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Case Report

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Kala-Azar Disease in A 5-Month-Old Male, A Case Report and Review of the Literature

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ABSTRACT

Background: Kala azar is a chronic parasitic disease which is prevalent in children such as adults, however, the number of in detail reports about the clinical manifestations, diagnostic methods and the treatment options in small babies are very limited. In this study, an under 6- month- old male and his characteristics have been described.

Case presentation: A five month and 6 days male has admitted to the pediatric ward, because of 12 days' fever, anorexia, weight loss and weakness. His physical examination findings included malaise and splenomegaly. Remarkable results in his laboratory tests have contained pancytopenia, negative results of all the performed related cultures and serologic tests. The diagnosis has been made by observing the bone marrow smear which included lots of Leishman body as extracellular and intracellular parasites within macrophages. He has responded to daily 3mg/kg Amphotericin B Liposomal for 7 doses as cumulative doses of 21mg/kg without occurring any adverse reactions or recurrence.

Conclusion: It sounds that the clinical presentation, diagnosis and treatment protocols for Kala azar disease in infants should be more studied and reported because of the several challenges this age group of children confronted to, such as different combinations of clinical presentations, diagnostic methods as well as therapeutic protocols.

Keywords: Kala azar; Infant; Amphotericin B liposomal; Diagnosis

INTRODUCTION

Kala-azar, Visceral Leishmaniasis (VL) or "black fever", is a zoonosis disease caused by protozoan parasites of the genus Leishmania. It is the most severe form of leishmaniasis and, is associated with high rate of morbidity and mortality if left untreated. The parasite is transmitted to humans through the bite of a sand fly, primarily infects the reticuloendothelial system and usually is found in the bone marrow, spleen, and liver. The incubation period is usually two to six months but may range from 10 days to few years [1-3]. The clinical manifestations of the disease include fever, hepatosplenomegaly, weight loss, pancytopenia and hypergammaglobulinemia [3-7]. It is a chronic disease which can cause various hematologic manifestations [1,3,4,6,7]. Dog and Canidae family considered as main reservoirs and different species of sandflies such as Phlebotomus major is the main vector for VL in Iran [7,8]. The specious which is common in Iran is leishmania Infantum [7-10]. Demonstration of parasites in a smear or culture of aspirate from spleen, bone marrow, or lymph node is required to confirm the diagnosis. During the last decade, Direct Agglutinin Test (DAT) has been used extensively for conducting sero-epidemiological studies of VL in human and animal reservoirs in

various parts of Iran, particularly in the endemic regions, considering the high sensitivity (96%) and specificity (95%) of the test [1,8]. Alternatively, serological evidence in a patient with recent onset of febrile splenomegaly in endemic areas will suffice [1]. It seems that the disease is not common in infancy, specially under 6- month- old infants. In this article, a 5- month- old male involved with the disease and his treatment presented.

CASE PRESENTATION

The case was a 5- month 6- day old male admitted to the pediatric ward with a history of prolonged fever. He was born in an Afghan family in Tehran. His chief complaint was 12 days' fever which occurred mostly in the evening, however, in the day time it was not prominent. The fever was detected by thermometer once in a clinic (Temprature: 38°C), however, the mother hasn't access to a thermometer at home for measuring the baby's temperature. During the feverish period, the patient has lost his appetite and had a weight loss of almost 500 grams. He was conscious and fully oriented, without any lethargy, agitation but with malaise and lassitude. There was no history of nausea, vomiting, diarrhea, coryza or coughing during the period. He was feeding with formula and his vaccination history was complete. His birth weight was 3600 grams and he was the fourth baby of the family. His weight was 6600 grams at the admission. There was no history of recent travel or fever among the family. His family have lived in a dirty and contaminated place somewhere in suburb of Tehran which has covered with lots of rubbish, stagnant waters, lots of mosquitos including sandfly as well as stray dogs.

