

CLINICAL REPORT

Cutaneous Leishmaniasis in Syria: Clinical Features, Current Status and the Effects of War

Kinan HAYANI^{1,2}, Anwar DANDASHLI^{2,3} and Elke WEISSHAAR¹¹Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital, Ruprecht-Karls University, Heidelberg, Germany, ²Department of Dermatology, University of Aleppo, Aleppo, Syria (formerly), and ³Saudi German Hospital, Dubai, United Arab Emirates (UAE)

Cutaneous leishmaniasis (CL) is a worldwide disease caused by an infection with the protozoan parasite *Leishmania* transmitted via sand flies. It is endemic in many of the poorest countries of all continents. “Aleppo boil” is one of the recognised names given to this disease in the medical literature. Although CL used to be well-controlled and well-documented in Syria, its incidence has dramatically increased since the beginning of the war; however, there is lack of documentation. Here, we present the past and current epidemiological situation of the disease in Syria. We also draw attention to gross and highly unusual clinical variants of CL presented to the Department of Dermatology in Aleppo covering the important differential clinical diagnoses, since this disease is already known to mimic other conditions. Diagnostic procedures and treatment as well as prevention are summarised. Due to the increased ability to travel, and especially the flight of Syrians to neighbouring countries, as well as to Europe, CL may become a new threat in formerly unaffected regions. Through this account, we hope to give weight to the aspiration that CL does not remain a neglected and often clinically overlooked tropical dermatosis. **Key words:** Aleppo boil; imported skin disease; leishmaniasis; old world cutaneous leishmaniasis; slit skin smear; meglumine antimonate; tropical dermatology.

Accepted Oct 20, 2014; Epub ahead of print Oct 24, 2014

Acta Derm Venereol 2015; 95: 62–66.

Kinan Hayani, MD, Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Ruprecht-Karls University, Thibautstrasse 3, DE-69115 Heidelberg, Germany. E-mail: kinan.hayani@med.uni-heidelberg.de

The transmission of endemic cutaneous leishmaniasis (CL) has been reported in a total of 98 countries, particularly those in development, and 3 territories on 5 continents, with an incidence of around 1.2 million new cases annually. Among the 10 countries with the highest estimated case counts stands Syria (1). CL is divided, based on its geographical distribution into Old World CL (OWCL) and New World CL (NWCL). CL is caused by members of the genus *Leishmania* and the clinical manifestations depend both on the species and the genetic,

immunological and cultural background of the patient (2–4). To make a diagnosis of CL different means are used; amongst them are skin smears with Giemsa staining, skin biopsy, culture of the parasite with various media and PCR. The therapeutic options, including evidence-based recommendations, for OWCL have been reviewed (5); however, the rise in the numbers of strains resistant to some of these medicaments is of great importance in all areas where CL is endemic. Syria, and specifically Aleppo, the source of one of the common names for CL, Aleppo boil, stands in a critical position in relation to the changing patterns of the disease. The current situation of CL in Syria, due to the war and massive population displacement, is changing dramatically. This paper aims to highlight the epidemiology, the uncommon clinical variants and the therapeutic aspects of the disease in Syria.

HISTORY OF THE DISEASE IN ALEPPO

History tells us about a skin lesion described by various middle-eastern physicians, which would last as long as one year, the so-called “one-year sore”. However, it was apparently documented for the first time in the Middle East in the ninth century under the name of “*Balkh sore*” (6). In 1756, the British physician Alexander Russell wrote a chapter on this disease in his book “The Natural History of Aleppo”, where he described it under different names, amongst which were *Il Mal d’Aleppo*, *Aleppo Boil* and *Aleppo Evil*. Interestingly, at that time the disease was thought to be transmitted by water (7). Also, in the era when Syria was a French mandate (1920–1946), CL, called “*bouton d’Alep*”, also attracted the special interest of many French and Syrian physicians.

