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Review Article

Cutaneous Leishmaniasis (CL) in Saudi Arabia: Current Status

Haytham Ahmed Zakai*

Faculty of Applied Medical Sciences, King Abdulaziz University, P.O. Box 80324, Jeddah-21589, Kingdom of Saudi Arabia.

Abstract: Cutaneous leishmaniasis (CL) is a major tropical infection of public health importance. It is caused by a group of protozoan intracellular parasites. Several factors contribute to the prevalence and transmission of CL. More than 1400 cases of CL were reported in Saudi Arabia in 2012. Although several studies have looked at CL in Saudi Arabia and emphasized on the Eastern province of the country, the highest prevalence of CL was reported in Al-Qaseem area. In this review, we report on the species of *Leishmania* parasites causing CL in Saudi Arabia, its distribution and its incidence in the past seven years. We also report on the methods used to diagnose this infection and the treatment protocols used to treat CL in the country.

Keywords: Cutaneous leishmaniasis, Saudi Arabia, *Leishmania.*

1. Introduction

Cutaneous leishmaniasis is a major tropical infection of public health importance. It is caused by a group of protozoan intracellular parasites belonging to the order of kinetoplastida. The disease is found in over 70 countries and 90% of cases occur in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia, and Syria. The disease is endemic in 18 out of 23 Middle Eastern countries [1, 2]. There are over one million cases of cutaneous leishmaniasis reported worldwide in the past five years [3]. In Saudi Arabia, there are over 19,000 cases of CL were reported in the past 7 years. Different species of the *Leishmania* parasite have been isolated and incriminated as the causative species [2, 4-9]. In this review we report on the current status of CL in Saudi Arabia, the diagnostic methods used in different health sectors, treatment, and control of the disease.

2. The parasite

There are more than 20 *Leishmania* species that are transmitted to humans by the bites of infected female phlebotomine sandflies [3]. A few species can cause visceral leishmaniasis, others cause cutaneous leishmaniasis and some may disseminate into mucocutaneous leishmaniasis (Table 1) [1]. Clinically, cutaneous leishmaniasis lesions usually appear as localized lesions. However, some species can cause diffused cutaneous lesions. Morphologically, there are two developmental stages of the parasite. Amastigotes are small spherical non-flagellated cells measuring from 2-4µm in diameter with a nucleus and kinetoplast that are surrounded by vacuolated cytoplasm. These forms are seen in mammalian hosts and are intracellular forms (Fig. 1). Promastigotes, or vector form, are thin, elongate cells with an anterior kinetoplast and an emergent free flagellum measuring from 5-14µm in length (Fig. 2). It is not possible to differentiate between species of *Leishmania* morphologically. However, *Leishmania* parasites can be differentiated according to the geographical, biological, molecular and clinical features of the disease.

Humans acquire CL infection through a bite of an infected female phlebotomine sand fly. Promastigotes enter the human circulation and are engulfed by macrophages and transform into amastigotes. The change in host temperature and surrounding pH triggers such transformation [10, 11].

*Corresponding author:
E-mail: hzakai@kau.edu.sa; Telephone: +966 0554334116.

Table 1. *Leishmania* species that cause cutaneous leishmaniasis [1, 12].

Leishmania species	Vertebrate host other than humans	Disease	Geographical distribution
L. aethiopica	Hyraxes	LCL, DCL	Ethiopia, Kenya
L. tropica	Dogs, rodents	LCL	Central Asia, middle east, parts of North Africa, Southeast Asia
L. tropica major	Dogs, rodents	LCL	Central Asia, North Africa, middle east, East Africa
L. peruviana	Dogs	LCL	Peru
L. mexicana mexicana	Rodents	LCL, DCL	Central America, Mexico, USA
L. mexicana amazonensis	Rodents	LCL, DCL	South America
L. mexicana pifanoi	Rodents	LCL	Venezuela
L. braziliensis	Rodents, sloths	LCL, MCL	Mexico, Brazil
L. panamensis	Rodents	LCL, MCL	Northern South America, Southern Central America
L. guyanensis	Rodents	LCL	South America
L. venezuelensis	Rodents	LCL	Northern South America

LCL = localized cutaneous leishmaniasis;
DCL = diffused cutaneous leishmaniasis;
MCL = Muco-cutaneous leishmaniasis.

