Case Report

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED WITH VISCERAL LEISHMANIASIS IN EARLY CHILDHOOD

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ABSTRACT

We describe a case of hemophagocytic lymphohistiocytosis which is related to visceral leishmaniasis in early childhood. As the condition is quite rare in early childhood and secondly there is close resemblance of the clinical features with visceral leishmaniasis the diagnosis of hemophagocytic lymphohistiocytosis is challenging in this age group. In our case, detection of the Leishmania donovani in the bone marrow and response to antimoniate therapy initially and followed by resistance to visceral leishmaniasis therapy and fulfillment of hemophagocytic lymphohistiocytosis criteria confirmed the diagnosis.

Key Words: Visceral leishmaniasis, hemophgocytic lymphohistioctosis.

INTRODUCTION

Visceral leishmaniasis (VL) is a chronic and frequently lethal disease caused by protozoan parasites of the Leishmania donovani complex. It is common and endemic in over sixty countries over five continents[1]. The clinical spectrum of VL is quite broad spectrum and manifest differently. The morbid and mortal nature of this condition is highly related to the delay in diagnosis and treatment. Several case reports have been published in pediatric age group; showing hemophagocytic lymphohistiocytosis (HLH) secondary to leishmaniasis that the clinical manifestations and laboratory features of VL and HLH overlap[2]. The HLH was first described in 1939 by Scott; this condition was subsequently classified into primary or genetic HLH and secondary or reactive HLH[3]. Either in its primary or secondary form, HLH is characterized by activation and uncontrolled non-malignant proliferation of T-lymphocytes and macrophages. Secondary HLH has been shown to be associated with a myriad of viral, bacterial, fungal, and parasitic infections, as well as autoimmune diseases and malignant disorders. An increasing number of HLH secondary to tropical infections have been reported, including those associated with VL. Because the hematologic features observed in VL may considerably overlap with those of HLH[4].

CASE REPORT

A 6 year-old male child, from North Waziristan, was admitted in children 'B' on May 5th 2017, with the history of recurrent fever with chills for the last 4 months, progressive generalized weakness 3 months, abdominal distension and loss of appetite for 2 months. The child was fine till 5 months earlier, when he started complaining of fever with chills on and off. The child was treated by local doctors from last 4 months. His hemoglobin progressively decreased over last 4 months from hemoglobin 11 to 8g/dl, total leukocyte counts were 13000/cmm, 8300/cmm, 4000/cmm respectively. The patient was given multiple antibiotics including cefixime, ciprofloxacin and ceftriaxone used without encouraging results. The patients was also prescribed anti-malarials (Artemether plus lumefantrine, dihydroartemesinin plus piperaquine and chloraquine phosphate) but no response. Afterwards Anti-tuberculous treatment started without any result being using for 2 weeks. The child weight was13.6 kg (< 5th Centile) the child was febrile running temperature of 102°F, he was toxic, emaciated and pale. He had several petechiae over the legs and having dark pigmentation. His systemic examination showed distended abdomen with huge hepatosplenomegaly spleen up to umbilicus (13cm) and liver 7 cm below the sub-costal margin. On chest examination there were few rales on right lower zone otherwise clear. The child was having grade 2/6 murmur at pulmonic area, and heart rate was 110/minute. Central nervous system examination was unremarkable with exception of being unable to walk because of extreme emaciation and illness. The differential diagnoses included were visceral leishmaniasis, leukemia, tropical splenomegaly, storage disorders and thalassemic syndromes. There was high possibility of malaria because of being highly endemic in Waziristan, resistant strains are identified and the negative evidences included already taken anti-malarials (on 2 occasions) optimal doses and duration and secondly huge heptosplenomegaly is unlikely in malaria. The possibility of visceral leishmaniasis could not be excluded because of huge hepatopslenomegaly, highly endemic in that area and no response to anti-malarial treatment. Special smear showed hemoglobin: 3.8g/