Endemic regions and prevalence

No records concerning the incidence of CL were found in Syria before 1950. In the middle of the 20th century, the control measures using DDT sprays (IRS: indoor residual spraying), used at that time to combat malaria, significantly reduced the incidence of CL in the following years. But thereafter, the number of CL cases increased sharply from the 80s onwards. Until 1960, the main endemic areas were Aleppo and Damascus and their surroundings, and also the banks of the river

Euphrates. Today, cases are reported yearly from different regions of the country (8–10).

The incidence of CL in Aleppo increased dramatically from 3,900 cases in 1998 to 6,275 in 2002. According to the World Health Organization (WHO) Report of 2010, Syria was one of the countries most affected by CL, with more than 25,000 cases per year (11). Of these, we documented, in Aleppo alone, more than 18,000 cases. In 2012, the Leishmaniasis Control Team of the World Health Organization published a report on the incidence of leishmaniasis. Syria had, according to the reports from 2004–2008, a constant annual incidence of CL of about 23,000 cases per year; however, this team assumed that there was likely to be an underreporting of the real incidence of CL, which should be 3–5 times higher (1).

Recent estimates of the Leishmaniasis Control Team showed an annual visceral leishmaniasis (VL) incidence of 14 cases per year, based on a 2–4-fold underreporting ratio (1). Few cases of VL are reported annually in Syria. Despite a seropositivity of up to 23% in some regions, full blown disease was only rarely seen and VL was never a threat in Syria (12).

Currently, an outbreak has been observed due to the war in Syria and the lack of measures to combat the disease, particularly in the besieged and medically underserved areas. New publications from the Ministry of Health reveal shocking statistics. There was an incidence rate of 53,000 cases in 2012 and 41,000 cases were reported in the first 2 quarters of 2013 (13). According to a recent telephone conversation with the head of the Leishmaniasis Centre in Aleppo (Dr. Ahmad Jatal, personal communication), 22,365 cases were reported in the previous year in Aleppo alone. One has to take into consideration that the city of Aleppo has been divided into 2 parts since 2012 and the government has control over only one part of the city. This has led to a dramatic loss in the means of control of CL. Besides, in seeking internal refuge, hundreds of thousands of civilians have been obliged to leave their homes to safer places inside the city of Aleppo; this has resulted in the spread of the disease to new, previously non-endemic parts of the city. Moreover, since then no more epidemiological statistics have been forthcoming from the other sector of the city.

Pathogens and transmission

In the north of Syria, in Aleppo and its surroundings, CL is of an anthroponotic type and is due to *L. tropica* ZMON-76 (14). In the suburbs of the capital Damascus, zoonotic CL is due to *L. major* ZMON-26 (15). Moreover, *L. infantum* has also been suggested as the causative agent in the Syrian Mediterranean area (16, 17).

The animal reservoirs include fat sand rats (*Psammomys obesus*), great gerbils (*Rhombomys opimus*) and dogs; however, these are only exceptionally found in the city of Aleppo, leaving infected individuals as

the probable main hosts of the disease in the city. This proposition has been supported recently with the spread of the disease, through the relocation of refugees, from one infected part of the city to new areas, previously unaffected with the disease.

The causative agent of the anthroponotic CL, *L. tropica*, is transmitted through the female sandfly *Phlebotomus sergenti*, and the agent of the zoonotic form of CL, *L. major*, through *P. papatasi* in Syria (2, 18).

Most cases of CL in Aleppo are diagnosed by means of slit skin smears with Giemsa staining and/or skin biopsies, sufficient to make the diagnosis. But, culture on Novy-MacNeal-Nicolle medium is less frequently used and there is little opportunity for the use of PCR in this situation.

CLINICAL COURSE

The clinical course of CL depends on the causative agents and the genetic, immunological and cultural background of the patient (19). There is no strict correlation between clinical presentation and the species of the parasite, since one single *Leishmania* zymodeme, as the case in Aleppo (ZMON-76), can produce clinically different skin lesions (20).

