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Leishmaniases in Maghreb: An endemic neglected disease

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ABSTRACT

Maghreb is known to be one of the most endemic areas of leishmaniases where both visceral and cutaneous forms are reported. Cutaneous leishmaniasis (CL) is older and has a higher prevalence than visceral one (VL). It is caused by four taxa (*Leishmania* (*L.*) *major*, *L. infantum*, *L. tropica* and *L. killicki*) which are responsible for a large clinical spectrum of lesions. Most transmission cycles of these taxa are known and many phlebotomine sandflies vectors and reservoir hosts are identified. The zoonotic transmission is well established for *L. major*. However, for *L. infantum* and *L. killicki* it needs more investigations to be proven. Regarding *L. tropica*, studies suggest it to be of both zoonotic and anthroponotic types. The isoenzymatic characterization of these four taxa showed a large enzymatic polymorphism varying from two zymodemes for *L. major* to 10 zymodemes for *L. tropica*. Cutaneous leishmaniasis is widely distributed and covers all bioclimatic stages with the coexistence of more than one taxon in the same foci.

Visceral leishmaniasis is the second form of leishmaniases in Maghreb. Only *L. infantum* is known to cause this disease. The transmission cycle of this parasite is zoonotic but still not well known. The isoenzymatic identification of *L. infantum* causing VL showed the presence of six zymodemes. Geographically, VL is distributed in all bioclimatic stages of Maghreb countries.

Despite all the previous studies realized on leishmaniases in Maghreb, they are still considered as neglected diseases because of the rarity or the absence of efficient control strategies.

Contents

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1. Introduction

Leishmaniases are parasitic diseases caused by Protozoa of the genus *Leishmania*, transmitted between mammals via an infected bite of female sandflies belonging to the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. They are known to be the ninth largest diseases burden among the 13 parasitic and bacterial neglected tropical diseases worldwide (Molyneux et al., 2005; Hotez et al., 2006). They occur in a total of 98 countries and three territories on five continents (Alvar et al., 2012).

According to the World Health Organization (WHO) reports, leishmaniases touch 12 million people worldwide and are estimated to cause 20,000–40,000 deaths per year (Alvar et al., 2006, 2012).

In natural conditions, transmission cycles of *Leishmania* implicate a large number of parasites, reservoirs and vectors. Therefore, considering geographical regions and foci, more than 30 *Leishmania* taxa, 62 mammal host species and 93 phlebotomine sandfly species are potentially implicated in the transmission of leishmaniases (WHO, 2010). However, despite this number of reservoirs and phlebotomine sandflies, parasitic cycle could only be established when all these hosts live in the same ecological environment. The complexity of transmission cycles result in identification difficulties of many parasites, vector and reservoir hosts.

In order to understand these complex diseases, many classifications based on their clinical forms and transmission modes are considered. In fact, three main clinical forms of the disease are reported worldwide: cutaneous leishmaniasis, visceral leishmaniasis and mucocutaneous leishmaniasis (MCL). Cutaneous leishmaniasis itself is grouped into three clinical forms: localized cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL) and leishmaniasis recidevans (LR) (Dedet and Pratlong, 2009; WHO, 2010). According to the last WHO statistics, approximately 0.2–0.4 million VL cases and 0.7–1.2 million CL cases occur each year. CL is more widely distributed; 10 countries are estimated to account for 70–75% of global CL incidence: Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru (Alvar et al., 2012).

Based on the implicated reservoir hosts in the transmission cycles, leishmaniases are considered as zoonotic diseases when reservoirs are domestic or wild mammals and as anthroponotic when the parasite is strictly transmitted between humans. These two transmission modes are recognized for both cutaneous (ZCL/ACL) and visceral leishmaniasis (ZVL/AVL) (WHO, 2010).

Since the use of isoenzymatic method for *Leishmania* characterization, a large set of data has been available and many complexes and zymodemes have been identified. Furthermore, this technique has allowed a better understanding of many *Leishmania* transmission cycles in different endemic foci. In addition to the biochemical approach, many molecular tools are used to characterize the parasite and to clarify the distribution of different *Leishmania* taxa. These techniques are based on the parasitic DNA amplification by PCR. Then, amplification products are analyzed by different techniques such as restriction fragment length polymorphism (RFLP), single strand conformation polymorphism (SSCP) and sequencing (Mimori et al., 1998; De Andrade et al., 2006; Rotureau et al., 2006; Haouas et al., 2010).

Mediterranean region is endemic for both VL and CL. Their estimated annual incidence ranges from 1200 to 2000 and 239,500 to 393,600 cases, respectively. In Maghreb, as well as in many developing countries in the world, leishmaniases are historical but still neglected diseases. They are largely spread in this region causing a serious public health problem. Clinically, both CL and VL are encountered in this region. Nevertheless, the cutaneous form is more endemic and more largely distributed implicating several *Leishmania* taxa. For visceral leishmaniasis, *L. infantum* is the unique causative agent of this clinical form. Regarding to the transmission mode, both zoonotic and anthroponotic CL are reported. However, only zoonotic VL is known (Kadiki and Ashraf, 1971; Dedet and Belazzoug, 1985; Chaffai et al., 1988; Harrat et al., 1996; El-Buni et al., 2000; Benikhlef et al., 2004).

The aim of this paper is to review epidemiological features of leishmaniases in Maghreb region. This includes existing clinical forms and their respective incidences, different transmission cycles and the current geographical distribution of each *Leishmania* taxa.

2. Cutaneous leishmaniasis

Cutaneous leishmaniasis refers to a dermal lesion which appears at the site of the infected sandfly bite generally on exposed parts of the body. Its clinical features tend to vary between and within regions, reflecting different species of parasite or the type of zoonotic cycle concerned, immunological status and also perhaps genetically determined responses of patients. The classical lesion is painless and characterized by the appearance of a nodule that can or not ulcerates and covered with an adherent crust. It heals gradually over months or years, leaving a depressed scar with altered pigmentation. In some cases, the infection involves the lymphatic system inducing nodules along the lymphatic channels (WHO, 2010).

The first suggestive description of CL in Maghreb countries dates from the 18th century (Bray, 1987). Nevertheless, the first real documented cases date from 1860 in Algeria (Hamel, 1860), 1884 in Tunisia (Deperet and Boinet, 1884), 1914 in Morocco (Foley et al., 1914) and 1930 in Libya (Onorato, 1931). More than 58.600 cases are reported yearly in these countries. Algeria is the most endemic with 44,050 reported cases per year followed by Tunisia with 7631 cases, Libya with 3540 and Morocco with 3430 cases (Alvar et al., 2012). The annual estimated incidence is higher and ranges from 164,200 to 269,800 (Alvar et al., 2012). These discrepancies result of the underreporting fact. This last one is linked to the spontaneous heal of lesions, the lack of diagnostic laboratories and physicians reports and the difficulties to access to medical centers.

Since the first description of human CL in Maghreb, many research teams have investigated its epidemiology, in order to better understand the structure of different *Leishmania* foci. These studies include parasite characterization, reservoirs and phlebotomine sandfly vectors identification.

