

A Travel Misadventure – Visceral Leishmaniasis in an Immunocompetent Patient

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Abstract

Visceral leishmaniasis is one of the world's most neglected diseases. Over 90% of the 500,000 annual new cases occur in only five countries: India, Nepal, Bangladesh, Sudan and North-Eastern Brazil, but the disease remains endemic in Southern Europe. We report a case of visceral leishmaniasis in an immunocompetent serviceman after a seven-day stay in the Marseilles region of South-Eastern France. This case is intended to alert clinicians to the possibility of visceral leishmaniasis in patients who develop a febrile illness after returning from travel in Southern European countries.

Introduction

In 1903, Leishman and Donovan separately described the protozoan now called *Leishmania donovani* in splenic tissue from patients in India with the life-threatening disease now called visceral leishmaniasis [1,2]. Over a century later, visceral leishmaniasis (VL) remains a significant public health-problem. This illness was included by the World Health Organisation in the list of neglected tropical diseases targeted for elimination by 2015 [3]. In recent years, visceral leishmaniasis has been diagnosed in at least five U.S. servicemen [4] and one U.K. serviceman [personal communication, Lt Col MS Bailey] with acquisition in both Operation Enduring Freedom and Operation Iraqi Freedom. However, this disease can be observed in travellers returning from less distant countries.

Case Report

A 52 year old infantry soldier was admitted to our hospital. He reported a febrile syndrome of three months' duration associated with a change in general physical condition (4 kg weight loss over this period). The patient was immunocompetent and had no relevant medical or surgical history. He had returned from a two-year stay in Djibouti, East Africa, followed by a few days in South-Eastern France in the Marseilles region, three months before the first symptoms appeared. Clinical examination on admission showed mucocutaneous pallor associated with hepatosplenomegaly, but no peripheral adenopathy. The patient had a fluctuating fever (maximum: 39.5°C), mostly at night, accompanied by sweating. Biological examination revealed pancytopenia (leukocytes $1.8 \times 10^9/l$, polynuclear neutrophils $0.88 \times 10^9/l$, haemoglobin 9.7 g/dl, platelets $102 \times 10^9/l$) associated with an inflammatory syndrome and polyclonal hypergammaglobinaemia (CRP 109 mg/l, IgG 25.3 g/l). Malaria investigation (using thick and thin blood films and antigen-detection tests) and HIV investigation (using serologic and p24 HIV antigen tests) were negative. The results for the remaining biological tests were in the normal range.

On the basis of these clinical and biological findings, bone marrow aspiration was performed. Visceral leishmaniasis was diagnosed following the detection of large numbers of *Leishmania amastigotes* on microscopic examination of a Giemsa stained bone-

marrow aspirate (Figure 1). Molecular biological techniques confirmed this diagnosis by detection of the 18S rRNA specific to the genus *Leishmania* in bone marrow and identified *L. infantum* as the species responsible by sequencing of the CYT-B gene [5]. Liposomal amphotericin B treatment (3 mg/kg on days 1- 5 and 10) was initiated. The progression of the disease was favourable, with the resolution of fever and organomegaly, and the normalisation of biological parameters within two months. Twenty-four months later, no relapse was observed. As *L. infantum* is not found in East Africa, we concluded that the patient was infected during his seven-day stay in the Marseilles region.

