Aspects of tropical ulcerating diseases
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Chapter 6

Changing pattern of imported cutaneous leishmaniasis in The Netherlands


Summary

Cutaneous leishmaniasis (CL) in western countries seems to be appearing more frequently. Our aim was to determine if there has been a shift in countries where CL is acquired and whether the incidence has changed, and to assess current diagnostic procedures and treatment modalities. In a retrospective study medical records of patients with the diagnosis of CL at the Departments of Tropical Dermatology and Tropical Medicine, Academic Medical Center, Amsterdam, the Netherlands, from 1990 to 2000 were analysed. CL was diagnosed in 78 patients. The majority was acquired in Belize, Surinam, French Guyana and Bolivia. Giemsa stains were positive for the parasite in impression smears from 43% and in biopsies from 71%. Seventy-eight percent of cases were culture-positive and 89% were PCR-positive. Sixty-two patients were treated systemically: pentavalent antimony (32), pentamidine isetionate (11), itraconazole (19), and 13 locally, the majority with a combination of cryosurgery and intralesional pentavalent antimony. Imported CL is becoming more frequent, with South and Middle American countries being important sources of infection. Multiple tests, of which PCR is the most sensitive, are required to confirm the diagnosis. Systemic treatment was given to the majority of the patients.
Introduction

Leishmaniases are visceral, cutaneous and mucocutaneous diseases caused by parasites belonging to the genus *Leishmania*.1 Although cutaneous leishmaniasis (CL) is the mildest clinical form, it can cause considerable morbidity, and after healing often leaves disfiguring scars.2,3 All varieties are transmitted to humans by phlebotomine sandflies.4 The disease occurs throughout the tropical and subtropical regions of the world with an estimated 1.5–2 million cases per year, of which the majority is CL.5 The clinical picture is diverse and may vary from one or more papules, to ulcers with or without a scab. Lymphangitis may be present.6 Mucocutaneous leishmaniasis, although uncommon, may develop as a complication of New World-CL. The clinical picture depends on the species involved, the immune response of the host, host genetics, and probably the transmitting vector.7,8 Indications for treatment and current recommended treatment regimes vary.9–11 There are only a few double-blind clinical trials in which the exact *Leishmania* species is known. However, some treatments are well established.12,13

In the Netherlands leishmaniasis is seen as an imported skin disease, with a rising incidence in the last 10 years. A Dutch study described 49 patients with CL in the period 1979–1989; Mediterranean countries were the most important sources of infection.14 We found it of interest to see if a change in this pattern had occurred in the following years, and additionally, how sensitive our diagnostic procedures were, which treatments were given and how effective the results of treatment were. For this reason, incidence, clinical picture, treatment modalities and response of patients diagnosed with CL from January 1990 to January 2000 in our hospital were studied retrospectively.

Patients and method

From the records of 78 patients diagnosed with CL from January 1990 to January 2000 at the Academic Medical Center, the following data were extracted: age; area visited, reason for visit, dates of visit in endemic area; date that a lesion was first noticed; number, size and site of the lesions; results of histological examination of the lesion, of culture, impression smear and, if performed, PCR. Treatment modalities used, dose, duration and side effects, if they occurred, were also recorded. Response to treatment was defined as resolution of the lesion as assessed by the physicians. All patients were closely monitored during treatment until at least 6 weeks after finishing treatment by physicians of the Department of Dermatology and/or the Department
of Tropical Diseases. Thereafter, patients were usually followed-up by their general medical doctors, and referred to our department if relapses occurred.

Results

from 1990 to 2000 CL was diagnosed in 78 patients (63 male, 15 female). The mean age was 31 years (range, 4–84 years). The endemic areas visited are shown in Fig. 1. CL was most frequently acquired in Belize \((n = 23, 30\%)\), Surinam \((n = 12, 15\%)\), French Guyana \((n = 11, 14\%)\) and Bolivia \((n = 10, 13\%)\); 61 \((78\%)\) patients acquired CL in the New World, 17 \((22\%)\) in the Old World, of which seven \((41\%)\) came from Afghanistan.

![Figure 1](image)

Figure 1 The endemic countries visited by patients diagnosed with Cutaneous Leishmaniasis. Nineteen patients visited more than one country where CL is endemic.

Most lesions were localized on the arms \((n = 29, 29\%)\), head \((n = 22, 22\%)\), legs \((n = 15, 15\%)\) and hands \((n = 12, 12\%)\).

Fifty-two patients \((67\%)\) presented with a solitary lesion and 26 patients \((33\%)\) had two or more lesions. Twenty-nine patients of the 78 patients \((37\%)\) had nodular lymphangitis. They all had acquired CL in the New World.

As shown in Fig. 2, PCR was the most sensitive diagnostic tool. This test was performed in 47 patients \((60\%)\); 42 \((89\%)\) were found to be positive. Twenty-one of these positive tests were specified: 19 \(L.\) braziliensis and two \(L.\) mexicana were found.

In 57 patients histopathological examination, impression smear and culture were obtained. In 29 \((51\%)\) patients all tests were positive.
Treatments given are shown in Fig. 3. Forty-five patients were treated with pentavalent antimony in the form of sodium stibogluconate (Sb), 30 administered intravenously (i.v.), two patients intramuscularly (i.m.) in a daily dose of Sb 15–20 mg/kg for 21 days ($n = 32$), whereas 13 patients were treated intraleisionally (i.l.), five to six times with 0.5–2 mL Sb (in 10 of these patients treatment was combined with cryotherapy). Although most patients on parenteral Sb treatment complained of malaise, myalgia and arthralgia only one patient had to stop systemic therapy at day 15 because of elevated liver enzymes and amylase.

