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Epidemiology of Cutaneous Leishmaniasis in Tunisia

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Abstract

In Tunisia, Zoonotic cutaneous leishmaniasis (ZCL) represents the most significant leishmaniasis form. The epidemic of ZCL emerged in Central Tunisia in 1982 and expanded to the whole central and southern parts of the country. Tunisian ZCL is caused by *Leishmania (L.) major* zymodeme MON-25 and transmitted by *Phlebotomus papatasi*. Rodents constitute the reservoir for ZCL. They include *Psammomys obesus*, *Meriones shawi* and *Meriones libycus*. ZCL occurs as seasonal epidemics and the annual incidence ranges from 2 to 10 thousand cases. Transmission of *L. major* by the phlebotomine sandfly vector occurs during the summer months, and active lesions in humans tend to emerge during the autumn and winter months. The symptoms of the disease are rather polymorphic, ranging from benign self-limited cutaneous sores to more protracted and extensive lesions that may cause severe disfigurement. Asymptomatic infection occurs frequently in endemic areas indicating a high level of immunity of the residents in these regions. The transmission of ZCL, its drastic increase and its spread are influenced by environmental changes affecting the reservoir and vector geographic distributions and by the lack of efficacy of the control tools available.

Keywords: Epidemiology, zoonotic cutaneous leishmaniasis, Tunisia

1. Introduction

Tunisia is the northernmost country in Africa, covering 165,000 km². It is bordered by Algeria to the west, Libya to the southeast and the Mediterranean Sea to the north and east. Tunisia's population was estimated to be just fewer than 11 million in 2014 (National census, 2014). It includes a contrasted relief with mountainous regions in the north where the Atlas range continues from Algeria, coastal plains along Tunisia's eastern Mediterranean coast and the desert in the southern region.

In this country, zoonotic cutaneous leishmaniasis (ZCL) is the most frequent form of cutaneous leishmaniasis (CL) and is caused by the parasitic protozoan *Leishmania major* (*L. major*) [1]. It is mainly transmitted by sandfly vectors, and rodents constitute the reservoir of the parasite.

The transmission dynamic of this zoonotic vector-borne disease is complex: the seasonal activity of the vector species directly impacts on the transmission process of the parasite, whereas the length of the activity period and sandfly vectors abundances are affected by the environmental conditions that influence their life cycle [2].

Since its emergence as an epidemic in Kairouan in 1982 [1], the disease has spread in several parts of Tunisia, particularly in the central and southern parts [3]. The epidemics are cyclic, and annually, 2000–3000 cases are reported. Although ZCL is usually self-curing and not life-threatening, individual cases may be psychologically and socially damaging, especially women with indelible scars that skin lesions leave on their faces. For these reasons, the epidemics are considered as a major public health priority, which remains an unresolved problem until now in Tunisia.

Disease prevention and control are difficult because of the complexity of CL epizootology, and the few options available for effective vector control [4]. Furthermore, ZCL dynamic is influenced by environmental, demographic and human behavioral factors. In fact, in the recent decade, several new foci have been reported indicating the potential spread of the disease in Tunisia. Understanding the epidemiology, the distribution and the ecological structure of the Tunisian ZCL is a crucial prerequisite for applying efficacious control measures.

2. Recall in the history of CL in Tunisia

"In Tunisia, CL was historically confined to the oasis of Gafsa and its surroundings (South-West Tunisia) where the disease was typically sporadic and occasionally epidemic, particularly in French soldiers that camped in the Gafsa region in the late 19th century. This cutaneous affection was named 'clou de Gafsa'. In 1982, a CL outbreak occurred near the dam of Sidi Saad (Kairouan governorate, Central Tunisia) that had been just finished" [2]. Over the next few years, the disease continued its contiguous spread to the western, eastern and southern parts of the country, leading to the emergence of several new foci every year [3]. Therefore, a notable increase in the incidence of CL cases was reported, ranging from 1 to 10 thousand new cases recorded annually depending on environmental changes and the pool of susceptible humans. This form of CL was identified to have a zoonotic transmission cycle.

