Chapter 7

Leishmaniasis in Tunisia: History and New Insights into the Epidemiology of a Neglected Disease

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Additional information is available at the end of the chapter

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Abstract

In Tunisia, both cutaneous (CL) and visceral leishmaniases (VL) are historical diseases that have been described since the nineteenth century. Cutaneous form is more prevalent than the visceral one. It is caused by three taxa (*Leishmania major, Leishmania infantum*, and *Leishmania killicki* synonymous *Leishmania tropica*) and six zymodemes (MON-1, MON-8, MON-24, MON-25, MON-80, and MON-317). Among these dermotropic zymodemes, sand flies vectors and reservoir hosts were identified for only three ones. Transmission cycles of *L. infantum* MON-24 and MON-80 and L. *killicki* MON-317 are still unknown. Zoonotic CL is largely distributed and covers mainly the sub-arid and arid bioclimatic stages. Nevertheless, it has recently spread to the humid and sub-humid stages in northern Tunisia. Sporadic and chronic CL are less prevalent with limited geographical distribution. Visceral leishmaniasis (VL) is mainly infantile that affects children of <13 years. It is caused by the single taxon *L. infantum*. Transmission cycle of this parasite is zoonotic but not well elucidated. Three zymodemes are responsible for the genesis of VL (MON-1, MON-24 and MON-80). Only the transmission cycle of *L. infantum* MON-1 is identified. Geographically, VL is mainly distributed in the humid, sub-humid, and semi-arid bioclimatic stages of the country. Despite the large progress of knowledge in the ecoepidemiology of leishmaniases in Tunisia, many parameters of the transmission cycles of these taxa are still unknown and need further investigations to identify them.

Keywords: *Leishmania*, cutaneous leishmaniasis, visceral leishmaniasis, epidemiology, Tunisia

1. Introduction

In the Mediterranean basin region, both cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) are well established diseases with an estimated annual incidence ranges from 239,500

to 393,600 and from 1200 to 2000 cases, respectively. In Tunisia (North Africa, South Mediterranean basin), leishmaniases are largely spread causing a serious public health problem. Clinically, both CL and VL are encountered in this region. Nevertheless, the cutaneous form is most prevalent and largely distributed. Visceral leishmaniasis is less prevalent in this region with a zoonotic transmission of the causative agent.

In Tunisia, leishmaniases are historical. Indeed, the first documented cutaneous case was reported in 1884, while the first VL case was in 1904. Nevertheless, these infectious diseases were stayed neglected for a long period and the epidemiological investigations were scarce. Indeed, an analysis of the published research on leishmaniases in Tunisia over about a century (1884–1980) showed around 20 published items. From the beginning of 1980s of the last century, the number of publications has increased from 5 publications (1981–1985), to 14 publications (1991–1995), 41 publications (2001–2005), and 85 publications (2011–2015).

The aim of this chapter is to review the history of leishmaniases in Tunisia and to present the new insights into the epidemiological features of this disease. This includes clinical forms, transmission cycles, and geographical distribution.

2. Body

As many other regions of the Mediterranean basin, Tunisia is an endemic focus for both cutaneous and visceral leishmaniases. Each of these two clinical forms has its own epidemiological profile.

2.1. Cutaneous leishmaniases

Cutaneous leishmaniasis refers to a dermal lesion which appears at the site of the infected sand fly bite. The lesion is usually painless and characterized by a gradual evolution. It firstly appears as a tiny erythema, which then develops into a papule and nodule that can ulcerate within 2 weeks to 6 months. It heals gradually over months or years. Although CL is mild and not life threatening, its disfiguring lesions and scars with altered pigmentation severely affect the social and psychological functioning of the affected individuals causing anxiety, depression, decrease in body satisfaction, and low quality of life [1–3]. The clinical form of CL lesions varies between patients, reflecting different species of parasite, different virulence degree inside the same species or a difference in the immunological status of patients.

The first real documented case of CL in Tunisia date from 1884 in the region of Gafsa, south Tunisia [4, 5]. Indigenous people named it "Habb El Seneh" (sore of a year) or "Bess El Tmeur" (evil of the dates) related to their supposition that the disease is the result of the consumption of dates, sting of palms or the drinking of the water [6]. In 1882, Achard, military physician in Gafsa, gave the infection the name of "Clou de Gafsa" (boil of Gafsa). It was only in 1905 that Nicolle and Cathoire made microbiological analysis of the sore scraping and reported the presence of small oval bodies sized of 4 μm similar to those already described by Wright in 1903 in the oriental sore [7–9]. While Wright proposed the name *Helcosomatropicum* to the

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reported protozoa, Nicolle as well as other authors named them *Leishmania tropica* [6]. In 1908, Nicolle made the first isolation of the parasite by using the Novy-MacNeal media and inoculated it to the monkey *Macacus sinicus* in order to reproduce the boil of Gafsa [10].

