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Visceral leishmaniasis: Very rare cases report from Kashmir valley (J&K) with Literature Review

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Abstract
Leishmaniasis is a disease caused by an intracellular protozoa parasite transmitted by the bite of a female sandfly (Phlebotomus species). This vector borne disease has wide clinical spectrum with visceral leishmaniasis being the most severe form. We report a case of visceral leishmaniasis from a Kashmir valley of Jammu and Kashmir (India) where the vector for leishmaniasis does not exist. Only one case of leishmaniasis has been reported from valley. This is the second case, which was reported because of rarity and delay in diagnosis even though it was imported. A 44 Year old male patient presented with intermittent, low grade fever associated with chills and rigors, night sweating for 3 years, took antibiotic and antipyretic, partially responded, was never evaluated properly. Patient had history of travel to outside state. In state like Jammu and Kashmir where tuberculosis is more prevalent visceral leishmaniasis is very unlikely to be diagnosed. On evaluation patient had pancytopenia and hepatosplenomegaly with bone marrow revealing inclusion bodies (LD bodies both intracellular and extra cellular) thus confirming the diagnosis of visceral leishmaniasis.

Keywords: Visceral leishmaniasis, hepatosplenomegaly, LD bodies, Jammu and Kashmir

Introduction
Visceral leishmaniasis also known as kala-azar.[1] Leishmaniasis is a complex group of disorders caused by unicellular eukaryotic obligatory intracellular protozoa of the genus Leishmania and primarily affects the host's reticuloendothelial system and capable of causing a spectrum of clinical syndromes.[2] It is classified as a Neglected Tropical Disease (NTD). The protozoa are transmitted to mammals via the bite of the female sandfly of the genus Phlebotomus. India constitutes 40-50% of disease. Without treatment, the fatality rate reaches 90%. Early diagnosis and treatment reduces mortality to 2–5%. Vector for leishmaniasis does not exist in Kashmir (J&K). Only one case of leishmaniasis has been reported from valley. This is the second case, which was reported because of rarity and delay in diagnosis even though it was imported.

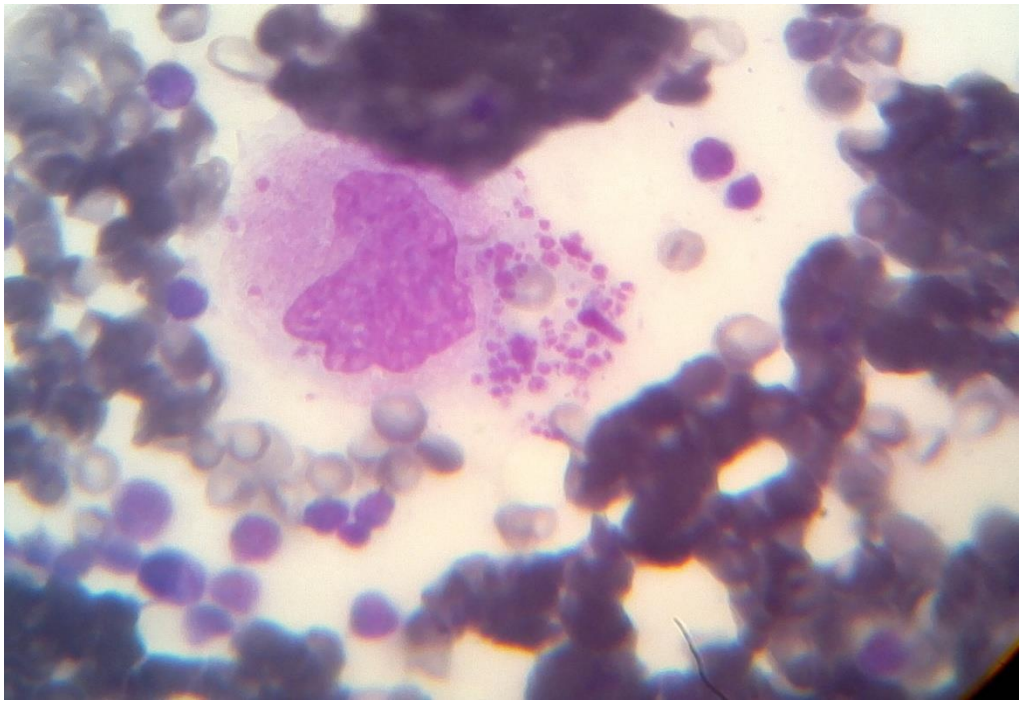
Case Summary
A 44 Year old male from Anantnag (Jammu and Kashmir), Businessman(field worker) by occupation was admitted in the department of gastroenterology on September 2013 with history of fever 3 years (low grade (101 F), intermittent, more during evening, associated with chills and rigors, night sweating), mostly during summer months, took antibiotic and antipyretic, partially responded, was never evaluated properly. Patient had history of travel to outside state for business multiple times (Bihar, U.P, Delhi). There was no history of any systemic infection, transfusion, jaundice, rash, bleeding diathesis, weight loss, anorexia, high risk behavior or animal contact.
Physical of the patient revealed pallor, temperature of 101F, hepatomegaly (3 cms below right costal margin) with liver span of 18 cms and massive splenomegaly (12 cms below left costal margin). Rest general and systemic examination was normal.
Investigations: Complete blood count revealed pancytopenia.

