

## VISCERAL LEISHMANIASIS TREATED WITH LIPOSOMAL AMPHOTERICIN B

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### ABSTRACT

Three children under 5 years of age with visceral leishmaniasis, responded dramatically to a short course of liposomal amphotericin B (L-AmB) and are presented and discussed in the view of literature.

**Key Words:** Leishmaniasis, Liposomal amphotericin B

### INTRODUCTION

Visceral leishmaniasis (VL) is an acute disease in most pediatric cases. It could be seen in immunocompetent and immunosuppressed patients.

VL, caused by *Leishmania infantum* is endemic in all countries bordering the Mediterranean basin. The typical presentation of progressive splenomegaly, hepatomegaly, anemia, wasting and fever is seen in both children and adults. Diagnosis is confirmed from bone marrow culture, microscopic visualization of the parasite in bone marrow aspirates and antibody detection. Microscopy, with or without culture remains highly sensitive and specific and is the diagnostic method of choice.

The pentavalent antimonials have remained standard treatment for VL for over 40 years (1). Because of increasing primary resistance and the long duration of therapy, Amphotericin B deoxycholate (AmB) is used as antileishmanial but remains a second line drug because of its toxicity. Liposomal amphotericin B (L-AmB) is less toxic than AmB and is shown to be highly effective against leishmania in vitro and in mice (2). It was approved as the first drug in the treatment of VL by the United States Food and Drug Administration (3).

We report three children under 5 years of age with VL who responded dramatically to a 10 day course of L-AmB with no side effects for showing the efficacy in treating this infection.

### CASE REPORTS

**Case 1:** A 4- year- old girl was admitted to our hospital with complaints of fever, malaise, cough and abdominal pain for a week. On physical examination, she was febrile (38.7 °C), had hepatomegaly (3cm), splenomegaly (8cm) and generalized lymphadenopathy. The haematological findings included a haemoglobin concentration of 7 gr/dl with hypochromic indices, white blood count 1400/mm<sup>3</sup> and platelets

69000/mm<sup>3</sup>. Erythrocyte sedimentation rate was 102 mm/hour, renal and liver function tests were within normal limits. The level of Ig G was 3890 mg/dl (N:345-1236 mg/dl), the markers of infectious and collagen tissue diseases (salmonella, brucella agglutination tests, ANA, AntidsDNA, C<sub>3</sub>) were negative. Ultrasound examination showed enlargement of the liver and spleen with no focal lesions. Leishmania antibody (ELISA) was found to be positive in serum but no evidence of leishmania infection was determined from bone marrow aspirate. The patient was started on L-AmB (3mg/kg/day intravenously for 10 days). She became afebrile in the second day of treatment. No adverse effect of treatment was observed. She has remained well with no complaints for over one year.

**Case 2:** A 13-month- old girl was admitted with complaints of weight loss and pale skin. She was afebrile (36 °C), had hepatomegaly (4 cm) , splenomegaly (8 cm) and cervical lymphadenopathy. Complete blood count showed haemoglobin concentration of 5.5 gr/dl, white blood count 2800/mm<sup>3</sup>, platelet 224.000/mm<sup>3</sup>. Her blood chemistry showed albumin concentration 2.8 gr/dl, aspartate aminotransferase (AST) 487 IU/L, alanin aminotransferase (ALT) 360 IU/L. The level of Ig G was 1891 mg/dl (N:345-1236 mg/dl). The infectious and collagen tissue disease markers (salmonella, brucella agglutination tests, ANA, AntidsDNA, C<sub>3</sub>) were negative. Erythrocyte sedimentation rate was 40mm /hour. Ultrasound examinations of the abdomen showed enlargement of the liver and spleen with normal echogenicity. Bone marrow aspirates showed leishmania bodies within the macrophages. Leishmania antibodies (ELISA) were present. L-AmB (3 mg/kg/day for 10 days) was started. One week after the treatment hematological parameters and biochemical profile returned to normal. She is lost to follow up after discharge.

**Case 3:** A 16- month- old girl was referred to our hospital with fever of unknown origin, for cough and wounds on her hands for four weeks. She was from the same region as Case 1. She had been treated with different kinds of antibiotics because of her complaints. On physical examination she was febrile (39 °C), had pale skin with hepatomegaly (4 cm) and splenomegaly (5 cm). She had ulcerative lesions on her hands. The

haematological findings revealed haemoglobin 5.3 gr/dl, white blood count 2400/mm<sup>3</sup>, platelets 86.000/mm<sup>3</sup>. Blood chemistry showed albumin 1.8 gr/dl, ALT 55 IU/L, AST 99 IU/L. The level of Ig G was 3062 mg/dl (N:345-1236 mg/dl). Erythrocyte sedimentation rate was 107 mm/hour. Diffuse hepatosplenomegaly was found in abdominal ultrasonography. Leishmania bodies were not seen in bone marrow aspirate but the agent was detected in the bone marrow culture. Her leishmania serology with indirect immunofluorescence antibody test (IFAT) was strongly positive. L-AmB (3 mg/kg/day) was started and continued for 10 days. She became afebrile on 5<sup>th</sup> day of the treatment and haematological parameters became normal a week later. She continues to be in remission six months after completion of the treatment.

## DISCUSSION

Early treatment for VL was attempted with pentavalent antimonials. As experience with these drugs has grown, the incidence of treatment failures has increased. The recommended dosages and duration of treatment exceeded the high rates of clinical failures and relapses. Some investigators have speculated that this increase is because of the development of relative resistance to antimonials (4,5).

Amphotericin B and its lipid formulations were shown to have efficacy in treating leishmania infections (2).

Amphotericin B is thought to act by binding with the parasite episterol precursors of ergosterol in preference to the host cholesterol, interrupting parasite cell wall synthesis (6). The toxicity of this drug has limited its clinical use. Preparations of amphotericin B lipid complexes have been thought to have potential utility in the treatment of VL because of its lower toxicity. The first case report of successful treatment of VL with L-AmB was reported in 1991 (7).

Investigators show that there is a lack of consistent treatment regimens of VL throughout Mediterranean countries. Pentavalent antimonials were accepted as the first line choice but L-AmB is included by WHO among the recommended therapies for VL regarding

toxicity, intolerance and unresponsiveness to the others (4). In our cases no side effects and toxicity were observed.

In other studies it was demonstrated that L-AmB is a well tolerated treatment for VL in immunocompetent patients including infants and those with previous relapses (8). It has also been demonstrated that bone marrow normally recovers and inflammatory markers subside very early after the beginning of the treatment with liposomal amphotericin B in immunocompetent children (9). Our patients were not immunocompetent. So they gave a good response clinically and laboratory parameters became normal in a short time.

Giacchino (10) administered L-AmB to an infant with relapses because of resistance to the conventional therapy. He concluded that treatment with L-AmB in liposomal solution appeared to be effective in the treatment of drug resistant VL and the drug could be considered as a first choice treatment in very young children as our two cases (case 2 and 3) Catania (11) also considered the L-AmB as a first line treatment.

Davidson et al in their study recommended the optimal regimen for immunocompetent patients with VL to be a total L-AmB dose of >20 mg/kg given in >5 doses and 3-4 mg/kg/day over >10 days (12).

Two infants who were initially felt to have alternative diagnosis in Northern Europe were presented as VL and responded to a short course of L-AmB (3 mg/kg/day for 10 days) as our patients (13).

In an other study low dose L-AmB (5 mg/kg) given either as a five day course or as an infusion seems to be effective to VL (14).

Short course regimens, fever adverse effects, short hospital stays enable us to use this drug as a first choice in the treatment of VL.

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