**Figure 2** Diagnostic tools used in the 78 patients studied.

**Figure 3.** Treatment modalities used.
All patients who were systemically treated with Sb had acquired CL in the New World.

Cryotherapy as a single treatment was given in four patients, three from the Old World and one from the New World.

For the last 5 years all patients who contacted CL in the Guyanas were treated with pentamidine isetionate administered i.v. or i.m., with four to seven doses of 4 mg/kg. Most patients complained of discomfort, most commonly pain at the injection site if administered i.m. Severe side effects were not seen. For the last 5 years pentamidine has been the treatment of choice for CL from this area. Only one patient who acquired CL from this area relapsed 4 months after treatment with pentamidine. He was subsequently successfully treated with the lipid formulation of amphotericin B (Abelcet®).

Nineteen (24%) patients were treated with itraconazol. Eleven patients had acquired CL in the New World, of which all were in Central America. Relapses were not seen. Lipid formulation amphotericin B (Abelcet®) was successfully used in four other relapses in patients who acquired CL in Bolivia, Brazil and Venezuela.

Discussion

CL is endemic in 88 countries. Patients diagnosed with CL at our hospital during the period 1990–2000 came from 21 countries, mostly from the Americas. The high number of cases from Belize and French Guyana was contributed by Dutch marines who went on jungle training in these countries. The patients from Surinam were mostly travellers. Historically there has been intensive traffic between the Netherlands and Surinam.

The majority of the patients were travellers. Preventive measures and information to travellers could be important in decreasing the numbers of imported CL. The majority of patients acquired the infection in the New World in contrast with our previous study in which most patients were infected in the Mediterranean area. The incidence compared with the previous study, which was performed in two university hospitals (period 1979–1989), has almost doubled and is still rising.14

Clinically, all patients were suspected as having CL. In our hospital PCR is the most sensitive single diagnostic tool followed by culture and histological examination.15 PCR has become available as a routine procedure only recently; species identification was limited at the time of this study.

As large double-blind studies are lacking it is not always clear which treatment regimen should be used for CL. For the Americas, CL caused by L. braziliensis (sensu lato), Sb seems still to be the drug of choice.12 In 1984, the WHO recommended for
CL a dose of Sb 10–20 mg/kg/day which should be given at least until the lesions are healed. However, from clinical experience it is known that lesions become drier and smaller during successful therapy but are hardly ever completely reepithelialized by the end of 21 days of therapy, as is generally used.\textsuperscript{12,16} For some endemic areas, a lower dose of Sb (10 mg/kg/day) or a shorter dose might be sufficient.\textsuperscript{17} In areas where mucocutaneous leishmaniasis is rare and when there are no clinical signs of dissemination of the disease, intralesional therapy with Sb in combination with cryotherapy has proven to be an effective and safe treatment.\textsuperscript{18,19}

We saw few relapses. As a second-line treatment after inadequate response to Sb or pentamidine, we treated five American CL patients with the amphotericin B lipid complex (Abelcet\textsuperscript{®}). In our limited experience this seems to be a good second-line treatment for relapsing new-world CL. For CL caused by \textit{L. mexicana} complex, itraconazole given orally or local therapy is often sufficient.

In 1995, we started to treat CL from the Guyanas with pentamidine. This decision was made because good clinical experience was obtained with pentamidine in this area. Pentamidine isetionate (300 mg) administered i.m. once a week for 3–4 weeks resulted in 90\% healing within 0–4 weeks after the last injection in a study in Surinam.\textsuperscript{20} Other dosing regimens of 2–3 mg/kg/dose for four injections on alternate days or for 3 successive days or an even shorter course of treatment have been

**Figure 4** Diagnostic procedures at the Academic Medical Center, Amsterdam, the Netherlands

<table>
<thead>
<tr>
<th>Clinical suspicion</th>
<th>histology</th>
<th>smear</th>
<th>culture</th>
<th>PCR</th>
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**Figure 5** Treatment options for cutaneous Leishmaniasis
reported from French Guyana, Guyana and Colombia.\textsuperscript{21,22} In most studies parasites were not cultured.

Old World-CL often does not require treatment because of the tendency of spontaneous cure. To speed up healing, intralesional Sb until blanching (generally 0.5–4 mL) on alternate days (four to five injections) is highly effective. It can be combined with cryotherapy. Itraconazole given orally 100 mg twice a day is reported to be effective; however, studies are limited.\textsuperscript{23} Our experience with itraconazole is too limited to draw conclusions. Recently, a study performed in Saudi Arabia showed that a 6-week course of oral fluconazole is safe and effective for CL caused by \textit{L. major}.\textsuperscript{24}

Flowcharts for diagnostic procedures and treatments given in our hospital are given in Fig. 4 and Fig. 5.

It can be concluded that in our hospital, imported CL is seen with a rising incidence. South American countries have become more important origins of infection. This rising incidence was caused by marines on training in the jungle and by travellers. PCR is the most sensitive single diagnostic test. If \textit{L. braziliensis} (\textit{sensu lato}) is suspected, Sb is still the drug of choice. The doses and duration of therapy with Sb might be lower or shorter in some endemic areas, but if the recommended dose and duration of treatment in a specific area is not known a schedule of 20 mg/kg/day for 21 days is almost always sufficient. For infection with \textit{L. mexicana}, itraconazole is our drug of choice. For \textit{L. braziliensis guyanensis} acquired in the Guyanas, four injections of pentamidine at 4 mg/kg seems to be the drug of choice.\textsuperscript{20-22} If facilities are available it is recommended that culture be performed to characterize and specify the parasite, so that treatment can be based on the species involved.

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References