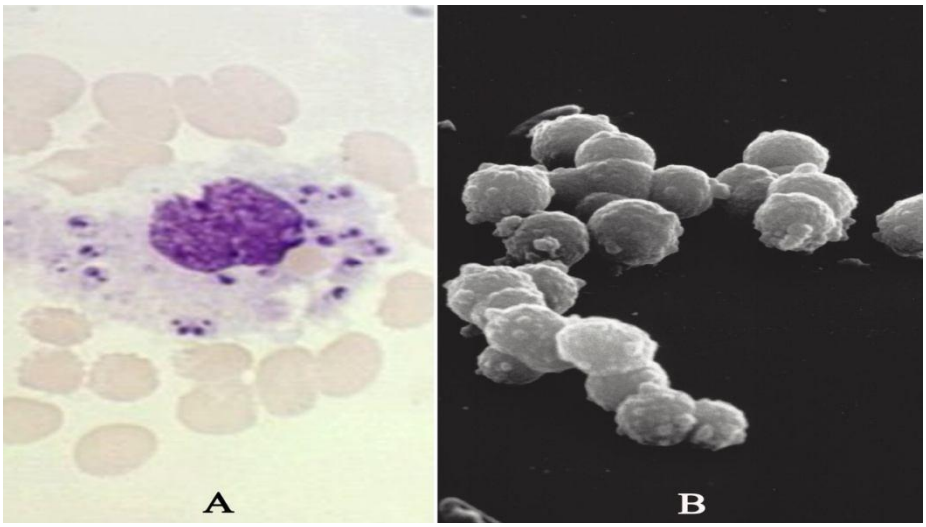

Fig. 1. Amastigotes of *Leishmania* (A = Light micrograph; B = Scanning Electron micrograph).

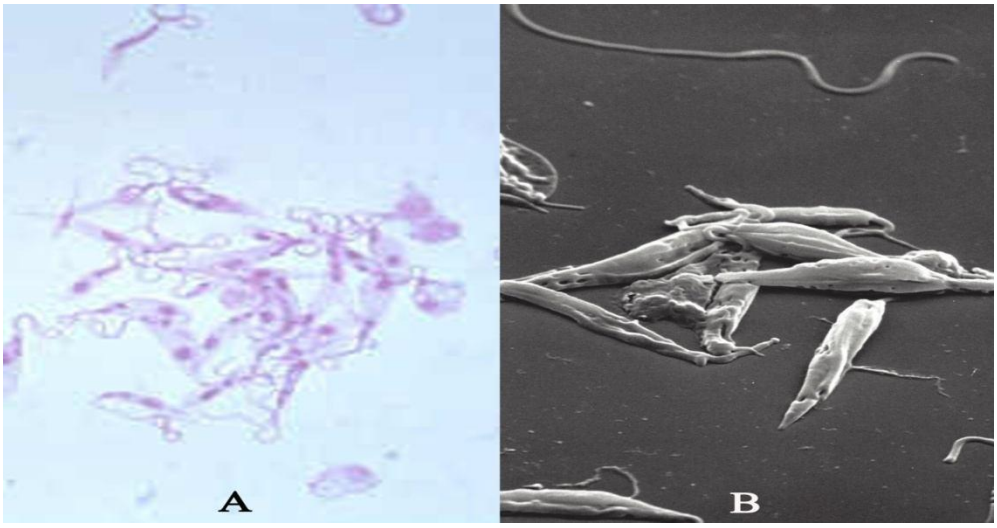

Fig. 2. Promastigotes of *Leishmania* (A = Light micrograph; B = Scanning Electron micrograph).

3. Current status of CL in KSA

In Saudi Arabia, CL is more common in males (77.5%) and appears to be more prevalent in adults (66.2%) [2, 4-9]. This could be due to the customs used by females in Saudi Arabia, which requires the reporting of most of the body and because males in Saudi Arabia tend to be more exposed to the sand fly

than females for most of the working force in Saudi Arabia are males. Overall, it is found in equal percentages between Saudis and non-Saudis. Saudi Arabia has 13 provinces. CL is more prevalent in Al-Qaseem area and least prevalent in Al-Jouf area. However, CL is known to be under reported. CL has been known in Saudi Arabia for a very long time. It was considered to be of minor importance until 1975. Later, it was considered one of the challenging diseases that were put on the control scope of the Ministry of Health [9]. At that time, no surveys were done to estimate the prevalence of CL in Saudi Arabia and data were collected from patients attending clinics [13]. Several factors have contributed to the increase in transmission of CL in Saudi Arabia, including rapid urbanization, migration, intensive agriculture, poor living conditions at farms, and massive immigration. After the setup of a national control program, number of cases of CL have dropped. However, several areas in Saudi Arabia are still considered endemic for CL [2, 4-9].