Given that the Gafsa boil was almost observed on the uncovered parts of the body, that the infection was restricted to some cities of Gafsa near water sources, and that patients reported the bite of insects few days before the onset of the lesion, Billet supposed that the infection is transmitted by the bite of the mosquito Pyretophorus chaudoyei [11]. It was only in 1921 that the brothers Sergent proved the transmission of CL by the female sand fly *Phlebotomus papatasi* [12]. Since that date, some studies were conducted on the phlebotomine fauna in some Tunisian regions such Tunis, Zaghouan, Kebili, El Kef, and Makhtar [13–18].

Nevertheless, few were the data available on the incidence of the disease, its geographical distribution and the causative species. Since the 1980s of the last century and by the introduction of both biochemical and molecular tools, many research teams have investigated the epidemiology of CL in many regions of the country focusing on the characterization of the parasite and the identification of both reservoirs and phlebotomine sand fly hosts.

The precise characterization of the parasite circulating in Tunisia started in 1981 using the gold standard method (isoenzymatic analysis) [19]. Since then, many research teams have been involved in the isoenzymatic analysis of *Leishmania* strains. Three taxa were identified to be responsible for the genesis of CL: *Leishmania major, Leishmania infantum*, and *Leishmania killicki*.

2.1.1. Cutaneous leishmaniasis due to Leishmania major

2.1.1.1. History

Zoonotic cutaneous leishmaniasis (ZCL) due to *L. major* was the first described form of leishmaniasis in Tunisia in 1884 by Deperet and Boinet in the region of Gafsa, southwest Tunisia. Between 1882 and 1893 outbreaks affected different regions of Gafsa and thereby autochthonous cases were recorded each year in this region [6].

In 1908, an extension of the Gafsa boil occurred from the southwest (Gafsa) to the west (Feriana, Kasserine) and southeast (Aioun, Tataouine) regions. Since then, the endemic area did not go beyond Kasserine (Sbeitla) [20]. The Tunisian Centre has been free from ZCL until a major outbreak in 1982 in the Sidi Saad Region (Kairouan) [21, 22]. Then, ZCL has spread to many foci in centre and south of Tunisia [23, 24]. Ruiz Postigo 2010 [25] reported an annual incidence of 2750 new case of ZCL. Nevertheless, the true incidence of this noso-geographical form of CL is underestimated due to multiple factors including the increasing prevalence of the disease, the unrecorded cases, and the expanding areas of endemicity.

2.1.1.2. Clinical forms

L. major is responsible for localized cutaneous lesions. It is always "wet" with a deep ulceration in the center and covered by a crust. It heals slowly leaving ugly scars that severely affect the social and psychological functioning of the affected individuals.

Although *L. major* is the main species responsible for CL in Tunisia, a very limited number of studies have investigated and explored the clinical spectrum of CL caused by this *Leishmania* species. Indeed, the published studies have described the clinical polymorphism of cutaneous leishmaniasis without any isoenzymatic or molecular identification of the causative species. Masmoudi et al. have studied the different clinical aspects of CL in some zoonotic CL foci of the centre and the south of the country. Eleven different clinical forms of ZCL (vegetative, impetiginoid, erysipeloid, necrotic, warty, erythematosquamous, lupoid, sporotrichoid, papulous, eczematoid, and recidivans) were reported but without any identification of the parasite. The ulcerocrusted form was the most predominant form (54.9%) followed by the sporotrichoid and lupoid aspects with 18.6 and 15.7%, respectively [26, 27]. A recent study conducted in 2012 in our laboratory has analyzed the clinical polymorphism of CL due to *L. major* based on the identification of the parasite by PCR sequencing. Thus, 12 clinical forms were noticed. The most common type was the ulcerocrusted form (38.66%) followed by the papulonodular form (16%) and the impetiginous form (13.33%). The ulcerated, mucocutaneous, lupoid, and sporotrichoid forms were less common. The eczematiform, erysipeloid, verrucous, psoriasiform, and pseudotumoral types were represented by a single CL case (1.33%) (unpublished data) (**Figure 1**).

