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Case Report

# Cutaneous Leishmaniasis in a Chinese man returning from the Amazon forest in Brazil

# 一名中國籍男子於巴西亞馬遜森林旅行後感染皮膚利甚曼病之案例

JTHT Yu 余浩德 and SY Wong 黃曉毅

A 60-year-old man presented with ulcerated infiltrative plaques over his face following an adventure trip to the Amazon rainforest in Brazil. The diagnosis was confirmed to be cutaneous leishmaniasis by histological examination and polymerase chain reaction assay of the skin biopsy. He was treated successfully with oral miltefosine. To the authors' knowledge, this is the first report of a Chinese patient with cutaneous leishmaniasis treated with miltefosine.

一名六十歲男子於巴西亞馬遜森林探險旅行後，面部出現潰爛及滲入性斑塊。皮膚活檢組織學及聚合酶鏈反應檢查確診爲皮膚利甚曼病，病人接受口服米替福新後得以康復。據作者所知，此乃首名華裔病人用口服米替福新治療皮膚利甚曼病的成功案例。

**Keywords:** Cutaneous Leishmaniasis, local treatment, systemic treatment, travel

**關鍵詞：**皮膚利甚曼病、局部性治療、系統性治療、旅行

## Introduction

Leishmaniasis is a disease caused by protozoan parasites belonging to the genus *Leishmania* and is transmitted by the bite of *phlebotomine sandfly*.[1] The three main forms of leishmaniasis are cutaneous, mucocutaneous and visceral. Cutaneous leishmaniasis is the most common form whereas visceral leishmaniasis is the most severe form, in which vital organs of the body are affected.[1]

## Case report

A 60-year-old Chinese man in Hong Kong, China, presented in February 2011 with a two-month history of non-healing skin lesions on his face. He was a keen hiker and had travelled to Manaus in northern Brazil for a three-week Amazon adventure tour navigating the labyrinth tributaries of the Rio Negro in November 2010. The first

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lesion developed as a small erythematous papule on his right cheek in December 2010 and it was treated by his general practitioner with oral doxycycline 100 mg twice daily for 14 days. Subsequently, two further lesions also developed together with right-sided cervical lymphadenopathy in January 2011. An ultrasound-guided fine needle aspiration arranged by his general practitioner showed reactive changes.

On physical examination in February 2011, there were three ulcerated infiltrative erythematous plaques on his right cheek and temple (Figure 1a) which were non-tender. The diameter of the largest plaque was around 3 cm. There were surrounding oedema and associated right-sided cervical lymphadenopathy. No mucosal involvement was detected.

The clinical differential diagnoses included bacterial skin infections, fungal skin infections, cutaneous mycobacterial infections, cutaneous leishmaniasis, sporotrichosis and sarcoidosis. Skin biopsy showed a dense infiltrate of lymphohistiocytic cells in the dermis (Figure 2a). Most of the histocytes contained small ring-shaped parasitic organisms approximately 1-2 micron in size with eccentric kinetoplasts which were better seen with Giemsa stain (Figure 2b). The diagnosis was granulomatous skin infection by leishmaniasis and it was subsequently confirmed by polymerase chain reaction (PCR) assay with kDNA (Department of Microbiology and Molecular Genetics, Hebrew University-Hadassah Medical School, Jerusalem, Israel). However, the internal transcribed spacer 1 (ITS1)-PCR assay,[2] which is less sensitive but would allow species identification, was negative.

The patient was started on oral itraconazole 100 mg twice daily and clarithromycin 500 mg twice daily. Two weeks later, oral miltefosine 50 mg three times a day and topical paromomycin twice daily were also added after the patient's family purchased the medications from a pharmacy at Frankfurt Airport, Germany in person, as it was not available in Hong Kong. There were no significant side-effects apart from mild nausea and abdominal discomfort initially. However, all oral treatments had to be stopped on Day 10 as laboratory investigations showed abnormal liver and renal function tests with alanine aminotransferase 739 U/L, aspartate aminotransferase 706 U/L, alkaline phosphatase 144 U/L, sodium 125 mmol/L and creatinine 122 $\mu$mol/L. Transabdominal ultrasound excluded any space-occupying lesions and obstructive lesions and the overall clinical picture was consistent with a diagnosis of drug-induced hepatitis. The abnormal liver and renal functions normalised subsequently upon stopping all oral treatments.

The patient was subsequently restarted on miltefosine 50 mg daily in April 2011. With careful laboratory monitoring, miltefosine was gradually stepped up to 50 mg twice daily and three times per day after two weeks. The patient completed a 28-day course of miltefosine 50 mg three times per day in June 2011 without any side-effects. During his last visit in November 2012, all the infiltrative plaques had resolved with minimal post-inflammatory hyperpigmentation and atrophic scarring (Figure 1b).

