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Review

Leishmaniasis in Northern Cyprus

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ABSTRACT

Leishmaniasis is a vector-borne disease that is caused by *Leishmania* parasites. Sandflies are the vectors, and dogs are the primary reservoir of *Leishmania* spp. Cutaneous leishmaniasis (CL) is the most common form of the disease, whereas visceral leishmaniasis (VL) is the most severe form and is generally fatal if left untreated. The disease is seen in 98 countries and distributed through three regions on five continents. The island of Cyprus is located in the eastern part of the Mediterranean region where leishmaniasis is endemic. The presence of sandflies, canine leishmaniasis (CanL), and human VL and CL cases has been documented in Northern and Southern Cyprus. CanL cases were found at various rates between 1.9% and 13.2% in Northern Cyprus. In 1990, Leishmanin skin test positivity was detected in Northern Cyprus, and *Leishmania infantum* was found to be the infecting agent. In 2016, three pediatric VL cases caused by *L. infantum* were reported in Northern Cyprus. More recently, in a study conducted in Kyrenia District, three seropositive individuals have been detected. In the study, seven individuals, including the seropositive persons, were found to have a history of CL. Consequently, these studies indicate the presence of leishmaniasis in Northern Cyprus. Therefore, vector and reservoir control programs should be implemented for prevention of the disease.

Keywords: Cutaneous leishmaniasis, *Leishmania donovani, Leishmania infantum*, Northern Cyprus, visceral leishmaniasis

INTRODUCTION

Leishmaniasis is a vector-borne disease that is caused by obligate intracellular protozoa belonging to *Leishmania* species. Vectors of *Leishmania* parasites are phlebotomine sandflies, whereas animals, primarily dogs, serve as a reservoir for parasites (1). In addition to dogs, mice, foxes, cats, and also humans can be a reservoir for leishmaniasis (2). Leishmaniasis is endemic in the tropical and subtropical regions, as well as the Mediterranean Basin (1). The disease is seen in 98 countries and distributed through three regions on five continents (3).

The disease has four clinical forms. These are visceral leishmaniasis (VL) (also known as kala-azar), post-kala-azar dermal leishmaniasis (PKDL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis. According to the World Health Organization, nearly 1.3 million new cases of leishmaniasis (300,000 visceral and 1 million cutaneous or mucocutaneous forms) occur annually (3).

Visceral leishmaniasis is the most severe form of leishmaniasis. It is generally fatal if it is left untreated. The disease is characterized by fever, weight loss, splenomegaly, hepatomegaly, and anemia (4). Approximately 90% of VL cases are reported from Bangladesh, Brazil, Ethiopia, India, Nepal, South Sudan, and Sudan. Annually, 20,000-50,000 people are estimated to die from VL (3). Occasionally, VL can develop into a cutaneous disease (PKDL) following treatment (3). In this case, macular, maculopapular, or nodular rash is present as skin lesions. Post-kala-azar dermal leishmaniasis is typically seen in Sudan and less frequently in other countries of eastern Africa and the Indian region. Owing to the high number of organisms in the lesions, these patients can be a reservoir for infection with sandflies and maintain transmission of VL (1).

The most common form of leishmaniasis is CL. The primary skin lesions are ulcers that leave scars and cause severe disfigurement. Approximately 95% of CL cases are reported in the Mediterranean Basin, the Middle East, Central Asia, and the region of the Americas (4). In mucocutaneous leishmaniasis, destructive lesions occur in the mucosa of the nose, mouth, and throat. Approximately 90% of cases are documented from Brazil, Peru, and Bolivia (4).

Leishmaniasis is an important concern for public health in the Eastern Mediterranean Region. Both CL and VL are endemic in this region (5). Owing to climate changes, the area covered by sandflies is expanding in the Mediterranean region, leading to the emergence of leishmaniasis in this region (6).

Cyprus is situated in the eastern part of the Mediterranean region between 34° and 35° northern latitudes and 32° and 34° eastern longitudes. The island has a Mediterranean climate, in which summers are generally hot and dry and winters are mild (7). In the island, canine leishmaniasis (CanL) was prevalent before 1945, and *Phlebotomus tobbi* was shown to be the vector of *Leishma-*

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nia infantum (8). The sandfly fauna consisting of *Phlebotomus* and *Sergentomyia* species in Cyprus was documented for the first time in the 1940s (7). However, the number of sandflies declined considerably due to the malaria eradication program implemented between 1940 and 1950. Additionally, the control program against echinococcosis between 1970 and 1975 resulted in a remarkable decrease in the number of dogs. For these reasons, the prevalence of CanL reduced substantially in Cyprus for more than two decades after these campaigns. However, discontinuation of these programs led to an increase in the number of sandflies and dogs, and as a result, CanL cases occurred again (8).

