	D.Repens	[76]
Tunisia	2010	40/F	Lip	D.Repens	[77]
Turkey	2002	62/M	Premasseteric soft tissue	D.Repens	[10]
UK	2010	32/M	Parotid	D.Repens	[78]
UK	1992	12/M	Parotid	D.Repens	[36]
USA	2016	79/M	Buccal Mucosa	D.Repens	[79]
USA	1993	56/M	Cheek	D. Tenui	[38]
USA	1995	66/M	Cheek	D. Tenui	[80]
USA	2004	73/M	Cheek	D. Tenui	[81]
M: Male; F: Female					

Table 1: List of Oral dirofilariasis cases reported in literature.

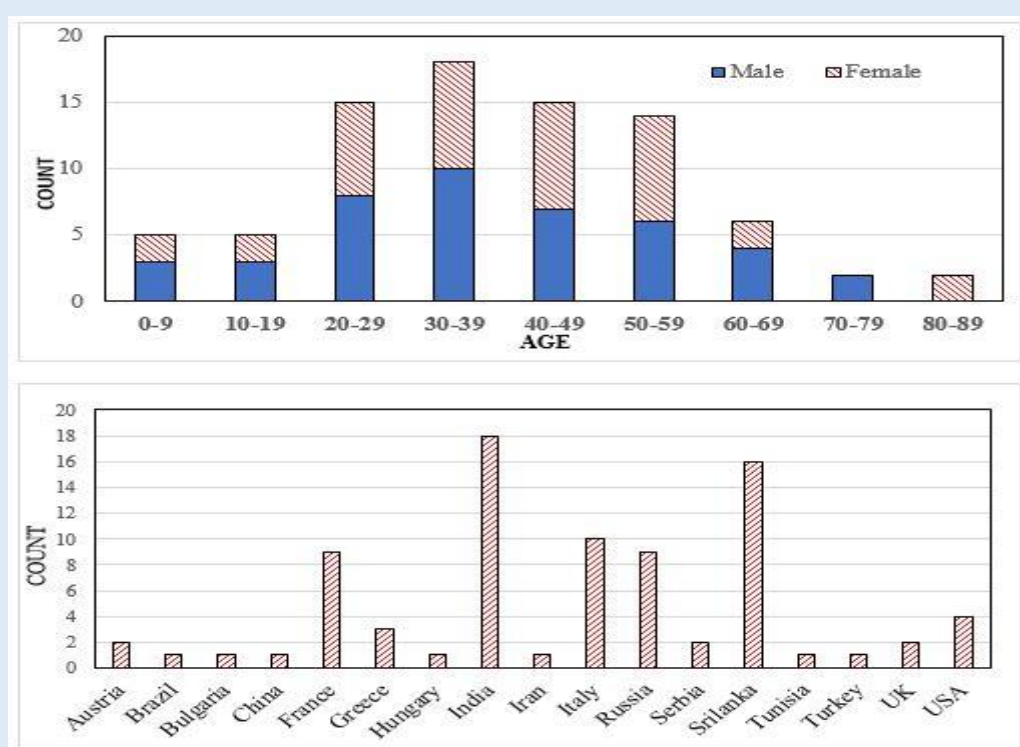


Figure 6: (Top) Age/ sex predilection of Oral dirofilariasis, (Bottom) Country-wise distribution of Oral dirofilariasis.

Diagnosis

Diagnosis of human dirofilariasis typically starts with patients reporting subcutaneous nodules, worm, oedema, pain or tenderness, itching, feeling discomfort and experiencing foreign or moving object [82]. Given there is no well-defined protocol for the diagnosis and there is no reliable laboratory technique to confirm clinical suspicion straight away, this needs to be approached on differential diagnosis method. The typical approach for oral surgeon is to suspect nodules as, cyst allergic reactions or malignancy of odontogenic or non-odontogenic origin [82]. On such a situation, it is better to ask the patient about the local or distance migration of the nodule. During history taking, it is also important for clinician to take travel history of patient months preceding the onset of symptoms into consideration particularly if the patient is from non-endemic areas [83]. In the endemic areas (Mediterranean regions of Europe and North Africa, the Caribbean and the southeastern US, South Asia) it is better for oral surgeons or physicians to inform the patients that “Oral dirofilariasis” as an emerging infection and is a possible differential to be considered [15,22,82].