CL caused by *L. major* has been reported in many parts of Saudi Arabia, including Al-Hasa, Al-Madinah Al-Munawarah, Al-Qaseem, Riyadh and the Eastern Province while CL caused by *L. tropica* is endemic in the southwestern part of the country only [13-15]. Moreover, *L. tropica* have been isolated from CL in canines in the Eastern Province [16]. Furthermore, *L. tropica* was implicated as the causative agent of visceral leishmaniasis in Gulf War veterans [17]. However, a 46 year retrospective study of leishmaniasis cases in the Eastern Province found no evidence of dissemination or viscerotopic syndrome in patients seen at the Saudi Aramco hospital in the Eastern Province [18] and the potential for dissemination due to cutaneous leishmaniasis was significantly higher in individuals from non-endemic areas than those living in endemic areas [19]. In the past seven years over 19,000 of CL have been reported in Saudi Arabia with the highest prevalence in Al-Qaseem province (Table 2 and Fig. 3) [2, 4-9]. However, Amin and colleagues reported a declining trend in the incidence of CL in Al-Hasa area [20]. *Phlebotomus papatasi* was incriminated as the transmitting vector in Al-Hasa area [13, 21] while *P. sergenti* was identified as the transmitting vector of *L. tropica* in the southwestern part of the country [22].

Table 2. Cases of CL reported in Saudi Arabia in from 2006 – 2012.

Area	Year							Total
	2006	2007	2008	2009	2010	2011	2012	
Riyadh	306	305	325	235	401	230	135	1937
Makkah Al-Mukarramah	64	51	57	35	21	14	18	260
Al-Madinah Al-Munawarah	643	619	287	626	1000	405	236	3816
Al-Qaseem	981	851	758	654	1464	534	368	5610
Eastern Province	900	833	397	460	470	227	289	3576
Aseer	145	148	137	181	271	204	139	1225
Tabouk	149	165	90	106	159	125	97	891
Hail	249	189	165	186	234	117	122	1262
Northern Borders	3	0	0	0	1	0	0	4
Jazan	46	51	63	28	81	75	31	375
Najran	70	30	12	15	15	11	18	171
Al-Baha	45	44	30	23	12	9	11	174
Al-Jouf	1	0	0	0	0	0	0	1
Total	3602	3286	2321	2549	4129	1951	1464	19302

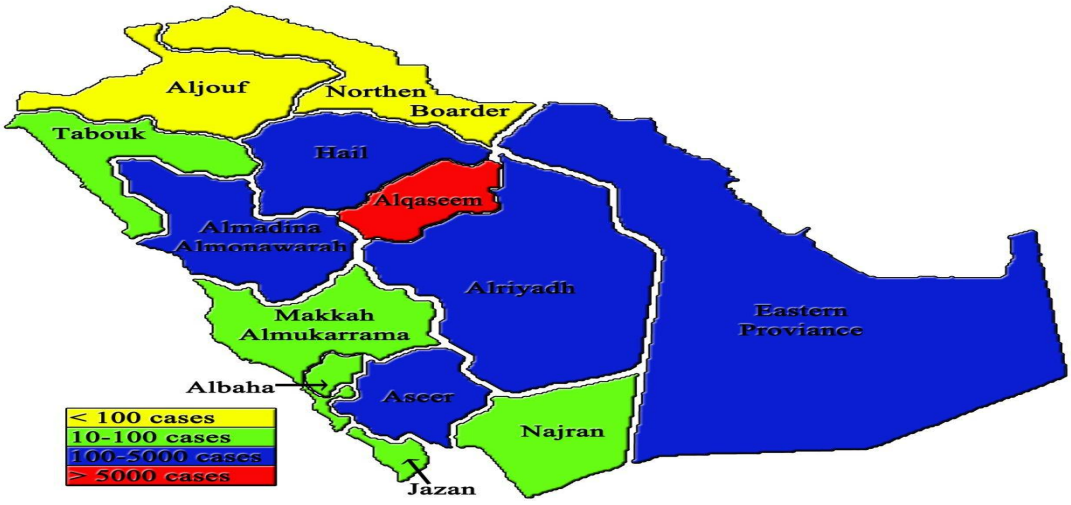

Fig. 3. Incidence of CL in different provinces of Saudi Arabia.