HB	TLC	DLC	PLT	MCV	MCH	MCHC	ESR	RETI
10.4	3.06	N63/L26/E2	56	92	32	34.6	26	3.95
10.2	3.2	64/20	51	94	32	34		

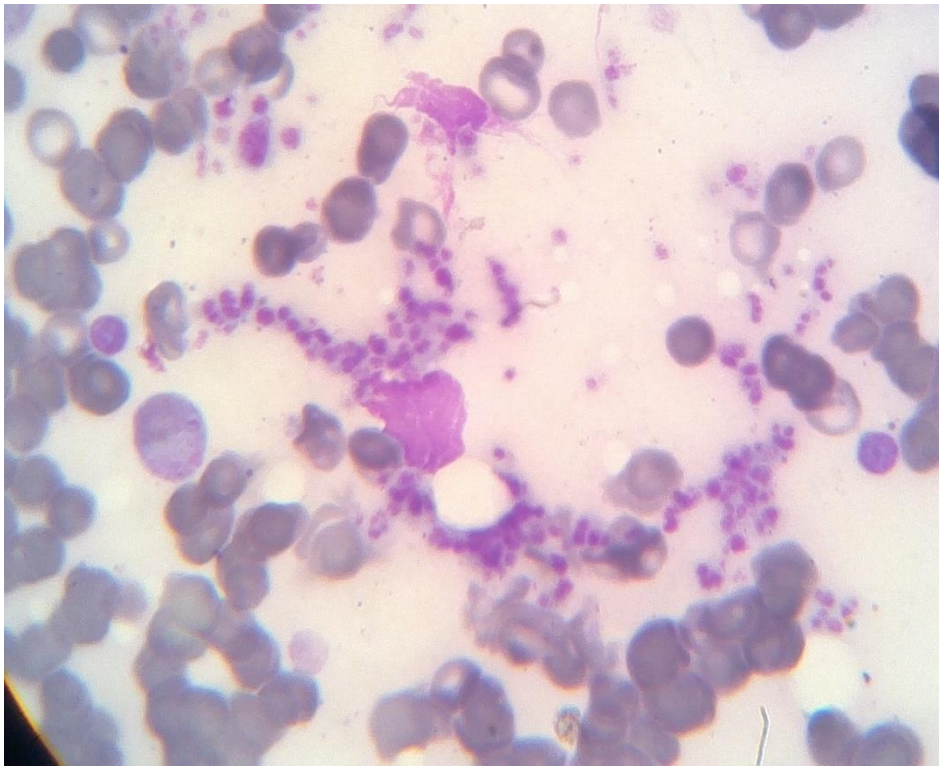
BIL	AST	ALT	ALP	TP	ALB	UREA	CR	LDH	CA
1.6	60	89	110	6.3	3.3	36	1	303	10.2

Lipid profile, urine exam and coagulogram were normal. Electrocardiography was showing normal sinus rhythm. Chest radiography and echocardiography was normal. Ultrasonography was showing massive splenomegaly and mild hepatomegaly. Mantoux, antiretroviral, brucella and widal serology was negative.

