Original Article

Visceral Leishmaniasis: A Cause of Pyrexia of Unknown Origin

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ABSTRACT

OBJECTIVE: To determine the cause of pyrexia of unknown origin.
STUDY DESIGN: Cross-sectional study.
SETTING: The subjects for this study were enrolled at the private setup in northern areas of Gilgit and Hyderabad from January 2006 to December 2007.
METHOD AND MATERIAL: All patients presenting with pyrexia unresponsive to antibiotic and antimalarial therapies with negative serology for salmonella, malaria, tuberculosis and brucellosis underwent bone marrow aspiration. The specimens were analyzed at Armed Force Institute of Pathology (AFIP) Rawalpindi and Department of Pathology, Liaquat University of Medical and Health Sciences (LUMHS) Jamshoro. Patients were treated on the basis of microscopic findings and observations were recorded.
RESULT: Among total 77 subjects 72 (98.51%) were of <8-years age and 5 (6.49%) were of 8-25 years age. Males were 53 (68.83%) and females were 24 (31.17%). Microscopic examination reported all 77 specimens as amastigote positive. Subjects became symptom-free after anti-leishmaniasis therapy.
CONCLUSION: Patients belonging to the Northern areas and Azad Kashmir living anywhere in Pakistan, not responding to antibiotics and antimalarial treatment with negative serology for salmonella, brucellosis, tuberculosis and malaria should be considered for visceral leishmaniasis and be investigated and treated promptly.

KEYWORDS: Pyrexia; Bone marrow; aspirate; Amastigote; Leishmaniasis.

INTRODUCTION

Visceral leishmaniasis occurs globally and is disproportionately common in Horn of Africa, South Asia and Brazil.[3,4] Although cutaneous leishmaniasis is more common in Pakistan, visceral leishmaniasis is endemic in Azad Kashmir, NWFP and areas of Punjab adjoining Azad Kashmir and NWFP [6]. Cases have also been reported from Sindh province.[7] Visceral leishmaniasis is an infectious disease characterized by irregular fever, hepatosplenomegaly, generalized weakness and emaciation with anemia, leucopenia and thrombocytopenia. It is predominantly a disease of childhood, insidious in origin, slow in development and fearful in effects. Bone marrow examination is a reliable method for diagnosis of visceral leishmaniasis with a sensitivity of 60-85%.[8]

Visceral leishmaniasis is a disease of major public health importance leading to severe morbidity and mortality up to 90%, if remains untreated. Being such a dreadful but treatable disease, physicians need to remain aware of the clinic-haemotological features of the disease for early diagnosis and prompt treatment. This becomes even more important keeping in mind the frequent and fast traveling in this modern age.[9]

The aim of this study was to present clinical and hematological features of visceral leishmaniasis in patients from Northern Pakistan referred to and diagnosed over a period of Three years at Armed Forces Institute of Pathology, Rawalpindi and Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro.

MATERIAL AND METHODS

This cross-sectional study was carried out from January 2006 to December 2009, at two places – northern areas of Gilgit and Hyderabad, Sindh. Regardless of age and sex, cases of pyrexia unresponsive to antibiotic and antimalarial therapies for two months with negative serology for salmonella, malaria, tuberculosis and brucellosis were included in this study after obtaining an informed consent. Bone-marrow aspiration was carried out in all study subjects. Specimens of the subjects from northern areas of Gilgit were sent to Armed Forces Institute of Pathology (AFIP) Rawalpindi. Subjects presented at Hyderabad actually belonged to northern areas and had recently visited there. The bone-marrow specimens of these subjects were sent to Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro. All subjects diagnosed as amastigote positive by microscopic examination. The subjects were then treated by anti-

leishmaniasis therapy and after that they became symptom free.

RESULTS

Among total 77 study subjects 70 (90.91%) presented at northern areas of Gilgit and 7 (9.09%) at Hyderabad, Sindh. The baseline characteristics of the study subjects are detailed in **Table I**.

Regarding laboratory parameters only 15 (19.48%) cases had Hb 9-11 g/dl, 54 (70.13%) cases had low RBC count, 11 (14.29%) cases had low WBC count, 20 (25.94%) cases had low platelet count, 31 (40.26%) cases had high reticulocyte count. The details of laboratory parameters is presented by **Table II**.

TABLE I: BASELINE CHARACTERISTICS (n=77)

Characteristics	Number of patients	Percentage
AGE		
1.6 to 8	72	93.51
8-25	5	6.49
Gender		
Male	53	68.83
Female	24	31.17
Fever	77	100
Spleenomegaly	77	100
Hepatomegaly	68	88.31
Pallor	67	87.01
Abdominal disturbance	51	66.23
Lymph Adenopathy	31	40.26
Bleeding	15	19.48

TABLE II: LABORATORY PARAMETERS (n=77)

Laboratory Parameters	Number of patients	Percentage
Hb		
3-6 gm/dl	13	16.88
6-9 gm/dl	49	63.64
9-11 gm/dl	15	19.48
RBC		
1.5-3*10 ^{9}/L	54	70.13
3-5.2*10 ^{9}/L	23	29.87
WBC		
1.5-4*10 ^{9}/L	11	14.29
4-7*10 ^{9}/L	50	64.94
7-11.50*10 ^{9}/L	16	20.78
Platelet Count		
4-70*10 ^{9}/L	21	27.27
70-90*10 ^{9}/L	23	29.87
90-117*10 ^{9}/L	33	42.86
Reticulocyte Count		
2-5%	9	11.67
5-11%	37	48.05
11-20%	31	40.26
Polymorph		
5-20%	13	16.88
20-35%	46	59.74
35-50%	18	23.38
Lymphocyte		
.44-65%	12	15.58
65-85%	41	53.25
85-90%	24	31.17
ESR at the end of 1st Hr		
22-35	15	19.48
35-65	30	38.96
65-90	32	41.55

