Visceral leishmaniasis and Coombs' positive hemolytic anemia: a rare association in an infant treated with liposomal amphotericin B

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SUMMARY: Dilber E, Erduran E, Işık Y. Visceral leishmaniasis and Cooms' positive hemolytic anemia: a rare association in an infant treated with liposomal amphotericin B. Turk J Pediatr 2002; 44: 354-356.

Visceral leishmaniasis is a worldwide, disseminated intracellular protozoal infection that usually manifests by fever, hepatosplenomegaly, anemia, thrombocytopenia, leukopenia and hypergammaglobulinemia. Although anemia is a usual finding, Coombs' positive hemolytic anemia has rarely been reported in association with this disease. Pentavalent antimonials have been the preferred treatment for this disease for decades, but increasing numbers of treatment failure with antimony are being reported. Liposomal amphotericin B is a new drug which is highly efficacious in the treatment of visceral leishmaniasis and produces minimal toxicity. Here we report an infant with visceral leishmaniasis associated with Coombs' positive hemolytic anemia who was successfully treated with liposomal amphotericin B.

Key words: visceral leishmaniasis, Coombs' positive hemolytic anemia, liposomal amphotericin B.

Visceral leishmaniasis (VL) is a protozoal infection that infects and multiplies in macrophages of liver, spleen and bone marrow[1]. It usually manifests by fever, hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, and hypergammaglobulinemia, and may cause a lethal disease if untreated.

Anemia, leukopenia and thrombocytopenia are the main hematologic abnormalities commonly seen in VL[1,2]. It has been confirmed that during the active phase of VL , the erythrocyte life span is shortened[2,3]. At this time, erythrocytes have been shown to be agglutinated by anti-complement and anti-non-γ-globulin (direct Coombs' test) sera. It has been postulated that an autoimmune mechanism was the likely explanation for the reduced erythrocyte survival in kala azar[3]. The pentavalent antimonials are the first-line drug in the treatment of VL[1,4]. They may cause serious toxicity especially on the heart and kidney and there is also increasing resistance to these drugs[4-6]. Liposomal amphotericin B (L-AmB) is a highly effective anti-leishmanial drug and causes less toxicity[4,7-10]. It has been successfully used especially in the treatment of resistant cases[4-6].

Here we report successful treatment with L-AmB of an infant with VL associated with Coombs' positive hemolytic anemia and discuss the effect of L-AMB in the treatment of VL.

Case Report

An eight-month-old girl was admitted to our clinic from Torul-Gümüşhane because of intermittent fever, anemia and hepatosplenomegaly. On admission she was pale and had a distended abdomen. Temperature was 37.6°C, liver was palpable 4 cm below the right and spleen 7 cm below the left costal margin. The laboratory investigation revealed a hemoglobin of 5 g/dl, leukocytes $9x10^9$/L, with 56% neutrophils, 40% lymphocytes, and 4% monocytes, platelet count of $50x10^9$/L, and reticulocyte count of 12%. Coombs' test was positive, albumin was 1 g/dl and globulin was 5.6 g/dl.

Initially, high dose methylprednisolone (HDMP-30 mg/kg for three days, 20 mg/kg for four days) was initiated for the treatment of Coombs' positive hemolytic anemia. During one week of treatment no improvement was noted either in clinical findings or laboratory

parameters, and a slight intermittent fever also appeared. At this time, bone marrow aspiration was done and multiple Leishmania amastigotes were shown in macrophages (Fig. 1). She was then given intravenous L-AmB at a dose of 3 mg/kg daily as an infusion over an hour and continued for 30 days. With this treatment hemoglobin increased to normal value and Coombs' positivity disappeared on the 25th day; platelets increased to normal on the 5th day. No Leishmania amastigote was seen on bone marrow aspirate at the 30th day of L-AmB treatment. At this time liver and spleen were palpable 1 and 2 cm below the costal margin, respectively. During treatment a transient hypokalemia was noted. Five months after completion of treatment the patient was healthy and all laboratory tests were normal.

