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VISCERAL LEISHMANIASIS AS FEVER OF UNKNOWN ORIGIN

GH. R. OMRANI, A. FARHADI, A. PARHIZGAR, S. ARDEHALI*, M. HAGHSHENAS

*From the Departments of Internal Medicine and * Microbiology, Medical School, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran.*

ABSTRACT

Visceral leishmaniasis is the second most common cause of fever of unknown origin in our study. This disease is not common in adults, although it's endemic among the pediatric age group. The majority of the affected individuals were young. High grade spiking fever, chills and splenomegaly were unique findings. Other common findings were neutropenia, anemia, abnormal liver function tests, sterile pyuria and microscopic hematuria. Except for 1 case, parasites were absent from tissue biopsies (e.g. bone marrow, liver, lymph node). Diagnosis was suggested by indirect fluorescent antibody (IFA) and confirmed by response to meglumine antimonate (Glucantime) and decline of IFA titer on follow-up.

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INTRODUCTION

Visceral leishmaniasis (VL) is endemic in Fars and East-Azarbaijan provinces and sporadic in the other parts of Iran; 96.5% of the cases in endemic foci are children under the age of 8 years.[1] The disease is quite uncommon in the adult population; and approximately half of affected adults have an unusual presentation of the disease intriguing the diagnosis. Till recently VL was not encountered among the common causes of fever of unknown origin (F.U.O.) in our hospitals. Detection of VL as a common cause of F.U.O. in adult patients will make our physicians more aware with VL and this could lead to early pick-ups of VL and avoidance of many unnecessary work-ups on these patients.

MATERIALS AND METHODS

In a 5 year prospective study, we gathered 66 cases of F.U.O.. Our patients were selected from all adult febrile patients who were admitted to one of the Shiraz University related hospitals and fulfilled the criteria of Petersdorf and Beeson[2] which included duration of the disease for more than 3 weeks, documented fever greater than 38.3°C on several occasions and a non-revealing diagnosis after 1 week of in-hospital study.

The diagnosis of visceral leishmaniasis was suggested by indirect fluorescent antibody (IFA), which was regarded positive when titers exceeded 1/128.[3,4] Confirmatory data for diagnosis was obtained by complete response of clinical and laboratory parameters with a course of therapy with meglumine antimonate (Glucantime). The drug was administered at the dose of 500mg as pentavalent antimonate compound (142mg base) in two intramuscular injections each day for a total of 30 days. The clinical responses included complete defervescence and shrinkage in splenic size, and laboratory responses were normalization of any abnormal complete blood count, urinalysis and liver function tests (LFTs), and a decrease in IFA titer. Bone marrow aspiration and biopsy were performed in all patients and liver biopsy in 3 patients, in a search for leishmania amastigotes.

Table I: Clinical Data in VL.

Case No	Age	Sex	Disease Duration	Hospital Stay	Pattern of fever	Symptoms	Signs	Response to trial
1	21	F	3 mo.	70 days	Hectic	Chills headache vomiting dry cough sore throat	Splenomegaly pallor flank tenderness	3 days
2	16	F	1.5 mo.	40 days	Hectic	Chills headache	Splenomegaly lymphadenopathy hepatomegaly	2 days
3	26	M	1.5 mo.	15 days	Inter-mittent	Chills headache anorexia vertigo	Splenomegaly axillary lymphadenopathy	10 days
4	35	M	1.5 mo.	15 days	Hectic	Chills vomiting dry cough sore throat	Splenomegaly	5 days
5	18	F	1 mo.	17 days	Hectic	Chills headache vomiting jaundice skin rash	Splenomegaly hepatomegaly generalized lymphadenopathy skin rash	8 days
6	37	M	1 mo.	15 days	Hectic	Chills headache arthralgia	Splenomegaly pallor	13 days

RESULTS

As in shown in Table I, all the affected patients were young with a mean age of 25 years. All were healthy prior to their present illness except for one patient (case no. 6) who had chronic renal failure and had undergone renal transplantation 9 months prior to admission. All of the patients had high grade spiking fever accompanied with true shaking chills and sweating. Headache was common. Other symptoms included pallor, significant weight loss, GI upset, sore throat, jaundice and generalized body pain. Splenomegaly was present in all patients and other physical findings included lymphadenopathy (3 cases), pallor (2 cases) and hepatomegaly (2 cases).