4. Diagnostic methods used to diagnose CL

In addition to clinical diagnosis, microscopic examination of skin biopsy or scraping can be used for the diagnosis of CL by identifying the amastigotes of *Leishmania* in the specimen. Biopsy and aspirate materials can be also cultured in NNN medium or Schneider's liquid medium to detect the promastigote stage of the parasite. Furthermore, such material can be injected into a suitable laboratory mouse or hamster and recover the parasites later on. However, Goto and his colleagues reported a low sensitivity of the direct examination techniques, culture techniques and animal inoculation techniques at approximately 50-70%, 44-58%, and 38-52% respectively [23-25].

Immunohistochemistry is a better technique in terms of sensitivity to detect *Leishmania* amastigotes and antigen reaching 41.4% and 88.5%, respectively [26]. These methods require skilled laboratory personnel and take a long time to accomplish. In addition, they are unable to identify the *Leishmania* species diagnosed. Therefore, the researcher's effort was aimed at developing molecular tools to assess in the detection of *Leishmania* DNA and hence diagnose the infection.

Leishmanin, or Montenegro test, is delayed-type hypersensitivity skin test that is used to diagnose leishmaniasis. However, this test cannot differentiate between active and past infections. Nowadays, this test is rarely used and its use is mainly confined to epidemiological studies. This is because it can give positive results in CL cases even after treatment and false positive results in cases that never showed any symptoms and live in endemic areas [23, 27-29].

Immunofluorescence and ELISA are more commonly used serological test to diagnose leishmaniasis. However, such laborious techniques can show a high degree of cross reactivity and are of low sensitivity reaching up to 88% [23, 30-33]. The direct agglutination test (DAT) is another serological test that can be used to diagnose leishmaniasis. The test is highly specific and sensitive when using homogenous species antigens but its specificity and sensitivity are questionable if using heterogeneous species antigen [23, 34].

Molecular techniques for the diagnosis of *Leishmania* parasites have emerged and evolved since the 80's [35-39]. Recently, Yehia and colleagues described a rapid and optimized protocol from DNA extraction to leishmaniasis sub-speciation, which sowed showed high sensitivity and specificity in confirming clinically suspected cases [40]. Molecular techniques have been used for the confirmation of clinically diagnosed CL cases in Saudi Arabia. El-Beshbishy and his group described the use of internal transcribed spacer 1 (ITS1) PCR-restriction fragment length polymorphism (RFLP) and kinetoplast DNA (kDNA) PCR to diagnose CL cases caused by *L. major* and *L. tropica* in Al-Madinah Al-Munawarah. In their study, they reported that kDNA PCR had a sensitivity of 90.7%, whereas ITS1 PCR had a sensitivity of 70.1%, while parasite culture alone detected 39.2% and smear alone 55.3% of the positive samples. With the exception of kDNA PCR, all other assays were 100% specific [41].

5. Treatment

CL is considered a self-healing disease. Lesions usually heal within 1-5 years. However, it is quite justified to use drugs to treat CL to minimize the resultant scar tissue caused by the lesion. Sodium stibogluconate, a pentavalent antimony compound, have been used to treat CL for 70 years. Today, pentavalent antimonials are the most widely used drugs to treat leishmaniasis. Pentamidine have been used to treat leishmaniasis as it acts on the kDNA of the parasite. However, this drug acts more slowly than pentavalent antimonials [42].

Antifungal compounds have been used also to treat CL. Ketoconazole, clotrimazole, miconazole, fluconazole and itraconazole, have been reported to have antileishmanial activity [42-46]. The use of oral rifampicin in the treatment of CL is reported to be a valuable, safe, easy to administer and cheaper modality for the treatment of CL. The advantage of rifampicin over other drugs is that it is more accepted than injectable drugs, especially by children [47].

Terbinafine was also tested *in vitro* and *in vivo* to evaluate its effect on *L. major* promastigotes and lesions in mice. Its efficacy in causing growth arrest in cultures and reducing the lesion size in mice is still questionable [43, 48]. Amphotericin B is one of the polyene antibiotics effective against various fungi and *Leishmania*. It was reported that this drug has leishmanicidal activity, but it is still rarely used due to its toxic effect [42]. Unfortunately, there is no consistent method used in treating CL. Moreover, there are no differences between treatment of single and multiple lesions [49]. This would emphasize the necessity to set clear guidelines for treatment of CL in Saudi Arabia and worldwide.

6. Conclusion

In conclusion, cutaneous leishmaniasis is still considered an endemic disease in Saudi Arabia even though its incidence is declining. More studies are required to reassess its epidemiology in the country and more effort should be made to control the disease and reduce its prevalence. Furthermore, strict guidelines for the treatment of CL and the drug dose to be used in Saudi Arabia should be implemented and enforced.

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