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A Successful Treatment of a Child with Clinical Relapse of Visceral Leishmaniasis Complicated with AH_1N_1

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Abstract: ***Introduction: Visceral leishmaniasis is associated with poor sanitary conditions in Albania as suggested by clinical relapses and frequency of comorbidities. New lipid formulations are costly and have only been used as the first choice in cases of clinical relapses or resistance from meglumine antimoniate. Case presentation: This is a retrospective case report of a 14 month old child diagnosed with visceral leishmaniasis and treated with meglumine antimoniate for 28 days. Six months later he was readmitted to the hospital for clinical relapse of VL. His status was complicated by interstitial bronchopneumonia and influenza AH_1N_1. In this situation we re-treated the patient using intravenous liposomal amphotericin B (L-AmB) with dosing 3mg/kg weight in days 1–5, 14 and 21. Due to the influenza AH1N1 complication, the child was also treated with oseltamivir for 5 days. L-AmB and oseltamivir were well tolerated by the child, no side effects were seen. Following treatment with L-AmB, bone-marrow aspirate resulted negative for VL and laboratory exam values were normal. Conclusion: L-AmB is considered the treatment of choice in clinical relapses of visceral leishmaniasis first treated with antimone based preparations.***

Keywords: VL- visceral leishmaniasis, (L-AmB) liposomal amphotericin B, meglumine antimoniate, relapse, AH_1N_1,

1. Introduction

Zoonotic visceral leishmaniasis (VL) is a disseminated protozoan infection transmitted by phlebotomine sandflies, caused by Leishmania infantum in areas of the Old and New Worlds[1].

It is estimated that 350 million people are at risk of VL with an incidence of 0.5 million and a prevalence of 2.5 million worldwide. According to our experience, VL in the pediatric age is a frequent occurrence in Albania with a mean of admitted per year of 93 patients [2]. The incidence of the disease in Albanian children 25/100,000 in the age group 0–6 years is much higher than in developed Mediterranean countries endemic for VL. The disease is associated with poor sanitary conditions in Albania as suggested by clinical relapses and frequency of comorbidities.

The objectives of treating VL should be to cure the patient of intracellular parasites, prevent relapse and keep the costs to a minimum. Current VL therapy is based on the long-term parenteral administration of pentavalent antimonials, which, despite being expensive and highly toxic, has been the standard treatment for over 60 years. Clinical relapse of VL usually occurs within 6 months after completion of therapy.

New lipid formulations,however, are costly and have only been used as the first choice (including in pediatric patients) [3] in places in which the medical costs are not a limiting factor, such as in southern Europe and developed Mediterranean countries [4].

We present here an interesting case report with clinical relapse of VL complicated with AH1N1 and bronchopneumonia where we use liposomal amphotericin B as treatment.

2. Case Presentation

A 14 month old child was admitted to the hospital because of intermittent fever, malaise, poor activity tolerance and decreased of appetite for approximately one month. During this period he was treated as an outpatient for iron-deficiency anemia but his general condition was not improving.

The patient presented with dry skin, slight jaundice, splenomegaly, hepatomegaly and cachexia. A diagnosis of visceral leishmaniasis was made based on laboratory findings and bone marrow aspirate. Laboratory values (Tab.1) associated with classic kala-azar included anemia (hemoglobin 6.2 mg/dL), thrombocytopenia, elevated hepatic transaminase levels, Lymphocytosis 52,8 % and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G (IgG).

Table 1: Laboratory indices

Erythrocyte	3.490.000/mm3
Leukocyte	8800/mm3
Hb	6.2gr/dl
Thrombocyte	97.000/mm3
Granulocyte	39.3%
Lymphocyte	52.8%
Monocyte	7.9%
Prothrombin	53.8%
Glycemic	87mg/dl
AST	714UI/L
ALT	248UI/L
Creatinine	0.31mg/dl
Total Protein Protein	7.7 mg/dl
Urea	11.8 mg/dl
Total bilirubin	1.7mg/dl

Coomb's Test Negative

Bone marrow aspiration: Leishmania positive

Upon diagnosis treatment was started with daily intramuscular injections of meglumine antimoniate 20 mg Sb/kg/24 h, for 28 days.