To date, ZCL represents the dominant Tunisian CL form in terms of burden of disease, and it is mainly distributed over the central and southern arid and semiarid regions of the country, where is responsible for seasonal epidemics and regional outbreaks [4].

3. Epidemiology and ecology

3.1. Disease burden and distribution

In 2002, 15 governorates from 23 were considered as endemic in Tunisia. Between 1998 and 2007, the total number of CL cases reported to health authorities during this period was 57,591. The global yearly incidence of CL is almost 20–30 per 100,000 persons [5].

As many CL forms are symptomless and misdiagnosed, the global burden of Tunisian CL is likely to be underestimated.

Most of cases are concentrated in rural area where public health human resources and infrastructure are limited. Sidi Bouzid, Gafsa and Kairouan governorates are the areas where ZCL is most endemic in Tunisia. Sidi Bouzid has the highest population infected by CL (18,508 cases between 1998 and 2007).

Over the past decade, the epidemiological situation of CL has changed significantly. The latest study conducted in 2009 for evaluating the prevalence and the determinants of *L. major* human infection in central Tunisia demonstrated the hyperendemicity of this region. In fact, the ZCL prevalence infection rate found was quite higher to those reported so far in previous surveys conducted elsewhere in the country reflecting the putative high ZCL transmission in Tunisia across space and time. The authors of the study concluded that the control program was not effective enough to stop transmission in endemic regions [6].

It is acquiring an increasingly epidemic status with geographic expansion to previously free areas and the emergence of new foci in several regions of Tunisia. In fact, the ecological niche model elaborated by Chalghaf et al. [7] predicts that CL will extend, within few years, to many new regions in Tunisia (the northwestern side of Sfax, the western part of Mahdia, the southern part of Zaghouan and the western side of Gabès), which will be at high risk for CL emergence.

The recorded increment in the distribution and number of cases is principally a response to environmental changes, either anthropogenic or natural, which favor the rise and establishment of vector species' populations in proximity to human settlements [8].

3.2. Epidemiology

Tunisian CL epidemiology is characterized by an autumn-summer seasonality with an incidence peak from October to December. Transmission of *L. major* by the phlebotomine sandfly vector occurs during the summer months, and active lesions in humans tend to emerge during the autumn and winter months.

A previous study conducted by Toumi and colleagues in Sidi Bouzid showed the seasonality of the incidence of ZCL during the same cycle with an inter-epidemic period ranging from 4 to 7 years [9].

A recent study on the epidemiology of CL was conducted in five neighboring villages in central Tunisia, which were classified into one old and four emergent foci [6]. The prevalence and the incidence findings of this study illustrated an interesting phenomenon long known about CL; two foci as close as a few kilometers apart can have disparate prevalence and incidence statistics. The major risk factor for CL infection found in this study was the past history of transmission in a given geographic area. These findings provide additional evidence that the prevalence of the infection increases with length of residence in endemic areas, as an indicator of time exposure to the parasite [10]. This study suggests that people who resided in the old focus acquired a relative protection due to the presence of continuous boost of the immune

system by exposure to infectious sandfly bites. Moreover, the higher rate of infection in the old focus may be due to a higher density and infection rate of rodent reservoirs and, consequently, a higher infection rate of vector sandflies.

They also demonstrate in this survey that CL prevalence typically increases with age, presumably because of the acquisition of immunity. Furthermore, in established endemic areas of CL in Tunisia, the risk of infection was found to be strongly associated with the presence of family history of disease and increases significantly with the number of past ZCL cases among other persons in the same household. This finding indicates a significant clustering of ZCL transmission within households.

It has been traditionally believed that *Leishmania* infection is associated with agricultural activities in Tunisia [6]. Environmental changes, whether natural or man-made, in land use and cover, urbanization and unplanned settlements, have probably created suitable conditions for domestic transmission cycle that shifted the risk of infection from sylvatic environment to rural settlements [11].

3.3. Parasitology

3.3.1. *Leishmania* parasite

The majority of *L. major* strains isolated in Tunisia belong to the MON-25 zymodeme [3, 12]. It is largely recognized that the population structure of pathogens is influenced by different evolutionary factors, particularly during invasion of new ecosystems [13].