Results of paraclinical workups of these patients are shown in Table II, and included anemia (5 cases), leukopenia (4 cases) abnormal LFT (4 cases), pyuria (4 cases) and microscopic hematuria (3 cases). No leishman bodies were detected in the bone marrow examination smears even after re-evaluation in any of the patients. The only finding in the bone marrow examination was a shift to the left in 2 cases.

Liver biopsy was performed in 3 cases which revealed non-caseating granuloma in all samples. Amastigotes of leishmania were seen in only one of the three biopsies. Splenic aspiration was performed in only 1 patient, which was negative. Lymph node biopsies were done in 2 cases which revealed nonspecific abnormalities.

Other abnormal lab data were positive CRP and rheumatoid factor and a prolonged prothrombin time (PT) in some patients.

IFA for VL was positive (> 1/128) in all cases. Response to therapy was observed from 2-13 days after initiation of treatment with a mean of 6.8 days. All patients were followed for at least 6 months and were in complete clinical and paraclinical remission in follow-ups. Decrease in IFA titers was observed within 6 months after treatment.

DISCUSSION

In this study we gathered 66 cases of fever of unknown origin. 30(45%) patients had infectious disease as the cause

Table II: Paraclinical Data in VL.

Case no.	CBC	LFT	U/A	Bone marrow	IFA Titer	Other abnormal lab data
1	Hb:9 WBC: 2700 Bandemia ESR: 83	SGOT: 52 SGPT: 78 Alk. phosphatase: N	Sterile pyuria	Shift to left	1/128	RF CRP
2	Hb: 10 WBC: 3000 Bandemia ESR: 42	SGOT: 152 SGPT: 40 Alk. Phosphatase: ↑↑	Pyuria Microscopic hematuria Bacteriuria	Shift to left	1/256	-
3	HB: 11.5 WBC: 14000 ESR: 32	SGOT: 6 SGPT: 3 Alk. phosphatase: N	Normal	Normal	1/256	-
4	Hb: 9.3 WBC: 2600 Platelets: 74000 ESR: 52	SGOT: 86 SGPT: 54 Alk. phosphatase: ↑	Sterile pyuria Microscopic hematuria Proteinuria	Dyserythropoiesis	1/256	PT: 16 sec
5	Hb: 9.1 WBC: 6400 ESR: 21	SGOT: 195 SGPT: 144 Alk. phosphatase: ↑↑	Sterile pyuria Microscopic hematuria	Normal	1/256	PT: 17 sec
6	Hb: 9.8 WBC: 2500 ESR: 28	SGOT: 8 SGPT: 13 Alk. phosphatase: N	Normal	Normal	1/512	CRP

of their febrile illness.

Neoplastic disease, collagen vascular disease and miscellaneous disease made up 18%, 17% and 9% of our patients respectively and finally 11% remained undiagnosed. Tuberculosis was the most common cause in the infectious category which was detected in 10 patients (33% of the infectious group). In order of frequency, other infectious causes of F.U.O. in our study were VL (6 patients), intraabdominal abscess (5 patients), typhoid fever (3 patients), bacterial endocarditis (3 patients), biliary tract infection (1 patient), brucellosis (1 patient), and malaria (1 patient).