Malarial antigen (card test) was negative. Urine and blood culture sensitivity was sterile. PBF was showing no malarial parasite, no leishmania amastagote form seen. Bone marrow revealed cellular marrow, normal erythroid maturation, adequate iron stores, inclusion bodies (LD bodies both intracellular and extra cellular)



Bone marrow picture 1: Demonstrating intracellular LD bodies



Bone marrow picture 2: Demonstrating extracellular LD bodies.

Treatment and follow-up.

With a final diagnosis of Visceral Leishmaniasis patient was to be started on amphotericin B (1mg/Kg) alternate days for a total of 15 infusions but patient lost follow up.

Discussion

Leishmaniasis is a complex group of disorders caused by protozoa and primarily affects the host's reticuloendothelial system and capable of causing a spectrum of clinical syndromes ranging from cutaneous ulcerations to systemic infections.[2] It is classified as a Neglected Tropical Disease (NTD). Currently, leishmaniasis occurs in 4 continents and is considered to be endemic in 98 countries, 72 of which are developing countries. Annual incidence is 500,000 cases of VL. 90% of all VL occur in Bangladesh, Brazil, India, Nepal and Sudan.[3] India constitutes 40-50% of disease. 15538 cases and 47 deaths due to VL were reported by NVBDCP in 2010. In India infection is concentrated in the states of Bihar, West Bengal, Uttar Pradesh, Assam and Jharkhand. The protozoa are transmitted to mammals via the bite of the female sandfly of the genus Phlebotomus in the Old World and Lutzomyia in the New World. Humans are generally considered incidental hosts.

Transmission occurs by 1.Anthroponotic (i.e., the vector transmits the infection from infected humans to healthy humans) 2.Zoonotic (i.e., the vector transmits the infection from an animal reservoir to humans) 3.Human-to-human transmission via shared infected needles has been documented in IV drug users in the Mediterranean region. After inoculation by a sand fly, promastigotes are phagocytosed by macrophages in the skin, convert to amastigotes, and multiply within acidic parasitophorous vacuoles.[4,5] Additional mononuclear phagocytes are attracted to the site of the initial lesion and become infected. Amastigotes disseminate through regional lymphatics and vascular system to infect mononuclear phagocytes throughout reticuloendothelial system (lymph node, liver, spleen, bone marrow and other organs).[6] This vector borne disease with wide clinical spectrum includes 1) Visceral 2) PKDL (post kala-azar dermal leishmaniasis) 3) Cutaneous 4) Diffuse cutaneous 4) Mucocutaneous 5) Viscerotropic

Visceral leishmaniasis also known as kala-azar,[1] a Hindi term meaning "black fever" caused by the L. donovani complex, which includes L. donovani and L. infantum (the latter designated L. chagasi in the New World); these species are responsible for anthroponotic and zoonotic transmission, respectively.

Clinical Manifestation: Visceral leishmaniasis has varied spectrum of severity and manifestations. The onset can be chronic, subacute, or acute. Although the incubation period generally ranges from weeks to months, asymptomatic infection can clinically manifest years to decades after the exposure in people who become immunocompromised. It is most severe form of the disease and affects internal organs (particularly, spleen, liver, and bone marrow). In endemic areas, the diagnosis often is made based on the history and physical examination. Patients present with recurrent high fevers, wasting, anorexia, night sweats, diarrhea, abdominal distress, and malaise. Physical examination reveals a patient is cachetic with abdominal distension due to massive hepatosplenomegaly. The liver and spleen are usually soft. Epistaxis and petechiae can occur due to severe thrombocytopenia.

Lymphadenopathy is common in most endemic regions of the world except the Indian subcontinent, where it is rare. Visceral disease from the Middle East is usually milder with less specific findings than visceral leishmaniasis from other areas of the world. Without treatment, the fatality rate reaches 90%. Early diagnosis and treatment reduces mortality to 2–5%. It causes secondary infections such as measles, pneumonia, tuberculosis, bacillary or amebic dysentery. HIV-coinfected patients may have atypical manifestations, such as involvement of the gastrointestinal tract and respiratory involvement in the form of GI ulcerations and pleural effusions.