This review will provide an overview of the literature on sandfly vectors, CanL, and human leishmaniasis cases reported on the island, with a particular focus on Northern Cyprus.

CLINICAL AND RESEARCH CONSEQUENCES

Sandfly Studies in Northern Cyprus

Various sandfly species have been demonstrated in Northern Cyprus. In the study conducted by Demir et al. (7), a total of nine *Phlebotomus* and three *Sergentomyia* species were identified among sandflies collected from 20 different residential settings in Northern Cyprus. The localities with the greatest number of sandfly species diversity were found to be Lapithos (Lapta) and Leonarisso (Ziyamet) with 12 and 9 different species, respectively (Figure 1). The highest number of *Phlebotomus* species was noted to be *Phlebotomus galilaeus*, which was followed by *Phlebotomus papatasi* and *P. tobbi* (7).

Töz et al. (9) collected sandflies from different localities in Kyrenia and Lapithos and detected six *Phlebotomus* and three *Sergentomyia* species. Among *Phlebotomus* species, *P. tobbi* was found at the highest rate, followed by *P. papatasi* and *P. galilaeus*. The authors did not detect any *Leishmania* promastigotes in sandflies (9). Notably, Ergunay et al. (10) identified *L. infantum* in eight pools of *P. tobbi* in Northern Cyprus. Among the positive pools of *P. tobbi*, three were obtained from Lapithos, whereas five were collected from Panagra (Geçitköy), a locality close to Lapithos (10). These residential settings are indicated in Figure 1.

CanL Cases in Northern Cyprus

Owing to the increased number of sandflies and dogs, a number of studies have been conducted to investigate CanL cases. In 2004, 3 (3.61%) of 83 dogs were found to be positive for CanL in Klepini (Arapköy), a village in the Kyrenia District. Of the 83 dogs, 2 were found to be positive by indirect fluorescent antibody test (IFAT) and rK39 test, and 1 was found to be positive by polymerase chain reaction (PCR) only. Additionally, borderline positive results were obtained in 13 (15.66%) dogs by IFAT. In the same study, three of five clinically suspected dogs were detected to be positive for CanL by PCR in 2012 (9).

In 2016, seropositivity in dogs was found to be 1.9% (n=2/105), whereas 1 (0.95%) dog was noted to be borderline positive by IFAT in Northern Cyprus. The seropositive dogs were noted to be from Kyrenia (n=1) and Famagusta (Magosa) (n=1), whereas the dog that was found to be borderline positive (n=1) was from Nicosia (Lefkoşa) (11). Another study published in the same year found CanL seropositivity to be 3.55% (n=10/281) by IFAT in Northern Cyprus. Rates of seropositivity were 1.72% (n=1/58) in Trikomo (İskele), 13.20% (n=7/53) in Kyrenia, 1.67% (n=1/60) in Famagusta, and 3.33% (n=1/30) in Morphou (Güzelyurt). The study found no CanL seropositivity in Nicosia (12).

Human Leishmaniasis Cases in Northern Cyprus

In Cyprus, human leishmaniasis was not investigated comprehensively in the past, and the presence of two infantile VL cases has been reported in humans since 1935 (8). Thereafter, only a few studies have investigated the presence of leishmaniasis. In 1990, Leishmanin skin test positivity was detected to be 10% in Kyrenia and 35% in Lapithos in Northern Cyprus. The causative agent was found to be *L. infantum* by DNA hybridization (13).

More than two decades later, in 2016, three pediatric VL cases were reported from Northern Cyprus. The first patient was a 16-month-old female from Vuno (Taşkent) in Kyrenia District. The second and third cases, both from Aytrias (Sipahi) in the Karpasia Peninsula, were 24-month-old female and 34-month-old male patients, respectively. All of three cases were detected to be positive by IFAT (1≥1/128), direct agglutination test (DAT; ≥1/400), and rK39 test. *Leishmania* amastigotes were identified in Giemsa-stained slides of each bone marrow aspirate. Furthermore, PCR and restriction fragment length polymorphism analyzes of the aspirates indicated that the causative agent was *L. infantum* in three VL cases. Patients were successfully treated with liposomal amphotericin B (14).