Parrot (1922), Gaud (1947), Croset et al. (1978) and El-Buni et al. (2000) were the pioneers in studying the phlebotomine sandfly fauna and their vector role in the transmission of CL in the region (Algeria, Morocco, Tunisia and Libya, respectively). These cited teams studied existing species and their distribution in different bioclimatic stages. They found that *Leishmania* parasites were transmitted by three main Sub-genera: *Phlebotomus*, *Paraphlebotomus* and *Larroussius.*

Concerning reservoir hosts, many studies carried out in Maghreb highlighted the implication of both rodents and domestic mammals in the transmission of *Leishmania* parasites (Rioux et al., 1982, 1986b; Belazzoug, 1983a,b; Dedet and Belazzoug, 1985; Ben Ismail et al., 1987a).

The precise characterization of the parasite circulating in this geographical area using the gold standard method (isoenzymatic analysis) started in 1981 (Lanotte et al., 1981). Since then, many research teams have been involved in the isoenzymatic analysis of *Leishmania* strains in different Maghreb foci. Four taxa were identified to be responsible for the genesis of CL: *L. major*, *L. infantun*, *L. tropica* and *L. killicki*.

2.1. Cutaneous leishmaniasis due to L. major

2.1.1. History and incidence

Cutaneous leishmaniasis due to *L. major* is the oldest leishmaniasis reported form in Maghreb. It was described in 1860 in Biskra (East of Algeria) and was known as "Clou de Biskra" (Hamel, 1860). Deperet and Boinet have named the lesion as "Bouton de Gafsa" in Gafsa (South West of Tunisia) in 1884. In Southern Morocco, this form was described in 1914 (Foley et al., 1914). Cutaneous leishmaniasis due to *L. major* is endemo-epidemic in all these countries. Approximately, 3431, 2000, 2750 and 1700 new cases were reported every year in Morocco, Algeria, Tunisia and Libya, respectively (Harrat et al., 1996; Ruiz Postigo, 2010).

2.1.2. Clinical forms

Leishmania major is known to cause localized cutaneous lesions (LCL). The classical lesion aspect caused by this parasite is of "wet" type with an infiltrated nodule, dug with a large ulceration in the center and covered by a crust. Lesions are often severely inflamed, ulcerated and heal within two to eight months. Frequently, they are multiple, especially in nonimmune immigrants, becoming confluent and secondarily infected. Such lesions are often slow to heal and may leave large, disfiguring or disabling scars. The incubation period is often less than four months (WHO, 2010).

In addition to this classical ulcerative form, a large but less frequent clinical polymorphism of lesions caused by *L. major* was observed (Rioux et al., 1986a; Ysmail-Dahlouk et al., 1994; El-Buni et al., 1997; Rhajaoui et al., 2007; Zait and Hamrioui, 2009; Er-Rami et al., 2012; Abdellatif et al., 2013). Tunisia is the country that represents the most important clinical polymorphism with 11 different forms (vegetative, impetiginoid, eryseloid, necrotic, warty, erythemato-squamous, lupoid, sporotrichoid, papulous, eczematoid and recidivans) (Masmoudi et al., 2005, 2006a, 2008a). A mucosal form was also reported in five cases in this country: lesions were localized on the mucosa of the lips (four patients) and the nose (one patient). This form is different from the mucocutaneous leishmaniasis due to *L. braziliensis* since the absence of mutilating lesions and the excellent response to treatment (Kharfi et al., 2003) (Fig. 1).

2.1.3. Identification of the parasite

Isoenzymatic characterization of *L. major* showed the presence of the main zymodeme MON-25 in Morocco, Algeria and Tunisia (Rioux et al., 1986a; Maazoun et al., 1986; Harrat et al., 1996; Pratlong et al., 2009; Haouas et al., 2012). However, Pratlong et al. (2009), have identified for the first time a new zymodeme MON-269 in Algeria. The isoenzymatic profile of this zymodeme differs from MON-25 by the only PGD (Phosphogluconatese dehydrogenase) enzymatic system. Unfortunately, in Libya no isoenzymatic analysis was carried out and parasite identification was only done by the molecular PCR-RFLP approach. 75.9% of the identified samples were *L. major* (Amro et al., 2012) (Table 1).

2.1.4. Epidemiology

The transmission cycle of *L. major* is the same throughout Maghreb countries (Dedet and Belazzoug, 1985) (Table 1).

2.1.4.1. Reservoir. Cutaneous leishmaniasis due to *L. major* is of zoonotic type (ZCL), the reservoir hosts are wild rodents *Psammomys* and *Meriones*. The fat sand rat, *Psammomys obesus*, is generally considered to be the main reservoir of *L. major* in North Africa (Ashford, 2000). The parasite-reservoir host combination was subsequently observed with formal identification of the parasite (Ashford et al., 1977; Belazzoug, 1983a,b; Ben Ismail et al., 1987a). This rodent is distributed in North Africa from the Atlantic eastward into the Red Sea (Daly and Daly, 1974). It is essentially diurnal and lives in burrows. *Psammomys obesus* is a Saharan herbivore feeding on the succulent salty leaves and stems of plants of the family *Chenopodiacea* (Petter, 1961; Amirat et al., 1977; Kam and Degen, 1989; Fichet-Calvet et al., 1999, 2000, 2003). In addition to this rodent, *Meriones* ssp. was also identified as reservoir of *L. major* in Morocco, Algeria and Tunisia (Rioux et al., 1982; Belazzoug, 1986a; Ben Ismail et al., 1987a; Ben Ismail and Ben Rachid, 1989; Ghawar et al., 2011). In Libya, *Meriones* ssp. has been found in

Table 1
Transmission cycles of different *Leishmania* taxa in Maghreb.