In drug history, only Acetaminophen and Ibuprofen were used by the patient, with no history of antibiotics consumption. His vital signs at the admission included: T:36.9° C, RR:33/minute, PR: 105/minute and Oxygen (O_2) saturation: 95%. The only abnormal finding in his physical examination was splenomegaly which the spleen was palpable 2 cm below the rib edge in left midclavicular line. The Laboratory tests were as following: Complete Blood Count (CBC): White Blood Cells (WBC): 3600, Neutrophil: 26%, Lymphocyte:71%, Monocyte:2%, Eosinophil:1%, Hb: 8gr/dl, Hct:24%, RBC: 3.4 million cells/ µL, Platelet: 48000/ µL, Erythrocyte Sedimentation Rate (ESR):62, C-reactive protein (CRP): 89, Reticulocytes: 0/8%, Lactate Dehydrogenase (LDH):1232 U/L (135-750), Total protein: 5.2 g/dl (6-8.3 g/dl), serum Albumin: 3.61g/dl (2.8-4.3 g/dl), D-dimer: >5000 ng/ml, serum Ferritin: 1027 ng/mL (50-200 ng/mL). Liver function tests, Blood Urea Nitrogen (BUN), Chromium (Cr), Sodium (Na) and potassium (K) were in normal ranges. Prothrombin Time, Partial Thromboplastin Time, and International Normalized Ratio all were in normal ranges. His serum Immunoglobulins included: IgM:187 mg/dl (40-150 mg/dl), IgA: 32 mg/dl (0-83 mg/dl), and IgG: 1405 mg/dl (700-1405 mg/dl).

The serologic tests including Wright, Coombs Wright, 2ME, and Vidal were negative. Blood culture, urine culture and stool culture results were negative. Moreover, Covid, Parvovirus, Tuberculosis and Influenza Polymerase Chain Reaction (PCR) tests were negative. Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Human Immunodeficiency Viruses (HIV), Hepatitis A, B, C viruses and Toxoplasmosis ab tests all had negative results. In peripheral blood smear, mild neutropenia with toxic granulation inside neutrophil were seen. Moreover, no parasite like Malaria or Borrelia was seen in the thick or thin smear of blood. Chest x ray was normal. Abdominal and pelvic ultra-sonography just has shown echogenic parenchymal echo pattern and splenomegaly (90 mm diameter in size) without any cystic or solid space-occupying lesion. Because of documentation of fever during his admission, plus loss of appetite, weight loss, anemia, mild neutropenia, thrombocytopenia and splenomegaly, broad spectrum antibiotics including Cefotaxime and Vancomycin were initiated for the patient and a pediatric hematology consultation has ordered.

Despite necessity of performing bone marrow aspiration for obtaining related cultures, unfortunately his father hasn't signed the informed consent for the test. After 3 days, the patient still was suffered from fever and anorexia. Therefore, cefotaxime has changed to Meropenem. After 7 days of his admission at the hospital, because of no response to antibiotics and negative results of his cultures, a pediatric hematology consultation has ordered again. At last, his father has signed the informed consent which resulted in his son's bone marrow aspiration for providing marrow cultures for Brucellosis, Typhoid fever, Atypical Mycobacteria and Tuberculosis; the results of all of the cultures were negative. Besides, the bone marrow smear has observed for Leishman body. The Smear has shown lots of Leishman body extra and intra macrophages (Figure 1&2).

