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Leishmaniasis: An Emerging Disease in Mumbai, Maharashtra, India.

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ABSTRACT

Leishmaniasis is caused by the infection of haemoparasite '*Leishmaniadonovani*'. Clinically it can present as Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (MCL) and Visceral Leishmaniasis (VL). In India it is a major health problem in the North & Central regions of India and is infrequently reported from western India. However, we encountered two clinically suspected cases of Leishmaniasis over a period of six months in the 2009. First case presented with Post Kala Azar Dermal Leishmaniasis (PKDL) and second presented as VL with secondary septicemia. In first case laboratory diagnosis was made by demonstration of LD bodies on histopathological examination and in second case anti-leishmanial antibodies were also detected. The reason for the emergence of the disease in an area from where it had not been reported earlier could be due to migration of people from areas where the disease is endemic to hubs of development in urban areas for their livelihood.

INTRODUCTION

Leishmaniasis is a vector-borne disease caused by obligate intra-macrophage protozoa - *Leishmaniadonovani*. Numerous possible combinations of leishmania species, geographical areas of acquisition of infection lead to different leishmanial clinical syndromes that exihibit diverse and complex characteristic. Clinical presentation, ease of diagnosis, natural history and response to therapy is found to be varying in each such occurrence[1,2].Bites inflicted by sand flies transmits the leishmania parasite causing this communicable disease[3].

The parasite finds its way into the viscera such as liver, spleen and bone marrow; unchecked it inevitably leads to death of the host.Common presenting signs and symptoms are fever, weight loss, mucosal ulcers, fatigue, anemia, considerable swelling of the liver and spleen. Association of Visceral Leishmaniasis with Human Immunodeficiency Virus is an emerging problem as per the World Health Organization (WHO) data. Leishmaniasis can be divided into five categories on the basis of clinical signs and symptoms[4].

Visceral Leishmaniasis (VL)

Ischaracterized by low-grade fever, considerable reduction of weight, enlargement of abdomen due to swollen liver and kidney, and progressive anemia. Fatality can reach up to 100% if this form of Leishmaniasis is left untreated, hence, of all the forms this is the most serious condition.[2]Referred to by popular name 'Kala Azar' or 'Black Sickness' more than 90 % of VL cases appear in India, Nepal, Bangladesh, Sudan and Brazil[2,5,6].

Cutaneous Leishmaniasis (CL)

Is the most common form of Leishmaniasis. In this form, permanent disfiguring scars affecting mostly the open parts of the body like face, legs and arms are produced by chronic non-fatal skin ulcers numbering at times up to 200 in a single patient[2,7].The anthroponotical transmission by sand flies spreads rapidly in high density populations with lowly housing conditions, overcrowding and lack of protection from blood sucking insects[8]. Different species of the sand fly vector and associated parasites haveproliferated in the reservoirs around the rural

settlements due to changes in the environment. Humans contract CL irrespective of age and sex after entering the zoonotic cycle of the Leishmania[9].

Mucocutaneous Leishmaniasis (MCL) (Epsundia)

Affects only the mucous membranes of facial regions like mouth, nose and throat cavities causing extensive tissue destruction that at times involves even the cartilages[10].An uncontrolled MCL can lead to a metastatic complication and facial disfigurement. This form is reported from Sudan[2].

Diffuse-Cutaneous Leishmaniasis (DCL)

It is a chronic type of skin infection, spreading all over the body, lesions looking similar to that of Leprosy and difficult to treat. This form is reported from Venezuela, Dominican Republic, Kenya and Ethiopia.

Post-Kala-Azar Dermal Leishmaniasis (PKDL)

It usually follows VL treatment within two years of complete course of VL, as mottling of the skin[4].

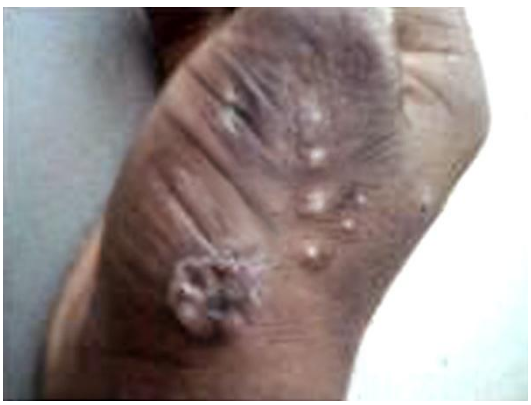
The limiting factor for geographical distribution of Leishmaniasis is the distribution of sand fly, the main vector of this disease. World over the disease is contracted byapproximately 2 million people, most of them residing in the developing countries[11].The Leishmaniasis has received renewed interest because of an upsurge of cases in traditionally Leishmanias is endemic areas and the emergence of new foci of disease[12].