Figure 1. Map of Cyprus indicating the localities of reported visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and canine leishmaniasis (CanL) cases; sandflies (only in particular settings) in Northern Cyprus. Positive Leishmanin skin test results: Kyrenia (K) and Lapithos (La). Three pediatric VL cases: Vuno (V) and Aytrias (A). CL in a traveler: Lapithos (La). Seven past CL cases, including three seropositive individuals: Kyrenia District. Seropositivity in dogs: Kyrenia (K), Klepini (Kl), Trikomo (T), Famagusta (F), and Morphou (M); borderline positive result in Nicosia. Highest number of sandfly species diversity: Lapithos (La) and Leonarisso (Le). *Leishmania infantum* (+) in *Phlebotomus tobbi*: Lapithos (La) and Panagra (Pa). Polis (CL case in a traveler) and Paphos (a family cluster of four CL cases) located in the Greek Cypriot territory are also indicated in the figure. (The map was adapted from: http://www.worldatlas.com/webimage/countrys/europe/outline/cy.htm)

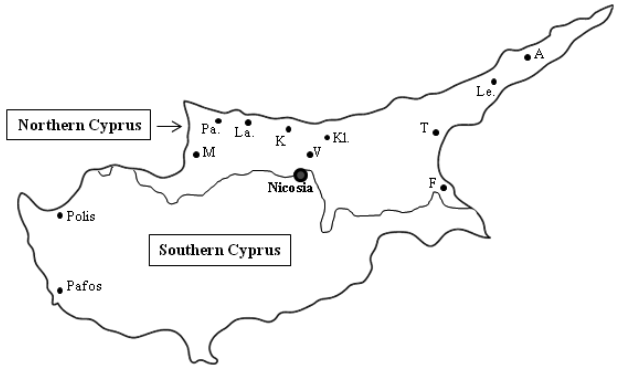

Table 1. Summary of reported human and canine leishmaniasis cases in Northern and Southern Cyprus in chronological order

	Northern Cyprus			Southern Cyprus		
Case	**Case definition**	**Reference**	**Ref. no.**	**Case definition**	**Reference**	**Ref. no.**
Human leishmaniasis	Positive Leishmanin skin test results in Kyrenia and Lapithos (1990). *L. infantum* is the causative agent.	Deplazes et al.	(13)	Three CL cases caused by *L. donovani* MON–37 (2006).	Antoniou et al.	(16)
	CL related with travel to Northern Cyprus. The causative agent is *L. donovani* complex.	de Silva et al.	(19)	Two VL cases caused by *L. infantum* MON–1 (2006).	Antoniou et al.	(16)
	Three pediatric VL cases caused by *L. infantum*.	Sayili et al.	(14)	CL associated with travel to Southern Cyprus. The causative agent is *L. donovani*/infantum complex.	Poeppl et al.	(18)
	Three (1.2%) seropositive individuals and 7 (2.8%) past CL cases (including the seropositive individuals) among 249 participants.	Ruh et al.	(15)	A family cluster of four CL cases caused by *L. donovani*.	Koliou et al.	(17)
Canine leishmaniasis	Three (3.61%) positive and 13 (15.66%) borderline positive results among 83 dogs (2004).	Töz et al.	(9)	CanL cases caused by *L. infantum* MON–1. Overall CanL seroprevalence was found to be 1.7% (1996).	Deplazes et al.	(13)
	Three CanL positive cases among five clinically suspected dogs (2012).	Töz et al.	(9)	Co–infection in a dog with L. infantum MON–1 and *L. donovani* MON–37.	Antoniou et al.	(16)
	Two (1.9%) seropositive and 1 (0.95%) borderline positive results in 105 dogs.	Beyhan et al.	(11)	CanL cases caused by mostly *L. infantum* MON–1. Seroprevalence was found to be 14.9%.	Mazeris et al.	(8)
	Ten (3.55%) seropositive results in 281 dogs.	Çanakçı et al.	(12)			

CL: cutaneous leishmaniasis; VL: visceral leishmaniasis; CanL: canine leishmaniasis

More recently, the presence of VL was evaluated in the Kyrenia District of Northern Cyprus, where CanL and sandflies were detected previously. Among 249 study participants, 3 (1.2%) were found to be seropositive, whereas the remaining 246 were found to be negative by serological tests. Two out of three participants (68- and 54-year-old males) were detected to be positive by DAT, and their serum antibody titers were 1:1600. The third case (18-year-old male) was detected to be positive by rK39 test. Furthermore, 7 (2.8%) of 249 participants, including the seropositive cases, had a history of CL (15).

The localities where human and CanL cases were reported in Northern Cyprus are indicated in Figure 1.

