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CUTANEOUS LEISHMANIASIS IN SYRIAN REFUGEE CHILDREN

A CASE SERIES

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Abstract: Cutaneous leishmaniasis is the most common presentation of infection by protozoan parasites of the genus *Leishmania*. Patients with cutaneous leishmaniasis may have one or several disfiguring skin lesions that resemble other dermatologic diseases. Old World cutaneous leishmaniasis is a major public health problem in the World Health Organization Eastern Mediterranean Region. Conflict and ensuing collapse of health systems leads to migration of leishmaniasis patients from countries like Syria. Pediatricians in nonendemic countries should be aware of this disease entity. We identify knowledge gaps and summarize treatment options for cutaneous leishmaniasis.

Key Words: cutaneous leishmaniasis, import pathology, Syria, infectious diseases

Accepted for publication March 12, 2020.

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The authors have no funding or conflicts of interest to disclose.

All authors made significant contributions to the design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DOI: 10.1097/INF.0000000000002676

Cutaneous leishmaniasis (CL) is the most common presentation of infection by protozoan parasites of the genus *Leishmania*. It is a potentially disfiguring disease.[1] People with CL may have one or several chronic skin lesions, usually without fever or systemic symptoms. Old World CL is a major public health problem in the World Health Organization (WHO) Eastern Mediterranean Region as control efforts for this neglected disease are failing.[2,3] The emergence of leishmaniasis is associated with conflict and unrest in the region.[4] In northern Syria, the incidence of CL peaked to 7599 cases in February 2015. The number of new cases was reduced to prewar levels of around 2500 cases per month after reactivation of both curative and preventive control efforts.[5] In this region, CL may be caused by 3 different *Leishmania* species, *L. tropica*, *L. major* and *L. infantum*.

Because of conflict and subsequent displacement of people, patients from this region may present with CL lesions in nonendemic countries, where the disease is not readily recognized. During the civil war in Syria (from 2010 and ongoing), many migrants from this region presented with leishmaniasis at the Institute of Tropical Medicine, Antwerp, Belgium. In this series, we describe the clinical management of 3 representative CL cases in Syrian children.

CASE REPORTS

Case 1

A 12-year-old girl presented at Institute of Tropical Medicine in November 2016 with painless papules and pustules on the left cheek for over 1 year (Fig. 1A). She was a refugee from Saraqeb, Idlib, who had arrived in Belgium 7 months before presentation. A biopsy of the lesion showed granulomatous inflammation. No microorganisms were identified with parasitologic microscopic examination of Giemsa-stained biopsy, neither with anatomopathologic analysis of the tissue. *Leishmania* was detected by real-time polymerase chain reaction (PCR). Species identification of *L. tropica was* based on heat-shock protein 70 sequencing.[6] The lesion was treated with 6 weekly intralesional injections of meglumine antimoniate (Glucantime; Sanofi-Aventis). Complete remission was seen without scar formation.

Case 2

The 13-year-old sister of case 1 had a painless ulcer on the right lower arm for 1 year (Fig. 1B). Histologic examination showed a hyperkeratotic epidermis with infiltrations of histiocytes, lymphocytes and plasma cells, but no amastigotes nor granulomatous inflammation. PCR was positive for *Leishmania.* At species level, *L. tropica* was identified. The lesion was infiltrated weekly with meglumine antimoniate during 5 weeks. Complete cure was recorded.

Case 3

An 11-year-old Syrian girl presented in October 2016 with a nonhealing lesion on the tip of the nose for 3 years (Fig. 1C). Because of the sensitivity of the lesion site, a swab was taken for PCR analysis and sequencing. A *L. tropica* infection was confirmed. To avoid painful injections in this anatomic location, oral treatment with fluconazole was initiated. Because the lesion did not heal, she received treatment with liposomal amphotericin B (total dose of 20 mg/kg). The lesion disappeared completely.

DISCUSSION

More than 98 countries are currently reporting endemic CL transmission. Between 0.5 and 1.2 million cases occur each year.[2,3,7] In the WHO Eastern Mediterranean Region, more than 100,000 new cases are reported annually. The true incidence is estimated to be 3 to 5 times higher.[2,3,8] Historically known as the "Aleppo Boil," Old World CL has always been prevalent in Syria.[9] The relationship between war and the emergence of infectious diseases, including leishmaniasis, is well known. Massive population displacement, breakdown of control measures, collapse of health systems and impeded access to health care facilities are only a few of the risk factors for a surge in the number of cases.[8] In Syria, CL incidence doubled in 2013 compared with the period preceding the civil war with a peak in 2015.[5,8,10] The highest incidence was recorded in the provinces of Idlib, Hama and Aleppo.[4,8] Intense transmission is concentrated around refugee settlements as well.[10] Neighboring countries receiving refugees such as Turkey and Lebanon also reported increasing numbers of CL.[10]