A chest X-ray and cardiac sonography were performed without evidence of any other lesion. Haematological and cultural examinations turned out to be negative also.

ECG: Sinus tachycardia, with flattening of the ST segment that may be related to hypokalemia.

The child's condition continues to be poor, pale, fatigued, while treated with perfusions, electrolytes KCL, thrombocytopenic measures, plasma in the immediate hours, and vitamin therapy.

Abdominal sonography:
The liver was structurally homogenous and enlarged 102 mm below costal margin, the spleen enlarged 92 mm below costal margin.

The condition of the child and the laboratory indexes began to improve. The child tolerated treatment with meglumine antimoniate for 28 days, without any side effects. The patient has well tolerated the treatment , without side effects. The biochemical indices throughout the treatment have yielded normal values.

By the end of the treatment *a second bone-marrow aspirate was performed and found to be negative.* The child was discharged from the hospital in healthy condition. The child was followed up after discharged with controls every month by clinical examination,biochemical analyses and abdominal sonography.We would like to perform PCR (polymerase chain reaction) like a gold standard for detecting relapse of VL but unfortunately we have not disponible PCR in our hospital.

Second admission

The child was readmitted to the hospital 6 months later because of intermittent fever and lack of appetite for approximately 1 month. In physical examination we found a pale skin. Heart with rhythmic tone. Respiration was hard with fine rales. Abdomen was soft with splenomegaly and hepatomegaly.No enlarged lymph nodes were palpated. *Bone marrow aspiration*: Leishmaniasis positive
Biochemical indices were normal
Laboratory findings included pancitopenia:
Erythrocyte =2.760.000/mm3, Leukocyte =3200/mm3, Hb=5.6gr/dl
Under these conditions, child receives matched whole blood transfusion.
Abdominal sonography:
Liver homogeneous in structure and enlarged 70 mm, spleen homogeneous in structure and enlarged 93 mm.
Chest X-ray follow up: Bilateral bronchopneumonia

Following the results of the X-ray, treatment started with Ceftriaxon. The condition of the child continued to be poor, pale in appearance, with a temperature of 37.5 C and cough. The liver was found by palpation to be enlarged approximately 3-4 cm. The spleen was palpated close to the iliac crest.

ECG: Normal
HIV serology results: Negative
In this poor state of the child with clinical relapse of visceral leishmaniasis treatment started with L-AmB with dosing 3mg/kg/weight. 7 doses were administered from days 1-5, with the 6th dose administered on day 14, the 7th dose administered on day 21. Biochemical indices were normal. The condition of the child continued unchanged, with a temperature of 39 degrees C, cough, and pale appearance.

A nasopharyngeal swab for AH1N1 was requested and was found to be positive. The analyses were performed at the Institute of Public Health.

Chest X-ray: Interstitial bronchopneumonia and right middle lobe infiltrate

In this worsened condition of the child complicated by the swine flu AH1N1, antiviral treatment was started with oseltamivir (tamiflu) 2 x 25mg p.os for 5 days. Because the condition of the child continued to be poor, with high fever, dyspnea, polypnea RR=60/min, and HR=140/min, the child is transferred to the Intesive Care Unit for better assistance.
Chest X-ray follow up: Bronchopneumonia of the superior right lobe

Laboratory indices: Hb=7.6gr/dl, leukocyte =2500/mm3, erythrocyte=3,450,000/mm3

Treatment was started with tazocine, perfusions, 100ml of plasma, and continued with L-Amb at the appropriate dose. After 10 days in the Intensive Care Unit the condition of the child improved and transfered to Pediatric Infectious Disease Service.