Usually, there is an incubation period of 2 weeks to several months. First, a small red-brownish papule appears, normally on areas of the skin not protected by clothes. In addition, nodes or plaques can develop in the course of the disease. Ulcerations are frequent. Within 12–18 months, and without treatment, CL normally heals with a an ugly scar. In a single study, the psychological burden of CL has been assessed in a Turkish city next to the Aleppo governorate. Here, it was shown that patients with CL (either CL active for more than one year or healed lesions with scars CL) have higher anxiety and depression scores, lower body image satisfaction scores and a decreased quality of life index (21).

As for many dermatological diseases, there is a variety of different clinical forms, where the CL may resemble common skin diseases such as e.g. psoriasis, eczema and erysipelas (22, 23). The following cases represent examples of unusual expression of CL:

Case 1. A 13-year-old girl with a known history of atopic dermatitis presented with eczematous, erythematous and slightly lichenified papules on her wrist that had been present for 8 months (Fig. 1A). Physical examination did not show any signs of atopic dermatitis, except for mild xerosis, which was our first differential diagnosis. Treatment with various corticosteroid- and antibiotic-containing ointments had no effect on the course of the lesions. The slit skin scrapings confirmed the diagnosis of CL.

Case 2. A 17-year-old patient (Fig. 1B left) presented to our clinic with a picture of mild acne composed of erythematous papules, small nodules and comedones. He was treated topically with isotretinoin cream and topical erythromycin. He revisited us for a follow-up after 2 months with no change in his lesions, and he was put on oral antibiotics for acne. On his third visit he brought his 2 brothers and stated that they were suffering from the same

disease. Slit skin smears with Giemsa staining from all 3 brothers confirmed the diagnosis of CL mixed in with acne in 2 of the 3 (left and right). One would expect to see an easy-to-diagnose “familial type” of CL in such an endemic area like Aleppo.

Case 3. A 3-year-old child presented with multiple papules and vesicles limited to his face for 2 weeks (Fig. 1C). The mother stated that she had unsuccessfully used various ointments, including corticosteroids. The main differential diagnosis here was chickenpox. Smear with Giemsa staining showed *Leishmania* amastigotes. The child responded very well to systemic meglumine antimonate (MA) treatment.

Case 4. A 22-year-old patient presented with a 5-month history of plaques and papules on his face, which were violaceous-brownish in colour and slightly scaly (Fig. 1D). There were

no other lesions on the skin of other body areas. Our first differential diagnosis was sarcoidosis. The patient was in good general condition without any fever, cough or joint pain. The chest X-ray was normal. Skin biopsy showed the non-caseating granulomas but with Leishman Donovan (LD) bodies which confirmed the diagnosis of CL.

Case 5. A 17-year-old girl presented to our department with rapid development of a pedunculated tumour on her face over one month (Fig. 1E). The main differential diagnoses included adnexal tumours of the skin, mainly syringomas and/or trichoepitheliomas. The node was excised and the dermatopathology examination revealed non-caseating granulomas with amastigotes. The remaining surrounding papules responded completely to systemic treatment with MA.



Fig. 1. Clinical spectrum of cutaneous leishmaniasis (CL). (A) Multiple small red papules and lichenification of the skin, partly covered with pustules, on the wrist of a patient with atopic dermatitis, due to CL. (B) The so-called familial type of CL in 3 brothers with additional acne lesions in two of them (left and right). (C) Multiple serous papules and nodules with crusts on the face of a child resembling chickenpox or impetigo. (D) Brownish violaceous plaques on the face resembling sarcoidosis. (E) A huge tumour on the nose with surrounding small papules. The differential diagnosis included adnexal tumours, but dermatohistopathological examination revealed CL. (F) Superficial basal cell carcinoma-like variant of CL on the forehead. (G) CL presenting as an oedematous plaque on the helix mimicking Kimura disease. (H) CL of the neck without any abnormality of the thyroid gland function. (I) A huge mutilating lesion affecting the skin and mucosae of the lips and lower face in a boy. Dermatopathology revealed CL. The patients/parents approved publication of all photos.