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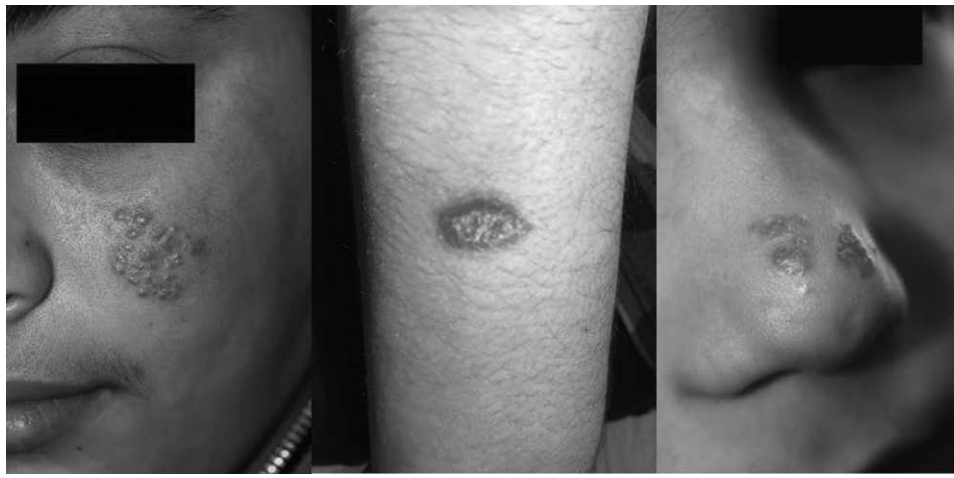

FIGURE 1. Skin lesions of the 3 patients. Lesions of patients 1 (A), 2 (B) and 3 (C) before treatment.

Chronic skin lesions can be caused by numerous conditions such as bacterial skin infections, insect bites, venous ulcers, cutaneous tuberculosis and syphilis.[2,11] CL should be included in the differential diagnosis in patients from endemic regions.[11] Days to months after the bite of an infected female sandfly[9] typical lesions are found on uncovered parts of the body. In localized CL, the lesion starts as a raised papule that becomes a nodule or plaque. Centrally a crust covers a painless ulcer. The edges are raised with variable surrounding induration. The number of lesions, their location, aspect and size can vary.[2] In contrast with infections in the New World (America) that may lead to mutilating lesions, those acquired in the Old World (Europe, Africa, Asia) are usually self-healing.[11] However, this process may take months or years, as illustrated by our 3 cases, and can result in disfiguring scars.[9,12] The most frequent species causing CL in Syria is the anthroponotic *L. tropica*, accounting for more than 90% of cases, and which was the causative species identified in our 3 cases.[3,8] *L. major*, a species primarily transmitted as a zoonotic disease, is much less frequent,[3,8,13] and *L. infantum* is rarely encountered.[2,11] The lesions caused by these species are clinically indistinguishable, although the course of *L. major* infection is usually milder and shorter than the others.

For confirmation of the diagnosis, demonstration of *Leishmania* parasites in skin samples is required. The diagnostic yield is highest in samples taken from the rim, which is the active site of the lesion. Sensitivity of microscopic techniques has been reported to range from 17% to 83% for CL depending on clinical presentation, parasite species, technical expertise and other factors.[14] Amastigotes can be seen after Giemsa staining (Fig. 2). In addition, non-necrotizing epithelioid granulomata with lymphocytes, histiocytes, plasma cells and scanty macrophages are classically found in the histologic examination of punch biopsies.[11] Samples can be obtained from the rim of a lesion by biopsy or needle aspiration for culture in a modified Novy-Nicolle-McNeal medium. This allows isolation and identification of promastigotes,[11] but the sensitivity of culture is low.[7] PCR has become the preferred test to confirm the diagnosis. Sensitivity is 53.8%–98.7% depending on the assay used with a specificity approaching 100%.[14] Because *Leishmania* species are morphologically indistinguishable by light microscopy, identification at species level is done by sequencing analysis of the PCR product.[2,11] Serologic tests do not contribute to the diagnosis of CL.[7,11] The diagnosis of CL was ascertained by PCR in our 3 cases because microscopic examination failed to demonstrate amastigotes in cases 1 and 2, while it could not be performed on the swab sample obtained in case 3.