Discussion

Visceral leishmaniasis is a disseminated intracellular protozoal infection that occurs worldwide. Infection of the macrophage of the reticuloendothelial system results in VL that is clinically present as fever, hepatosplenomegaly and pancytopenia[1-3]. Anemia, leukopenia and thrombocytopenia are the main hematologic abnormalities commonly seen in VL. The anemia appears to be due to a combination of factors, including hemolysis, marrow replacement with Leishmania-infected mononuclear phagocytes, hemorrhage, splenic sequestration of erythrocytes and hemodilution. In addition, reversible myelodysplasia has been reported in association with VL[11]. Although anemia is a usual finding, Coombs' positive hemolytic anemia has rarely been reported in association with VL[2,3,12]. In a previous report it was suggested that an autoimmune mechanism was the likely explanation for reduced erythrocyte survival in kala azar[2]. In that study the red blood cells of three patients with kala azar gave a positive anti-non-γ-globulin reaction, and agglutination with anti-complement sera was also demonstrated in two patients at the time of proven reduced erythrocyte survival. In our case the association of VL and Coombs' positive hemolytic anemia was not recognized initially, and HDMP was initiated for the treatment.

In Turkey, VL is endemic in the southeast region[13]. Another region where VL is sporadically reported is Torul-Gümüşhane[13]. In a previous report, it was suggested that a landslide that occurred in 1988 could have led to the development of climate conditions favourable to the growth of sandflies in this region[14].

Pentavalent antimonial agents have been the preferred treatment for VL for decades, but an

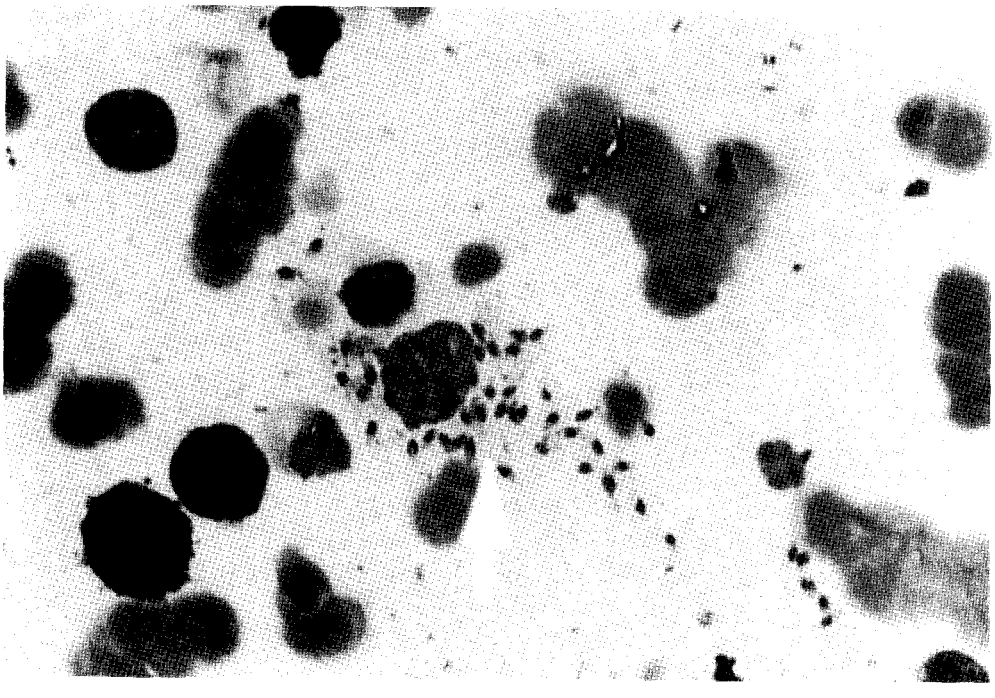

Fig. 1. Multiple leishmanial amastigotes in bone marrow aspiration.