Country	Taxon	Zymodeme	Clinical form	Proven or suspected *Phlebotomus* vector	Proven or suspected reservoir	Reference
Algeria	*L. major*	MON-25 MON-269	CL	*P. papatasi*	*Meriones* ssp. *Psammomys obesus*	Belazzoug (1983a,b, 1986a) Harrat et al. (1996) Izri et al. (1992) Pratlong et al. (2009) Sergent et al. (1921)
	L. infantum	MON-1 MON-24 MON-80 MON-33 MON-34 MON-77	CL, VL	*P. longicuspis* *P. perfiliewi* *P. perniciosus*	Dog *Canis aureus*	Aït-Oudhia et al. (2009, 2011) Belazzoug et al. (1985a), Belazzoug (1987) Benikhlef et al. (2001, 2004, 2009) Bessad et al. (2012) Dedet et al. (1977) Harrat et al. (1992, 1996) Harrat et al. (1996) Izri et al. (1990) Izri and Belazzoug (1993) Marty et al. (1998) Parrot et al. (1941)
	L. killicki	MON-301 MON-306	CL	*P. sergenti*	Unknown	Boubidi et al. (2011) Harrat et al. (2009) Mansouri et al. (2012)
Libya	*L. major*	unidentified	CL	*P. papatasi*	*Psammomys obesus* *Meriones* ssp.	Amro et al. (2012) Ashford et al., (1977) El-Buni et al. (2000)
	L. infantum	unidentified	CL, VL	unknown	unknown	Belal et al. (2012) Dar (1978) Dedet (1979) Mehabresh and El-Mauhoub (1992) Mehabresh (1994)
	L. killicki	MON-8	CL	*P. sergenti*	Unknown	Aoun et al. (2006) El-Buni et al. (2000)
Morocco	*L. major*	MON-25	CL	*P. papatasi*	*Meriones* ssp.	Maazoun et al. (1986) Rioux et al. (1982, 1986a)
	L. infantum	MON-1 MON-24	CL, VL	*P. ariasi* *P. longicuspis* *P. perniciosus*	Dog	Dereure et al. (1986) Guessous-Idrissi et al. (1997b) Haralambous et al. (2007) Nejjar et al. (1998) Rami et al. (2003) Rioux et al. (1984, 1996)
	L. tropica	MON-102 MON-107 MON-109 MON-112 MON-113 MON-122 MON-123 MON-263 MON-264 MON-279	CL	*P. sergenti*	Dog Human	Dereure et al. (1991) Guilvard et al. (1991) Lemrani et al. (2002) Rhajaoui et al. (2004) Pratlong et al. (1991, 2009)
Tunisia	*L. major*	MON-25	CL	*P. papatasi*	*Psammomys obesus* *Meriones* ssp.	Ben Ismail et al. (1987a,b) Ben Ismail and Ben Rachid (1989) Ghawar et al. (2011) Haouas et al. (2012) Maazoun et al. (1986) Pratlong et al. (2009) Rioux et al. (1986a)
	L. infantum	MON-1 MON-24 MON-80	CL, VL	*P. perfiliewi* *P. perniciosus* *P. langeroni*	Dog	Aoun et al. (2000, 2001, 2008) Belhadj et al. (2000, 2002, 2003) Benikhlef et al. (2009) Ben Ismail et al. (1986, 1993) Gramiccia et al. (1991) Guerbouj et al. (2007) Haouas et al. (2007, 2012) Kallel et al. (2008a,b) Lanotte et al. (1981)

Table 1 (*Continued*)

Country	Taxon	Zymodeme	Clinical form	Proven or suspected *Phlebotomus* vector	Proven or suspected reservoir	Reference
	L. killicki	MON-8	CL	*P. sergenti*	*Ctenodactylus gundi*	Aoun et al. (2008) Bouratbine et al. (2005) Bousslimi et al. (2012) Haouas et al. (2005, 2012) Jaouadi et al. (2011, 2012) Kallel et al. (2005) Pratlong et al. (1986, 2009) Rioux et al. (1986a,b) Tabbabi et al. (2011)

L. major endemic areas but their reservoir role has not been proved yet (El-Buni et al., 2000). This mammal is restricted to the Atlas Mountains of Morocco and Algeria and Coastal North Africa from Egypt to Southwestern Morocco (Duvernoy and Lereboullet, 1842). These hygrophilic and nocturnal rodents are granivorous and build their burrows in jujube trees surrounding cereal fields (Ben Ismail and Ben Rachid, 1989; Ben Rachid et al., 1992) (Table 1).

2.1.4.2. Vector. Phlebotomus papatasi was proven to be the vector of this parasite in 1921, which corresponds to the first description of the transmission of a *Leishmania* by a sandfly (Sergent et al., 1921). *Leishmania major* promastigotes were isolated from infected females of *P. papatasi* in Morocco, Algeria and Tunisia (Sergent et al., 1921; Adler and Ber, 1941; Rioux et al., 1986a; Ben Ismail et al., 1987b; Izri et al., 1992). In Libya, *P. papatasi* was found as the most abundant sandfly in endemic areas (El-Buni et al., 2000). However, *L. major* parasites have not been isolated from *P. papatasi* in this country yet. This sandfly is essentially spread in semi-arid, arid and Saharan bioclimatic stages of these countries (Dedet et al., 1984; Boudabous et al., 2009; Boukraa et al., 2010) (Table 1).

2.1.5. Geographical distribution

Zoonotic cutaneous leishmaniasis due to *L. major* is widespread and confined to arid Saharan regions. In Morocco, this disease is present in the desert region south of the Atlas Mountains in a strip bordering the Sahara Desert (Rioux et al., 1986a; Rhajaoui et al., 2007). In Algeria, *L. major* is distributed from the large steppe regions of arid and semi-arid zones to the Algerian highlands (Harrat et al., 1996). Recently, a new focus of CL due to *L. major* has emerged on the Northern part of the chain of the Tell Atlas, in the basin of the Soummam (Boudrissa et al., 2011). This form covers the whole central and Southern parts of Tunisia (Haouas et al., 2012). In Libya, the latest realized study identified *L. major* in 12 districts of North Western part of the country. These districts have typical Mediterranean costal climate in the upper Northern districts like Tripoli, and semi-arid and arid climate in Al Jabal Al Gharbi and Wadi al Hayaa to the South (Amro et al., 2012) (Fig. 2).

2.2. Cutaneous leishmaniasis due to L. infantum

2.2.1. History and incidence

Leishmania infantum is known as a viscerotropic taxon implicated in the genesis of VL in both Old and New Worlds. Nevertheless, the first observations of cutaneous leishmaniasis due to *L. infantum* in Maghreb were reported in Tunisia, Algeria, Morocco and Libya, respectively (Nicolle and Blanc, 1917; Sergent and Gueidon, 1923; Rioux et al., 1996; Belal et al., 2012). This disease has been sporadically reported in these countries with only

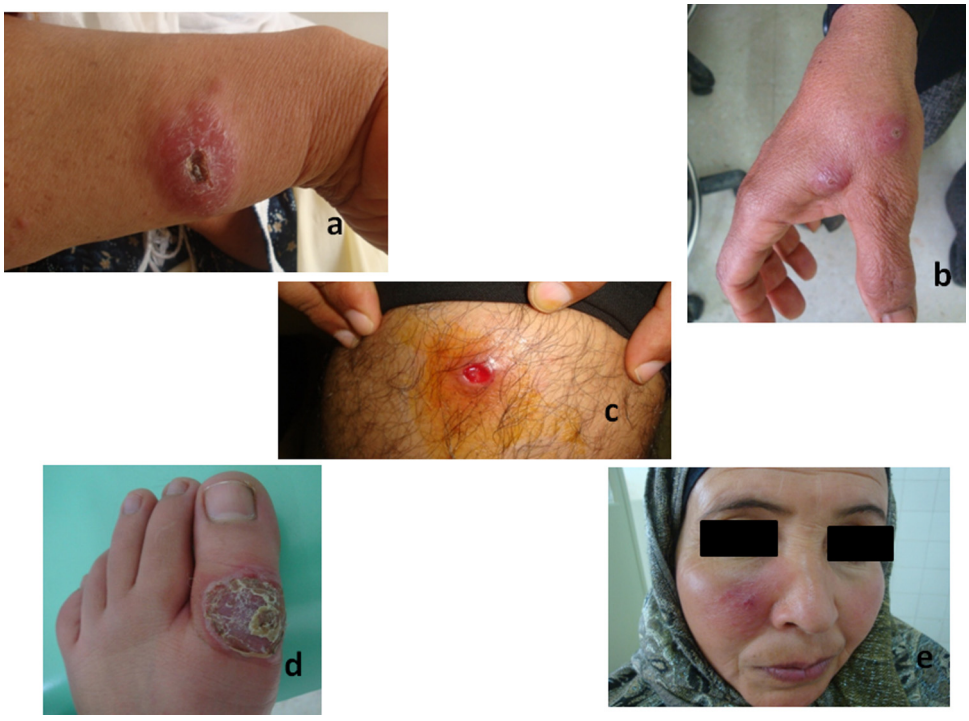

Fig. 1. Clinical polymorphism of cutaneous lesions caused by *L. major*: (a) Ulcero-crusted (b) nodular, (c) ulcerous, (d) erythemato-squamous and (e) nodulo-papulous.