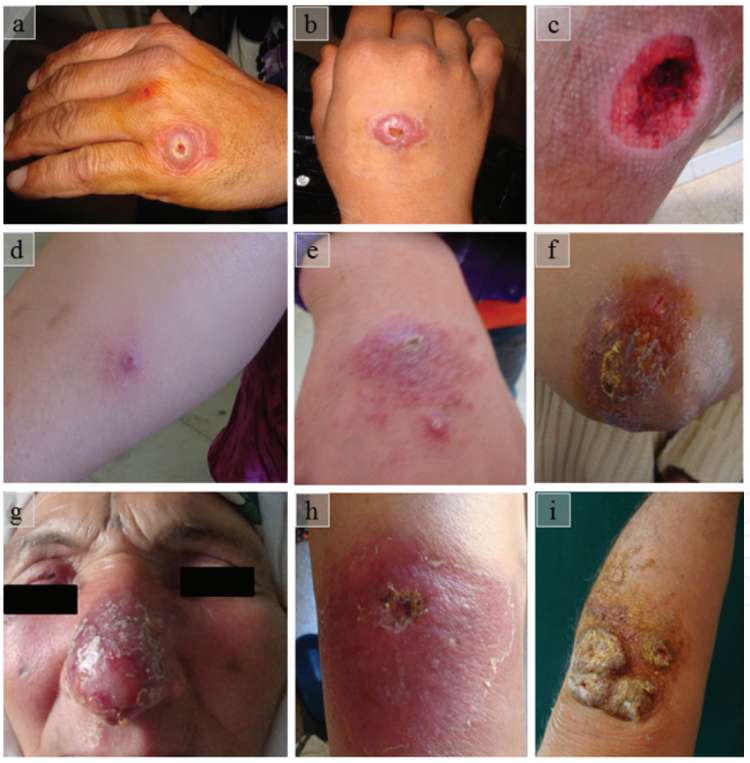

Figure 1. Clinical forms of CL lesions caused by *L. major*: (a, b) ulcerocrusted, (c) ulcered, (d) nodular, (e) papulonodular, (f) warty, (g) lupoid, (h) erysipeloid, and (i) vegetative. (Laboratory of Parasitology-Mycology, Faculty of Pharmacy, University of Monastir, Tunisia).

This clinical polymorphism seems to be rather high, which could reflect the complexity of the disease involving several factors related to the parasite (virulence, parasitic load, and the

presence of other pathogens), the type and duration of clinical lesion, the geographic location, the disease reservoir, and the host immune status [28, 29].

2.1.1.3. Causative species

The precise characterization of the parasite circulating in Tunisia foci started only in 1981 [19]. Since then, many research teams have been involved in the isoenzymatic analysis of *Leishmania* strains from ZCL foci. All the strains were identified as *L. major* with the single zymodeme MON-25. This genetic homogeneity gathered with the wide distribution of MON-25 suggests the rapid diffusion of this zymodeme in many Tunisian provinces [23, 24, 30, 31].

2.1.1.4. Transmission cycle

L. major has a zoonotic transmission cycle. The fat sand rat *Psammomys obesus* and the gerbils *Meriones shawi* and *Meriones libycus* are reservoir hosts [32, 33]. Recently, a natural infection with *L. major* zymodeme MON-25 has been reported in a specimen of least weasel (*Mustela nivalis*) suggesting its potential role as reservoir host of ZCL [34].

In 1987, Ben Ismail et al. [33] proved that *Phlebotomus* (*P.*) *papatasi* is the vector of *L. major* in Tunisia. Indeed, the isoenzymatic identification of isolated promastigotes from infected females of *P. papatasi* revealed the zymodeme MON-25 already identified in human CL cases (**Figure 2**). In Tunisia, This sand fly species is essentially spread in semi-arid, arid, and Saharan bioclimatic stages [35, 36].