Differential Diagnosis of VL: Malaria, typhoid fever, tuberculosis, brucellosis, schistosomiasis, histoplasmosis, leukemia and lymphoma.

Laboratory findings include anemia (normocytic normochromic), leucopenia, thrombocytopenia and hypergammaglobulinemia. Eosinopenia is frequently observed. Hypergammaglobulinemia, circulating immune complexes and rheumatoid factors are present in serum of most patients with visceral leishmaniasis.[7]There is evidence of polyclonal B-cell activation. The globulin level may be as high as 9g/dl; the ratio of globulin to albumin is typically high. The erythrocyte sedimentation rate is usually elevated. The kidneys may show evidence of immune complex deposition. Mild glomerulonephritis can occur,[8] but the renal failure is rarely seen.

Histilogical diagnosis: The diagnosis can be confirmed by demonstrating amastigotes in the tissues-L.D. bodies(sensitivity of spleen aspirate >95%, bone marrow 70-85%, lymph node 56-65%, buffy coat or blood 70%) or isolating promatigote in the culture (Schneider's and NNN media). Splenic aspiration[9] for Wright-Giemsa stained smears and for culture is the most sensitive method for parasitic identification. Bone marrow aspiration is safer, but less sensitive. Lymph node aspiration or biopsy may be diagnostic when enlarged nodes are present. Amastigotes may also be seen within mononuclear cells in Wright-Giemsa stained smears of the buffy coat or in biopsy specimens of various organs. The latter is particularly true for the patients of AIDS in whom amastigotes in macrophages have been identified in bronchoalveolar lavage, pleura effusions, or biopsy specimens of the oropharynx, stomach or intestine.[10]

Tissue Culture: This method is used for diagnosis and to help identify Leishmania species. These are available in only reference laboratories. Specimens may be cultured on Novy-MacNeal-Nicolle (NNN), Schneider Drosophila medium, or a multitude of specialized media to induce promastigote growth. Cultures usually take a few days to 2 weeks with sensitivity of 75%. Cultures can also be performed by inoculating tissue into the footpad and nose of hamsters strains (ie, in vivo cultures via animal inoculation). This is a sensitive method, especially in difficult cases, but results can take several weeks to months.

Serologic Studies: Serologic detection of antibodies to recombinant K39 antigen[11] using a direct agglutination test (DAT), immunofluorescence assay (IFA), or enzyme-linked immunosorbent assay (ELISA) has been shown to be highly sensitive and specific in diagnosing visceral leishmaniasis and post–kala-azar dermal leishmaniasis.[12] A nitrocellulose dipstick test has also been used with K39

testing. Recombinant K39 reactivity appears to correlate with active visceral disease caused by L donovani, L chagasi, and L infantum and is absent in cutaneous and mucocutaneous infections. Cross-reactions can occur with leprosy, Chagas disease, malaria, and schistosomiasis. K39-based antigen testing is the FDA approved for diagnosing visceral leishmaniasis.[13,14]

Polymerase Chain Reaction: PCR can identify parasite using sequences from the variable region of kinetoplast DNA.[15] It is highly sensitive and rapid diagnosis of specific Leishmania species. However, a negative serologic test does not exclude the possibility of a leishmanial infection. Currently limited to military and reference laboratories.[16,17]

Leishmanin Skin Test (Montenegro Test): The Leishmanin skin test (LST) is similar to the purified protein derivative (PPD) used for Mycobacterium tuberculosis. This test used to determine delayed-type hypersensitivity reactions. Killed promastigotes are injected intradermally; a 5-mm area of induration over 48-72 hours suggests past infection. Results are negative during active visceral leishmaniasis; positive results occur 2-3 months after infection, usually after successful therapy. The test results are also positive in patients with post–kala-azar dermal leishmaniasis. This test is not used to distinguish between active and resolved disease.

