A Rare Presentation of Leishmaniasis

Ritesh Prajapati*, Ashish Kumar*, Praveen Sharma*, Vikas Singla*, Naresh Bansal*, Shashi Dhawan†, Anil Arora*

*Department of Gastroenterology & Hepatology, Sir Ganga Ram Hospital, New Delhi, India and †Department of Pathology, Sir Ganga Ram Hospital, New Delhi, India

Leishmaniasis or kala-azar is a protozoan disease that can present as cutaneous, mucocutaneous, visceral, and disseminated disease. In India, it is usually localized in distinct areas of Bihar, Jharkhand, West Bengal, and parts of Eastern Uttar Pradesh. Visceral leishmaniasis (VL) involves the visceral organs, mainly the liver, the spleen and bone marrow. VL is characterized by prolonged fever, massive splenomegaly, weight loss, progressive anemia, pancytopenia, and hypergammaglobulinemia, and can be complicated by serious infections. In most of the patient the diagnosis is made on bone marrow biopsy or splenic aspirate. We hereby present an unusual case of kala-azar in a 52-year-old patient non-resident of endemic area presenting with pyrexia of unknown origin, in whom bone marrow biopsy was negative for Leishmanin Donovan (LD) bodies, and diagnosis was made by liver biopsy in which LD bodies were seen. (J CLIN EXP HEPATOL 2016;6:146–148)

Leishmaniasis or kala-azar is a protozoan disease that can present as cutaneous, mucocutaneous, visceral, and disseminated disease. In India, it is usually localized in distinct areas of Bihar, Jharkhand, West Bengal, and parts of Eastern Uttar Pradesh.¹ Visceral leishmaniasis (VL) involves the visceral organs, mainly the liver, the spleen, and bone marrow. VL is characterized by prolonged fever, massive splenomegaly, weight loss, progressive anemia, pancytopenia, and hypergammaglobulinemia, and can be complicated by serious infections. In most of the patient the diagnosis is made on bone marrow biopsy or splenic aspirate.²

We hereby present an unusual case of kala-azar in a patient non-resident of traditional endemic area, presenting with pyrexia of unknown origin (PUO), in whom bone marrow biopsy was negative for Leishmanin Donovan (LD) bodies, and diagnosis was made by liver biopsy, in which LD bodies were seen.

CASE REPORT

A 52-year-old patient, practicing as doctor in a health center in Haldwani, Uttarakhand, India, presented with high-grade fever, without rigors, for last 20 days. There was no history of visit to any usual endemic area of leishmaniasis in near past. There was no history of respiratory, urinary, abdominal or neurological complaints. There was no history of skin rash, animal contact, recent travel or any co-morbidity. Clinical examination showed icterus and hepato-splenomegaly but no lymphadenopathy. The spleen tip was just palpable.

His laboratory parameters were as follows: hemoglobin 10.6 g/dL, WBC $6.5 \times 10^3/\mu\text{L}$ (P: 54, L: 42, E: 2), platelets $100 \times 10^3/\mu\text{L}$, total bilirubin 2.7 mg/dL, direct bilirubin 1.8 mg/dL, AST 194 IU/L, ALT 81 IU/L, ALP 356 IU/L, GGT 378 IU/L, albumin 3.37 g/dL, total protein 8.4 g/dL, normal kidney function test, ESR 96 mm (1st h), and negative Mantoux test. Anemia profile was suggestive of anemia of chronic disease. Peripheral smear for malarial parasite, IgM Dengue serology, routine urine examination, blood culture, urine culture, widal, HIV, HBsAg, and anti-HCV were negative. His IgM Leptospira, Brucella titres, Weil felix reaction, ANA, Rheumatoid factor, and dsDNA were also negative. His 2D-echo was negative for any evidence of infective endocarditis. Chest X-ray was normal and USG abdomen showed grade-1 fatty liver with mild splenomegaly with minimal ascites. CT abdomen with thorax showed features of early chronic liver disease with mild splenomegaly and mild ascites. Etiologic work up for chronic liver disease was negative. Bone marrow examination showed cellular marrow, normal hematopoietic elements, prominent histiocytes, plasma cells, and eosinophils. Positron emission tomography scan showed hepatosplenomegaly with chronic liver disease with diffusely increased marrow uptake with mild ascites.

Keywords: kala-azar, protozoan disease, visceral leishmaniasis, pyrexia of unknown origin, Leishmanin Donovan bodies

Received: 15.11.2014; **Accepted:** 6.01.2016; **Available online:** 14 January 2016

Address for correspondence: Dr. Ashish Kumar, Associate Professor, Department of Gastroenterology & Hepatology, Ganga Ram Institute of Post-graduate Medical Education & Research (GRIPMER), Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110 060, India.
Tel.: +91 9312792573; fax: +91 11 25861002.