When diagnosing such patients, techniques like Enzyme-Linked Immunosorbent Assay (ELISA), Indirect Hemagglutination (IHA) and DNA detection by PCR have been reportedly used as screening tests for zoonotic *Dirofilaria* infections which has not proven sensitive or specific enough for humans. Ermakova used ELISA technique to determine the diagnostic accuracy of serological procedure and found its sensitivity (the proportion of individuals with a positive test result among patients with surgically removed helminths) and accuracy (a correct test result in the total number of results, both positive and negative) to be only ~75% and 83% [94]. Similarly, Katharina Riebenbauer, showed that antibodies and eosinophilia were detectable only on 74% and 56% of patients with confirmed dirofilariasis in Austria, respectively [84]. Moreover, the antibody levels were found to be moderate. High false negative result is a serious issue with serological tests.

The other problem with serological tests is lack of specificity between *D. Repens* and other nematodes. The specificity of the tests is very much dependent upon careful selection of dirofilaria antigens [14]. The antigens chosen for such tests in humans must be shown not to react with antibody in humans against *Toxocara canis*, *Ascaris lumbricoides*, *Strongyloides Ancylostoma duodenale* and *Necator americanus* [12]. All of these nematodes potentially expose humans to antigens and will, therefore, stimulate an antibody response. Detection of antibodies against the dominant *Wolbachia* Surface Protein (WSP) is another way to improve the specificity of serology [41]. Moreover, lack of circulating microfilaria in blood in most cases eliminates the possibility of using DNA detection of the parasite as a reliable tool for diagnosis. Given the low pretest probability of detecting dirofilariasis from serological

analysis, this technique should only be used in combination with other techniques [3,72]. There is a need for a serological diagnosis that is reliable, quick and simple to perform.

Imaging techniques like Orthopantomograms (OPG), CT and Magnetic Resonance Imaging (MRI) can all be used in eliminating other possible differentials which are both odontogenic and non-odontogenic in origin. Orthopantomograms using digital planimetry is most useful clinically for diagnostic problems requiring broad coverage of the jaws which can be used to rule out of cysts and tumors in and around oral cavity [85]. CT is useful in assessing acute inflammatory processes and abscesses as well as cysts and neoplasia in and adjacent to salivary glands. MRI is the diagnostic tool for soft tissue imaging and contrast resolution with details of adjacent vital structures with superior display. So far only one case was able to use MRI for figure out dirofilariasis [86]. Low probability detection of filariasis and the expensive nature of this method makes it less desirable technique for diagnosis of dirofilariasis as an independent technique.

Compared to other imaging techniques, USG combined with color Doppler charting allows for a pre-surgery specific diagnosis of filariasis [41]. This technique is the least expensive with high impact. USG can reveal the inner contents of the nodule. Fig. 7 shows an example of USG. The presence of live worms is indicated by the winding hyperechoic textures, sometimes with visible spontaneous writhing movements. Live worms look like multiple continuing and sharp but fine tubular textures [87]. Dead worms show the same structures but they are motionless, non-continuous, mostly blurred and broken, with areas of high and low echo density. This characteristic allows the attribution of the origin of the nodule to a helminthic origin, probably *Dirofilaria*, when epidemiological data is known. Once the worms are detected, microfilaria in the blood can be detected using fresh blood, filter test and modified Knott tests. Among these tests, Modified Knott test is widely used because of its sensitivity and specificity [17,24]. While Fig. 8 shows the possible methods in management of Oral dirofilariasis, Table 2 shows a list of diagnostic tools widely used and their advantages and disadvantages in detecting dirofilariasis.

In most of the cases, the final diagnosis of oral dirofilariasis was done through the histological examination of worm and infected tissue either collected through Fine Needle Aspiration Cytology (FNAC) or surgery. The microscopic features of the biopsy sample can be characterized into four possible groups as described by Pampiglione [1]:

1. Most common- Inflammatory reaction leading to a necrotic lesion with neutrophils, eosinophils and chronic inflammatory cells (Histiocytes, Plasma cells, Histiocytes and Giant cells) with or without dead and degenerated worm inside the nodule
2. Pitted centralized area with segments of nematodes which was delimited by an acute and chronic inflammatory cells

Sreenandini AR| Volume 3; Issue 1 (2022) | JDHOR-3(1)-045 | Review Article

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3. Less common category- Necrotic worm which is surrounded by scant reactive tissue. Central area was delimited with formation of dense fibrous ring made of fibroblastic tissue which was surrounded occasionally by non-specific inflammatory cells
4. Rarely, some nodules are similar to reactive lesion caused by a foreign body