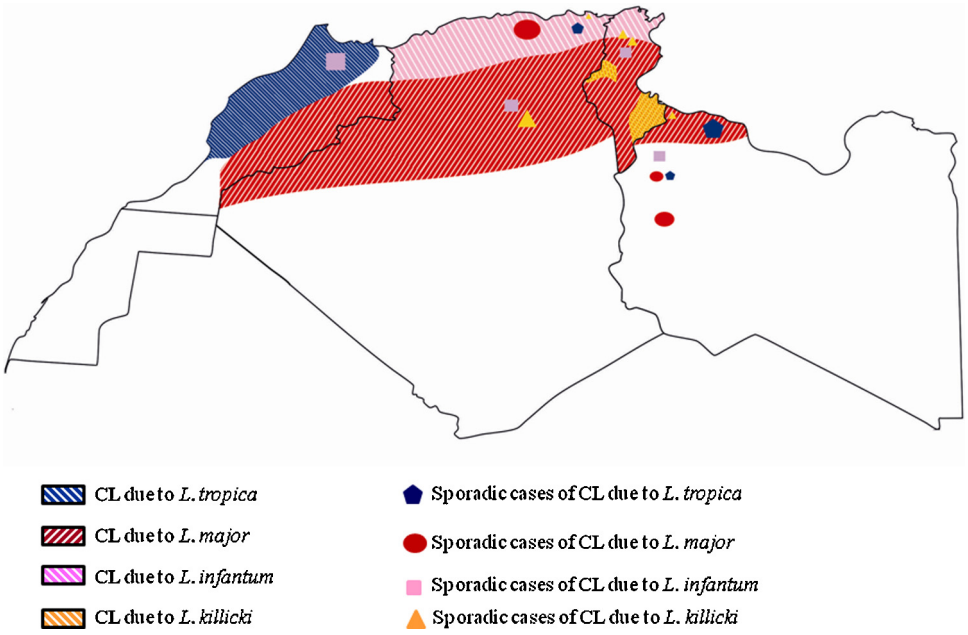

Fig. 2. Geographical distribution of different *Leishmania* taxa causing cutaneous leishmaniasis in Maghreb.

few cases per year. In Tunisia, the annual incidence is estimated to 30 cases per year (Aoun et al., 2000).

2.2.2. Clinical forms

The classical lesion caused by this parasite is located (LCL) and characterized by a small single ulcerated or lupoid lesion of the face that lasts up to three years (Chaffai et al., 1988; Rioux et al., 1996; Bachi, 2006). In addition to this classical aspect, a clinical polymorphism was observed in Tunisia, Morocco and Algeria with erythematous, papulonodular, nodular and mucosal lesions (Belhadj et al., 2003; Kallel et al., 2005; Rhajaoui et al., 2007; Benmously-Mlika et al., 2008; Zait and Hamrioui, 2009) (Fig. 3).

2.2.3. Identification of the parasite

Isoenzymatic characterization of this taxon has shown the presence of three zymodemes. The zymodeme MON-24 is the most frequent one. It was found in Morocco, Algeria and Tunisia (Belazzoug et al., 1985a; Gramiccia et al., 1991; Rioux et al., 1996; Kallel et al., 2008a). The second identified zymodeme is MON-1. It's known to be the etiological agent of visceral leishmaniasis. However, its ability to cause CL is also well known. The dermotropic zymodeme MON-1 was identified in Algeria and Tunisia (Marty et al., 1998; Kallel et al., 2008b). The last one is the zymodeme MON-80, also identified in Algeria and Tunisia (Harrat et al., 1996; Haouas et al., 2012) (Table 1).

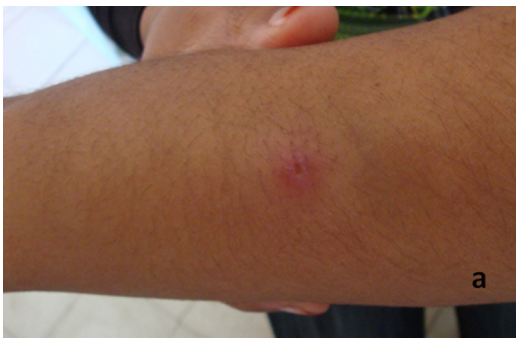

Fig. 3. Nodular lesion caused by *L. infantum*.

2.2.4. Epidemiology

2.2.4.1. Reservoir. The transmission cycle of this parasite is zoonotic and not completely elucidated. Many studies realized in Maghreb countries have isolated *L. infantum* from dog suggesting it to be the reservoir of this disease. The zymodeme MON-1 was isolated from this mammal in Algeria, Morocco and Tunisia (Belazzoug, 1987; Nejjar et al., 1998; Haouas et al., 2007; Aït-Oudhia et al., 2011). A recent study realized in Algeria has reported the isolation of *L. infantum* MON-1 from a golden jackal (*Canis aureus*) in Malou (North of Algeria) (Bessad et al., 2012). Nevertheless, its reservoir role has not been proven yet. The zymodeme MON-24 was also isolated from dogs in Morocco and Algeria but never in Tunisia (Benikhlef et al., 2004; Haralambous et al., 2007). Benikhlef et al. (2009) have reported the first identification of *L. infantum* MON-80 from the dog in Algeria and Tunisia, but its role as reservoir is still in doubt. Unfortunately, no study concerning reservoir hosts of *L. infantum* in Libya was carried out (Table 1).

2.2.4.2. Vector. *Phlebotomus perfiliewi* was found naturally infected with *L. infantum* MON-24 in Algeria (Izri and Belazzoug, 1993). In Tunisia, this sandfly is suspected to be the vector of this parasite because of its abundance in *L. infantum* CL foci (Ghrab et al., 2006). Nevertheless, no *L. infantum* have been isolated from this phlebotomine sandfly species yet. In Tunisia, another suspected vector was reported: indeed, Guerbouj et al. (2007) have detected *L. infantum* DNA from a *Phlebotomus langeroni* specimen using the PCR-hybridization technique. Though, neither parasite isolation from sandflies nor *L. infantum* isoenzymatic identification were carried out in Tunisia, Morocco and Libya. No data are available concerning the vector of *L. infantum* MON-80 (Table 1).