Case 6. A 62-year-old woman presented with a 2-month-old ulcerated lesion on the forehead (Fig. 1F). Taking the age of the patient and the location of the lesion into account, we considered the possibility of a superficial type of basal cell carcinoma. Interestingly, there was a history of a healed CL lesion in the scarred area 2 years ago. Skin biopsy from the active lesion showed a recurrent lesion of leishmaniasis, and no histological evidence for a basal cell carcinoma.

Case 7. A 41-year-old patient presented with red-yellow-brownish plaques on the left helix for 2 months (Fig. 1G). He had no lymphadenopathy and did not report any pain sensation. Kimura's disease was considered as a differential diagnosis, which fitted with the localisation of the lesions. Skin biopsy showed non-caseating granulomas with LD bodies.

Case 8. A 34-year-old patient had an ulcerated plaque for months which was localised to the lower hairline of his beard area (Fig. 1H). The lesion had been traumatised continuously by shaving and by his neck posture. Screening for enlargement of his thyroid gland yielded normal results. Skin biopsy confirmed the diagnosis of CL that responded very well to intralesional MA; however, residual scarring could not be avoided.

Case 9. A 13-year-old boy from the country had been mistreated by the traditional "health practitioners", initially for herpes and then for a bacterial infection. He showed a huge disfigurement of the mouth and lower face (Fig. 1I). A skin biopsy showed non-caseating granulomas with the LD bodies. The patient was treated systemically for CL and eventually admitted to the department of plastic surgery for reconstruction of the lips and the perioral region. CL is in some cases a cause of severe mutilation.

THERAPY

A local scheme is now applied for the treatment of CL in Aleppo. The choice of therapy depends on size, number and location of the lesion(s), as well as on the species of the causative *Leishmania*. Usually, however, identification of *Leishmania* to species level is rarely applied in this situation and identification is based on the epidemiologic database for the area from which the patient originates. OWCL in Syria has higher spontaneous cure rates compared to those of the NWCL; therefore, they only exceptionally need any systemic treatment (24). According to the classification proposed by Bailey et al. (25), the CL lesions in Aleppo were also classified into simple and complex lesions. Complex lesions are defined as those that are greater than 40 mm in size, show evidence of dissemination, carry a risk of cosmetic or functional problems, or do not respond to initial treatment as a simple lesion; however, and contrary to Bailey's classification, complex CL lesions in Aleppo are those comprising 5 or more lesions. Systemic treatment is usually administered for those with complex lesions. Alternatively, simple CL lesions are single nodules and simple plaques that do not require more than local treatment. Three or less sporotrichoid CL lesions are also considered as simple CL lesions and these are treated intralesionally. Otherwise, systemic therapy should be necessary.

All the aforementioned recalcitrant and complex cases of CL responded well to MA, either intralesionally

or systemically. Despite the documentation of resistance elsewhere, the pentavalent antimonial preparations yielded the best cure rate in the Department of Dermatology at the University Hospital of Aleppo and are the drug of choice. MA is preferred for intramuscular (i.m.) and sodium stibogluconate (SSG) for intravenous (i.v.) administration. The usual recommended dosage is 20 mg antimony (Sb^{5+})/kg/day for 14–21 days, which is administered as an i.v. infusion (SSG only) or i.m. injection (both SSG and MA). Pentavalent antimonials are commonly used as intralesional (i.l.) injections for simple lesions. The technique of i.l. treatment has been described previously (26).

Neither miltefosine nor the liposomal amphotericin are available in Syria. By reviewing the internal documentation of the University Hospital of Aleppo, different therapies have been tried in Aleppo, amongst which: oral azole agents, oral metronidazole, i.l. zinc sulphate, topical paromomycin as well as cryotherapy, to name but a few. All these modalities were less effective than the pentavalent antimonials (unpublished data).