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dL, platelet count: 14000/cmm, total leukocytes: 4800/cmm neutropils: 20%, lymphocytes: 73% and no blast cell. MP slide was negative, retic count: 0.5% and ESR: 90 mm/1st hour. SGPT: 78, serum creatinine: 0.9, Urine R/E: Normal, Typhidot: Negative. LDH: 470 while the rest of initial investigations were unremarkable. X-rays chest was normal. U/S abdomen showed hepatosplenomegaly. Bone marrow showed adequacy: with normal erythropoiesis, few normoblasts, increased megakaryopoiesis and LD bodies identified. Initially the child was treated with Antibiotics, Antipyretics, IV fluids, packed-cell transfusion and platelets transfusion. After diagnosis of visceral leishmaniasis, the child was put on meglumine antimoniate (Glucantime) in a dose of 20 milligrams (mg)/kg of body weight per day injected into a muscle and discharged with a total treatment for twenty-eight days and advice to come after 4 weeks. After 04 weeks of follow-up the patient showed a good response to the treatment, his appetite improved, there were no petechial rash, vomiting but still running low-grade fever. Platelet count increased up to 69000/ml and hemoglobin level was 8.4 g/dL. The liver size at 4 weeks was 5cm (at admission: 7cm) and spleen size (9cm). The attendants of the child were asked to come for follow up visit after a month. The parents brought the child after 2-3 weeks. This time the child had high grade fever, increased toxicity, decreased appetite, occasional vomiting and weight loss. On examination, liver size had increased from 7 cm to 9.5cm and spleen size had increased from 9cm to 13cm. The child was readmitted and work up done. This time the hemoglobin was 7.6, platelets: 40,000/cmm, TLC: 3200/cmm, N: 38%, and L: 52%. MP: Negative, Typhidot: IgM Negative, CRP: 23, ESR: 102mm/1st hour, Urine: Albumin +, Pus cell 6-8/HPF, RBC 2-3/HPF and no casts. X-rays chest showed bilateral hilar minimal lymphadenopathy, ALT: 102, Bilirubin: 4.8, Serum alkaline phosphatase 58, Urea 56, Creatinie: 0.9 and US abdomen showed hepatosplenomegaly with minimal pelvic ascites. The complexion of the patient was dark. We conducted other investigations including serum ferritin: 2800ng/ml, fasting triglycerides: 436mg/100ml, Fibringen level: 56mg/100ml. Hemophagocytes were found in the bone marrow repeated second time showing hemophagocytes. The patient was willing to get consultation of pediatric oncologist but unluckily died after two weeks of diagnosis.

DISCUSSION

Secondary HLH caused by VL is rare condition but found in visceral leishmaniasis endemic regions as compared to endemic ones. Pakistan and especially the mountainous built of Khyber Pakhtunkhwa is highly endemic area for this infectious condition[6]. In our case we found that initial diagnosis was fulfilling the criteria of visceral leishmaniasis. Additionally, the age of onset suggested primary, familial HLH. However, the diagnosis of VL associated HLH was made, sparing the patient

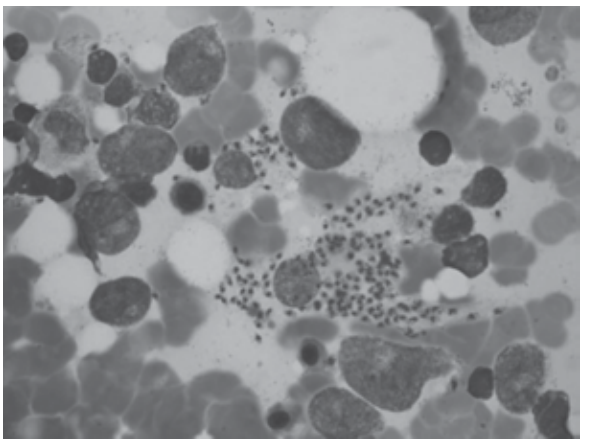

Figure 1. Bone Marrow showing Leishmania Donovani

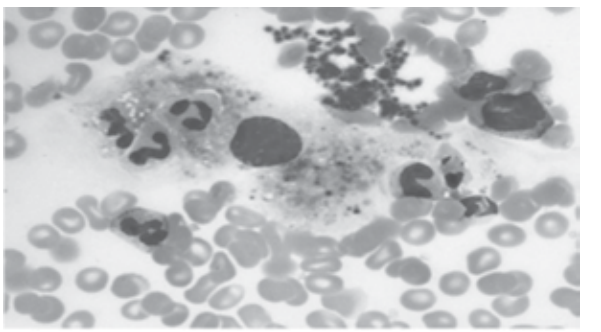

Figure 2. Bone Marrow showing hemophagcytes

from highly toxic immunosuppressive and cytotoxic treatment used in primary HLH. Leishmanisis must be included in the differential diagnoses of pyrexia of unknown origin especially in endemic area. Repeated bone marrow aspiration, splenic aspirate blood cultures and serological analysis can contribute to the diagnosis. Initial bone marrow examination may often yield negative results. In such cases splenic aspirate may help to confirm the diagnosis[7], but the bone marrow finding is the gold standard for diagnosis. Antiprotozoal treatment is the therapy of choice in secondary HLH caused by VL in most cases. Pentavalent antimony salts and amphotericin B are most frequently used in the treatment of VL in children. Meglumine antimoniate treatment in our patient led to almost complete recovery in the first admission. Resistance of Leishmania to pentavalent antimony salts is increasingly becoming a significant problem[8]. In such cases, use of amphotericin B and its liposomal formulations is recommended due to lower toxicity and shorter duration of treatment[9]. Additionally, amphotericin B lipid formulation is superior to antimony salts in secondary HLH because lipid-associated amphotericin B is taken up by macrophages and targets the drug to the site of infection, leading to very high concentrations in the liver and spleen. Use of intravenous immunoglobulins (IVIG) in VL associated HLH has been reported to have variable benefits and is probably related to the delay in initiation of therapy[10]. Hyperferritinemia implies the ongoing macrophage

activation, and additional therapy with IVIG, guided by clinical judgment, is warranted[11]. Some case reports have shown and found the successful use of etoposide[12]. However, the use of steroids and etoposide may be at times showing untoward results, especially in conditions when tuberculosis, malaria or VL might are the exacerbating factors for HLH[13].

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