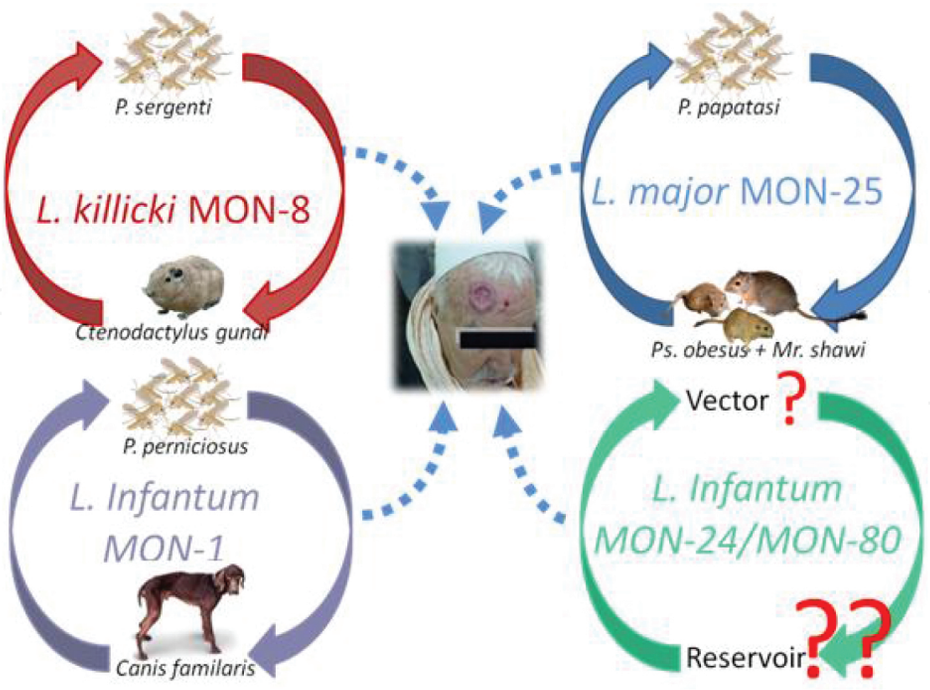

Figure 2. Transmission cycles of the dermotropic *Leishmania* zymodemes in Tunisia. (Laboratory of Parasitology-Mycology, Faculty of Pharmacy, University of Monastir, Tunisia).

2.1.1.5. Geographical distribution

Zoonotic CL due to *L. major* is the main noso-geographic form widespread in whole central and southern part of Tunisia. In 2002, 15 of 23 Tunisian provinces were considered as endemic for ZCL with two to three thousand cases annually [37]. Since 2012, *L. major* has been reported in 19 provinces. Out of them, seven were in the north of the country. Key factors leading to the spread of this disease are presently unknown. Dynamics of rodent populations, vector dispersal, and climate change may be involved in the spatiotemporal dynamics of the disease [24] (**Figure 3**).

Figure 3. Geographical distribution of dermotropic *Leishmania* taxa [24].

2.1.2. Cutaneous leishmaniasis due to Leishmania infantum

2.1.2.1. History

L. infantum is primary known as a viscerotropic species responsible for the genesis of visceral leishmaniasis. Nevertheless, the first case of CL due to this species in Tunisia was described in

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1916 in Sakiet Sidi Yousef, El Kef (north of Tunisia) by Nicolle and Blanc (1918) [20]. This disease has been sporadically reported with an annual incidence of approximately 20 or 30 cases per year [38]. The geographical distribution of this sporadic form overlaps with that of VL.

2.1.2.2. Clinical forms

Unfortunately, the low prevalence of sporadic CL (SCL) as well as the absence of published data concerning the clinical polymorphism of this noso-geographical form of CL prevents us to make a define description of the lesion. Previous studies reported that in over 80% of cases, CL caused by *L. infantum* is characterized by a single small lesion on the face. The ulcerocrusted form is the most common [38, 39]. Nevertheless, lupoid with a striking infiltrated patch, erythematous and squamous forms were also reported.

2.1.2.3. Causative species

The precise identification of the causative agent of SCL using the golden standard method has been started in the beginning of the 1990s of the last century. Thus, three zymodemes of the *L. infantum* taxon were identified as responsible of SCL. *L. infantum* MON-24 was the first identified dermotropic zymodeme [40]. Currently, it is the most isolated one from SCL lesion in Tunisia [24, 39, 41]. Its represents between 90.56 and 92.85% of all SCL cases in Tunisia [24, 41]. The second identified dermotropic zymodeme is MON-1. The first case of SCL caused by *L. infantum* MON-1 was reported by Aoun et al. in 2000 [38]. This dermoviscerotropic zymodeme is less frequent than *L. infantum* MON-24. Indeed, it represents between 7.14 and 8.5% of the SCL cases in Tunisia [24, 41]. The last one is the zymodeme MON-80. Only a single sporadic case of CL due to this zymodeme was reported in 2012 in Zaghouan, north Tunisia [24] (**Figure 3**).

2.1.2.4. Transmission cycle

The transmission cycle of *L. infantum* is not completely elucidated. While *L. infantum* MON-1 was isolated from the domestic dog *Canis familiaris* suggesting that this animal is the reservoir of this zymodeme, the reservoir hosts of the other zymodemes MON-24 and MON-80 are still unknown (**Figure 2**). In 2009, Benikhlef et al. [42] reported three cases of canine VL in Tunisia due to *L. infantum* MON-80; nevertheless, its role as reservoir for this zymodeme is still discussed. The zymodeme MON-24 was also isolated from dogs in Morocco and Algeria but never in Tunisia [43, 44].

