Foamy histiocytes in a patient with visceral leishmaniasis after treatment with liposomal amphotericin B

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A seven-year-old patient was admitted to our hospital with the complaints of fever, malaise, and abdominal distention. In the bone marrow aspiration smears, leishmania amastigotes were observed. The patient was diagnosed as having visceral leishmaniasis (VL) and treated with liposomal amphotericin B (L-AMB). The authors report their observation of foamy histiocytes seen in the bone marrow aspiration smears of the patient with VL after L-AMB treatment. This effect of L-AMB needs to be recognized, since L-AMB may represent a further condition in addition to the other diseases that are associated with foamy histiocytes in the bone marrow.

Key words: foamy histiocytes, visceral leishmaniasis, liposomal amphotericin B.

Visceral leishmaniasis (VL) is a systemic disease caused by the dissemination of the protozoa, leishmania, throughout the reticuloendothelial system (RES). This infection is endemic to the tropics, subtropics, and most Mediterranean countries including Turkey. *L. donovani* and *L. infantum* are the most common species in Turkey and dogs are thought to be the most common reservoirs. Visceral leishmaniasis should be suspected in patients with fever, splenomegaly, pancytopenia, hypergammaglobulinemia, lymphadenopathy and potential exposure in an endemic area[1,2].

Liposomal amphotericin B (L-AMB) may be considered as the first- or second-line treatment in immunocompetent patients with VL. Incorporation of amphotericin B into small unilamellar liposome forms the liposomal form of the drug. This form alters the pharmacokinetic properties of the drug, but allows retention of significant in vitro and in vivo drug activity. Liposomal amphotericin B is generally well tolerated and this form of the drug decreases the side effects. Few patients require discontinuation or dose reduction because of the side effects[3].

We describe an observation of foamy histiocytes in the bone marrow aspiration smears of a patient with VL after L-AMB treatment.

Case Report

A seven-year-old boy was admitted to our hospital with the complaints of fever, malaise, and abdominal distention. The family and past medical histories of the patient were unremarkable. The physical examination of the patient revealed the presence of splenomegaly 8 cm below the left costal margin. The lymph nodes and the liver were not enlarged.

On admission, laboratory findings were as follows: hemoglobin, 7.3 g/dl; hematocrit, 22.7%; mean corpuscular volume, 66.3 fl; red cell distribution width, 18.9%; white blood cell count, $1.8x10^3/mm^3$ with 44% neutrophils, 6% monocytes, 50% lymphocytes; platelet count, $105x10^3/mm^3$; reticulocyte count, 2.8%; and erythrocyte sedimentation rate, 49 mm/h. The ferritin level was 24 ng/dl (N: 28-365); triglycerides, 204 mg/dl (N:<200); cholesterol, 132 mg/dl (N: <200); and fibrinogen, 477 mg/dl (N: 144-430). Liver and renal function tests and electrolytes were

normal. There was no serological evidence for Epstein-Barr virus, cytomegalovirus, toxoplasmosis, parvovirus B19, salmonella, or brucella infections. Abdominal ultrasonography revealed the presence of splenomegaly. The first bone marrow aspiration smear showed normocellularity and characteristic leishmania amastigotes (Fig. 1). The diagnosis of VL was established on the basis of these clinical and laboratory findings.

The treatment with intravenous L-AMB, 3 mg/kg/day for 21 days, was administered. After the treatment was started, the fever resolved in a short period of time and his general condition improved. However, splenomegaly only gradually decreased. After three-week treatment with L-AMB, bone marrow aspiration was performed to determine presence or not of leishmania amastigotes. On the second bone marrow aspiration smear, there were no leishmania amastigotes but many foamy histiocytes (Fig. 2). On discharge, physical examination of the patient was normal except for a mildly enlarged spleen. At his last follow-up examination, his spleen was not palpable and multiple foamy histiocytes had disappeared on the bone marrow aspiration smear performed one year after the diagnosis.