2.2.5. Geographical distribution

Cutaneous leishmaniasis due to *L. infantum* is sporadically distributed in Maghreb. In Morocco, it was identified in Taounate in the South (central Rif) (Rioux et al., 1996) and in Sidi Kacem in the North of the country (Rhajaoui et al., 2007). In Algeria, this disease occurs essentially in the North. In fact, the dermotropic zymodeme MON-1 is mainly distributed in the sub-humid bioclimatic zone in Northern Algeria (Marty et al., 1998). However, a single sporadic case of *L. infantum* MON-1 was reported in the

region of Biskra (South of the country) which is an arid area (Harrat et al., 1996). The parasite *L. infantum* MON-24 is largely distributed in Northern Algeria (Belazzoug et al., 1985a; Harrat et al., 1996). The zymodeme MON-80, was mainly observed in the Centre of the country (Harrat et al., 1996). In Tunisia, sporadic cutaneous leishmaniasis occurs in humid, sub-humid and semi-arid bioclimatic stages. The zymodeme MON-24 is essentially spread in the North (Gramiccia et al., 1991; Belhadj et al., 2003). However, recent studies have shown the extension of this zymodeme to the Centre and the South of the country (Kallel et al., 2008a; Haouas et al., 2012). Sporadic cases of CL due to *L. infantum* MON-1 are distributed in the North of the country (Aoun et al., 2000; Kallel et al., 2005). The zymodeme MON-80 was identified from Northern foci (Aoun et al., 2008; Haouas et al., 2012). In Libya, The only study based on the PCR-RFLP molecular technique has reported the presence of *L. infantum* in the North West of the country (Belal et al., 2012) (Fig. 2).

2.3. Cutaneous leishmaniasis due to L. tropica

2.3.1. History and incidence

Among Maghreb countries, CL due to *L. tropica* is essentially encountered in Morocco. The first case of this disease was identified in 1987 from a child who stayed in the province of Azilal (Central Morocco) (Marty et al., 1989). In this country, CL due to *L. tropica* is one of the most endemic CL forms. In fact, 1697 new cases were reported in 2008 (Ruiz Postigo, 2010).

2.3.2. Clinical forms

Clinically, *L. tropica* causes localized cutaneous lesions (LCL). A classical lesion is usually described to be dry, lupoid, small (two cm in diameter), unique, self-healing, mainly located on the face and can lasts up to a year (Marty et al., 1989; Chiheb et al., 1999). A clinical polymorphism of this cutaneous form was also observed. In fact, impetiginized, ulcerocrusted, noduloulcerative, sever, vegetant inflammatory, large, multiple and limbs infections were described (Guessous-Idrissi et al., 1997a; Rhajaoui et al., 2007).

2.3.3. Identification of the parasite

Isoenzymatic analysis revealed an important diversity within this complex in Morocco. A total of 10 zymodemes were identified from humans, dogs and sandflies: MON-102, MON-107, MON-109, MON-112, MON-113, MON-122, MON-123, MON-263, MON-264 and MON-279 (Dereure et al., 1991; Guilvard et al., 1991; Pratlong et al., 1991, 2009). Out of these, seven zymodemes were identified from humans (MON-102, MON-107, MON-109, MON-112, MON-113, MON-263 and MON-264) with a dominance of the zymodeme MON-102 (Pratlong et al., 1991; Rhajaoui et al., 2004). In phlebotomine sandflies only four zymodemes were identified: MON-102, MON-123, MON-122 and MON-107. This last one is the most isolated zymodeme (Guilvard et al., 1991; Pratlong et al., 2009). Both zymodemes MON-102 and MON-113 are responsible for canine cutaneous leishmaniasis in Morocco (Dereure et al., 1991; Pratlong et al., 1991). Recently, *L. tropica* MON-279 has been identified from a dog with canine visceral leishmaniasis in the province of El Houcima (Lemrani et al., 2002). According to Pratlong et al. (1991), this enzymatic diversity could be the result of an hypoendemic equilibrium: a single zymodeme, more virulent, predominates during hyperendemic or epidemic periods. In addition to this isoenzymatic method, *L. tropica* was also identified by the ITS1-PCR-RFLP approach (Rhajaoui et al., 2012; Arroub et al., 2013) (Table 1).

2.3.4. Epidemiology

2.3.4.1. Reservoir. The transmission cycle of CL due to *L. tropica* in Morocco is still not well elucidated. In fact, the isolation of *L. tropica* (MON-102 and MON-113) from dogs suggests that this mammal could be the reservoir host and therefore a zoonotic transmission cycle. Nevertheless, the small number of canine cases and the short duration of the lesions make it difficult to define the precise role of the dog in the epidemiological cycle (Dereure et al., 1991). The transmission cycle of this parasite in Morocco was also suggested to be anthroponotic (ACL). Indeed, the study realized by Pratlong et al. (1991) showed the existence of the zymodeme MON-102 in many distant localities and the concomitant presence of the zymodeme MON-107 in the North of the High-Atlas and in the South of the Anti-Atlas would support the anthroponotic dispersion of this disease. This same study showed the sympatric presence of clearly distinct parasite groups with anthroponotic and zoonotic cycles (Table 1).

2.3.4.2. Vector. The proved vector of *L. tropica* is the *Phlebotomus sergenti* (Guilvard et al., 1991). It is reported to be largely widespread throughout the country (Gaud, 1947; Rioux et al., 1984) and has a considerable genetic diversity (Yahia et al., 2004). Its vector role was proven for four *L. tropica* zymodemes (MON-102, MON-107, MON-122 and MON-123). Whereas, zymodemes MON-112, MON-113, MON-109, MON-263, MON-264 and MON-279 have not been isolated from any phlebotomine species yet (Table 1).

2.3.5. Geographical distribution

Concerning geographical distribution, CL due to *L. tropica* is largely widespread in Morocco. It occurs in semi-arid, arid and perarid bioclimatic stages (Pratlong et al., 1991). It extends from Agadir-Guelmim in the South via Essaouira, Chichaoua, Salé in the West, Beni Mellal, Azilal, Marrakech in the Centre, Ouarzazate in the East to Taza in the North.

Outside Morocco, sporadic cases of CL due to *L. tropica* were reported in Algeria and Libya. In fact, a recent study carried out in North Eastern Algeria (Constantine City) using molecular techniques (Real-time PCR and sequencing) detected *L. tropica* from cutaneous lesions (Mihoubi et al., 2008). Similarly, Amro et al., 2012 identified *L. tropica* using the molecular PCR-RFLP technique in many districts in Libya (Al Jabal Al Gharbi, Misrata and Tarhuna). Nevertheless, no isoenzymatic prove was given to identify the causative zymodeme (Fig. 2).

2.4. Cutaneous leishmaniasis due to L. killicki

2.4.1. History and incidence

In Maghreb countries this cutaneous form was first identified in 1980 in South Eastern Tunisia (Rioux et al., 1986a,b) and in 2006 in Libya (Aoun et al., 2006). In Algeria, a *Leishmania* close to *L. killicki* was identified in the North of Sahara in 2009 (Harrat et al., 2009). In Tunisia, the annual incidence of this disease is estimated to 10 cases per year (Ben Rachid et al., 1992).