Studies from Southern Cyprus

The presence of sandflies, CanL, and human leishmaniasis in Southern Cyprus (Greek Cypriot territory) was also demonstrated by several studies. In 1996, CanL cases caused by *L. infantum* MON-1, the predominant zymodeme in the Mediterranean region, were detected in Southern Cyprus. In that study, the overall seroprevalence of CanL was found to be 1.7% (13). A later study reported the seroprevalence of CanL as 14.9% in Southern Cyprus. The parasite isolates collected from dogs were identified as *L. infantum* MON-1 and *L. infantum* MON-98 with rates of 98.4% and 1.6%, respectively. Additionally, in the study, *P. tobbi*, *P. galilaeus*, and *P. papatasi* were documented to be prevalent among *Phlebotomus* species collected (8).

In 2006, three CL (44-, 50-, and 55-year-old) and two VL cases (9-month-old and 73-year-old) were detected in humans in Southern Cyprus. These isolates were defined as *Leishmania donovani* MON-37. Additionally, in a dog living in the region where the three human CL cases were found, *L. infantum* MON-1 and *L. donovani* MON-37 were detected. This was interpreted in terms of a co-infection with two parasite species in the dog (16). In a village of the Paphos District in Southern Cyprus (Figure 1), a familial cluster of four CL cases developed by *L. donovani* was documented in 2014. Cases included a 6-year-old male patient,

a 60-year-old female patient, a 60-year-old male patient, and a 40-year-old female patient, respectively. The lesion in the third case self-resolved, whereas the other patients were administered liposomal amphotericin B (17).

Leishmaniasis Cases Associated with Travel to Cyprus

In the literature, there are also reports of CL cases that are related to travel to Cyprus. One of the patients (59-year-old female) had a history of a 2-week stay in Polis in the Greek Cypriot territory (Figure 1) 8 months before the diagnosis. The causative agent was identified as *L. donovani*/*infantum* complex, and the patient was successfully treated with miltefosine (18). Another case of CL (54-year-old male) spent 3 days in Lapithos in Northern Cyprus (Figure 1) 6 months before the onset of disease. The causative agent was detected to be *L. donovani* complex, and the patient was successfully treated with sodium stibogluconate (19).

Reported cases of human leishmaniasis and CanL in Northern and Southern Cyprus are summarized in Table 1.

Possible Transmission Cycles in Northern Cyprus

Previously, it was postulated that there are two cycles of leishmaniasis transmission in Cyprus. One of them involves *L. infantum* that causes CanL, and the second transmission is anthroponotic where *L. donovani* causes CL and VL in humans (17). The findings obtained in Southern Cyprus are consistent with this (8, 13, 16, 17). However, the types of transmission cycles in Northern Cyprus are yet to be cleared, as there are limited data on the molecular characteristics of *Leishmania* species infecting humans and dogs. Zoonotic transmission of *L. infantum* to humans is likely to occur, since *P. tobbi* (7) and CanL (9, 11, 12) have been demonstrated in different localities in Northern Cyprus. Nevertheless, considering that *P. tobbi* can be the vector for both *L. infantum* and *L. donovani* (8), the possibility of *L. donovani* transmission in humans cannot be ignored in Northern Cyprus. This hypothesis is strengthened by two facts. First, *L. donovani* is present in Southern Cyprus (16, 17). Second, a close genetic relationship was found between *L. donovani* isolates in Southern Cyprus and the strains in Turkey. It was also suggested that Turkey might be the origin of the Cypriot isolates (17, 20). Therefore, detailed analyzes should be conducted to better understand the molecular characteristics of *Leishmania* species in Northern Cyprus.

CONCLUSION

Previous and recent studies on leishmaniasis indicate that the disease is present in both humans and dogs in Cyprus (8, 9, 11-17). In Southern Cyprus, *L. donovani* MON-37 was found to be the primary zymodeme responsible for both CL and VL cases in humans (16). While a dog was found to be co-infected with both *L. donovani* MON-37 and *L. infantum* MON-1 (16), the major cause of CanL cases was detected to be *L. infantum* MON-1 in Southern Cyprus (8, 13). Studies from Northern Cyprus did not identify the detailed molecular characteristics of CanL cases (9, 11, 12), whereas *L. infantum* was reported as the infecting agent in human cases in this territory (13, 14). Moreover, *L. donovani* complex was shown to be responsible for a CL case in a traveler who visited Northern Cyprus (19).

Consequently, results obtained from the studies highlight that leishmaniasis is of concern not only in the south but also in the north of the island. Moreover, the presence of sandflies (7, 9, 10) and CanL cases (9, 11, 12) suggests that vector and reservoir control programs should be implemented in Northern Cyprus. In addition to the preventive measures, more studies are essential to investigate leishmaniasis in additional localities of the Turkish Cypriot territory. Furthermore, detailed molecular characteristics of *Leishmania* species should be identified in Northern Cyprus to evaluate their relationship with the parasites in Southern Cyprus and the neighboring countries.

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