Kala-Azar and leukemia: A rare association

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Abstract

Visceral leishmaniasis is an infectious disease that infects and multiplies in macrophages of the liver, spleen, and bone marrow. The most common clinical features are fever, splenomegaly, and anemia. Anemia, leucopenia, and thrombocytopenia are the main hematologic abnormalities commonly seen in visceral leishmaniasis. These findings can be seen in several types of hematologic disorders. The findings are similar to most hematologic disorders and so may make diagnosis problematic. It is difficult to confirm when it is seen except in epidemiologic areas. It can be fatal if it is not treated and appropriate treatment can be lifesaving. In this article a 12 year-old male patient who was followed-up with diagnosis of acute lymphoblastic leukemia and received maintenance therapy while being under remission after BFM-ALL-2000 treatment protocol and diagnosed with hemophagocytic lymphohistiocytosis due to Kala-azar during this period was presented

Keywords: Leukemia, pancytopenia, visceral leishmaniasis

Introduction

Visceral leishmaniasis (VL) is a protozoal disease that infects the reticuloendothelial system and can cause death, if left untreated. It may be confused with multiple hematologic diseases. The diagnosis may be difficult when it occurs in areas other than those where it is frequently epidemiologically observed. In this article, we present a rare association of kala-azar and acute lymphoblastic leukemia (ALL) in a 12-year-old boy who presented with fever and pancytopenia while receiving maintenance treatment with a diagnosis of ALL.

Case

A 12-year-old boy who was being followed up with a diagnosis of acute lymphoblastic leukemia (ALL) whose maintenance treatment was initiated with remission following BFM-ALL-2000 treatment protocol presented to our clinic with intermittent fever, which had been continuing for 10 days. On physical examination, the

liver edge was palpable 1.5 cm below the right costal margin. The laboratory findings were as follows: white blood cells (WBC): 1300 /mm³, neutrophil count: 800/mm³, hemoglobin: 8,9 g/dL, platelet count: 156 000/mm³, C-reactive protein (CRP): 16.5 mg/L (normal: 0-5 mg/L). On peripheral blood smear, the WBC differential count showed 60% neutrophils, 33% lymphocytes, 3% eosinophils, and 4% monocytes. Hepatic and renal function tests were found to be within the normal limits. Bone marrow examination showed no findings of recurrence of ALL. The patient's maintenance treatment was discontinued and intravenous meropenem treatment was initiated with a diagnosis of febrile neutropenia. On the fifth day of treatment, the hepatomegaly and neutropenia improved. Subsequently, maintenance treatment was initiated again and the patient was discharged. One month later, the patient presented once again with fever and malaise. In a physical examination, the spleen edge was palpable 5 cm below the left costal margin. The laboratory findings were as follows: WBC: 2100/mm³, neutrophil count: 1500/mm³,

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hemoglobin: 9.7 g/dL, platelet count: 302,000/mm³, ferritin: 1299 ng/mL (normal: 30-400 ng/mL), fibrinogen: 456 mg/dL (normal: 200-400 mg/dL), triglyceride: 118 mg/dL (10-200 mg/dL), albumin: 3.27 g/dL (normal: 3.5-5.2 g/dL), globulin: 4.61 g/dL (normal: 2.9-3.1 g/dL). In the peripheral blood smear, the WBC differential count showed 70% neutrophils, 25% lymphocytes, 3% eosinophils, and 2% monocytes. No serologic evidence related with salmonella, Brucella, and viral pathogens could be found. Lymphadenopathy could not be found on abdominal ultrasonography. A bone marrow aspiration was performed once again. Although *Leishmania* amastigotes were not observed on the previous bone marrow examination, multiple *Leishmania* amastigotes and hemophagocytic hystiocytes were observed on bone marrow samples this time (Picture 1).

Growth occurred in culture of bone marrow samples in Novy-MacNeal-Nicolle (NNN) medium. A diagnosis of infection-related hemophagocytic lymphohistiocytosis (HLH) was made and intravenous immunoglobulin (1 g/kg/day) was administered for two days and intravenous liposomal amphotericin B (3 mg/kg/day) was given in association. On the fourth day of treatment, the patient's body temperature returned to normal values and the spleen edge was palpable 1 cm below the left costal margin. A total of seven doses of liposomal amphotericin B were given to the patient. Subsequently, the patient had no fever, malaise, hepatomegaly, splenomegaly or decreased blood cell counts. Additionally, maintenance treatment was reinitiated 25 days later. Two months after completion of liposomal amphotericin B treatment, the patient presented again with fever. Splenomegaly and reduction in all three series of blood cells were found in the patient. Bone marrow aspiration was repeated with a suspicion of recurrence

