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Case Report: Acute Renal Injury as a Result of Liposomal Amphotericin B Treatment in Sodium Stibogluconate Unresponsive Visceral Leishmaniasis

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Abstract. We report an unusual case of visceral leishmaniasis occurring in a patient from Sichuan China. The patient presented with a remitting fever, anemia, and pancytopenia. The case was confirmed as visceral leishmaniasis by microscopical detection of the *Leishmania* species amastigote in bone marrow aspirate. The patient was treated with 10 mg/kg/day of sodium stibogluconate for 5 days, with no therapeutic response. As a result, the patient was treated with liposomal amphotericin B (LAB) at 10 mg/day as an initial dosage. After treatment with an increasing drug dosage for 7 days, acute renal injury was evident as indicated by increased serum creatinine and urea nitrogen. LAB administration was discontinued until serum creatinine and serum urea nitrogen regressed on Day 15. Two maintenance treatments of 100 mg/day LAB were given on Days 19 and 26 (total 870 mg, 14.5 mg/kg). Bone marrow aspirate and clinical examination suggested total remission.

INTRODUCTION

Visceral leishmaniasis (VL) is a zoonotic disease caused by a protozoan of the *Leishmania* genus. In China, VL is caused primarily by the sub-species *Leishmania donovani*, and is transmitted by the bite of the sand fly *Phlebotomus chinensis*. Visceral leishmaniasis was eliminated in China in the late 1950s; however, over the past few years sporadic cases have been reported in Xinjiang, Inner Mongolia, Gansu, Sichuan, and Shaanxi provinces.[1] The clinical characteristics associated with VL are irregular fever, weight loss, anemia, massive splenomegaly, hepatomegaly, pancytopenia, and hypergammaglobulinemia. A clinical diagnosis is determined if amastigotes are found in aspirate from liver, spleen, lymphaden, or bone marrow. Uncommon sporadic cases can lead to missed or erroneous diagnoses. Sodium stibogluconate is the most common first-line treatment used in China, despite some cases of reported parasitic resistance. Because of its high cost, liposomal amphotericin B (LAB) is a second-line drug reserved for cases where resistance is present and is highly efficacious.

CASE REPORT

The case presented here involves a 36-year-old man who was born in Tongnan County, Chongqing, China. Before admission into our hospital, the patient had been working in Wenchuan county, Sichuan province from March 2009 to January 2010, during which time he had remitting fever up to 40°C (particularly in the afternoon and night) and fatigue in January 2010. During this time he had no cough, nausea, abdominal pain, or weight loss. Two weeks of hexadecanol and antiviral therapy was effective in reducing the symptoms. However, the fever returned (reaching 40°C) after cessation of the oral prednisone. After this treatment, the patient underwent bone marrow aspiration and *Leishmania* species amastigotes were found on the Giemsa-stained smear (Figure 1), and was diagnosed with VL in a different hospital. For further treatment, the patient was admitted to Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University in March 2010 with complaints of high-grade fever that had persisted for 2 months.

The patient weighed 64 kg, with a fever of 39.5°C, pallor, non-tender hepatomegaly, and splenomegaly (palpable 3 cm below the costal margin) at the time of admission. Superficial lymph nodes were too sensitive for evaluation by touch. Laboratory tests revealed anemia, pancytopenia, hypergammaglobulinemia, hypoalbuminemia, increased serum alanine aminotransferase, and aspartate aminotransferase (Table 1), and normal renal function. The hepatitis B virus test was negative. Tuberculosis was excluded because of a negative chest x-ray examination. The patient was treated with an intravenous infusion of 10 mg/kg/day sodium stibogluconate on the fifth day after admission. After 5 days of treatment there was no amelioration of clinical manifestations or laboratory tests (Table 1), and the patients highest body temperature was 40.4°C. Thus, the patient was considered to be unresponsive to antimonial therapy. We therefore discontinued the use of sodium stibogluconate therapy because of the apparent resistance. Subsequently, we initiated an intravenous infusion of liposomal amphotericin B (LAB), beginning with a dosage of 10 mg/day and increasing to 40, 70, 100, 150, 150, and 150 mg on Days 2, 3, 4, 5, 6, and 7, respectively. The patient was afebrile after 3 days of treatment, but he manifested nausea and vomiting beginning on Day 6. Laboratory tests indicated that most of the hematological values improved except for the increased serum creatinine (Cr) and serum urea nitrogen (BUN) (Table 1), which indicated acute renal injury. The LAB therapy was discontinued after 7 days. Immediately following cessation of LAB treatment, the nausea and vomiting disappeared. Serum Cr and BUN regressed through the eighth day after LAB treatment was discontinued. Two maintenance treatments of 100 mg/day LAB were administered, along with an intravenous injection of 5 mg hexadecanol on Days 19 and 26. The patient continued to improve and almost all laboratory values returned to normal. There were no detectable parasites in his bone marrow aspiration smear on Days 14 and 29 after LAB treatment. Treatment resulted in a clinical cure and remission without relapse.