VL was the second most common cause of fever of unknown origin and comprised 20% of the infectious category. This disease is not common in adults, although it's endemic among the pediatric age group. It's obvious that many cases acquire infection without overt clinical disease in childhood in endemic areas and Badero et al found that subclinical infection with leishmania species is much more frequent than clinical leishmaniasis.[5,6] He also stated that the ratio of infected children to those with clinical leishmaniasis was 18.5:1. This ratio indicates that factors other than exposure to parasite determine progression of the disease. On the other hand, the organism persists and remains viable even in healthy people for a long period.[7] It has also been shown that latent infection can progress to overt disease under the influence of stresses which upset the immunological balance[8] and there are increasing reports of VL in immunocompromised hosts.[7,11] Obviously there was no clue of immunological disturbance in 5 of our patients and all had no problem prior to or after their acute illness. Whether the disease was a newly acquired infection or reactivation of a latent infection, immunosuppression is not an essential background for overt disease in patients in an endemic area.

It is not surprising that VL is not limited to endemic areas of the world. This is due to an increasing number of immunocompromised hosts and a predisposition of immunosuppressed patients to this disease as an opportunistic infection.[7,11] Immunosuppression was present as a predisposing factor in one of our patients. Case number 6 had chronic renal failure, for whom renal transplant was performed and immunosuppressive medication had begun 9 months prior to his febrile illness. It was interesting that from all samples of tissue biopsies only the liver biopsy of

this patient contained parasites surrounded by granuloma formation. Presenceof VL in recipients of kidney transplants had also been reported previously. The causative organism of VL in this region is suspected to be *L. infantum*. Further studies on isolation and characterization of leishmania organisms from adults need to be performed in order to see if the causative organism is indeed *L. infantum* or other species of leishmania.

Although VL is not a well-known cause of fever of unknown origin in the literature, it should be considered in the differential diagnosis of fever of unknown origin, especially in endemic areas.[12,13] It has also been recommended to search for amastigotes of leishmania and to measure antibody titers to this organism in all immunocompromised patients who have ever lived in an area endemic for leishmaniasis and present with F.U.O. unassociated with an enlarged liver and/or spleen.[7,10]

REFERENCES

1. Edrissian GH: Kala-Azar in Iran. Med J Islam Repub Iran. 4: 235, 1990.
2. Petersdorf RG, Beeson PB: Fever of unexplained origin. Report of 100 cases. Medicine 40: 1-30, 1961.
3. Behforouz N, Rezai HR and Gettner S: Application of immunofluorescence to detection of antibody in Leishmania infections. Ann Trop Med Parasit 70: 293, 1976.
4. Behforoz N, Amirhakimi GH, Rezai HR, et al: Immunological findings in Kala-Azar, Iran. Trop Georgraph Med 35: 27, 1983.
5. Badaro R, Jones TC, Lorenco R, et al: A prospective study of visceral leishmaniasis in an endemic area of Brazil. J Infec Dis 154: 639, 1986.
6. Badaro R, Jonest TC, Carvalho EM, et al: New perspective on a subclinical form of visceral leishmaniasis. *J Infec Dis* 154: 1003, 1986.
7. Badaro R, Carvalho EM, Eocha H, et al: *Leishmania donovani*: An opportunistic microbe associated with progressive disease in three immunocompromised patients. Lancet 1: 647, 1986.
8. Ma DDF, Concannon AJ, Hayes J: Fatal leishmaniasis in renal transplant recipient. *Lancet* 11: 311, 1979.
9. Harrison LH, Naidu TG, Drew JS, et al: Reciprocal disease, visceral leishmaniasis. Rev Infec Dis 8: 497, 1986.
10. Fernadez Guerro ML, Aguado JM, Bunzo L, et al: Visceral leishmaniasis in immunocompromised hosts. Am J Med 83: 1098, 1987.
11. Bereguer J, Moreno S, Cercenado E, et al: Visceral leishmaniasis in patients infected with human immune def. virus (HIV). *Ann Intern Med* 111: 129, 1989.
12. Barbado FJ, Vasques JJ, Pena JM, et al: Fever of unknown origin: A survey of 133 patients. J Med 15: 185, 1984.
13. Siegman-Igra Y, Waizbard E, Rubinstein A, et al: Visceral leishmaniasis presenting as fever of unknown origin. Trop Geograph Med 39: 10, 1987.