of leishmaniasis. *Leishmania* amastigotes were also observed on this examination. Maintenance treatment was discontinued and liposomal amphotericin B treatment was initiated. Following seven doses of liposomal amphotericin B (3 mg/kg/day), the laboratory findings were as follows: WBC: 1900 /mm³, hemoglobin: 11.8 g/dL, platelet count: 243,000/mm³ (peripheral blood smear: 60% neutrophils, 35% lymphocytes, 4% eosinophils, and 1% monocytes), albumin: 4.6 /dL, globulin: 5 g/dL. On physical examination, the spleen was palpable 1 cm below the left costal margin. With these results, it was thought that this treatment was inadequate and intravenous liposomal amphotericin B treatment was continued twice per week for one month (3 mg/kg/day). One month later, the laboratory results were as follows: WBC: 3120 /mm³, hemoglobin: 10.9 g/dL, platelet count: 244,000/mm³ (peripheral blood smear: 65% neutrophils, 33% lymphocytes, 2% monocytes), albumin: 4.9 g/dL, globulin: 3 g/dL. No organomegaly was found on physical examination. Antibiotic treatment was discontinued because the patient was in remission. The patient has been under control for eight months and no relapse has occurred. Verbal consent was obtained from the patient's family.

Discussion

Visceral leishmaniasis is an infectious disease that invades macrophages in the bone marrow, liver, and spleen (1). The most common clinical findings include fever, splenomegaly, and anemia. Hepatomegaly is observed with a lower frequency compared with splenomegaly (2). The most common sign is fever and it may be intermittent or remittent. In contrast, fever may not be observed in immunocompromised patients (3). In visceral leishmaniasis, anemia, leukopenia, and thrombocytopenia are common hematologic anomalies (1). These findings may also be observed in many other hematologic diseases. Recurrence of leukemia was primarily considered in our patient who developed fever, pancytopenia, and splenomegaly while receiving maintenance treatment. Although there were no pathologic findings on the first bone marrow examination, a second bone marrow examination was made one month later with the same clinical findings. Secondary hemophagocytosis was also considered in the differential diagnosis because increased ferritin level was found in association with fever, pancytopenia, and splenomegaly. It should be kept in mind that the most common triggering protozoal cause of acquired HLH is *Leishmania* parasites (4).

Picture 1. Hemophagocytic hystiocytes

In visceral leishmaniasis, one of the common laboratory findings is reduced serum albumin associated with increased serum globulin. An increase in the polyclonal B lymphocyte count is observed as a result of the high number of amastigotes in macrophages and stimulation of the reticuloendothelial system (5). In parallel to the increase in immunoglobulin (Ig)-G level, the globulin level is also increased. It was thought that the absence of increased globulin level in our patient was related with immunosuppressive drugs given as a maintenance treatment. The diagnosis was confirmed with the growth of *Leishmania* in NNN medium on the fourth day in the bone marrow culture, which we performed for the second time. Kala-azar was not primarily considered in the patient who presented with fever and pancytopenia because Gaziantep was not an epidemic area in terms of leishmaniasis. It was learned that the patient was in contact with Syrian immigrants and it was thought that the infection was transmitted in this way. Moreover, *Leishmania* amastigotes were not observed when the first bone marrow samples were retrospectively examined considering that they might have been overlooked on the first bone marrow examination.

As reported before, NNN medium positivity is observed with a frequency ranging between 16.6% and 14.2% in young children in Turkey (5-7). The most specific and sensitive test to detect *Leishmania* antibodies and measure their level is enzyme-linked immunosorbent assay (ELISA). In addition, there are other diagnostic tests [polymerase chain reaction (PCR), immunofluorescence antibody test (IFAT), complement fixation, hemagglutination) (8). Visceral leishmaniasis can be successfully treated with liposomal amphotericin B. Liposomal amphotericin B selectively accumulates in the reticuloendothelial tissue and is less toxic compared with other drugs (9, 10). Therefore, liposomal amphotericin B (3 mg/kg/day) was given in seven doses primarily as recommended by the World Health Organization. Subsequently, the patient recovered, but later the disease recurred. During the recurrence, treatment was prolonged; liposomal amphotericin B was administered twice per week for one month after it was given in seven doses. At the end of the one-month period, the clinical findings and laboratory tests returned to normal. Therefore, it was thought that liposomal amphotericin B was more effective when administered for a longer period and at higher doses in immunocompromised patients.

Clinical and laboratory findings similar to different hematologic disorders are observed in visceral leishmaniasis. If left untreated, visceral leishmaniasis may have a

fatal course. Appropriate treatment is life-saving. Liposomal amphotericin B can be given for a longer period and at higher doses in immunocompromised patients to prevent recurrence of kala-azar.

Informed Consent: Informed consent was obtained verbally from parents of the patient.

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