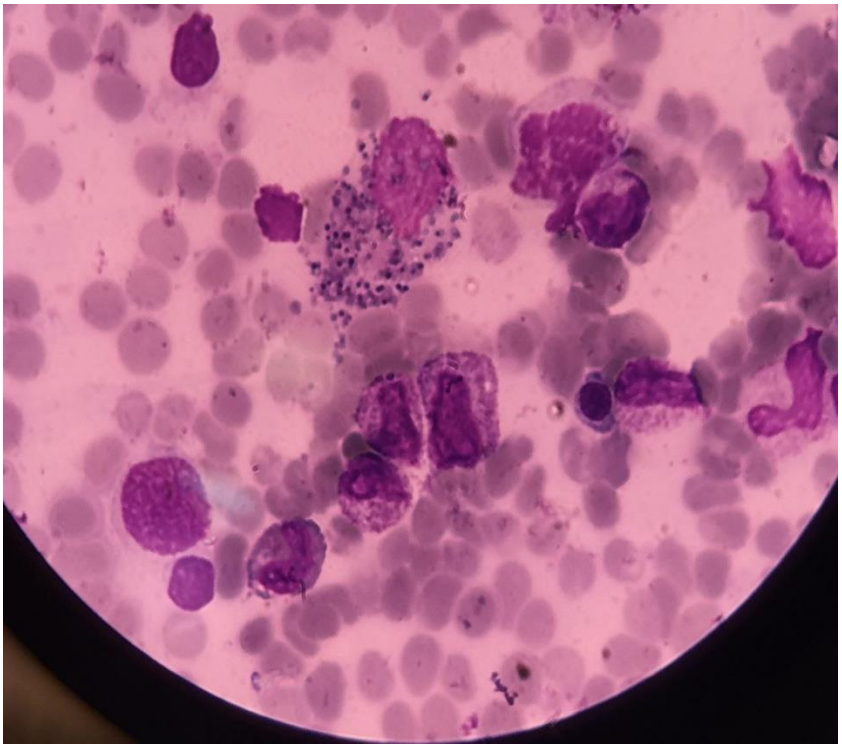

Figure 1: Amastigote forms of Leishmania in our patient's Giemsa-stained bone marrow smear. 400x magnification.

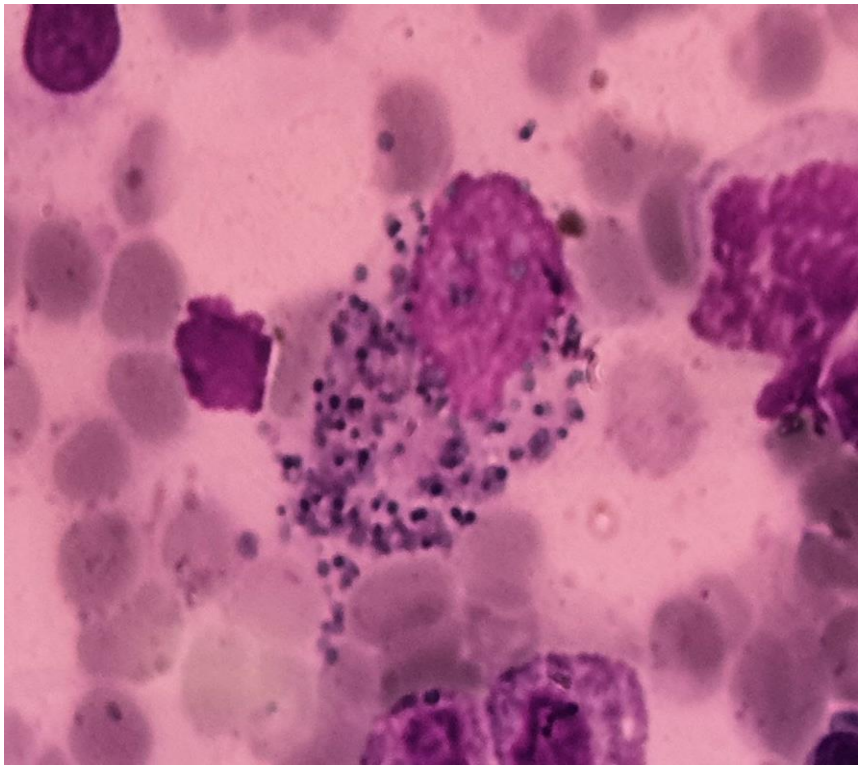

Figure 2: Amastigote forms of Leishmania in our patient's Giemsa-stained bone marrow smear. 1000x magnification.