## Discussion

As travel to endemic areas has become more popular, leishmaniasis is increasingly seen among returning travellers.[1] Based on its geographical distribution, leishmaniasis can be divided into Old World (including southern Europe, the Middle East, parts of south-west Asia and Africa) and New World (from southern United States of America through Latin America) species. While Old World species mostly cause benign and often self-limiting cutaneous disease, New World species cause a broad spectrum of conditions from benign to severe manifestations, including mucosal involvement.[1] Mucocutaneous disease is more commonly found in *Leishmania braziliensis*, *Leishmania panamensis*, *Leishmania guyanensis* and *Leishmania amazonensis*.[1]

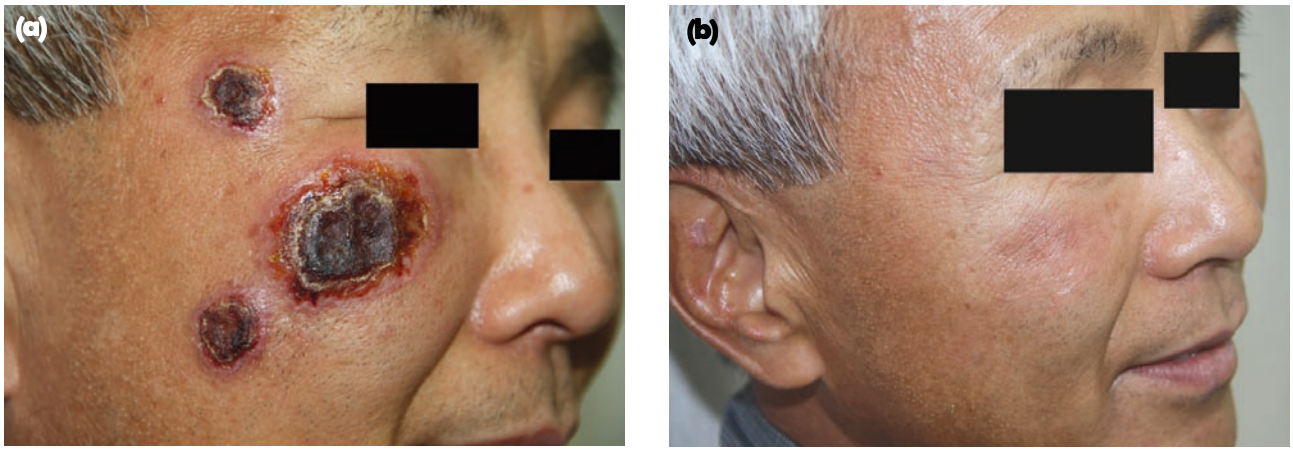


**Figure 1.** (a) Three ulcerated infiltrative erythematous plaques on the right cheek and temple with crusting. (b) Postinflammatory hyperpigmentation on the right cheek and temple with mild atrophic scarring.

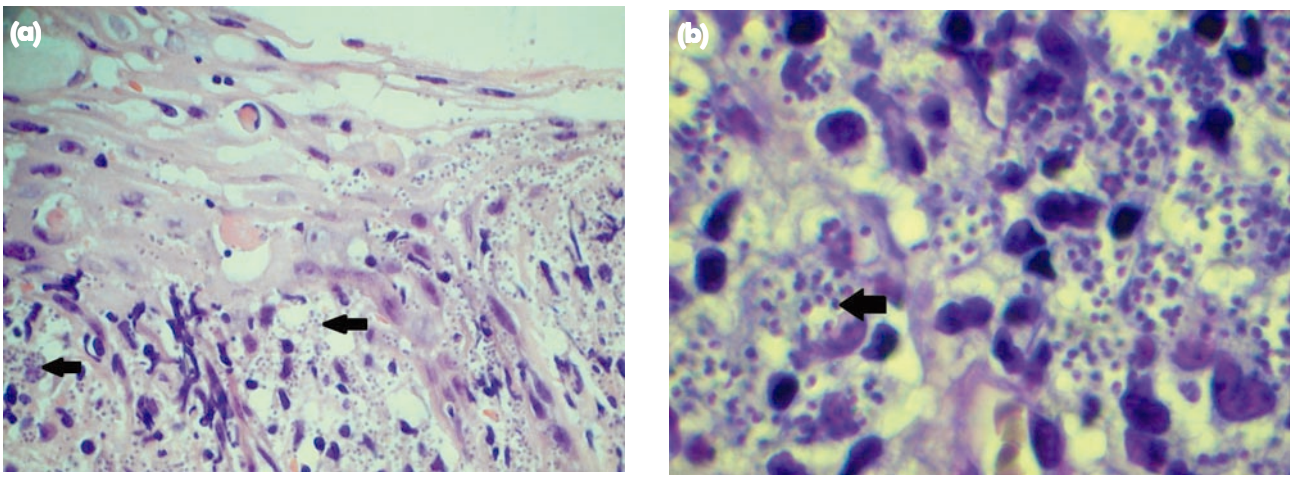


**Figure 2.** (a) Microscopic examination of the skin biopsy showing that the skin surface is partly eroded with inflammatory exudate and spongiosis. Numerous small rounded parasites are noted in the histiocytes as well as in the inflammatory exudate (arrows) (H&E, Original magnification x400). (b) High power view showing round to oval bodies with clearing and eccentric kinetoplasts consistent with leishmania parasites that are present within the histiocytes (arrow) (Giemsa stain, Original magnification x1000).