E-mail: ashishk10@yahoo.com

Abbreviations: ALT: alanine aminotransferase; ALP: alkaline phosphatase; ANA: anti-nuclear antibodies; AST: aspartate aminotransferase; CT: computerized tomography; E: eosinophils; ESR: erythrocyte sedimentation rate; GGT: gamma glutamyl transferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; L: lymphocytes; LD: Leishmanin Donovan; P: polymorphs; PET: positron emission tomography; PUO: pyrexia of unknown origin; VL: visceral leishmaniasis; WBC: white blood count

<http://dx.doi.org/10.1016/j.jceh.2016.01.001>

Figure 1 Liver biopsy stained with Hematoxylin and Eosin showing numerous L D bodies (arrow) in portal tracts (resolution 400×).

Liver biopsy was done in view of continuous fever, deranged liver function tests and negative work-up for cause of fever till now. Liver biopsy showed extensive portal inflammation and bridging fibrosis, dense lymphocytes admixed with few histiocytes, neutrophils in portal tracts with histiocytes showing many LD bodies in them (Figures 1 and 2). IgG leishmania antibody was 2.9 units (normal <0.9 units). On the basis of liver biopsy a diagnosis of VL was made, and the patient was started on Liposomal Amphotericin B (3 mg/kg on days 1, 2, 3, 4, 5, 14, and 21), following which the patient became afebrile, and his liver function tests returned to normal.

DISCUSSION

Leishmaniasis is a protozoan disease that is categorized into Old World disease (Africa, Middle East, Asia, and the

Figure 2 Liver biopsy stained with Hematoxylin and Eosin showing numerous L D bodies (arrow) in portal tracts (resolution 1000×).

Mediterranean) and New World disease (Central and South America). Bihar, Jharkhand, West Bengal, and parts of Eastern Uttar Pradesh constitute the endemic area. However sporadic cases have been reported from Gujarat,³ Himachal Pradesh and Uttarakhand.^{4,5} Our patient belonged to Uttarakhand, traditionally a non-endemic area. The incidence of disease is increasing in Uttarakhand due to construction activities, horticulture development, and establishment of new residential, large water resources schemes leading to destruction of forests and intrusion into the sylvatic cycle. The laborers employed are mainly from the known endemic areas of Bihar, Jharkhand, Uttar Pradesh, and Nepal.⁶

The VL involves mainly the liver and spleen and bone marrow leading to fever, malaise, weight loss, anemia, pancytopenia and hypergammaglobulinemia.¹ In a study of 100 cases of PUO, infections constituted 53% and visceral leishmania constituted 5%.⁷ Hepatosplenomegaly is a common finding. Patients usually have moderate hepatomegaly and marked splenomegaly. In a case series of 10 patients with VL moderate to marked hepatosplenomegaly was seen in all patients.

The diagnosis of this disease depends on the demonstration of the LD bodies in spleen, bone marrow, lymph node or buffy coat smears. Histoplasmosis is the differential diagnosis on histology. H&E stains the entire protozoan and does not show the halo produced by the fungal cell wall. Kinetoplasts (a hematoxylin-stained bar to the side of the nucleus) are observed in the patient with leishmaniasis, which is absent in histoplasmosis. The cell wall of histoplasma is highlighted with PAS stains.⁸ Bone marrow and splenic aspirates are mostly sufficient for diagnosis. Bone marrow aspiration is a safer, but is a less sensitive method (76%) in the diagnosis of VL as compared to splenic aspiration (95%).^{2,9} Splenic aspirate is associated with risk of fatal hemorrhage in inexperienced hands. Imaging has very minimal role in confirmation of Leishmaniasis other than to rule out other causes of fever mimicking as leishmaniasis. Montenegro leishmaniasis skin test and cellulose acetate electrophoresis (for typing the protozoan species) were used previously. This has been replaced by the new serological test, rK39, and PCR methods to detect the species of infecting organism.^{9,10} Enzyme-linked immunosorbent assay tests with a kine-sin-like antigen, have good sensitivity and specificity for the diagnosis of VL in immunocompetent persons and titers correlate directly with disease activity.¹¹ A rK 39 rapid diagnostic test is a ready to use strip test. According to a recent metaanalysis the rK39 immunochromatographic test has an overall sensitivity of 91.9% and specificity of 92.4%.¹² Persistence of antibodies well beyond cure and inability of some patients to produce enough antibodies are inherent limitations with all antibody-based diagnostics. In a case series of liver biopsies in confirmed leishmaniasis by el Hag et al., parasites were