Besides the infected tissue, the worm was collected and analyzed for the morphological features, diameter of the body, presence of external the thickness of the cuticle and its structure, the presence of external cuticular ridges, the digestive tract, the male or female sexual tubules, the male genital cells, the female genital cells and, in pregnant females, the microfilaria inside the uterus of the worm all of which can be used in identifying sex, maturity and type of dirofilarial species [88]. For example, the adult females and males of worms can be 100-170 mm (4.6-6.3 mm diameter) and 50-70 mm (3.7-4.5 mm in diameter) in length, respectively. Pampiglione et al. presented histological cross sections of males and females of worms that were in different states of preservation at time of removal [88]. Positive identification of the worm is dependent on the extent of the preservation of the worm inside the nodule [88]. It is not uncommon for the filaria to die inside the inflammatory nodule where inflammatory cells destroy parasite destroying morphological characteristics leading to diagnostic difficulty [88]. In such cases, it can be suggested to use PCR [89]. PCR can also be used on live worms which can confirm the species of dirofilaria.

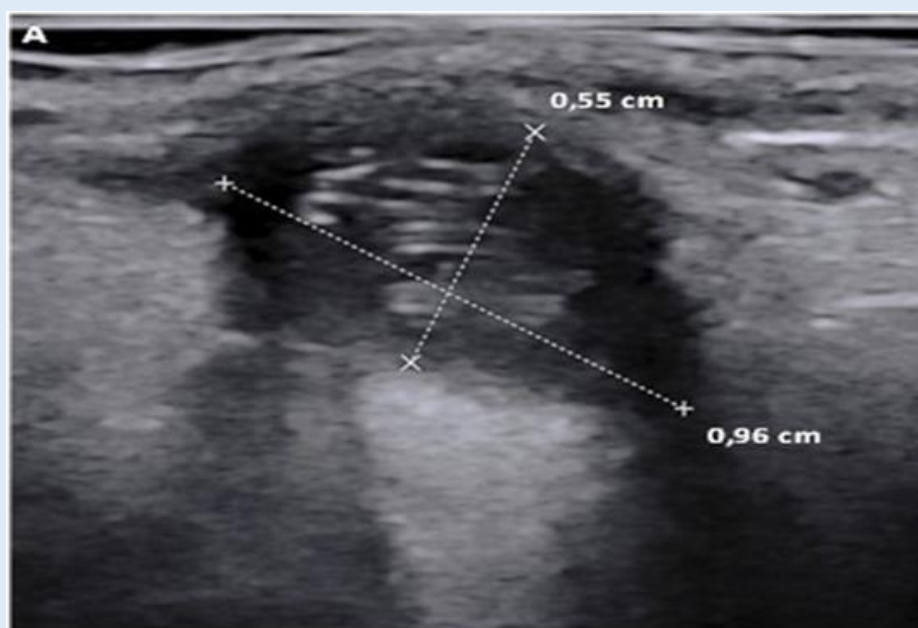


Figure 7: USG of cystic lesion approximately of 1 cm in diameter, localized in the submucosa of the left superior maxillary vestibule, containing an echogenic fluid and a solid filiform mobile worm-like structure with echogenic posterior reinforcement taken from Trunfio et al. [87].