Phlebotomus perniciosus was described as the vector of *L. infantum* MON-1. However, the vector species of MON-24 and MON-80 are still unidentified. In Tunisia, *P. perfiliewi* is abundant in *L. infantum* CL foci and was thereby suspected to be the vector of *L. infantum* [35]. Nevertheless, no *L. infantum* strain has been isolated from this phlebotomine sand fly species yet. Also, *L. infantum* DNA was detected from a *P. langeroni, P. longicuspis, P. perfiliewi, P. papatasi*, and *Sergentomyia minuta* using molecular tools [45, 46]. However, neither parasite isolation from these sand flies species nor *L. infantum* isoenzymatic identification were carried out in Tunisia yet to confirm their role as vector of *L. infantum* taxon.

2.1.2.5. Geographical distribution

Geographical distribution of SCL is apparently restricted to the humid and sub-humid bioclimatic areas. Its distribution overlaps with that of VL in north and central Tunisia. Indeed, Haouas et al. reported that 95.3% of dermotropic *L. infantum* strains were isolated from the north of Tunisia, 2.83% from the centre (Kairouan and Sidi Bouzid) and 1.9% from the south (Sfax) [24]. The sporadic cases reported in the south of the country suggested an extension of SCL to the arid bioclimatic areas [24, 41]. Also, *L. infantum* MON-24 was unevenly distributed from the northern areas of the country: It was mainly isolated in Siliana, Manouba, Béja, Bizerte, and Jendouba provinces. The dermoviscerotropic zymodeme MON-1 was isolated in northern Tunisia, mainly in Siliana province, and the single CL *L. infantum* MON-80 strain was isolated in Zaghouan province (**Figure 3**).

2.1.3. Cutaneous leishmaniasis due to Leishmania killicki (synonymous L. tropica)

2.1.3.1. History

Chronic cutaneous leishmaniasis (CCL) due to *L. killicki* was discovered for the first time on the basis of 30 strains isolated in 1980 when an outbreak of cutaneous leishmaniasis occurred in the microfocus of Tataouine in southeast Tunisia [32, 47]. The annual incidence of this disease was estimated to 10 cases per year [48].

The taxonomic status of *L. killicki* is not well defined yet. Indeed, it was initially characterized within the *L. tropica* complex [49]. By the revision of the *Leishmania* genus classification, *L. killicki* was considered as a separate phylogenetic complex [50]. In 2009, an update study by Pratlong et al. confirmed the inclusion of *L. killicki* within the *L. tropica* complex [51]. Phenetic and phylogenetic studies using multilocus microsatellite typing [52], PCR sequencing [53], and multilocus sequence typing (MLST) [54] also classified *L. killicki* within the *L. tropica* complex. A recent study on the evolutionary history of *L. killicki* relative to *L. tropica* suggested that *L. killicki* emerged from a single founder event and evolved independently from *L. tropica*. Thereby, they suggested naming this taxon *L. killicki* (synonymous *L. tropica*) [55, 56].

2.1.3.2. Clinical forms

Clinically, the lesion is frequently unique, ulcerous with a scab of 1–3 cm in diameter located on the face, with chronic evolution that can last for 4 years [57, 58] (**Figure 4**).

2.1.3.3. Causative species

The first description of CL due to *L. killicki* in 1980 was based on the isoenzymatic identification of about 30 strains from southeastern Tunisia. All of them were characterized as *L. killicki* zymodeme MON-8 [32]. Since this date and over a period of 36 years, only about 90 *L. killicki* strains were identified using the golden standard method [24, 30, 32, 51, 56]. The isoenzymatic analysis showed the presence of two zymodeme inside *L. killicki* taxon. Zymodeme MON-8 is the most frequent one. However, a new zymodeme MON-317 has been recently identified from two patients in Metlaoui, southwestern Tunisia [56].

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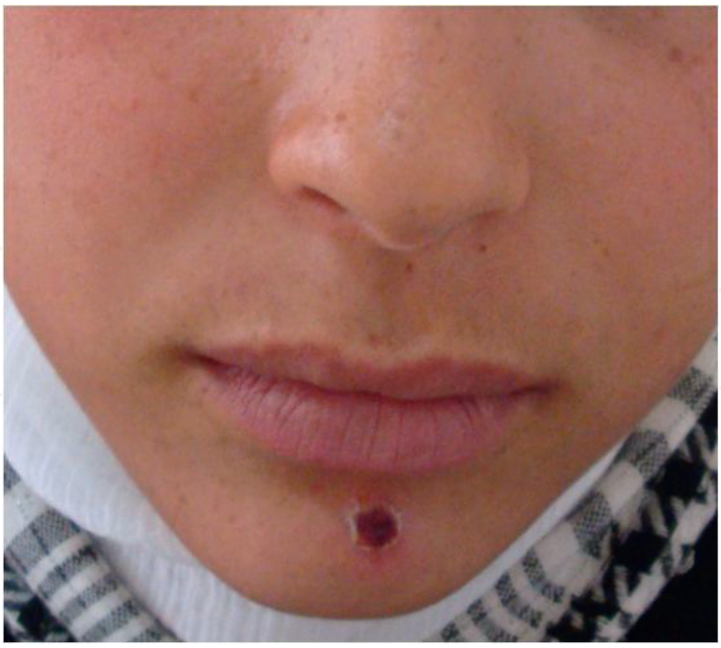