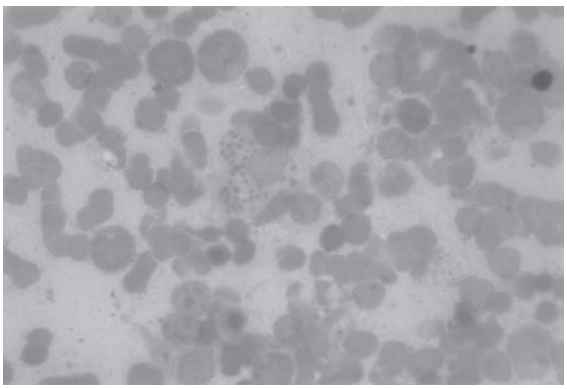

Fig. 1. Leishmania amastigotes in the bone marrow aspiration smears (x100-Wright).

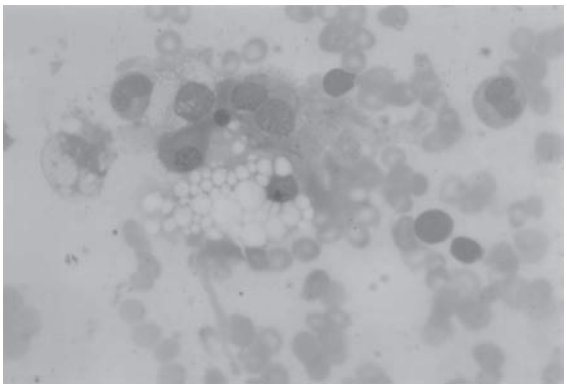

Fig. 2. Foamy histiocytes in the bone marrow aspiration smears (x100-Wright).

Discussion

Liposomal amphotericin B is a complex of amphotericin B with hydrogenated phosphatidylcholine, distearoyl phosphatidylglycerol, and cholesterol. Liposomal amphotericin B seems to be less toxic than other lipid formulations. Common side effects of nausea, vomiting, fever, hypokalemia, abdominal pain, cramping, and nephrotoxicity are usually mild. However, severe side effects such as anaphylactic reactions, reversible hepatic dysfunction, and hyperphosphatemia have rarely been reported[4-8]. As has been reported previously, L-AMB reaches higher concentrations in plasma and remains in the circulation longer than the other forms of the drug. Similar to the other lipid formulations, L-AMB concentrates in the RES. Elimination of L-AMB from serum is biphasic, which suggests that L-AMB is first concentrated in RES cells and then redistributed[9]. We noticed foamy histiocytes in the bone marrow aspiration smears of the patient after he received three-week L-AMB treatment. We suggest that it resulted from the nature of the drug, which is composed of unilamellar lipid vesicles. After histiocytes phagocytosed the drug, degradation products derived from the unilamellar liposomes may have given rise to the foamy histiocytes.

Frances et al.[10] reported that histologic examination of skin lesions in a patient treated for recurrent Hodgkin's disease showed nodular infiltration of the dermis with very few Leishman-Donovan bodies and foamy, Virchow-type histiocytes. It was reported that these skin lesions were observed in immunodepressed patients with kala-azar[10]. However, our patient was immunocompetent and did not have any underlying diseases or skin lesions.

Liposomal amphotericin B is broadly used in patients with hematological malignancies or bone marrow transplantation, but there is no report about foam cell occurrence. Foam cells may occur because of the following:

(a) enhanced uptake of native or modified lipoproteins or lipids; (b) alterations in intracellular lipid metabolism; (c) failure of export systems to maintain cholesterol homeostasis; or (d) combinations of the aforementioned mechanisms[11]. The expression of many genes is likely modulated during macrophage transformation into a foam cell[12]. The occurrence of foamy histiocytes may be due to the genetic background of our patient. It is also possible that foamy histiocytes occur in patients receiving L-AMB for other reasons, but bone marrow aspiration is not routinely performed at the end of therapy.

Such foamy histiocytes may also be seen in patients with different diseases and conditions including Niemann Pick disease, Wolman disease, Tangier disease, long-term total parenteral nutrition, hypercholesterolemia, and hyperlipoproteinemia[13-14]. These should be considered in the differential diagnosis.

In conclusion, to our knowledge, the occurrence of foamy histiocytes in the bone marrow after L-AMB treatment has not been reported previously. Liposomal amphotericin B should now be considered in the differential diagnosis of foamy histiocytes in the bone marrow. The frequency and the underlying mechanisms should be further assessed.

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