increasing number of treatment failures with this drugs are being reported throughout the world[4-6]. These drugs may also cause significant toxicity, particularly to the heart and kidney[6]. One of the alternative drugs that has been shown to be the most active anti-leishmanial agent in use is L-AmB[4,7-10]. It is a new and well tolerated drug for VL. It is also highly lipophilic and selectively concentrates in reticuloendothelial tissue, the site of disease in the case of VL[7,8]. It is an important alternative especially in patients who did not respond to conventional pentavalent antimony therapy given alone or in combination with other agents[7]. After an initial HDMP treatment, L-AmB was initiated and continued for 30 days. With this treatment laboratory abnormalities improved and hepatosplenomegaly decreased. Treatment with L-AmB may cure leishmanial infection even in a shorter time. In this case initial HDMP treatment may have prolonged the treatment period. The only side effect noted in our case was transient hypokalemia.

This is one of the youngest patients with VL associated with Coombs' positive hemolytic anemia who was successfully treated with L-AmB. We believe this drug may be the first choice of treatment in VL even in very young infants.

REFERENCES

1. Pearson RD, Sausa AQ. Clinical spectrum of leishmaniasis. Clin Infect Dis 1996; 22: 1-13.
2. Miescher PA, Belehu A. Leishmaniasis: hematologic aspects. Semin Hematol 1982; 19: 93-99.
3. Woodruff AW, Topley E, Knight R, Downie CG. The anemia of Kala Azar. Br J Haematol 1972; 22: 319-329.
4. Sundar S, Agrawal NK, Sinha PR, Horwith GS, Murray HW. Short-course low-dose amphotericin B lipid complex therapy for visceral leishmaniasis unresponsive to antimony. Ann Intern Med 1997; 127: 133-137.
5. Mishra Mm, Biswas UK, Jha DN, Khan AB. Amphotericin versus pentamidine in antimony unresponsive kala azar. Lancet 1992; 340: 1256-1257.
6. Jha TK, Gri YN, Singh TK, Jha S. Use of amphotericin B in drug-resistant cases of visceral leishmaniasis in north Bihar, India. Am J Trop Med Hyg 1995; 52: 536-538.
7. Berman JD, Hanson WL, Chapman WL, Alving CR, Lopez BG. Antileishmanial activity of liposome-encapsulated amphotericin B in hamster and monkeys. Antimicrob Agents Chemother 1986; 30: 847-851.
8. Seaman J, Boer C, Wilkinson R, et al. Liposomal amphotericin B (Ambisome) in the treatment of complicated Kala Azar under the field conditions. CID 1995; 21. 188-193.
9. Davidson RN, Di Martio L, Gradoni L, et al. Liposomal amphotericin B (Ambisome) in Mediterranean visceral leishmaniasis: a multi-center trial. Q J Med 1994; 87: 75-81.
10. Croft SL, Davidson RN, Thornton EA. Liposomal amphotericin B in the treatment of visceral leishmaniasis. JAC 1991; 28 (Suppl): 111-118.
11. Erduran E, Aslan Y, Mocan H, Gedik Y, Anyacı FM, Ökten A. Reversible myelodysplasia due to kala-azar. Turk J Med Sci 1996; 26: 511-513.
12. Gagnaire MH, Galambrun C, Stéphan JL. Hemophagocytic syndrome. A misleading complication of visceral leishmaniasis in children-a series of 12 cases. Pediatrics 2000; 106: e58.
13. Hiçsönmez G, Özsoylu S. Kala-azar in childhood. A survery of clinical and laboratory findings and prognosis in 44 childhood cases. Clin Pediatr 1972; 11: 465-467.
14. Mocan H, Gedik Y, Ökten A, Erduran E, Gacar N. Kala Azar in Trabzon (Eastren Black Sea) region of Turkey. Indian J Pediatr 1993; 60: 775-778.