There the conditions appeared good, child continued to be afebrile. On auscultation lung fields were improved, heart had a rhythmic tone. Soft abdomen, liver palpated at 2cm, spleen palpated at 3cm. Treatment continued with the 7^{th} dose of L-AmB. During treatment, the levels of creatinine, urea, K^+, Na^+ have been monitored. Normal urine output was maintained. Child has also been under observation for allergic reactions throughout treatment.

After treatment : We found reduction in spleen size and correction of haematological parameters.Bone marrow aspirate resulted negative for Leishmania. In chest X-ray lung fields were greatly improved.

Patient follow up 6 months after the second admission

Follow up 1:
Laboratory indices were normal. Bone marrow aspirate was negative. Upon palpation liver and spleen were soft, smaller in size. Child's condition was good.

Follow up 2:

Child had no temperature, and was in good condition.
Laboratory indices were normal. Liver and spleen were soft, and smaller in size.

3. Discussion

Pentavalent antimony compounds (sodium stibogluconate and meglumine antimoniate) have been considered the standard antileishmanial treatment for about 70 years [5], and, notwithstanding the emergence of a high level of resistance in some parts of India (especially in North Bihar), they are still the first-line drugs in the other VL foci in the Indian subcontinent;[6,7] however, antimonials need a long period of hospitalization (28 days) and are characterized by non-negligible adverse effects.

In 1997, the US Food and Drug Administration approved L-AmB for the treatment of VL, with a regimen consisting of seven doses of 3 mg/kg (total dose 21 mg/kg).[8]

Liposomal amphotericin is a lipid formulation of a polyene antibiotic that binds preferentially to ergosterol (the major sterol in *Leishmania*), and is currently the first-line treatment for visceral leishmaniasis in Europe.[11] L-AmB has proven to be highly effective and safe as a monotherapy and as a single-dose treatment[12-14]

In this retrospective case report we confirm and extend previous results regarding the efficacy and safety of that 7 day schedule of L-AmB as the first line treatment in clinical relapse of VL.Our finding indicate that a total dose of 21 mg/kg of L-Amb was well tolerated. Moreover, several studies have shown that time of defervescence, reduction in spleen size and correction of haematological parameters occurs more quickly among patients (adults and children) treated with L-AmB in comparison with those treated with meglumine antimoniate.[15,16] The main objection to the use of L-AmB for the treatment of VL in countries where resistance to antimonials has been rarely reported is the high cost of the drug. However, for developing countries, such as Albania, the cost, despite being more affordable, is still considered too high.
It should be remembered that regional differences in response to treatment have been observed, probably related to the infecting Leishmania strain; in fact, Brazilian infection caused by L. chagasi seems to be less responsive to L-AmB than Indian Kala-azar (caused by L. donovani).[17]

In a Retrospective Analysis of 1,210 Consecutive Hospitalized Pediatric Patients (1995–2009) with Visceral Leishmaniasis that we have performed in Albania [2], eight patients (0.67%) showed a clinical relapse of VL, confirmed parasitologically, within
6–12 months from therapy and needed re-treatment with L-AmB, at the dose of 3 mg/kg/day in days 1–5, 14 and 21 [18], which successfully cured these patients as assessed by 1-year post-therapy follow-up. Patients treated with liposomal amphotericin B did not show adverse events.

A key development that now allows L-AmB to be considered for use as a first-line drug in countries where VL is endemic was the preferential pricing agreement secured by WHO in 2007, reducing the cost of treatment to 10% of its original price in developing countries [19] . It has also been indicated that a single intravenous dose of 10 mg/kg. L-AmB results in a 95.7% cure rate at 6 months of follow-up, with a lower frequency of adverse events than observed with other available VL treatments [20].

4. Conclusion

Our case report confirms the safety and efficacy of a total dose of 21 mg/kg of L-AmB for the treatment of VL in children with clinical relaps, as assessed by 1-year post-therapy follow-up. We hope to use L-AmB as first line drug in pediatric VL in Albania to provide long term cure of disease.

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