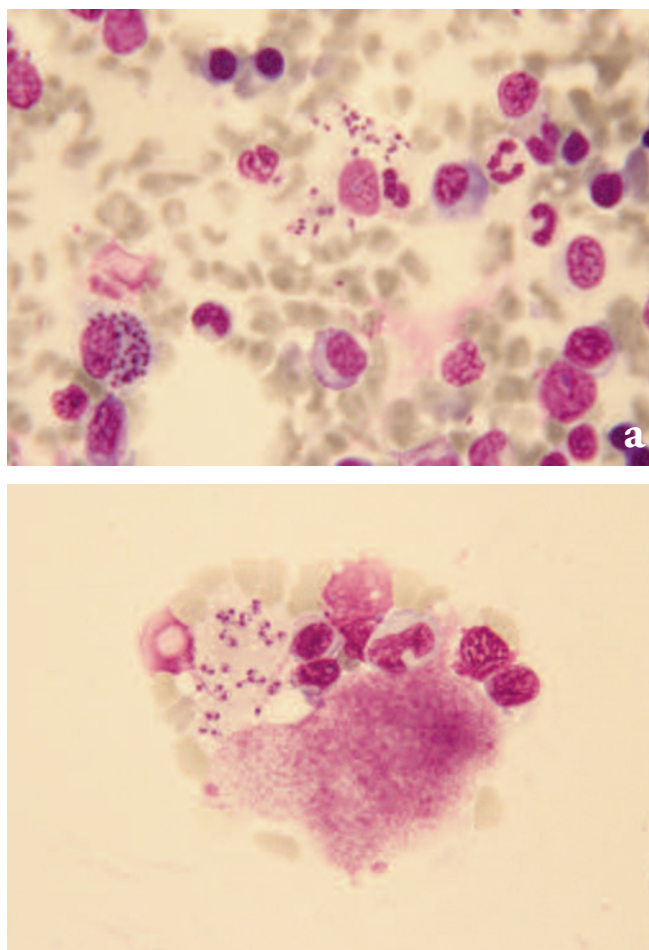


Figure 1. Amastigote forms of *Leishmania infantum* (Giemsa stained bone-marrow aspirate x 500 (a) and x 1,000 (b)).

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Discussion

Visceral leishmaniasis is a systematic protozoan disease that is transmitted by sandfly bites. Initially described in India at the end of the 19th century under the name Kala-Azar (Hindi for 'black fever'), VL has a large geographical range, extending from China to South America. This disease is present in more than 80 countries, forming five major epidemic foci: the Chinese, Indian, Central Asian, East African, Mediterranean and South American foci (Figure 2). The Chinese focus is pretty minor now after an eradication campaign. There are an estimated 500,000 new cases of VL and more than 50,000 deaths from the disease each year, a death toll that is surpassed among the parasitic diseases only by malaria. Over 90% of cases occur in only five countries: India (especially the Ganges and Brahmaputra plains), Nepal, Bangladesh, Sudan and North-eastern Brazil [6]. Turkey, Italy, Spain, Greece and France are the most affected among the European Mediterranean countries. Visceral leishmaniasis cases in returning travellers from these countries are regularly reported [7]. In France, 206 cases of visceral leishmaniasis were reported between 2001 and 2008, 116 of which were autochthonous. Most of them were observed in immunocompromised individuals (mainly HIV/AIDS-infected or transplant patients) or children under age 6 [8].

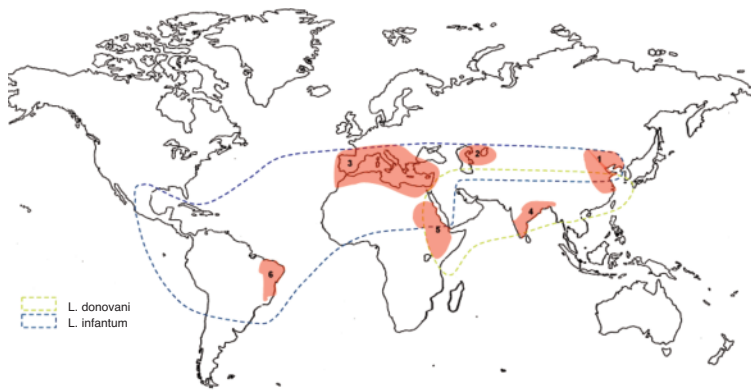


Figure 2. Distribution of visceral leishmaniasis worldwide and location of the main endemic foci: (1) Chinese (2) Central Asian, (3) Mediterranean, (4) Indian and (5) East African foci [14].

Visceral leishmaniasis is caused by the *Leishmania donovani* complex: *L. donovani* sensu stricto in East Africa, Asia and the Indian subcontinent and *L. infantum* in Europe, North Africa and Latin America (where this species is also known as *L. chagasi*). Other species have also been implicated: *L. archibaldi*, a species belonging to the *L. donovani* complex (Sudan, Ethiopia, Kenya), and *L. tropica* (Middle-East) and *L. amazonensis* (South America), which have been identified in only a very small number of cases. In our case, this difference of geographical distribution of *Leishmania* species and identification of *L. infantum* as causative agent allow us to conclude that this was an indigenous infection.