A serologic test Indirect Immune Fluorescence assay (IFAT), the only serologic test for Kala azar disease available in our reference laboratories' group for visceral leishmaniasis was ordered in the patient which the antibody titer reported 1/64 (up to titer 1/128 was normal). For rule outing congenital Kala

azar in the patient, the mother was interviewed and has been undergone a thorough physical examination. The findings were all unremarkable. Furthermore, CBC, ESR and CRP plus a serologic test for Kala azar were performed in her which the results were as follows: CBC: WBC: 4000/ul, Polymorphonuclear: 55%, Lymphocyte: 39%, Monocyte: 3%, Eosinophil: 3%, Hb: 12.8 g/dl, Hct: 38.8%, MCV:85.7, MCH: 28.3, MCHC: 33, RDW:12.9, Platelet:212000, ESR: 12, CRP: 3.2, Kala azar Ab titer: 1/16 (up to titer 1/128 was negative). After observing Leishman body in the patient's bone marrow smear, the specific treatment has been started.

Unfortunately, Miltefosine, an oral specific drug for Kala azar, was not accessible in Iran, therefore treatment with a protocol included Intravenous Amphotericin B Liposomal 3mg/kg per day initiated for the patient and primarily continued for 5 days [6,7,9,11-14]. Control of vital signs as well as Electrocardiogram (ECG) monitoring have been performed during the drug infusion and then every 4 hours after ending the daily infusion. Serum BUN, Cr, Na, K, Mg, Ca, glucose, liver function tests and Bilirubin has been checked in the patient every other day and in the 14th and 21st days after initiating the specific treatment. The patient's CBC, ESR, and CRP have been checked in the 6th, 14th and 21st day of initiating the specific treatment. After 3 days of starting the drug, the patient became afebrile and his appetite improved. After 5 days, his spleen was not palpable. No adverse effects consisted mostly of infusion site's local reactions, electrolyte disorders, nephrotoxicity or arrhythmias were recorded in the child. Afterwards, the patient has discharged without any drug.

At 14th day of initiating specific drug, he came back for receiving the sixth dose of Intravenous Amphotericin B Liposomal 3mg/kg. His CBC was as follows: WBC:7000, Polymorphonuclear: 26%, Lymphocyte: 70%, Monocyte: 2%, Eosinophil: 2%, Hb: 11.2 g/dl, Hct:33.8%, MCV: 75, MCH: 24.9, MCHC: 33.1%, platelet: 293000, RDW:16.3 (10.5-14.5), CRP: 39.8, and ESR: 52. During his post-discharge period, he was afebrile and his appetite has become normal. His weight was 7050 grams. His last admission for receiving the 7th dose of Intravenous Amphotericin B Liposomal 3 mg/kg was performed at 21st day of initiating specific treatment. His last CBC was as follows: WBC:10900, Polymorphonuclear: 23%, Lymphocyte: 70%, Monocyte: 3%, Eosinophil: 4%, Hb: 11.4 g/dl, Hct: 34.2%, MCV: 75, MCH: 24.9, MCHC: 33.1%, platelet: 321000, RDW: 17.5(10.5-14.5), CRP: 9.0, and ESR: 48. During this post-discharge period, he was still afebrile. His weight was 7300 grams. The patient has been recommended to come back 2 weeks later for the next follow up visiting. At that visit (5 weeks after initiating specific drug), his growth and development were normal. He was still afebrile and his physical examination as well as review of systems were normal. His weight was 7600 grams. His CBC, ESR and CRP all were in normal ranges. At the last follow up visit of the baby (performed 6 months after ending the treatment) when he was 13 months, he was completely well with normal growth and development. His weight was 10,200 kg. His review of system and physical examination results were normal.

DISCUSSION

Visceral Leishmaniasis is a chronic parasitic disease which transmitted by the insect vectors which are species of sandfly. In Iran, most of the cases are sporadic in the areas like Tehran that the disease is not endemic [9]. In this study, a 5-month-old male admitted to our ward, because of 12 days' remittent fever, anorexia and weight loss, malaise, lassitude, and splenomegaly was described. In his laboratory tests, he had showed anemia, thrombocytopenia and mild neutropenia. The results of all the serologic tests, blood and bone marrow cultures were negative. In smear of his bone marrow, lots of intra and extra macrophages amastigote were seen. In our knowledge, this case was the fifth infant and the third under 6- month- old baby has been reported in the literature. Four other cases reported as infants included a four-month-old male, a five-month-old female, a 9-month-old male, and a 10-month-old male [15-18]. Despite it sounds that Kala azar is prevalent in childhood, according to the reports from different parts of the world including Iran, just a few studies have mentioned the characteristics of the involved babies especially in infancy, their specific diagnostic tests or their response to the specific treatments [3,9,12,13,15-19].