found only in 44% of liver biopsies.¹³ In liver biopsy, there is hypertrophy and hyperplasia of Kupffer cells, ballooning degeneration is seen in two thirds of patients. Parasites are seen mainly within the Kupffer cells followed by histiocytes in portal tracts.¹³ In our patient parasites were seen only in portal macrophages. Cirrhotic changes has been described in liver biopsy which is not true cirrhosis but diffuse fibrosis isolating small groups of hepatocytes with evidence of regeneration (diffuse intralobular fibrosis).¹⁴ Koshy et al. reported that liver biopsy was diagnostic even when the bone marrow examination did not yield the diagnosis of VL in two adult cases.¹⁵ Khaldi et al. showed hepatic involvement in 16 children in a series of 180 cases of VL over 14 years.¹⁶

Though rare but in a patient of PUO, who is resident of non-endemic area of kala-azar, and in whom bone marrow biopsy is negative, liver biopsy can be useful to diagnose kala-azar as cause of PUO.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

- Oren R, Schnur LF, Ben Yehuda D, Mayner V, Okon E, Rachmilewitz EA. Visceral leishmaniasis: a difficult diagnosis and unusual causative agent. *J Infect Dis.* 1991;164(October (4)):746–749.
- Philips CA, Kalal CR, Kumar KNC, Bihari C, Sarin SK. Simultaneous occurrence of ocular, disseminated mucocutaneous, and multi-visceral involvement of leishmaniasis. *Case Rep Infect Dis.* 2014. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3965941/> [cited on 15.07.14].
- Sharma U, Redhu NS, Mathur P, Singh S. Re-emergence of visceral leishmaniasis in Gujarat, India. *J Vector Borne Dis.* 2007;44(September (3)):230–232.
- Naik SR, Rao PN, Datta DV, et al. Kala-azar in north-western India: a study of 24 patients. *Trans R Soc Trop Med Hyg.* 1979;73(1):61–65.
- Singh S, Biswas A, Wig N, Aggarwal P, Sood R, Wali JP. A new focus of visceral leishmaniasis in sub-Himalayan (Kumaon) region of northern India. *J Commun Dis.* 1999;31(June (2)):73–77.
- Raina S, Mahesh DM, Kaul R, et al. A new focus of visceral leishmaniasis in the Himalayas, India. *J Vector Borne Dis.* 2009;46(December (4)):303–306.
- Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. *J Postgrad Med.* 2001;47(June (2)):104–107.
- Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev.* 2011;24(April (2)):247–280.
- Mittal V, Bhatia R, Sehgal S. Serodiagnosis of Indian kala-azar: evaluation of IFA, ELISA and CIEP tests. *J Commun Dis.* 1991;23(June (2)):131–134.
- Chappuis F, Mueller Y, Nguimfack A, et al. Diagnostic accuracy of two rK39 antigen-based dipsticks and the formol gel test for rapid diagnosis of visceral leishmaniasis in northeastern Uganda. *J Clin Microbiol.* 2005;43(December (12)):5973–5977.
- Ben-Ami R, Schnur LF, Golan Y, Jaffe CL, Mardi T, Zeltser D. Cutaneous involvement in a rare case of adult visceral leishmaniasis acquired in Israel. *J Infect.* 2002;44(April (3)):181–184.
- Boelaert M, Verdonck K, Menten J, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. *Cochrane Database Syst Rev.* 2014;6:CD009135.
- el Hag IA, Hashim FA, el Toum IA, Homeida M, el Kalifa M, el Hassan AM. Liver morphology and function in visceral leishmaniasis (kala-azar). *J Clin Pathol.* 1994;47(June (6)):547–551.
- Duarte MI, Corbett CE. Histopathological patterns of the liver involvement in visceral leishmaniasis. *Rev Inst Med Trop Sao Paulo.* 1987;29(June (3)):131–136.
- Kumar PV, Omrani GH, Saberfirouzi M, Arshadi C, Arjmand F, Parhizgar A. Kala-azar: liver fine needle aspiration findings in 23 cases presenting with a fever of unknown origin. *Acta Cytol.* 1996;40(April (2)):263–268.
- Koshy A, Al-Azmi WM, Narayanan S, et al. Leishmaniasis diagnosed by liver biopsy: management of two atypical cases. *J Clin Gastroenterol.* 2001;32(March (3)):266–267.