Figure 4. Ulcerocrusted lesion of the neck caused by *L. killicki*. (Laboratory of Parasitology-Mycology, Faculty of Pharmacy, University of Monastir, Tunisia).

2.1.3.4. Transmission cycle

In the last century, the transmission cycle of *L. killicki* in Tunisia was considered as anthroponotic. However, in 2011, two epidemiological studies realized in the southwest and southeastern of Tunisia described the natural infection of *Ctenodactylus gundi* with *L. killicki* using molecular techniques suggestion a zoonotic transmission of this taxon [59, 60]. By the detection of *L. killicki* in its mid gut, *P. sergenti* was suspected to be the probable vector of this taxon [36, 61].

2.1.3.5. Geographical distribution

L. killicki was firstly described in the focus of Tataouine (southeast of Tunisia) [47]. For more than 20 years, no case was described outside this focus. Since 2004, some cases have been reported in Kairouan and Sidi Bouzid (centre of Tunisia), in Gafsa in the southwest and in Siliana in the north of the country [31, 62, 63]. A recent study focusing on the evolutionary history of this parasite using the microsatellite typing has supported the hypothesis of a zoonotic transmission cycle for *L. killicki* (syn. *L. tropica*) and suggested that Gafsa could be the historical focus of this parasite [56].

2.2. Visceral leishmaniases

Visceral leishmaniasis refers to the dissemination of the parasite *Leishmania* to the spleen, liver, lymphatic nodes, and bone morrow of the patient. A multitude of clinical features of the disease ensue gradually, the most important being splenomegaly, recurring and irregular fever, anemia, pancytopenia, weight loss, and weakness.

2.2.1. History

The first case of VL in Tunisia was reported by Laveran and Cathoire in 1904 [64] in the region of La Goulette, north of the country. Between 1904 and 1908, Charles Nicolle reported two new VL cases of children living in Tunis (north of the country). Since this date and till 1935, Charles Nicolle and collaborators reported 120 new VL cases mainly distributed in the north (Tunis, Bizerte, Zaghouan, Grombalia, Beja, and El Kef), the centre (Sousse and Kairouan) with one case in Tozeur (south of Tunisia) [65]. Some outbreaks of VL were reported in centre Tunisia mainly Kairouan where 247 cases were reported between 1984 and 1996 [66].

Since the description of VL in Tunisia, the annual incidence has increased progressively going from three cases in beginning of the twentieth century to 57 in the 1980s of the same century [66]. Currently, VL in Tunisia shows a stable incidence of about 100 cases per year [67, 68].

2.2.2. Clinical forms

As many other Mediterranean basin countries, LV in Tunisia has an infantile form affecting mainly children under 5 years. Indeed, the age of infected children ranged from 2 months to 13 years with a median, 18 months. The most common clinical symptoms at admission were splenomegaly, fever, and hepatomegaly. The principal biological disturbances were anemia, thrombocytopenia, and leucopenia [69].

While infantile VL is the most common form in Tunisia, cases of VL in both immunocompetent and immunocompromised (with HIV infection) adults were also reported in Tunisia [24]. Twenty-two (22) cases of adult VL (including six patients infected with HIV virus) were recorded over a period of 20 years [70]. Within this group, the triad of VL symptoms (fever, anemia, and splenomegaly) was less stable.

2.2.3. Causative species

The isoenzymatic identification of the isolated parasite have revealed three zymodemes of a single taxon *L. infantum*: The zymodeme MON-1 is the most identified one (89.12% of the VL cases). It was isolated in both infantile and adult VL cases [24]. The second zymodeme responsible for VL is *L. infantum* MON-24. The first case of VL due to this zymodeme was reported in 2000 [71]. Currently, *L. infantum* MON-24 is responsible for 8.08% of VL cases in Tunisia [24]. Finally, *L. infantum* MON-80 was identified in some sporadic VL cases in centre Tunisia (Zaghouan and Kairouan). It is responsible for 2.07% of VL cases [24].