There are two types of visceral leishmaniasis, which differ in their transmission characteristics. Anthroponotic VL (AVL) is transmitted from human to vector to human, whereas zoonotic VL (ZVL) is transmitted from animal to vector to human. In the last, humans are occasional hosts and animals, mainly dogs, are the reservoir of the parasite. AVL is observed in areas of *L. donovani* transmission whereas ZVL is found in areas of *L. infantum* transmission [9].

Importantly, infection does not always equate with clinical illness. In endemic countries, among immunocompetent people, there are 5-10 subclinical infections for every overt case. Risk factors for development of clinical disease include malnutrition, immunosuppressive drugs and especially HIV co-infection. Indeed, among HIV/AIDS-infected patients, the risk of clinical visceral leishmaniasis increased by 100-1,000 times.

Classically, in clinically expressed visceral leishmaniasis, symptoms appear after an incubation period which lasts 2-6 months. Clinical features include signs of systemic infection (fever, asthenia, weakness, loss of appetite, continued weight loss) and parasitic invasion of the blood and reticulo-endothelial system (adenopathy, hepatosplenomegaly). Pancytopenia and hypergammaglobulinemia (mainly IgG from polyclonal B-cell activation) with hypoalbuminemia are characteristic. Hyperpigmentation, which probably led to the name kala-azar, has only been described in VL patients from the Indian subcontinent. Today, this symptom is uncommon and was perhaps a feature of prolonged illness in the era when effective treatments were not available. With time, untreated disease can produce profound cachexia, multisystem disease, bleeding from thrombocytopenia, susceptibility to secondary infections, and death [9].

The clinical pattern of visceral leishmaniasis may be similar to other infectious or non-infectious diseases such as malaria, typhoid fever, miliary tuberculosis, brucellosis, lymphoma and leukaemia. Thus, the differential diagnosis could be difficult especially in non-endemic areas where delayed diagnosis is common.

The diagnosis of VL can be confirmed by one of the following laboratory methods: demonstration or isolation of the parasite, DNA detection and serology. The amastigote forms of the parasite (called Leishman-Donovan (LD) bodies) can be seen on microscopic examination of Giemsa-stained blood or aspirates from lymph nodes, bone marrow or spleen. Amastigotes appear as round or oval bodies measuring 2-3 μm in length with characteristic organelles (nucleus and kinetoplast). The sensitivity is highest for splenic aspiration (as high as 98% compared with < 90% for other organs), but so is the risk (rarely haemorrhage). In recent years, molecular approaches to diagnosis have been developed. They are more sensitive than microscopic examination and allow detection of leishmanial DNA in peripheral blood and serum. However, use of a quantitative PCR may be necessary to differentiate asymptomatic infections and acute-phase infections [10]. Actually, these techniques are restricted to a few laboratories. A relatively new serodiagnostic assay is the rK39 antibody dipstick test. This assay uses the recombinant *Leishmania chagasi* antigen rK39 to identify the presence of host antibodies to the parasite's dominant, kinesin-like amastigote antigen. A positive result from this immunoassay is highly sensitive and specific for active visceral leishmaniasis in immunocompetent individuals [11].

Currently, liposomal formulations of amphotericin B are the first treatment of choice in Southern Europe endemic countries as well as in other developed countries, because of their rapid and up to 100% cure rates with short regimens, improved convenience for the patient, and reduction of health-care costs. In Europe, for immunocompetent patients, the most common routine scheme is 3 mg/kg/d, to be given on days 1 to 5 and 10 [12]. An alternative dosage regimen recommended by the Food and Drug Administration is 3 mg/kg/d, to be given on days 1 to 5, 14, and 21. Most patients feel better and become afebrile during the first week of treatment but splenomegaly and biochemical abnormalities do not resolve for weeks to months in some cases. Freedom from clinical relapse for at least six months is the best indicator of cure. In immunocompetent patients, relapses are exceptional [13].

Conclusion

Visceral leishmaniasis has to be considered as a differential diagnosis in patients with prolonged fever of unknown origin who have returned from travel in Southern Europe. Early diagnosis of visceral leishmaniasis is crucial for patient therapy and outcome. However, this diagnosis could be difficult especially in non-endemic areas where delayed diagnosis is common.

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