Over the past few decades, we reported the emergence of newly evolved *L. major* species that are genetically best adapted to the environment in Tunisia. The result of this selective process may explain the increasing chances of parasitic transmission to humans and the rise of ZCL cases in endemic regions over the last years.

Indeed, a recent study conducted in Sidi Bouzid to evaluate the temporal organization of *L. major* genetic diversity in Tunisia [14] showed that the historical *L. major* population was genetically less diverse than the current one with a significant genetic differentiation across time. In 20 years, the genetic drift in *L. major* population has played a major role in the increase in species diversity.

The same study suggested also that the parasite transmission process does not follow a vertical south-north gradient as presumed from results of other research. In fact, the disease seems to have spread from Gafsa to Kairouan and then to Sidi Bouzid. Human settlement strategies and rodent population dynamics could lead to this nongradual spatial spread.

3.3.2. Vector

Leishmania parasites are transmitted from a vertebrate host to another vertebrate host by a tiny 2- to 3-mm-long insect vector, the phlebotomine sandfly. Only the female sandfly bites vertebrates can therefore transmit the parasite.

Phlebotomus papatasi Scopoli (Diptera: Psychodidae) is the main vector of *L. major* in Tunisia.

The geographical distribution of this vector was assessed by Chelbi I. et al. in September 2006 by setting CDC light traps placed in peridomestic areas in a transect from the north to the south of Tunisia [15]. Their data verify the remarkably spatial correlation between the sandfly vector density and ZCL cases. Both of them were abundant in the arid and Saharan bioclimatic zones and rare in the humid, subhumid and semiarid bioclimatic zones.

In the same period, another study was conducted in central Tunisia to assess the population density of *P. papatasi* using sticky traps (ST) [16]. Based on the sticky traps capture data, *P. papatasi* showed a peak of density in early spring and again in the autumn, while the lowest densities were recorded in the late summer. However, the peak incidence of ZCL cases in the governorate of Sidi Bouzid took place in December, three months after the fall of sandfly density, indicating a close temporal relationship with the abundance of *P. papatasi* [16].

In Tunisia, the percentage of *P. papatasi* females naturally infected with *L. major* likely increases over the summer and peaks to 7.9% in the fall [17], corresponding to seasonal prevalence peak in *P. obesus* of 70% [18].

3.3.3. Reservoir

Many ecological studies to investigate Tunisian CL reservoir hosts were realized. Three rodent species carrying *L. major* in Tunisia were identified: *Psammomys obesus* Cretzschmar 1828 (*P. Obesus*) with a major part in amplifying the transmission, *Meriones shawi* Duvernoy 1842 (*M. shawi*) and *Meriones libycus* Lichtenstein 1823 (*M. libycus*).

Psammomys Obesus is the main reservoir host of *L. major* and the source of epidemics in the central Tunisia [19]. It was naturally infected in Tunisia [18, 20]. Its local distribution is governed by that of the halophytic Chenopodiaceae on which it depends for food [21–22]. *Meriones libycus* was suggested to have a role to propagate the parasite between *P. obesus* colonies because of their common migration, thus increasing the distribution of the parasite [23].

In the other hand, *M. shawi* is the reservoir host of *L. major* in some parts of Tunisia [5, 24]. This rodent has a particular ability to tolerate long period of water deprivation that allow survival in clay and sandy deserts, arid steppes and mountain valleys. It may also be found in cultivated fields [25].

It is a terrestrial rodent, mainly active at night, that nests in deep and complex underground burrows with several food storage cavities [26]. These saline ecological biotopes are discontinuous in distribution in the center and south of Tunisia, thus leading to a fragmentation of the populations of sand rat.

Furthermore, natural infection by *L. major* has been identified in a specimen of least weasel (*Mustela nivalis*) in Sidi Bouzid [27]. This finding might imply just an incidental infection of the *Mustela nivalis* by the *L. major* parasite. However, further research on larger samples of this animal is needed to verify its role as a potential reservoir host for CL caused by *L. major*.