The diagnosis of cutaneous leishmaniasis relies on the demonstration of *Leishmania* in skin biopsy under microscopy. PCR assay on skin biopsy specimen helps to distinguish between specific species and confirm the diagnosis, thereby enabling a species-oriented treatment.[2] For visceral leishmaniasis, definitive diagnosis requires the demonstration of the parasite by smear or culture in tissue, usually from bone marrow or spleen.

The incubation period for cutaneous leishmaniasis ranges from a few weeks to several years. The lesion usually starts as an erythematous granulomatous nodule but will eventually ulcerate in most cases. Local lymphadenopathy can occur, especially with species of the *L. braziliensis* complex.[1] Spontaneous healing can occur but it may require months to years. Mucocutaneous leishmaniasis can occur years after healing of primary cutaneous leishmaniasis, most commonly

due to parasites of the *L. braziliensis* complex,[1] and may cause destruction of mucosal structure such as the nasal septum and palate leading to devastating facial mutilation. Delay in treatment of the antecedent localised cutaneous lesion is associated with a higher risk of mucocutaneous leishmaniasis.[1]

Treatment of cutaneous leishmaniasis can be divided into local and systemic. The choice of local or systemic treatment of cutaneous leishmaniasis is guided by the risk of developing mucosal disease. The aim of treatment is to prevent mucosal invasion by metastatic spread of the infection to the oropharyngeal site and to promote healing of the skin lesions to avoid disfiguring scars. The proposed indications for local treatment include lack of risk of developing mucosal lesions such as in Old World cutaneous leishmaniasis, *L.mexicana* cutaneous leishmaniasis, small, single lesion and absence of lymph node metastasis. The indications for systemic treatment include presence of mucosal lesion or lymph node metastasis, New World cutaneous leishmaniasis, except *L.mexicana* lesions and lesions unresponsive to local treatment.[3] The past health and immunological status of the patient, side-effects profile and local availability of drugs and the logistics of administration especially for parenteral systemic drugs also influence the ultimate treatment plan.

The mainstay of systemic therapy had been parenteral pentavalent antimony. The recommended intravenous dose for sodium stibogluconate (Pentostam®, GSK) is 20 mg/kg for 20 days diluted in 120 ml of 5% dextrose given over two hours.[4] Fatigue, musculoskeletal pain and gastrointestinal symptoms are common adverse effects. Laboratory abnormalities include raised levels of liver and pancreatic enzymes and haematological abnormalities such as leucopaenia and thrombocytopaenia. Reversible ECG alterations (T waves changes) can be seen and may occur without evidence of myocardial damage.[4]

Miltefosine (Impavido®, Paladin Labs Inc.), a phosphocholine analogue, was initially developed as an antineoplastic agent but subsequently found to have antiprotozoal properties. It has shown promising effects on *Leishmaniasis panamensis*[5] and *Leishmaniasis braziliensis* infections[6] and is given orally at a dose of 2.5 mg/kg/day with a maximum dose of 150 mg per day (divided into three doses) and the standard course of treatment is 28 days. The advantage of miltefosine is that it is given orally and is usually well tolerated. The most common side-effects are gastrointestinal such as nausea and vomiting. We suspect that the cause of abnormal liver function tests may be related to the concomitant use of itraconazole in our case.

Liposomal amphotericin B is useful in the treatment of visceral leishmaniasis but has the disadvantage of a high incidence of adverse reactions including hyperpyrexia, severe malaise, hypotension, thrombophlebitis, renal tubular damage, hypokalaemia, anaemia and hepatitis.[4]

The use of oral antifungal drugs[1] such as fluconazole, ketoconazole, itraconazole have been reported in the treatment of cutaneous leishmaniasis. They have the advantage of oral administration and fewer adverse effects but are less effective.

Local treatments include a wide range of physical methods, including direct infiltration of the lesion with pentavalent antimony, cauterisation, surgical excision, cryosurgery and the application of local heat. Topical ointment containing 15% paromomycin has also been found to be effective against cutaneous leishmaniasis.[7]

Personal protection against the vector sandflies is crucial for travellers. Insect repellents, long-sleeved shirts and impregnated fine-mesh bednetting will reduce the risk of infection. However, sandflies are much smaller than mosquitoes, thus standard bednets might be useless. Permethrin-impregnated clothing is helpful as shown in a study of Colombian military personnel.[8]

In conclusion, as travel to exotic tropical destination is getting more popular, tropical skin diseases will present more frequently. A high level of clinical suspicion is required and PCR is helpful in establishing the diagnosis. Oral miltefosine should be considered a first-line treatment for cutaneous leishmaniasis due to the simplicity of administration and the relatively benign side effect profile.

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