

Successful treatment of visceral leishmaniasis with liposomal amphotericin B

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Abstract. We report a case of a 26-year-old female from Kenya who suffered from intermittent fever of unknown origin for one month. The major findings on admission were pancytopenia associated with considerable splenomegaly. The diagnosis was established by visualisation of amastigotes in bone marrow biopsy and by detection of antibodies to *Leishmania spp.* in blood. The infection was treated intravenously with liposomal amphotericin B for five days. The patient was afebrile after the first infusion. No relapse was reported. (www.actabiomedica.it)

Key words: Fever of unknown origin, visceral leishmaniasis, liposomal amphotericin B

Introduction

Propagated by female sandflies, *Leishmania spp.* are obligatory intracellular protozoans, which cause a wide range of clinical manifestations: visceral (VL, kala-azar), cutaneous and mucocutaneous leishmaniasis. Encountered in subtropical and tropical regions leishmaniasis has a prevalence of 12 million cases and an approximate incidence of 0.5 million cases of VL and 1.5 million cases of cutaneous leishmaniasis. Disseminated VL is fatal if left untreated.

The typical incubation period of VL varies from 3 to 8 months (longer periods up to several years have been reported). Common clinical manifestations are: fever (intermittent, remittent with two daily temperature spikes, or even continuous), cachexia, pancytopenia, hypergammaglobulinemia, hepatomegaly and a striking splenomegaly.

The main complications are: anaemia (due to the combination of hemorrhagic bleeding, haemolysis, compression of the bone marrow and hypersplenism)

and secondary bacterial infections. Most patients die due to intercurrent bacterial infection or tuberculosis.

The gold standard of diagnosis remains direct microscopy (visualization of the parasite in affected tissues, mostly in bone marrow aspirate).

Case description

A 26 year old, formerly healthy female from Kenya sought medical attention for intermittent fever from which she had suffered for almost one month.

The woman was born in Kakamega, Kenya, and had been living in Austria for one year.

Three month after a stay in her home country, the patient becomes febrile with fever spikes up to 40°C. Further symptoms were chronic fatigue, weight loss, night sweats and headache.

The patient was referred to our hospital because of fever of unknown origin.

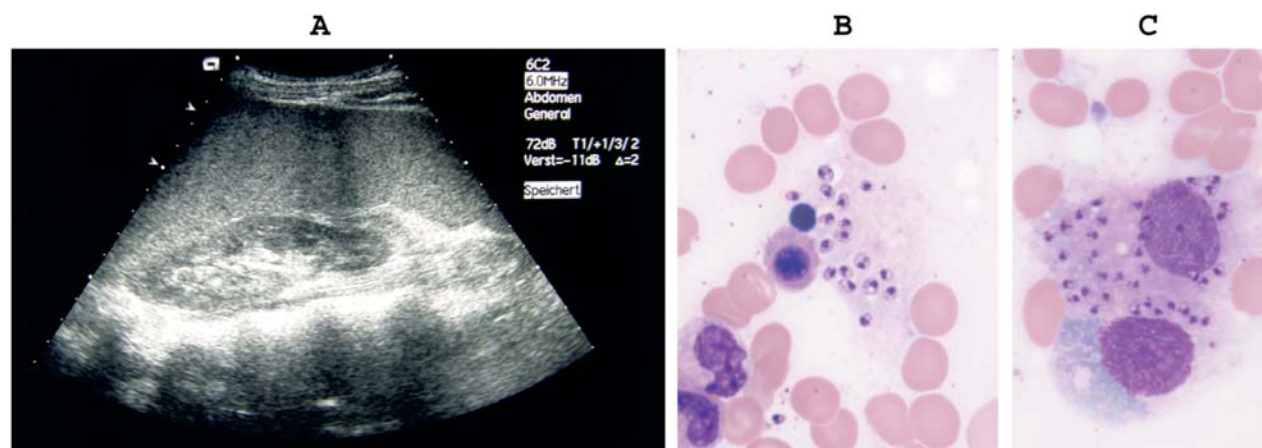


Figure 1. Ultrasound of splenomegaly (~ 20 cm) [A], bone marrow biopsy revealed numerous protozoan parasites (*Leishmania* spp.) either extracellularly [B] or within bone marrow macrophages [C]

An elevated body temperature of 39.6°C and a soft nontender spleen 20 cm in diameter (Figure 1) were the major findings on admission. Lymphadenopathy was neither found on physical examination nor on abdominal sonography. Echocardiography revealed normal findings.

Laboratory results showed an elevation of C-reactive protein, erythrocyte sedimentation rate and lactic dehydrogenase (Table 1). A marked polyclonal hyperglobulinemia (IgG 2350 mg/dl) and pancytopenia with a pronounced leucopenia was noted.