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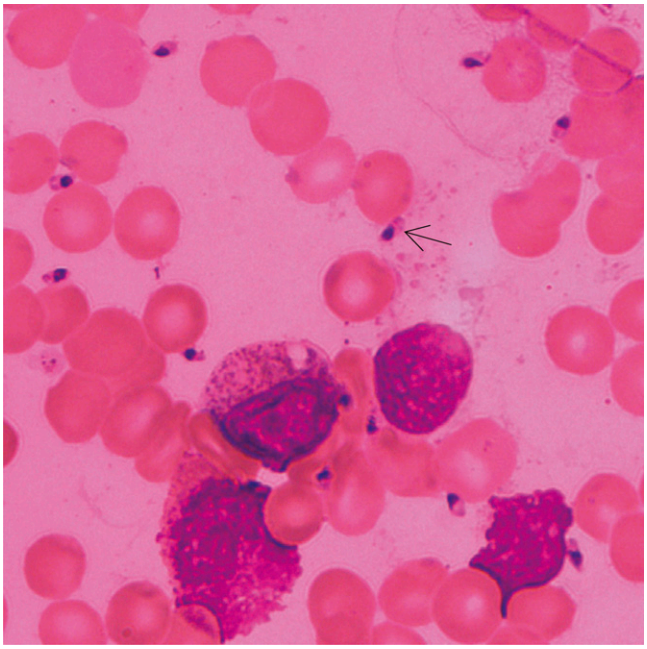

FIGURE 1. Bone marrow biopsy revealed characteristic *Leishmania* amastigotes either extracellularly or within bone marrow macrophages (Giemsa stain; original magnification, ×400).

DISCUSSION

Visceral leishmaniasis, also known as kala-azar, is endemic in more than 60 countries with tropical and subtropical climates and in Mediterranean countries. There are ~500,000 new cases and more than 50,000 deaths worldwide each year.[2] In China, increasing sporadic cases have been reported for the past few years, which have coincided with an increasing population of domestic dogs. Ineffective treatment of VL can lead to bad prognosis and high fatality. Occasionally VL may manifest as acute hepatitis or hemophagocytic syndrome, thus resulting in misdiagnosis, especially if cases are not common in that region. The patient presented in this case was misdiagnosed at first, which delayed treatment. He was diagnosed as VL 2 months later when *Leishmania* species amastigotes were found in his bone marrow aspirate. This case is a reminder that VL should be suspected in persons who live or have lived in a VL endemic area, especially when they present with clinical features such as prolonged and irregular fever, anemia, pancytopenia, and hepatosplenomegaly.

Currently, the drugs used to treat VL are Pentavalent antimonial, Amphotericin B, Liposomal amphotericin B, Miltefosine, Paromomycin, and Pentamidine, all of which have drawbacks such as toxicity, variable efficacy, parenteral administration, or high cost.[3] Recently, Sundar and colleagues[4] found that combination therapy is efficacious and well tolerated even when administered over a short duration. In China, monotherapy with antimonial is still the first-line treatment of VL because of its low cost. A retrospective clinical analysis suggested that a total dosage of 120–150 mg/kg sodium stibogluconate, separated into six equal portions given intravenously daily, for 6 days provided a cure rate of 95.3%.[5] The patient was treated with sodium stibogluconate at first, but decreases in hemoglobin content, leukocyte and erythrocyte count, and no amelioration on the clinical manifestations after treatment indicated that the patient was resistant to antimonials. Immediately, LAB was used to treat this patient because of its high efficacy and low toxicity. According to reports,[6–8] a total dosage from 7.5 to 15 mg/kg body weight is well tolerated and effective, and higher initial doses (> 5 mg/kg) provide better penetration and longer tissue persistence than do frequent low doses. The World Health Organization (WHO) recommends a total dose of 20 mg/kg administered intravenously at 5 mg/kg doses on Days 0, 1, 4, and 9.[9] However, considering the nephrotoxicity, a low initial dose of 10 mg/day was selected and was increased to 40, 70, 100, 150, 150, and 150 mg on Days 2, 3, 4, 5, 6, and 7, respectively. As the dose increased to 2.5 mg/kg/day, the patient had gastrointestinal side effects such as nausea and vomiting, and increased serum Cr and BUN, which indicated an acute renal injury. We concluded LAB treatment because of the threat of acute renal injury. As serum Cr and BUN regressed, two maintenance treatments of 100 mg/day LAB was given intravenously followed with an intravenous injection of 5 mg hexadecanol on Days 19 and 26. The patient received a total of 870 mg (14.5 mg/kg) during LAB treatment, which led to clinical improvement. Six months after discharge an abdominal ultrasound indicated normal liver and spleen sizes and no relapse were reported.

This is the first report of nephrotoxicity associated with administration of LAB at the relatively low dose of 2.5 mg/kg/day to treat unresponsive VL. Although 2.5 mg/kg/day is close to the labeled dose of 3 mg/kg/day, the advent of single doses of 10 mg/kg for VL[7] signifies that our final dose of 2.5 mg/kg/day can now be viewed as low. The results in this case suggest that serum Cr and BUN should be monitored

TABLE 1
Laboratory results before and after therapy

Parameter	Normal values	Before therapy	Treated with antimonial	Treatment with LAB		
				7 Days	15 Days	End therapy
Highest body temperature (°C)	< 37	40	40.4	36.6	36.8	36.6
Hemoglobin (g/L)	110–160	107	96	87	90	119
Leukocyte count ($\times 10^9$/L)	4–10	1.94	1.72	4.16	4.55	6.64
Erythrocyte count ($\times 10^{12}$/L)	3.5–5.5	3.75	3.39	2.99	3.11	4.1
Platelet count ($\times 10^9$/L)	100–300	30	57	223	244	194
Albumin (g/L)	38–51	34.9	28.8	33.5	–	42.8
Globulin (g/L)	25–38	41.7	43	45.1	–	29.6
Alanine aminotransferase (IU/L)	0–42	76	57	37	–	13
Aspartate aminotransferase (IU/L)	0–42	80	74	38	–	16
Blood urea (mmol/L)	1.7–8.3	3.21	–	9.62	4.36	7.24
Serum creatinine (μmol/L)	40–97	81	–	156.2	101.7	101.1

early and continuously when administrating LAB. Finally, low dosage and long duration LAB therapy was effective and safe for the treatment of VL in this patient.

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