Treatment

Treatment is complex, as the optimal drug, dosage, and duration vary with the endemic region.[1] A pentavalent antimonial is the drug of choice in most endemic regions of the world, but there is widespread resistance to antimony in the Indian state of Bihar, where either amphotericin B (AmB) deoxycholate or miltefosine is preferred. Dose requirements for AmB are lower in India than in the Americas, Africa, or the Mediterranean region.

Pentavalent Antimonial Compounds

Two pentavalent antimonial (Sb^V) preparations are available: Sodium stibogluconate (100 mg of Sb^V/mL) and meglumine antimonate (85 mg of Sb^V/mL). The daily dose is 20 mg/kg by rapid IV infusion or IM injection, and therapy continues for 28–30 days. Cure rates exceed 90% in Africa, the Americas, and most of the Old World but are <50% in Bihar, India, as a result of resistance. An adverse reaction includes arthralgia, myalgia, elevated serum levels of aminotransferases and chemical pancreatitis. Electrocardiographic changes are common. Concave ST segment elevation is not significant, but prolongation of QT_c to >0.5 s may herald ventricular arrhythmia and sudden death.

Amphotericin B

AmB is currently used as a first-line drug in Bihar. In others parts of the world, it is used when initial antimonial treatment fails. Conventional AmB deoxycholate is administered in doses of 0.75–1.0 mg/kg on alternate days for a total of 15 infusions.

Liposomal AmB

This is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of VL; the regimen is 3 mg/kg daily on days 1–5, 14, and 21 (total dose, 21 mg/kg). The total dose requirement for different regions of the world varies widely. In Asia, it is 10–15 mg/kg, in Africa, 18 mg/kg; and in Mediterranean/American regions, not less than 20 mg/kg. Sundar et al found that the efficacy of a single infusion of liposomal amphotericin B was equivalent to a conventional amphotericin B infusion (15 alternate-day infusions) for visceral leishmaniasis[18] Single-dose treatment with AmBisome has shown a 91% cure rate in India but is still considered too expensive for general[19] treatment and oral formulations are currently under development to increase access and facilitate distribution of the efficacious drug in the field.[20]

Paromomycin

Paromomycin (aminosidine) is an aminocyclitol-aminoglycoside antibiotic with antileishmanial activity.Its mechanism of action against Leishmania has yet to be established. It is approved in India for the treatment of VL at an IM dose of 11 mg of base/kg daily for 21 days; this regimen produces a cure rate of 95%.

Miltefosine

It is an alkylphosphocholine, first oral compound approved for the treatment of leishmaniasis.[21,22] Has long half-life (150–200 h) and its mechanism of action is not clearly understood. The recommended therapeutic regimens for patients on the Indian subcontinent are a daily dose of 50 mg for 28 days for patients weighing <25 kg, a twice-daily dose of 50 mg for 28 days for patients weighing >25 kg.[23,24]

Multidrug therapy

Multidrug therapy for leishmaniasis is likely to be preferred in the future.[25] Potential advantages in VL include (1) better compliance and lower costs associated with shorter treatment courses and decreased hospitalization, (2) less toxicity due to lower drug doses and/or shorter duration of treatment, and (3) a reduced likelihood that resistance to either agent will develop. Trials of multidrug therapy are under way in Asia and Africa. Sundar et al suggested that varied combinations of drugs, including liposomal amphotericin B, miltefosine, and paromomycin (for durations as short as 7-10 days), provide effective, safer, and cheaper regimens compared with the conventional 30-day amphotericin B regimen for visceral leishmaniasis.[26]

Prevention

Suppress the reservoir: dogs, rats, rodents etc.

Suppress the vector: Sandfly

Prevent sandfly bites: Personal protective measures, most important at night which includes sleeves down, insect repellent with DEET, permethrin treated uniforms and bed nets.

Vaccine

Till now there is no effective vaccine for prevention of any form of leishmaniasis. First generation vaccine was prepared using whole killed parasites combined or not with BCG. 2nd generation vaccines include recombinant proteins, DNA vaccines & combinations.[27]

Prognosis and follow-up

VL always fatal if not treated. In most patients fever disappears by 7 days, spleen starts to regress within 2 weeks and parasite disappears at the end of treatment.

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