DISCUSSION

Today, CL remains a real dermatological challenge in Syria and the Middle-Eastern countries. Its occurrence appears to be increased due to the conflict in Syria although there is no documentation for most parts of the country. Knowledge of this disease is also necessary for any dermatologist practising in Europe or other world regions. The potential for different clinical variants of CL should always be kept in mind, when considering dermatoses in travellers or migrants (19). CL is presenting an alarming problem for the whole area of the Middle East (27). Because of the current complicated and grim situation of the Syrian war, prevention measures of CL no longer are undertaken, a situation which has led to the spread of CL to new areas in Syria, that were previously not affected by the disease. In the portfolio of the Tropical Disease Research team – hosted at the WHO, Geneva – priorities were previously defined on the basis of a comprehensive analysis of research needs and research opportunities for each of the 10 major tropical diseases. In leishmaniasis, the principal neglected tropical disease control strategy was case identification, treatment, and control of vectors and animal reservoirs; however, the need for lengthy, complex and expensive treatments, practical limitations of laboratory diagnostics and poor health systems in the affected countries are major challenges that face this control strategy (28). In a recent study of the *aleppine* CL patients' knowledge and attitudes about the disease, most of the respondents referred to the disease as "one-year sore", linking it to insect bites. Most believed that it was not contagious and that it was preventable by using mosquito nets and insecticides. They also knew

the treatments available (29). Therefore, a strengthened international collaboration under the supervision of the WHO is necessary in order to reduce the incidence and to improve the treatment of CL. In anthroponotic foci, as is the case for many patients with CL in Syria, such an intervention would have a major impact on morbidity and transmission (30). Refugees in neighbouring countries (Lebanon, Iraq, Jordan and Turkey), and also in Europe, pose a risk, given the availability of vectors, for the transmission of the disease to new as yet unaffected countries.

ACKNOWLEDGEMENTS

We thank Ahmad Jatal, MD, the head of the Leishmaniasis Centre in Aleppo, for his help in providing the newest statistics on the disease in the city.

All photos presented in this manuscript are in the possession of Anwar Dandashli, MD, former director of the Department of Dermatology, Aleppo, Syria. They were taken after informed consent by the patients was obtained. This included the permission to publish them for scientific articles.

The authors declare no conflict of interest.