2.4.2. Clinical forms

Clinically, the skin lesion is frequently an ulceration covered with crust, unique, localized on the face or limbs, lasting up to six years. A clinical polymorphism was also observed with lupoid, ulcerative budding, warty and nodular erythematous lesions (Rioux et al., 1986b; Chaffai et al., 1988; Harrat et al., 2009; Aoun et al., 2012) (Fig. 4).

2.4.3. Identification of the parasite

The taxonomical position of *L. killicki* is still unobvious. In fact, a numerical taxonomic analysis realized by Pratlong et al. (1986) included *L. killicki* within the *L. tropica* complex. This classification was supported by Rioux et al. (1990). Nevertheless, after the revision of the classification of the genus *Leishmania*, *L. killicki* was considered as a separate phylogenetic complex (Rioux and Lanotte, 1993). The isoenzymatic analysis showed that *L. killicki* is

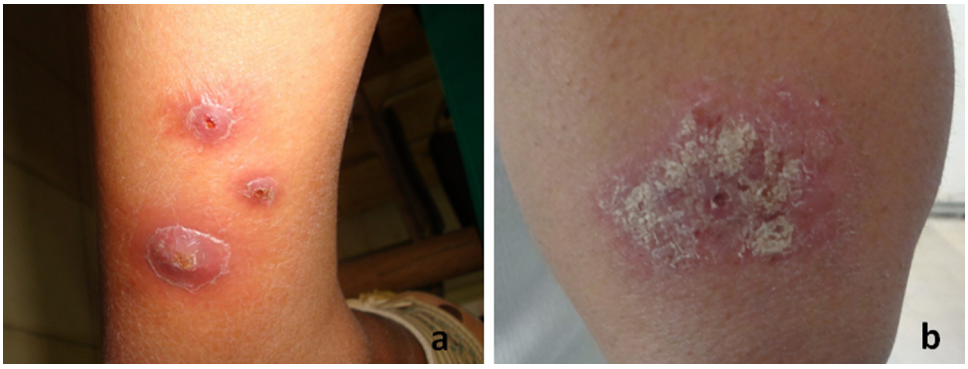

Fig. 4. Clinical polymorphism of cutaneous lesions caused by *L. killicki:* (a) Ulcero-crusted and (b) psoriasiform.

monomorphic with a single zymodeme MON-8 in Tunisia and Libya (Pratlong et al., 1986; Rioux et al., 1986a,b; Bouratbine et al., 2005; Haouas et al., 2005, 2012; Kallel et al., 2005; Aoun et al., 2008). In Algeria, four strains were identified by isoenzyme electrophoresis as belonging to the zymodeme MON-301. This cited zymodeme shares 11 isoenzymes of the 15 studied with the zymodeme MON-8 (Harrat et al., 2009). Recently, Mansouri et al., 2012 have identified a new zymodeme, MON-306, in the area of Annaba (Eastern Algeria) which shares 12 isoenzymes with the zymodeme MON-8 and 14 isoenzymes with the zymodeme MON-301 (Mansouri et al., 2012) (Table 1).

2.4.4. Epidemiology

2.4.4.1. Reservoir. Until 2011, the transmission cycle of *L. killicki* in Tunisia was thought to be anthroponotic. In this year, an epidemiological study realized in the South West of Tunisia described the first identification of *L. killicki* from *Ctenodactylus gundi* using molecular techniques (PCR-RFLP and PCR sequencing) (Jaouadi et al., 2011). In 2012, Bousslimi et al., showed the natural infection of this same rodent by *L. killicki* in South Eastern Tunisia. These two findings support the hypothesis of Haouas et al. (2012) who presumed that the low prevalence of *L. killicki* compared to *L. major* involve the existence of a zoonotic reservoir for *L. killicki*. Nevertheless, the isolation of this parasite and its isoenzymatic identification will confirm the reservoir role of this rodent. *Ctenodactylus gundi* Rothmann, 1976 has a short stocky body, short ears and proportionally short tail. The gundi's unique feet pads and stiff bristles around the claws make it readily distinguishable. This species is restricted to the edge of the Sahara, from Morocco eastward to Libya. In Tunisia, it is known only from rocky habitats in the central part of the country. Lataste (1887) indicated that it was abundant in Southern Tunisia, both on mountains and Roman ruins. This rodent lives in rocky areas. It is adapted to high temperatures and it can feed on dry food as well as succulent halophytes (Table 1).

2.4.4.2. Vector. Leishmania killicki DNA was identified using molecular techniques from *P. sergenti* females in the Southeast and the Southwest of Tunisia (Tabbabi et al., 2011; Jaouadi et al., 2012) and in Algeria (Boubidi et al., 2011). These findings emphasize the probable vector role of this species in the transmission of *L. killicki*. Nevertheless, the isolation and the isoenzymatic identification of *L. killicki* from *P. sergenti* will be the proof of the vector role of this phlebotomine species. *Phlebotomus sergenti* was found in arid and Saharan bioclimatic stages in Algeria, Tunisia and Libya (El-Buni et al., 2000; Boubidi et al., 2011; Jaouadi et al., 2012) (Table 1).

2.4.5. Geographical distribution

Geographically, *L. killicki* is distributed in independent foci. In Tunisia, it was firstly described in the focus of Tataouine (Southeast of Tunisia) in 1980 (Rioux et al., 1986a,b). For more than 20 years, no case was described outside this focus. Since 2004, some cases were reported in Kairouan and Sidi Bouzid (Centre of Tunisia), in Gafsa in the South West and in Siliana in the North of the country (Bouratbine et al., 2005; Haouas et al., 2005; Kallel et al., 2005). Based on these observations, an epidemiological investigation was carried out in the South West of Tunisia emphasizing the presence of a second *L. killicki* micro-focus in the district of Metlaoui, Gafsa (Jaouadi et al., 2012). In Algeria, the four *L. killicki* MON-301 strains were identified in the region of Gardaia (North of the Sahara) (Harrat et al., 2009). *Leishmania killicki* MON-306 was identified in Annaba. In Libya this parasite was found on the mountains of Jebel Naffoussa in the North West of the country (Aoun et al., 2006).

3. Visceral leishmaniasis

Visceral leishmaniasis is a systematic disease caused by the dissemination of *Leishmania* parasites throughout the reticuloendothelial system. It is a severe disease characterized by prolonged fever, splenomegaly, hypergammaglobulinemia, lymphadenopathy, emaciation and pancytopenia. Patients become gradually ill over a period of a few months, and nearly always die if untreated (WHO, 2010).

3.1. History and incidence

In Maghreb countries, this disease has been known since 1904 in Tunisia, where the first case of Mediterranean VL was described, 1910 in Libya, 1911 in Algeria and 1921 in Morocco (Laveran and Cathoire, 1904; Tashim, 1910; Lemaire, 1911; Klippel and Monier, 1921). In these countries, VL is less frequent than CL, with approximately 355 reported cases per year (Alvar et al., 2012). Morocco seems to be the most endemic, with 152 reported cases per year followed by Algeria with 111 cases then by Tunisia with 89 cases per year and finally by Libya with three reported cases per year (Alvar et al., 2012).