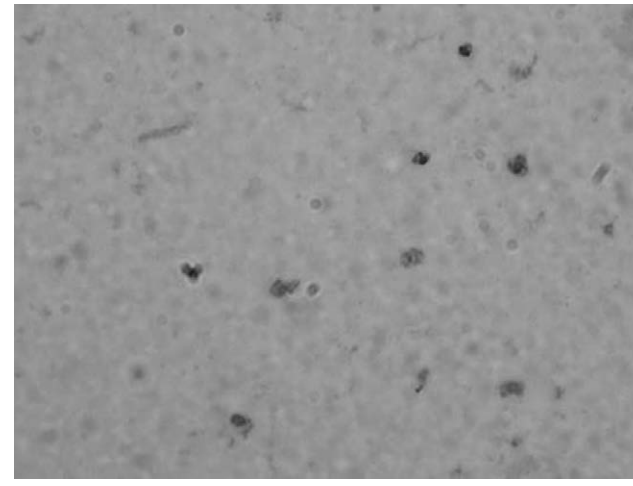

FIGURE 2. Small (2–4 μm diameter), oval *Leishmania tropica* amastigotes with a nucleus, kinetoplast and plasma membrane after Giemsa staining. Copyright microbiology laboratory, Institute of Tropical Medicine.

The management of CL differs from region to region and is primarily based on observational studies and expert opinion.[7,12] The Infectious Diseases Society of America proposes a step-wise approach depending on the size and number of the lesion(s).[15]

Lesions can heal spontaneously, and therefore, expensive and potentially toxic treatment is sometimes unnecessary. Treatment is justified when lesions are multiple, nonhealing, located on cosmetically sensitive sites, in case of mucosal involvement or in immunosuppressed hosts.[15] The localization of the lesions on uncovered areas of the body (as in the 3 cases reported here) and possible disfiguration has psychologic consequences warranting treatment. It is recommended to refer the patient to specialized centers.[11] The infecting *Leishmania* species affects treatment outcomes as prognosis and susceptibility to some drugs vary among species.[12,16] Treatment can be based on geographic

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origin, but this may be inadequate when multiple *Leishmania* species cocirculate, as is the case in Syria.[7] The preferred initial therapeutic approach for small (<4 cm), up to 4 CL lesions, is topical treatment with intralesional injections of pentavalent antimonials (Sb(V)) or application of liquid nitrogen (cryotherapy).[11,12,15,17] The combination of both treatment provides the highest cure rate (>90%). Both treatments have few side effects. Sb(V) must be injected intradermally. This can be painful and requires some expertise. Treatment should be given every 5–7 days, 2–5 times.[2,7,11,17] In case of cryotherapy, several sessions are often needed.[18] Topical paromomycin is not available in Belgium. The WHO criteria for topical treatment[2] were met in cases 1 and 2, and a good treatment response was observed after intralesional infiltration with Sb(V).

Systemic treatment is indicated if there is lymphatic spread, if the criteria for topical treatment are not met or if previous topical treatment failed.[2,17] Intravenous antimonials have classically been administered in endemic regions. This drug treatment shows high cure rates with few recurrence. However, the potential toxicity of intravenous antimonials includes pancreatitis, leukopenia, thrombocytopenia and electrocardiogram alterations (eg, QT interval prolongation and T-wave changes), and patients should be admitted for monitoring.[2,11] Oral miltefosine is a promising option especially for complicated *L. major* infections. Unfortunately experience with miltefosine is limited to small cases series in adults only, and access to this expensive drug is limited.[7,19] Liposomal amphotericin B is increasingly considered an alternative treatment, at least in Europe, with very few side effects, but is expensive and not reimbursed in Belgium for this indication.[7] Fluconazole and itraconazole have some antileishmanial activity against *L. tropica* and *L. major,* but studies have been inconclusive due to contradictory results,[2,7,11] and therefore, azoles are usually not used in first-line treatment. Because the localization of the lesions of case 3 did not allow antimonial infiltrations, oral fluconazole was first selected, with no improvement. Treatment with liposomal amphotericin B was given, and the lesion cured completely.

CONCLUSION

The current conflict in Syria contributes to the influx of CL patients in nonendemic countries such as Belgium. A systematic approach in diagnosis and treatment is of great importance. Molecular methods are currently the preferred tests for diagnosis and allow species identification that guide clinical management. Topical treatment is preferred whenever possible, although infiltrations may be uncomfortable in younger children. Indications for systemic therapy of CL in children are still poorly defined. Additional research into evidence-based therapeutic interventions for CL, and improved access to antileishmanial drugs is urgently needed.

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