2.2.4. Transmission cycle

The domestic dog has been incriminated in the transmission of VL since the first report of canine leishmaniasis in 1908 [72]. By the introduction of the isoenzymatic analysis, all strains isolated from infected dogs throughout the country were identified as *L. infantum* MON-1 [24, 30]. This result confirms the dog as the reservoir host of zoonotic VL caused by the zymodeme MON-1. In 2009, Benikhlef reported three cases of canine VL in Tunisia due to *L. infantum* MON-80; nevertheless, their role as reservoir for this zymodeme is still discussed [42].

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At the middle of the twentieth century, *P. perniciosus* has been reported to be the vector of *L. infantum* MON-1 and the complete life cycle was demonstrated [73]. However, the vector hosts of the two other zymodemes MON-24 and MON-80 are still unknown (**Figure 5**). Recently, *L. infantum* DNA was detected in the sand flies mid gut of the *Larroussius* (*P. langeroni*, *P. longicuspis*, *P. perfiliewi*) and *Phlebotomus* (*P. papatasi*) subgenera as well as the *Sergentomyia* genus (*S. minuta*) [45, 46]. However, neither parasite isolation from these sand flies species nor *L. infantum* isoenzymatic identification were carried out in Tunisia yet to confirm their role as vector of *L. infantum* zymodemes.

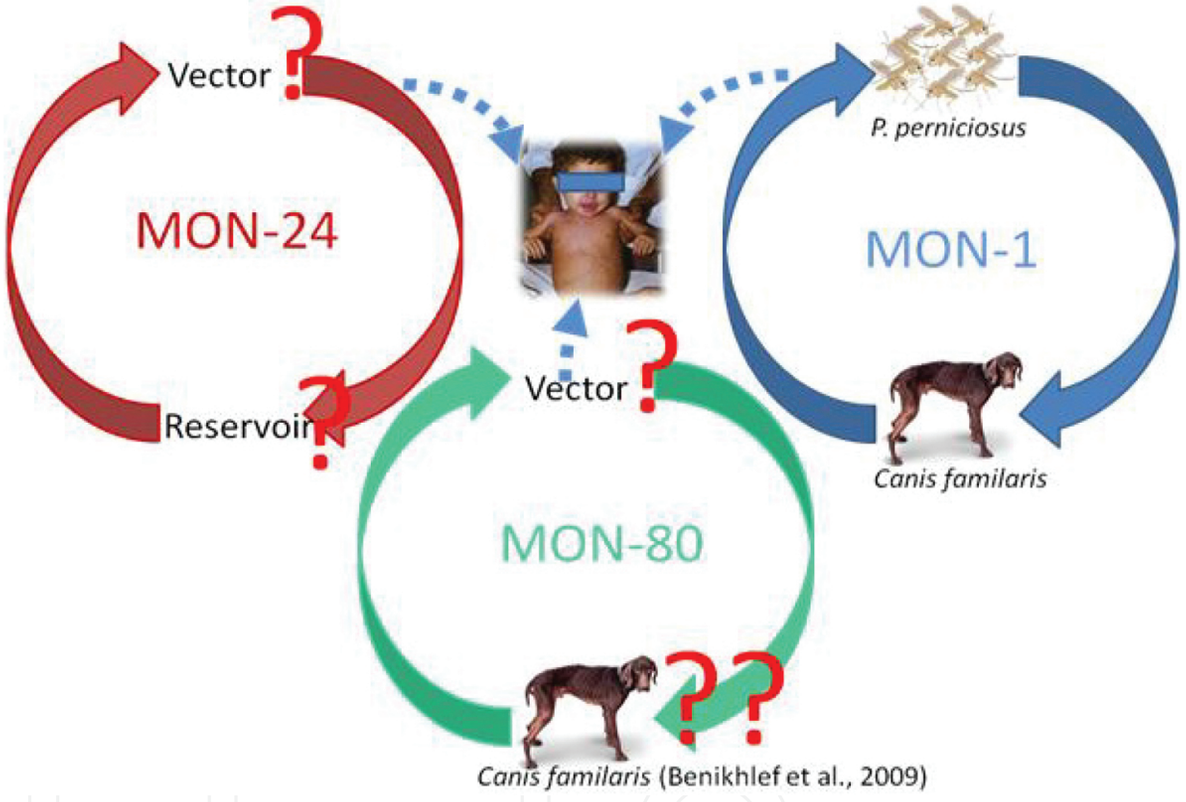

Figure 5. Transmission cycles of the viscerotropic *Leishmania infantum* zymodemes in Tunisia. (Laboratory of Parasitology-Mycology, Faculty of Pharmacy, University of Monastir, Tunisia).