3.2. Clinical forms

In Maghreb, VL is especially known under its infantile Mediterranean form. It develops in 95% of cases in children under five years (Dedet, 1979; Belazzoug et al., 1985b; Mehabresh, 1994; Belhadj et al., 2000; Lakhdar Idrissi et al., 2007; Zait et al., 2012). Nevertheless, some VL cases from both immuno-competent and immuno-compromised adults have been reported over the last few years in Morocco, Algeria and Tunisia (Ezzouine et al., 2010; Belkaid and Harrat, 1997; Essabbah Aguir et al., 2012).

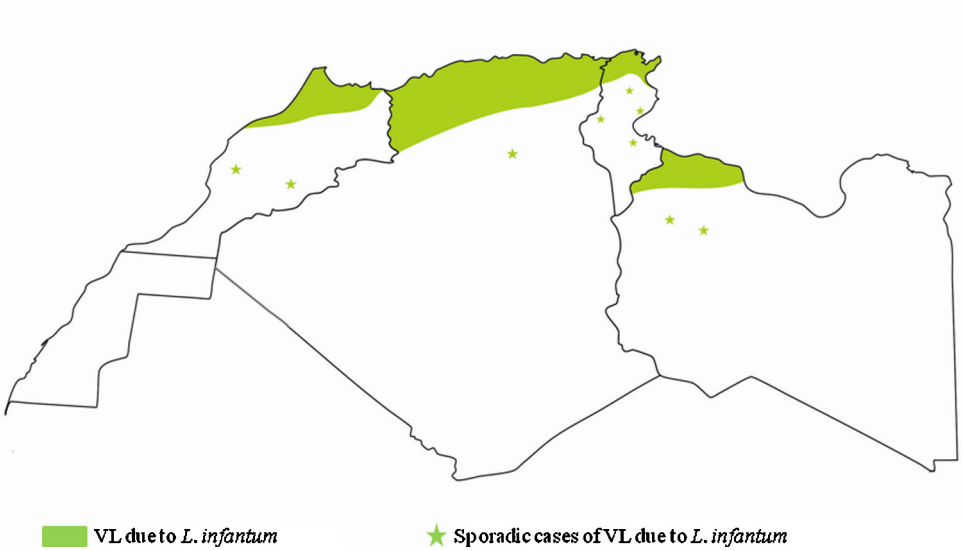

Fig. 5. Geographical distribution of *L. infantum* causing visceral leishmaniasis in Maghreb.

3.3. Identification of the parasite

Such as in all Mediterranean basin countries, *L. infantum* is the single aetiological agent of VL in Maghreb. Isoenzymatic analysis of this parasite proved that zymodeme MON-1 is the most common in this region. It was identified in Morocco, Algeria and Tunisia (Guessous-Idrissi et al., 1997b; Lanotte et al., 1981; Harrat et al., 1996; Haouas et al., 2012). In addition to the zymodeme MON-1 other zymodemes were also identified. Zymodemes MON-24 and MON-80 were isolated from human VL in Algeria and Tunisia (Harrat et al., 1996; Belhadj et al., 2000; Aoun et al., 2001, 2008; Benikhlef et al., 2001). The three zymodemes MON-33, MON-34 and MON-77 were sporadically identified in only Algeria (Harrat et al., 1996) (Table 1).

3.4. Epidemiology

3.4.1. Reservoir

The transmission cycle of this disease is zoonotic (ZVL). In fact, domestic dogs have been implicated as the main reservoir hosts of *L. infantum*. Zymodeme MON-1 was isolated from infected dogs in Morocco (Dereure et al., 1986; Nejjar et al., 1998; Rami et al., 2003); Algeria (Dedet et al., 1977; Aït-Oudhia et al., 2009) and Tunisia (Nicolle and Comte, 1908; Aoun et al., 2008). Zymodeme MON-24 was identified in infected dogs in Morocco and Algeria (Benikhlef et al., 2004; Haralambous et al., 2007). Both zymodemes MON-34 and MON-77 were identified in dogs in Algeria (Harrat et al., 1996). Infected dogs with L. infantum MON-80 were reported in Algeria and Tunisia (Benikhlef et al., 2009) (Table 1).

3.4.2. Vector

Many phlebotomine sandfly species were suspected to be the vector of *L. infantum* in Maghreb countries. In Morocco, *P. ariasi*, *P. perniciosus* and *P. longicuspis* are supposed to be responsible for the transmission of this parasite (Rioux et al., 1984; Dereure et al., 1986) but no infested female by *L. infantum* was identified until now. The vector role of *P. perniciosus* and *P. longicuspis* was well established in Algeria (Parrot et al., 1941; Izri et al., 1990). In Tunisia, *P. perniciosus* vector role was proven (Ben Ismail, 1993; Chargui et al., 2013) (Table 1).

3.5. Geographical distribution

Geographically, VL in Maghreb covers humid, sub-humid, arid and semi-arid bioclimatic stages. In Morocco, this disease is widespread in semi-arid and arid bioclimatic stages. It is mostly localized in the North but some sporadic cases were also described in the South of the country. In fact, three main areas were described as the most endemic for VL: the Northern area covers Rif in Ouazzane, Tetouan, Al-Hoceima and spread until Nador; the central area is spread in Oujda, Taza, Casablanca, Fès, Meknès, Khénifra and Marrakech and the Southern area covers Ighrem, Tafilalet, Arfoud (Dereure et al., 1986; Agoumi et al., 1991; Geussous-Idrissi et al., 1997b; Lakhdar Idrissi et al., 2007; Hassani et al., 2011). In Algeria, VL covers humid, sub-humid, semi-arid and arid bioclimatic stages. It has extended from the North to the South of the country. The foci of Grand-Kabylie, Constantine, Jijel, Tizi Ouzou, Boumerdes and Mila are the most endemic in the North of the country (Dedet et al., 1977; Belazzoug et al., 1985b; Harrat et al., 1992). In the South, some cases were described in the foci of Biskra, Hoggar and Tassili N'ajjar (Belazzoug, 1986b; Belkaid and Harrat, 1997). In Tunisia, VL is distributed in humid, sub-humid, semi-arid and arid bioclimatic stages. It was first endemic and largely distributed in the North of the country and then it extended to the Centre and the South. Many provinces of the North are known to be endemic for this form of leishmaniasis like Zaghouan, Kef, Jendouba, Seliana, Nabeul, Beja and Tunis (Ben Ismail et al., 1986; Khaldi et al., 1991; Bouratbine et al., 1998; Belhadj et al., 2002; Haouas et al., 2012). Other cases were also reported from the centre and the South provinces such as Kairouan, Monastir Kasserine, Sfax, Gabes, Sidi Bouzid and Tozeur (Ayadi et al., 1991; Besbès et al., 1994; Ben Salah et al., 2000; Belhadj et al., 2002; Kallel et al., 2008b; Haouas et al., 2012). In Libya, VL was first known in the Northern coastal areas near Tripoli and the Green Mountain area (Dar, 1978; Dedet, 1979). Since 1985, there have been new cases of the disease from the Southern part of Libyan the Saharan and sub-Saharan areas (Mehabresh and El-Mauhoub, 1992; Mehabresh, 1994) (Fig. 5).