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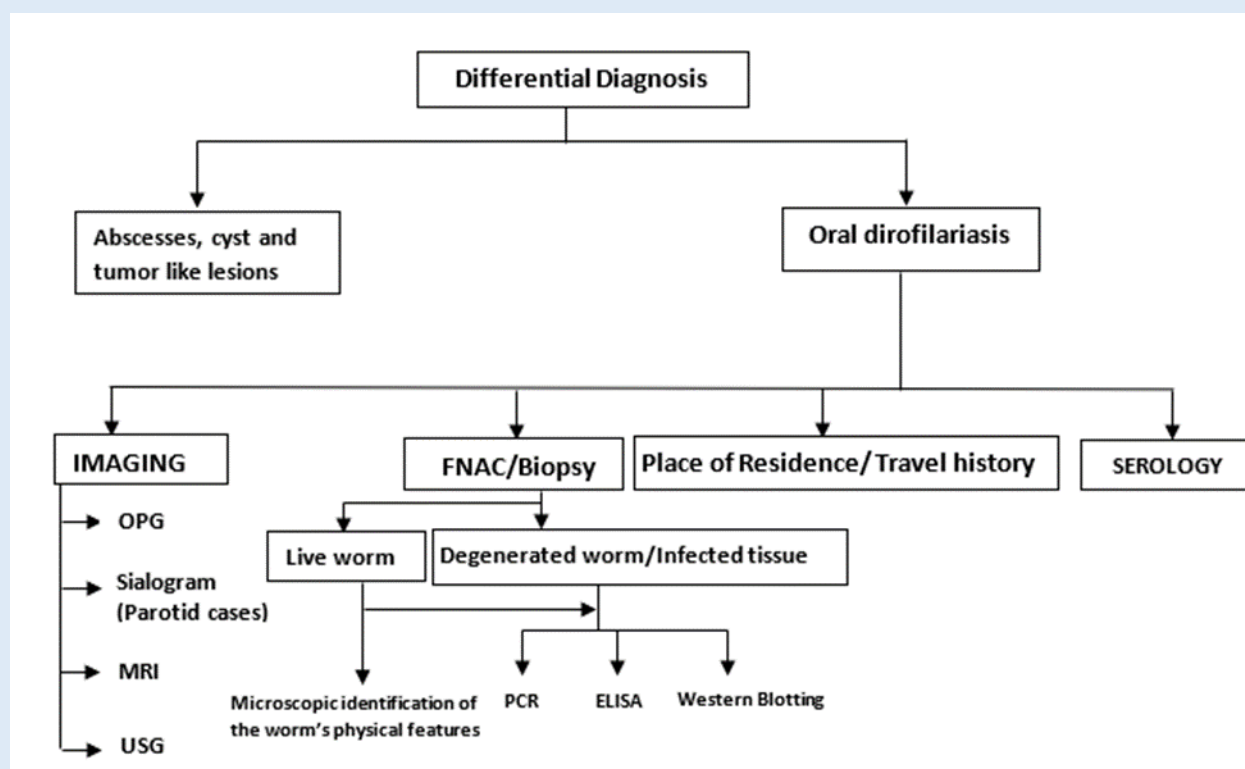


Figure 8: Flow chart for differential diagnosis of Oral dirofilariasis [17,41,90].

Technique	Objective	Advantages	Disadvantages	Comment
Fresh blood smear	To find microfilaria	✓ Rapid ✓ Inexpensive	✓ Very low sensitivity ✓ Frequent false negative ✓ No species diagnosis ✓ Need a trained operator	✓ Widely used on dogs and not on humans. ✓ Intensity of microfilaria in blood is not correlated to adult worm
Modified Knott test	To find microfilaria	Sensitive and specific: microfilaria belonging to different species can be differentiated	✓ Time consuming, ✓ Need of a skill operator with good knowledge of microfilaria morphology	✓ Widely used on dogs and humans. ✓ Intensity of microfilaria in blood is not correlated to adult worm.

				✓ Can be performed on blood before and after surgery ✓ Morphological features of the microfilaria of <i>D. repens</i>: 300-360 μm, width: 6-8 μm ✓ Recommended to use larger than 1 ml blood sample (Pupić-Bakrač et al. 2021)
Filter test	To find microfilaria	✓ Rapid and sensitive and less specific ✓ No need for a centrifuge apparatus	✓ Expensive (tests are sold as kit, Difil Test Evsco); ✓ The lysate solution shrinks the microfilaria and new measurement standards are required to differentiate species	Intensity of microfilaria in blood is not correlated to adult worm.
Microscopic technique	To determine the nematode and sex	Inexpensive and readily available	✓ Time consuming ✓ Need of a skill operator with good knowledge of microfilaria morphology ✓ Not an effective technique against dead or degenerated worms	Need PCR if the worm is dead or degenerated to determine the nematode