3.3.4. Transmission of CL

ZCL is transmitted to humans by sandflies vectors when they are in close contact with infected reservoir hosts, as a result of activities including agricultural practices, housing and residence in close proximity to active colonies of rodents [28].

Meriones species, even though a minor reservoir of *Leishmania* in Tunisia, is thought to contribute to the dispersal of *Leishmania* because of their large range compared to *Psammomys* which is more restricted. In addition, *Meriones* species of rodents tend to live in close proximity to human settlements, and their main food source is gramineae.

Human activities that interfere with the ecologic niche of reservoirs such as deforestation and destruction of natural habitats can change the epidemiology of ZCL. Emergence of ZCL epidemics can take place when humans invade the territory of *Psammomys* [29] or the incidence can be reduced when burrows of rodents and chenopods are properly destroyed.

Epidemics of CL in Tunisia may be associated with migration and the introduction of nonimmune people into lands with existing transmission [30]. Prediction of such outbreaks depends on the availability of ecological information and one valuation of development areas before implementation of projects or population movements. Noticeable increase in the number of CL cases has been observed when susceptible population migrate to formerly unsettled areas located near *L. major* reservoir host biotopes [5].

Poverty and CL transmission risk are tied closely together. Poor hygiene and inadequate sanitation facilities (e.g., lack of wastewater treatment and disposal, open sewerage) may favor the proliferation of sandflies which increase human-vector exposure. Crowding and proximity of people play also a role in attracting sandflies.

CL is a climate-sensitive disease, occupying a characteristic “climate space” that is strongly affected by changes in rainfall, atmospheric temperature and humidity [31]. Climate conditions affect the leishmaniasis complex components (parasite-reservoir-vector) and their ability to interact, persist and establish in new ecosystems.

In Tunisia, there are two climate types. It is typically Mediterranean in the north where the terrain is mountainous, with hot, dry summers and mild winters, whereas the southern part close to the Sahara experiences a hot desert climate with high humidity. Annual average precipitation in the northern region reaches a high of 1500 mm, while rainfall in the extreme south averages less than 200 mm [7].

A previous Tunisian study [31] indicated that the occurrence of significant environmental changes driven by agricultural development projects created suitable conditions that did not previously exist for the emergence of ZCL. Toumi and colleagues confirmed in their study [9] that the risk of disease in Sidi Bouzid is mainly influenced by the humidity related to the months of July to September during the same season and mean rainfall lagged by 12–14 months.

Another Tunisian study [7] showed that the most important climate risk factors explaining the variability of CL incidence over time are precipitation and temperature. The decadal increase in the number of ZCL occurrence in the region suggests that changes in climate increased minimum temperatures sufficiently and created conditions suitable for endemicity that did

not previously exist. The gradual warming trend in Tunisia resulted in the extension of the hot season, and as a consequence, there was an elongation of the transmission period and the exposure to the parasite bites [7].

Climate change may influence geographical distribution of both sandflies and rodent densities. Ambient temperature is one of the most important factors affecting developmental times and survival of sand flies [32].

Low and high temperatures are key in limiting the distribution of *P. papatasi* and its activity [33, 34]. It cannot tolerate the extreme conditions of temperature and low humidity. Temperatures above a critical range suppress ZCL incidence by limiting the vectors' reproductive activity. The highest densities of *P. papatasi* are associated with temperatures between 25 and 28°C [16]. In fact, sand flies have adaptations to help them live in thermal preference conditions. They spend most of their lives in protected refuges, such as rodents burrows, animal shelters, wells, cracks and crevices in walls and floors [35, 36], to avoid prolonged exposure to extreme weather events.

In the other hand, higher rainfall in endemic area in Tunisia would generally increase the vegetation abundance such as chenopods, a halophytic plant that represents the strict diet of *P. obesus*. These environmental conditions are suitable for both rodents and sandflies to reproduce in large numbers and survive in abundance throughout the winter diapause to the following cycle. Therefore, following an extension of the sand rat and sandflies populations, the pool of the parasite transmissible from the reservoir to the vector could lead to a higher human exposure risk to Leishmania-infected sandfly bites over the next season [9].