The diagnosis of VL was made by examination of a bone marrow biopsy. Numerous protozoan parasites (*Leishmania* spp.) either extra cellular or within bone

marrow macrophages were noticeable (Figure 1). Antibodies against *Leishmania infantum* were detected in the patient's serum by both an indirect immune fluorescence test and an enzyme-linked immunosorbent assay. All other radiological, serological and microbiological examinations including *Plasmodium spp.*, Dengue Virus and human immunodeficiency virus remained repeatedly negative.

The patient was treated with a total dose of 20 mg/kg body weight liposomal amphotericin B (AmBisome®) over five days. The daily dose of 200 mg (4 mg/day/kg body weight) was well tolerated and the patient was afebrile after the first infusion. The patient responded rapidly with clinical signs and laboratory

Table 1. Laboratory results at admission and day 1 and 5 of the Therapy with liposomal amphotericin B (AmBisome®) 200 mg once daily intravenously and day 11 und 34 after therapie

	Day at admission	1. day of therapy	5. and last day of therapy	11. days after therapy	34. days after therapy
C-reactive protein <1 mg/dl	12,16	17,16	3,79	<0,5	<0,5
Erythrocyte sedimentation rate after one hour 10 mm-20 mm	70	70	80	70	24
Erythrocyte 3,8-5-2 T/l	3,3	2,4	3,2	3,6	4,2
Thrombocytes 150-350 G/l	75	50	70	254	202
Neutrophils 4-10 G/l	1,7	0,9	3,5	4,4	4,3
Lactic dehydrogenase <247 U/l	452	557	549	240	158
Serum creatinin <1,2 mg/dl	0,98	0,88	1,44	0,84	0,96
IgG 700-1600mg/dl		2350			
Ferritin µg/l		3524			

values returning to normal (Table 1). No relapse until now was reported.

Discussion

Over 90% of VL worldwide occurs in five countries across three continents: north eastern India, Bangladesh, Nepal, Sudan and north eastern Brazil (1). Leishmaniasis causes 2.4 million disability-adjusted life years and around 70.000 deaths per year (2).

As visceral Leishmaniasis mainly occurs in poor and remote areas where access to medical care is very limited, advances in treatment, diagnosis and vector control could help to break the vicious circle of poverty and disease.

An intact cellular immunity is necessary to prevent the disease from affecting the entire reticuloendothelial system. Therefore malnourished and immunocompromised persons are the most affected. Even in southern Europe, where potent antiretroviral therapy is provided, VL is a common AIDS-related infection. Interestingly 90% of HIV-associated VL represents reactivation of prior subclinical infection (3).

In Europe Kala Azar is very rare, but in the clinical setting of fever of unknown origin with a corresponding travel history, especially in immunocompromised patients it should always be taken into consideration as an important differential diagnosis.

Current options for the treatment of Kala Azar are antimony salts, amphotericin B and its lipid formulations, pentamidine, miltefosine and paromomycin (4).

Pentavalent antimony drugs are associated with adverse reactions and require long treatment periods (30 days). Antimony-resistant VL, especially in Bihar in India (45% of the world's cases) makes treatment even more difficult (5). Miltefosine (the first effective oral treatment, testing still in progress) and the aminoglycoside Paromomycin, which has shown good results in India and is currently being evaluated in East Africa, could provide a therapeutic alternative to antimony worldwide (6).

Although antimony drugs remain effective in Europe (cure rate of about 90%) (1), most patients are now treated with liposomal amphotericin B, which is

safe and very effective in a short time (7). Reduction of the toxic effects by using lipid formulations allows the infusion of higher doses of amphotericin B. So far in Bahir 476 cases have been published (in six studies: two of which were comparative, three dose-finding, and one non-comparative) in whom liposomal amphotericin were highly effective, associated with high cure rates even at very low doses (8). In practical terms, the choice of which of these agents to use frequently comes down to cost and availability.

In patients with impaired immunity and re-treating antimony failures liposomal amphotericin B (AmBisome®) might be the drug of choice. The described patient was cured with a high dose of 4 mg/kg/day actually recommended for immunocompromised patients (9), the treatment was started at a point of unknown immunity and finished at day 5 because of negative HIV test. Various studies demonstrated that low dose and single dose liposomal amphotericin B were effective in the treatment of VL (10). A single dose treatment of 5-7.5 mg/kg show cure rates of about 92% while a total dose of 2 mg/kg/day for 5 days can achieve a cure rate of roughly 99 % (4). Other liposomal preparations, including amphotericin B colloidal dispersion (ABCD) and amphotericin B lipid complex (Abelcet) (7) have also been used in VL, although there is less experience with these compounds.

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