2.2.5. Geographical distribution

Until 1980s, geographical distribution of VL in Tunisia was limited to the humid, sub-humid, and semi-arid bioclimatic stages. The main endemic foci were localized in the north of the country including Zaghouan, Kef, Jendouba, Seliana, Nabeul, Beja, and Tunis [24, 74, 75]. However, more recently, VL has extended to the arid areas in central and southern Tunisia including Kairouan, Monastir, Kasserine, Sfax, Gabes, Sidi Bouzid, and Tozeur [24, 41, 66, 75–77] (**Figure 6**). Such extension could be the result of many factors including the travel of the reservoir host and the environmental changes sustaining sand flies populations.

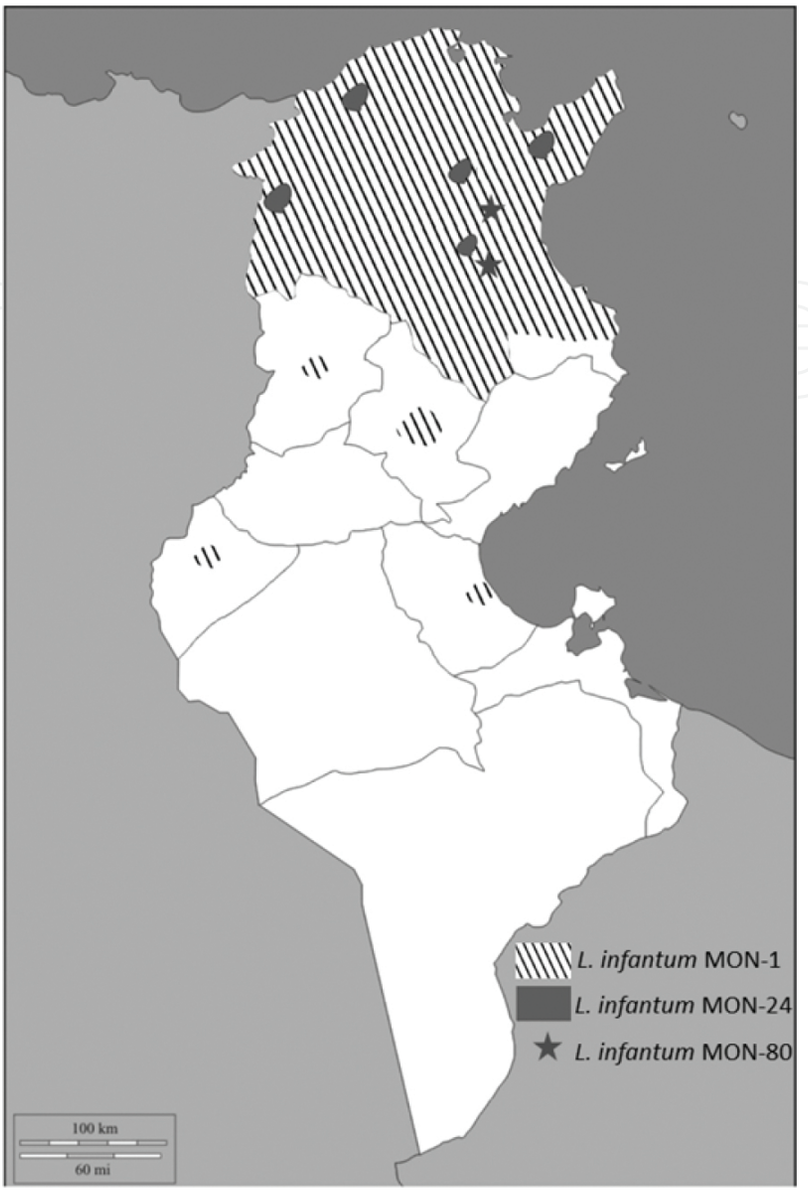

Figure 6. Geographical distribution of viscerotropic *Leishmania infantum* zymodemes [24].

3. Conclusion

Both cutaneous and visceral leishmaniases are old infectious diseases in Tunisia. Over more than a century since the discovery of the disease, we have witnessed an extraordinary progress in the knowledge of the epidemiology of *Leishmania* infection. At least six transmission cycles are present in this geographical area. Unfortunately only the life cycle of *L. major* MON-25, *L. infantum* MON-1, and *L. killicki* MON-8 are elucidated. Many other investigations are urgently needed to understand the dynamic of the different zymodemes in the Tunisian foci. The absence of data on the vector and the reservoir hosts of some zymodemes prevent us to follow

and predict the spatiotemporal evolution of the disease and consequently to establish effective control strategies.

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