REFERENCES

- Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J. Leishmaniasis worldwide and global estimates of its incidence. *PLoS ONE* 2012; 7: e35671.
- World Health Organization. Control of the leishmaniasis. World Health Organization Technical Report Series, 2010; (949): xii–xiii, 1–186, back cover.
- Desjeux P. Worldwide increasing risk factors for leishmaniasis. *Med Microbiol Immunol* 2001; 190: 77–79.
- Desjeux P. The increase in risk factors for leishmaniasis worldwide. *Trans R Soc Trop Med Hyg* 2001; 95: 239–243.
- Monge-Maillou B, López-Vélez R. Therapeutic options for old world cutaneous leishmaniasis and new world cutaneous and mucocutaneous leishmaniasis. *Drugs* 2013; 73: 1889–1920.
- Elgood C. The early history of the Baghdad boil. *J Roy Asia Soc* 1934; 66: 519–533.
- The Natural History of Aleppo; London: A. Millar. ISBN 10: 1230350187; 1756; p. 262–266.
- Desjeux P. Information on the Epidemiology and Control of the Leishmaniasis by Country or Territory. Switzerland: World Health Organization, 1992; p. 29.
- Ashford RW, Rioux JA, Jalouk L, Khiami A, Dye C. Evidence for a long-term increase in the incidence of Leishmania tropica in Aleppo, Syria. *Trans R Soc Trop Med Hyg* 1993; 87: 247–249.
- Tayeh A, Lama J, Cairncross S. Twenty years of cutaneous leishmaniasis in Aleppo, Syria. *Trans R Soc Trop Med Hyg* 1997; 91: 657–659.
- Anonymous, WHO Working to overcome the global impact of neglected tropical diseases. First WHO report on neglected tropical diseases, 2010: p. 91–96.
- Al-Nahhas S, Shabaan M, Hammoud L, Al-Taweel A, Al-Jorf S. Visceral leishmaniasis in the Syrian Arab Republic: early detection using rK39. *East Mediterr Health J* 2003; 9: 856–862.
- National reports for the Ministry of Health, Syrian Arab Republic. (2012, 2013) <http://www.moh.gov.sy>.
- Belazzoug S, Pratlong F, Rioux JA. Un nouveau zymodeme de Leishmania tropica, agent du Bouton d'Alep (Syrie). *Archives de l'Institut Pasteur, Algérie*, 1988, 56: 95–99.
- Khiami A, Dereure J, Pratlong F, Martini A, Rioux J'A. La leishmaniose cutane humaine à Leishmania major MON-26 aux environs de Damas (Syrie). *Bull Soc Exp Pathol* 1991; 84: 340–344.
- Rioux JA, Lanotte G. Leishmania infantum as a cause of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1990; 84: 898.
- Knio KN, Baydoun E, Tawk R, Nuwayri-Salti N. Isoenzyme characterization of Leishmania isolates from Lebanon and Syria. *Am J Trop Med Hyg* 2000; 63: 43–47.
- Adler S, Theodor O. The distribution of sandflies of the erected-haired group in relation to oriental sore. *Ann Trop Med Parasitol* 1929; 23: 269–302.
- von Stebut E, Schleicher U, Bogdan C. Cutaneous Leishmaniasis as travelers' disease. Clinical presentation, diagnostics and therapy. *Hautarzt* 2012; 63: 233–246.
- Pratlong F, Dereure J, Ravel C, Lami P, Balard Y, Serres G. Geographical distribution and epidemiological features of Old World cutaneous leishmaniasis foci, based on the isoenzyme analysis of 1048 strains. *Trop Med Int Health* 2009; 14: 1071–1085.
- Yanik M, Gurel MS, Simsek Z, Kati M. The psychological impact of cutaneous leishmaniasis. *Clin Exp Dermatol* 2004; 29: 464–467.
- Raja KM, Khan AA, Hameed A, Rahman SB. Unusual clinical variants of cutaneous leishmaniasis in Pakistan. *Br J Dermatol* 1998; 139: 111–113.
- Hayani K, Dandashli A, Weissshaar E. Außergewöhnliche klinische Manifestationen der kutanen Leishmaniasis. *Hautarzt* 2014; 65: 889–894.
- Blum J, Hatz C, Junghans T. The therapy of cutaneous and mucocutaneous leishmaniasis. *Dtsch Med Wochenschr* 1994; 119: 1169–1172.
- Bailey MS, Green AD, Ellis CJ, O'Dempsey TJ, Beeching NJ, Lockwood DN. Clinical guidelines for the management of cutaneous leishmaniasis in British military personnel. *J R Army Med Corps* 2005; 151: 73–80.
- Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. *J Am Acad Dermatol* 2007; 57: 335. e1–29.
- WHO warns of increased risk of disease epidemics in Syria and in neighbouring countries as summer approaches, 2013 3rd June. <http://www.emro.who.int/press-releases/2013/disease-epidemics-syria.html>.
- Remme JH, Blas E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, et al. Strategic emphases for tropical diseases research: a TDR perspective. *Trends Parasitol* 2002; 18: 421–426.
- Abazid N, Jones C, Davies CR. Knowledge, attitudes and practices about leishmaniasis among cutaneous leishmaniasis patients in Aleppo, Syrian Arab Republic. *East Mediterr Health J* 2012; 18: 7–14.
- Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis* 2004; 27: 305–318.