4. Disease presentation: clinical symptoms

ZCL is characterized by a painless skin ulceration, which is an erythematous papule that becomes darker and develops a crust in the center over the course of several weeks. The lesions at the site of inoculation are usually situated on exposed areas such as the face and extremities, ranging from benign self-limited cutaneous sores to more protracted and extensive lesions that may cause severe disfigurement. Generally, these lesions are self-healing within 4–6 months.

It has been shown by several Tunisian epidemiological studies that the majority of human infections by Leishmania parasites remain asymptomatic, especially in endemic areas, indicating a high level of immunity of the residents in these regions [30]. Asymptomatic *L. major* infection constitutes a relatively frequent mode of natural immunization, and the ratio of asymptomatic infection to patent ZCL may reach approximately one-third, especially in the context of low transmission rates [30].

5. Disease control

Since the onset of ZCL epidemic in 1992 in the town of Sidi Bouzid, many control interventions were planned and evaluated by Pasteur Institute of Tunis with the cooperation of local health authorities. The control program was based essentially on manual pulling of chenopods

around the town where *P. Obesus* was very dense, deep plowings of colonies of the rodent and their poisoning. These interventions led to a significant reduction in the incidence among humans with a prevention fraction of disease exceeding 90%.

Consequently, in 2000, the Tunisian National Control of Parasitic Diseases Program (PDP) introduced ecological surveillance of areas at risk for ZCL before the occurrence of the epidemics based on the surveillance of the emergence of rodent colonies, such as *P. obesus*. Despite this significant effort, and the analysis of transmission dynamics of the disease in other regions, control strategies remain unsatisfactory, as indicated by the number of annual cases [5]. In fact, such actions are demanding and expensive, and consequently are often partially and intermittently performed. As such, it was therefore not possible to reduce the temporal and spatial spread of the disease [4].

Thereby, the national strategy for Leishmaniasis prevention and control has mainly focused on passive case detection and free diagnosis and treatment rather than on the reservoir and sandfly control.

Since ZCL is polymorph in terms of disease severity (number and size of lesions, duration for healing), we can hypothesize that some immune factors, depending on their intensity, will not protect against the development of the disease but rather against the severe forms. Their identification could help the development of a vaccine that protect against a severe disease, which could constitute an interesting option. The rationale for vaccine development is provided by the evidence that most individuals that had leishmaniasis or symptomless infection are resistant to subsequent clinical infections. The only proven CL vaccine (practiced for centuries) is the deliberate inoculation of virulent *Leishmania* parasites, so-called leishmanization [37].

In order to decrease the CL incidence in Tunisia during future years, some points are recommended and should be considered such as health education and awareness about disease, traffic control of immigrants and travelers to endemic regions, personal protection from sandfly biting by curtains and bed nets, eliminating and destroying habitats of the reservoir rodent and spraying insecticides in habitats of sandflies [38]. Therefore, the high awareness among the community, health decision and policy makers were key elements for sustainability of surveillance and control measures in Tunisia. Constructing a risk map of geographical spread of ZCL across Tunisian regions is also important to guide such programs [39]. Indeed finding areas with high probability of presence for both vectors and reservoirs of ZCL will be beneficial to prevent human infection by planning relevant activities [28].

6. Conclusions

The prevalence and the incidence of ZCL infection are increasing, which may reflect the higher endemicity of ZCL transmission in Tunisia over time and across geographic space. This suggests that the control strategy was not effective enough to reduce man vector contacts in endemic regions. The lack of efficacy of the control tools available is partly explained by the complexity of the transmission cycle and the insufficient knowledge of the epidemiology and the natural history of the disease. Due to its limited health resources, prioritization of

successful public health interventions and identification of populations likely to be exposed to sandflies are essential in disease management in Tunisia.

In the absence of a safe and efficacious vaccine, control measures should be adapted according to the epidemiological characteristics of the foci concerned. More researches are needed to study the diversity, the dynamics and the ecology of infectious agents and endemic foci in the country. There is also a need to develop more appropriate and effective treatment.

Finally, collaboration among medical physicians, veterinarians, researchers and public health authorities is critical to find a suitable platform and strategy for the control and prevention of CL in Tunisia.

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