DISCUSSION

Visceral leishmaniasis is endemic in 62 countries with World Health Organization estimates of 500,000 cases of visceral leishmanisis occurring each year.[10] The disease mainly affects children, although adults may also be infected.[6,11-13]. In our study more than 93.5% were children upto 8 years of age and only 5 (6.49%) adults diagnosed as visceral leishmaniasis.

Visceral leishmanisis is a chronic inflammatory disease characterized by fever, Hepatomegaly, pancytopenia, and wasting. However at times patients with visceral leishmaniasis may not have the typical clinical features.[14] All the patients in this study had history of fever and splenomegaly. Hepatomegaly and pallor were present in majority and abdominal disturbance, lymphadenopathy and bleeding were relatively less common.

Splenomegaly was present in all the patients at the time of diagnosis. In 19 patients it was massively enlarged and extended upto iliac fossa. As the disease involves reticuloendothelial system of the body, spleen is an initial site for the generation of cell mediated immune response. However ultimately it becomes a site of parasite persistence with associated immunopathological changes. The progressive development of splenic pathology is largely associated with high levels of TNF and interleukin (IL)-10.[15]

All patients in our study had fever; the pattern of fever was persistent but irregular. The presence of fever is usually related to stimulation of the body's immune response. Fever can support the immune system's

attempt to gain advantage over infectious agents and it makes the body less favorable as a host for replicating organisms which are temperature sensitive. However, prolonged fever may result in cellular stress, infarctions, necrosis, seizures and delirium.

Lymph node enlargement was present in 40% patients, 98.5% of whom had lymphadenopathy localized only to cervical region. Other studies have also shown minimal involvement of lymph nodes.[5,12,16,19] Although bleeding diathesis, gastrointestinal complaints and cough are occasionally reported.[18]

Jaundice with grossly deranged liver functions tests and acute renal failure are considered bad prognostic signs.[17,18] Malaria, typhoid fever, tuberculosis, lymphoma and leukaemia should be considered in all patients presenting with fever, hepatosplenomegaly and haematological disorders. Pancytopenia is the most consistent haematological finding in patients with visceral leishmaniasis.[19] Pancytopenia is defined as haemoglobin <10g/Di absolute neutrophil count <1.5x10^9/l and platelet count <100x10^9/l.[19] There is usually neutropenia with lymphocytosis.[12] ESR was raised in 100% of cases and in more than 70% cases it was more than 50mm fall at the end of first hour. Rise in ESR is due to chronic nature of illness associated with hypergammaglobulinemia, hypoalbuminemia and altered albumin/ globulin ratio.[20,21] Formol gel test used to be performed previously had the same basis. In 5.16% visceral leishmaniasis cases, reteculocyte count is either normal or raised. Blood count in this study are comparable to the study carried out by Altaf et al.[5] Hematologic parameters are characteristic for visceral leishmaniasis on the basis of which diagnosis can be readily established being confirmed by other tests.[22] Several advanced sophisticated and costly sera diagnostic tests are available to diagnose visceral leishmaniasis which are beyond the reach of a standard/field clinical diagnostic laboratory especially in under developed countries like ours where diagnosis is established by demonstrating the parasite (LD bodies) in stained smears of bone marrow. [23,26]

Visceral leishmaniasis is endemic in northern areas of Pakistan and represents a severe public health problem. Any patient from endemic area with fever, anemia with hepatosplenomegaly and pancytopenia associated with normal or high reticulocyte count must be subjected to bone marrow examination to rule out possibility of leishamania infection. The disease has been eradicated successfully from some areas of the world.[27]

Strong commitment is required to formulate a control strategy to eradicate the deadly disease by a combination of approaches like early recognition, treatment, and control of vectors and health education of the population.[28]

In study of Rai Manzoor Alahi 2008 et al majority of the patients (98.57%) presented with fever followed by abdominal distension (47%) Pallor, (44%) weight loss (43%) diarrhea (17%), vomiting (15%) and epixtasis (8%). Hepatosplenomegaly was found in about 83% along with lymphadenopathy (20%) purpura (13%) and peripheral oedema (11%). Laboratory findings revealed anaemia in all the cases followed by neutropenia in 43%, lymphocytosis in 86% with thrombocytopenia in 79%. Bone marrow in most of these cases showed myeloid hyperplasia with increased magakaryocytosis.[29]

Gani Zaniab et al showed that out of 146 suspected visceral leishmaniasis cases, 124 (84.9%) were proved by the examination of bone marrow aspirate, 132 (91.1%) were positive by direct agglutination test (DAT) and only 3 (2%) were positive by immunochromatographic strip test. The sensitivity and specificity of DAT were (100%).[30]

CONCLUSION

Visceral leishmaniasis is endemic in northern areas of Pakistan and majority of the patients are children. Splenomegaly, persistent irregular fever and pancytopenia are the consistent clinico-haemotological features of these patients. Patient not responding to antibiotics and antimalarials should be investigated for visceral leishmaniasis.

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