4. Control

Despite all the epidemiological interest given to leishmaniases in Maghreb, most strategies for treatment, vector and reservoir control are still limited to pilot research studies and have not

been applied yet. This could be explained by many socioeconomic aspects like the high cost of these strategies, poverty and the weakness of health systems in hyperendemic areas in these countries (WHO, 2010).

4.1. Treatment

The meglumine antimoniate (Glucantime®) is the most commonly product used for treatment of both cutaneous and visceral leishmaniasis in Maghreb. Nevertheless, many adverse effects, especially for cutaneous leishmaniasis treatment have been reported (Belazzoug and Neal, 1986c; Masmoudi et al., 2006b). In order to find and effective cure with lower side effects than Glucantime®, several research teams have tested other drugs for cutaneous leishmaniasis like the metronidazole, doxycycline, paromomycin-gentamicin and paromomycin alone, which showed a cure rate ranging from 66% for the metronidazole to 82% for paromomycine alone, and lower side effects than the meglumine antimoniate (Masmoudi et al., 2007, 2008b; Belhadjali et al., 2009; Ben Salah et al., 2013). In addition to these chemical treatments other therapy methods for cutaneous leishmaniasis have been used like cryotherapy associated or not to Glucantime® (Chaabane et al., 2008; Abdellatif et al., 2013). The main difficulty for evaluation of the efficiency of the different drugs tested is the spontaneous cure of the *L. major* lesions.

4.2. Vector and reservoir control

In Maghreb, zoonotic cutaneous leishmaniasis due to *L. major* is the most endemic form, which shows periodic epidemic outbreaks. The majority of vector and reservoir control projects aimed at controlling this cited disease. These projects are generally not well applied in these countries because of the high cost and the rare compliance of the population. Vector control consists in using insecticides for indoor residual spraying, impregnation of nets or systemic and feed-through insecticide (Benzerroug et al., 1992; Moroccan Ministry of Public Health, 1997; Faraj et al., 2012; Derbali et al., 2012). Reservoir control is based on the reduction of the *Psammomys obesus* populations by clearing halophytic vegetation and destroying the burrows (Ben Ismail, 1994; Cherif et al., 2012). In Morocco, poisoned grains with anticoagulants and zinc phosphide are used to control *Meriones* sp. populations (Moroccan Ministry of Public Health, 1997). For the domestic dog, known to be the reservoir of VL in Maghreb, the applied control method in these countries is the euthanasia of infected dogs.

5. Discussion

In Maghreb, leishmaniasis epidemiology features seem to be in a continuous evolution. In fact, epidemiological investigations are revealing geographical extensions, new reservoir hosts, new vectors and new zymodemes of existing taxa. Socioeconomic, environmental and climate changes are considered to be responsible for these changes.

Out of the four *Leishmania* taxa present, two are widely distributed in all Maghreb (*L. major* and *L. infantum*) and two have restricted distribution areas (*L. tropica* and *L. killicki*).

Leishmania major is the most widely distributed. It covers semi-arid, arid and Saharan bioclimatic stages. The transmission cycle of this parasite is the same in all Maghreb foci reflecting the large distribution of both vector (*P. papatasi*) and reservoir hosts (*Psammomys* and *Meriones*) of this parasite. This unique transmission cycle explains the rapid circulation and the high incidence of cutaneous leishmaniasis due to *L. major*. In addition, the presence of the principal zymodeme MON-25 indicates the genetic stability of this taxon (Pratlong et al., 2009). The circulation of only MON-25 zymodeme and the large clinical polymorphism prove the absence of correlation between zymodeme and clinical features. Nevertheless, recently, a new variant of the zymodeme MON-25 have been described showing the probable beginning of the *L. major* polymorphism (Pratlong et al., 2009).

Concerning *L. infantum*, it is responsible for both cutaneous and visceral leishmaniasis in Maghreb. The geographical distribution of this parasite is sporadic and covers essentially humid, sub-humid and semi-arid bioclimatic stages. Nevertheless, a few sporadic cases have recently been described in arid regions. The transmission cycle of this parasite is not fully known; many phlebotomine sandflies are suspected to be the vector (*P. perfiliewi*, *P. langeroni*, *P. ariasi*, *P. perniciosus* and *P. longicuspis*) and the domestic dog is proved to be the reservoir of the MON-1 zymodeme. However, for the other identified zymodemes, reservoir hosts are still unknown. This ambiguity could be explained by the presence of more than one vector and reservoir implicated in the transmission of this taxon. So, more epidemiological and entomological investigations are crucial to elucidate the transmission cycles of these zymodemes.

Cutaneous leishmaniasis due to *L tropica* is mostly restricted to Morocco where it represents a large geographical distribution. *Phlebotomus sergenti* is the proved vector for some zymodemes; however, reservoirs are still unidentified. The presence of a large enzymatic polymorphism of this parasite indicates the probable presence of more than one reservoir and different transmission cycles (Pratlong et al., 1991).

Leishmania killicki is a recently described taxon compared to other taxa in Maghreb. The geographical distribution of this parasite was limited to the microfocus of Tataouine (South East of Tunisia). Recent epidemiological studies highlighted its extension to other microfoci in the South West, the Centre and the North of the country. This restricted geographical distribution is most likely related to the specific biotope where the suspected reservoir *Ctenodactylus gundi* lives. The geographical distribution of this rodent shows its presence in Morocco, Algeria and Libya which could suggest it to be involved in the transmission of *L. killicki* in Algeria and Libya and also *L. tropica* in Morocco.

Unfortunately, described cutaneous cases caused by *L. tropica* in Algeria and Libya were all identified using molecular approaches which could not distinguish between the two taxa *L. killicki* and *L. tropica*. Only the enzymatic analysis is able to differentiate between them. Actually, the taxonomic status of *L. killicki* is still an important and debated question. This parasite was first classified within *L. tropica* complex (Pratlong et al., 1986). However, Rioux and Lanotte (1993) have considered it as a separate phylogenetic complex. Indeed, current data on *L. tropica* and *L. killicki* are unable to give an obvious taxonomical position one relative to the other and to understand how they have evolved. Then, more phylogenetic and population genetics studies are necessary to better understand their genetic organization.

Finally, the low number of reported cases in Libya doesn't reflect the real situation of leishmaniasis in this country because of the rare epidemiological investigations carried out until now.

6. Conclusion

Although the epidemiological studies carried out until now, leishmaniases in Maghreb are still neglected diseases. Their incidence and geographical spread are increasing because of the environmental changes, urbanization and the absence of an efficient antileishmanial treatment. For this reason, more epidemiological studies and many surveillance and control systems are required to be established.

Conflicts of interests

This work has no conflict of interest

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