PCR	To find specific nematode and its sex	An alternative method for diagnosing cases where, microfilaria testing is positive but antigenic testing is negative.	Less sensitive as immunological reaction is mainly triggered by microfilaria in humans, in cases without microfilaremia low titers and antibodies cross reactivity is highly possible	The biopsy material as well as parasites intended for PCR should not be stored in formalin due to its destructive effect on fragments of genomic DNA and the polymerase. More effective on worms and not on
ELISA	To detect female adult worm's antigens	✓ Rapid and easy to perform ✓ Reasonably sensitive.	✓ Expensive. ✓ Can generate many false positive/negative results especially when male worms are present ✓ Can only be used as a complementary technique	✓ Factors affecting sensitivity of the tests - age, number of female worms versus number of male worms ✓ Can be used to assess the efficacy of adulticide therapy ✓ Specificity with complex antigens can be improved by using antigenic complexes of 26-40 kDa polypeptides in <i>D. Repens</i> (ESDA 2017)
Ultrasonography (USG)	Imaging technique to identify live worm activity	✓ Easily available ✓ Inexpensive	Not helpful in identifying the specific nematode.	Can be used only on superficial regions

	inside the nodules			
MRI	Imaging technique helpful when nodules are in deeper region like soft palate	Easily available	✓ Expensive ✓ Not helpful in identifying the specific nematode or live worms	Gives detailed description of the nodule in all the three planes with possible description of vital structures

Table 2: Diagnostic tools for Dirofilariasis [17,91].

Management of Oral Dirofilariasis

The treatment of choice for oral dirofilariasis is surgery. Complete excision of the nodule in toto is both diagnostic and therapeutic. In cases where the nodule is static, no additional chemotherapeutic treatment is required as microfilaria is extremely rare in blood sample. Furthermore, localization of nodule and the worm depends on the immunological response of each patient [24]. However, active migration of the nodules can make the surgery complicated. Ermakova, et al., found that the usage of albendazole and doxycycline stopped the migration of the worm and resulted in formation of fixed nodule, after which the nodule was removed surgically [92]. Jelinek recommended usage of oral ivermectin plus diethylcarbamazine as an effective therapy post-surgery [93]. Lechner, et al., also found initial trial with doxycycline to be effective against filarial diseases such as onchocerciasis and lymphatic filariasis through eliminating Wolbachia, resulting in a long-term embryo static effect and sterility of adult female worms, with a sustained reduction in micro filarial loads [94]. In above mentioned cases, there was no recurrence of oral dirofilariasis or microfilaria was seen in blood even after a year post surgery. From author's perspective, due to lack of understanding of role by immunodeficiency on recurrence of infection or lack of guidelines for treatment, it is safe to recommend few doses of ivermectin and doxycycline post-surgery.

Control and Prevention of Human Dirofilariasis

Control and prevention of human dirofilariasis need a multipronged approach:

1. Reduce mosquito population by improving sanitation, close open wafer storage and increased use of mosquito larvicides [31]

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2. Reduce mosquito bites in humans by applying repellants and wearing protective clothing
3. Preventing infection in dogs by having a routine check-up of the dogs for circulating microfilaria and administration of diethylcarbamazine during and after summer season [3]
4. Educating epidemiologists, pathologists, veterinarians and clinicians about spread of human dirofilariasis can be helpful [15]. Creating a working group among them can draw attention towards the source of the problem i.e., to eliminate the zoonotic infection from canines and felines
5. Creating a centralized database, updating of epidemiological and clinical data regarding human dirofilariasis, generally or in particular region, can raise the attention of clinicians to consider this infection in differential diagnosis of unexplained nodules [41]
6. In non-endemic regions, it is critical to ask for travel history of the patient to endemic areas to include this as part of differential diagnosis [95]
7. In endemic areas, physicians should inform about the emerging infection to reduce the psychological pain of the patients [12,41]

Conclusion

Oral Dirofilariasis is a zoonotic disease that is emerging into a global problem. Global warming has led to increase the zoonotic transmission capability of vector (mosquito) from animals to humans. This expanded the geographical distribution of the disease. The rapid expansion of the disease in addition to limited awareness of clinical presentation and infection risk among the dentists exacerbated the problem. This article aims to spread awareness of oral dirofilariasis to dentists by showing the clinical presentations of this zoonotic infection, advantages and disadvantages of various diagnostic tools and the need to consider oral dirofilariasis as part of differential diagnosis for effectively countering the disease. The article also stresses on the importance of creating central reporting system, educating all the stake holders, together with digital documentation of reference laboratory data of every confirmed case to increase the pre-surgery clinical diagnosis. Creating a collaborative working group of dentists, clinicians, epidemiologists, pathologists and veterinarians can not only help in diagnosis but also eliminate zoonotic disease from canines and felines.

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Conflict of Interest

There are no conflicts of interest.

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Sreenandini AR | Volume 3; Issue 1 (2022) | JDHOR-3(1)-045 | Review Article

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