Furthermore, several studies including a World Health Organization (WHO) study reported the most frequent clinical manifestations of the Kala azar in the involved babies as fever, splenomegaly, anemia or pancytopenia, weight loss or malaise similar to our case, however, hepatomegaly hasn't occurred in the case in contrary to other studies [1,3-7,13-16,19]. In present study, the disease has been diagnosed by observing the parasites in the smear of the case's bone marrow smear. The only serologic test was available in our reference laboratories was IFAT which became negative for Kala azar antibody in the case. In other reported four cases, two cases have been diagnosed by bone marrow smear, one case by PCR for detecting rK39 and the last case by Indirect Immune Fluorescence Assay (IFAT) [15-18]. It is noteworthy that it sounds bone marrow

smear is still a gold standard test for diagnosing Kala azar in infancy, despite the procedure is aggressive, needs the parents' informed consent, and obtaining the sample and interpreting the smear require lots of professional skills and expertise.

On the other side, performing serologic tests for diagnosing the disease although is cheaper, safer, and easy to use, their accuracy depends on lots of factors like the endemic region, the antigen used, and the age and immunity condition of the patient; Besides, they are not available everywhere [20]. Another challenges for Kala azar in infants are treatment options, because lots of different drugs and protocols introduced by authorities, however, all of the drugs are not available in different endemic regions. Moreover, some of the drugs are very expensive or difficult to obtain, and their effectiveness or adverse reactions are not cleared extensively in lots of small babies.

For example, Pentavalent antimony, Paromomycin, or Miltefosine are not available in Iran. Amphotericin B Liposomal vials are very expensive and hard to find, and the adverse reactions to the drug in infants have not been scrutinized in detail. Though, there are several protocols for consuming the drug in different doses and duration, based on an approved successful protocol in some reports, the seven doses of the drug as mentioned in the article previously has been prescribed [6,7,9,11-14]. Despite a few adverse reactions such as local reactions including thrombophlebitis in the infusion area, serum electrolytes disorders such as hypokalemia, elevation in liver function tests, GI symptoms such as abdominal pain or distension as well as vomiting, arrythmia or nephrotoxicity documented in a few case series following the Amphotericin B Liposomal infusion, fortunately, our patient has confronted with none of them like the results of a case series in Turkey [12-14,21].

CONCLUSION

Actually, the case was the third case of Kala azar reported in under 6- month age babies in the literature. Despite it sounds a rare disease in this age group, the true incidence of the disease is not clear, because it is difficult to diagnose, treat, or control due to their deceptive or evasive nature, making them elusive threats, so-called the disease named a trickster one. The term highlights the disease's ability to hide, appear in different forms, or present subtly, requiring clever strategies to overcome. Therefore, the disease should be considered especially in endemic area when an infant complaint of prolong fever, weight loss, pancytopenia and splenomegaly with regards to unhealthy family location for residence. Besides it is recommended reporting the clinical manifestations, diagnostic methods with emphasis on serologic tests, and different therapeutic protocols which are effective, accessible, safe and easy to afford in infancy.

DECLARATION

Conflicts of interest

The author declares no conflict of interest.

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Authors' contribution

The author solely contributed to the conception, design, analysis, and writing of this manuscript and approved the final version for publication.

Ethical approval

This article does not contain any studies with human participants or animals performed by the author. Ethical approval was not required for this study.

Patient consent for publication

Written informed consent for publication of the case report and any accompanying images, without any potential identifying information, was provided by the parents of the patient.

Data availability

Not applicable.

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