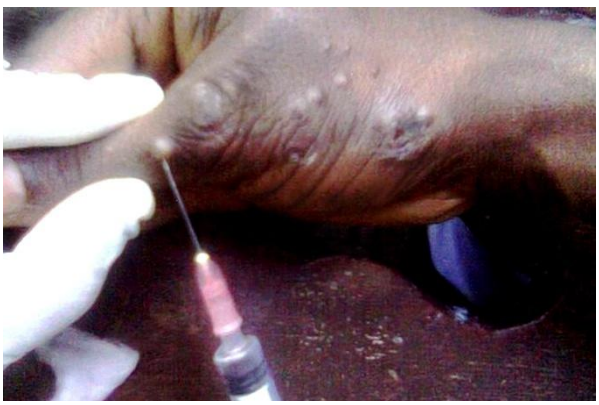
In India, this disease is commonly reported from the northernand central provinces. It is rarely reported from the western region. We encountered two clinically suspected cases of Leishmaniasis in Mumbai city over a period of six months.

Case 1

A 21 year old, unmarried male came to Skin &Venereal Disease OPD in Sir J.J. Group of Hospitals, Mumbai with complaints of a red popular rash on face, which persisted for 8 months. He migrated to Mumbai 5 years back from Madhubani district of Bihar state. In Mumbai, he was working as a Tailor inthe HandloomMills. He had fever 2 years back when he went to his hometown, for which he was hospitalized and treated. After one month of his discharge, he developed light colored spots on his face which gradually increasedin size, disappeared and fresh spots appeared. No past history of any major illness was given. On examination, he was a febrile, pulse was 88/minute, and BP was 120/70 mm Hg. Icterus, and Hepatosplenomegaly were present. On examination, multiple, soft, well-defined, discrete skin colored papules were present over chin, upper-lip, cheeks, noseand hand(Fig. 1a & 1b). Leonine face was suspected. Sensation was normal. Ear examinations revealed few skin- coloured papules over right pinna. Genital examination showed few well-defined, soft papules over glans penis. Lymph node examination showed bilateral, inguinal lymph node of 4-5 cm in diameter, non- tender and firm in consistency. During his hospital stay, his routine laboratory investigations such as hemogram and Liver function tests (LFT) were found to be normal. Chest X-ray was alsonormal. Patient was HIV as well as Venereal disease research laboratory (VDRL) negative.

Figure 1a & 1b: Papules and lesions over dorsum of right thumb.





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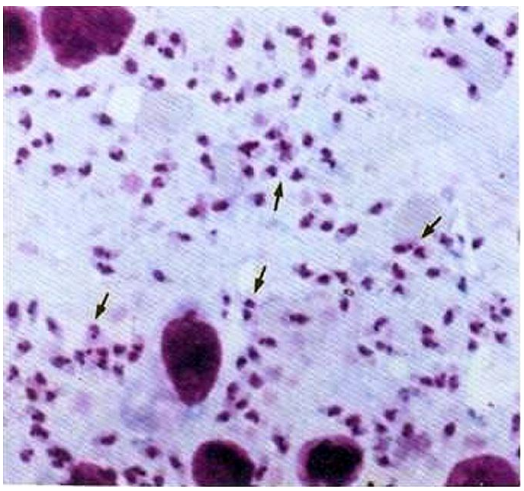
Microscopic examination of the skin biopsy showed minimal thinning of the epidermis with blunting of late ridges. Dermis showed dense inflammatory infiltrate reaching the overlying epidermis. Epidermis was retracted from dermis by a narrow zone of normal collagen which was seen extending in the underlying subcutaneous tissue.

Infiltrate was composed of plenty of plasma cells, few epitheloid cells, granuloma with multinucleate giant cells.Differential diagnosis considered was Borderline tuberculoid leprosy, CL and Cutaneous Histoplasmosis. Subsequently, bone marrow aspirate and aspirate from nodules were collected and stained with Giemsa.

The Slit-skin smear examination was negative for Acid-fast bacilli by Ziehl-Neelsen staining. Bone marrow aspirate and aspirate from nodules showed *Leishmaniadonovani*(LD) bodiesin Giemsa stain (Fig. 2). The patient was diagnosed as "Post Kala Azar Dermal Leishmaniasis".

Figure 2: Bone marrow aspirate showed LD bodies (Giemsa stain, 1000 x).



After the diagnosis of PKDL, 3cc Sodium Antimony Stibogluconate injection (Sodium Stiboglucaonate 30ml IP equivalent to 100mg Pentavalent Antimony in each ml/vial) was givenintramuscular in each buttock for 7 days along with the antibiotics.On follow up examination, decrease in the size of papules on arm and face was observed. Marked decrease was seen in the size of hypopigmented macules on forearms and buttocks which were covered by scaling.Patient recovered from PKDL.

Case 2

An 8 year old migrant from Bihar state was admitted to Pediatric Intensive Care Unit (PICU) in our hospital with complaints of high grade fever. Marked hepatosplenomegaly (Fig.3) was present. On examination, rash was present on chest and trunk(Fig.4). He was investigated for Pyrexia of Unknown Origin (PUO). Blood culture grew *Klebsiella pneumoniae.* Splenic aspirate (Fig.5) and bone marrow aspirate were positive for LD bodies by Giemsa staining respectively.

Figure 3: Marked Hepatosplenomegaly.

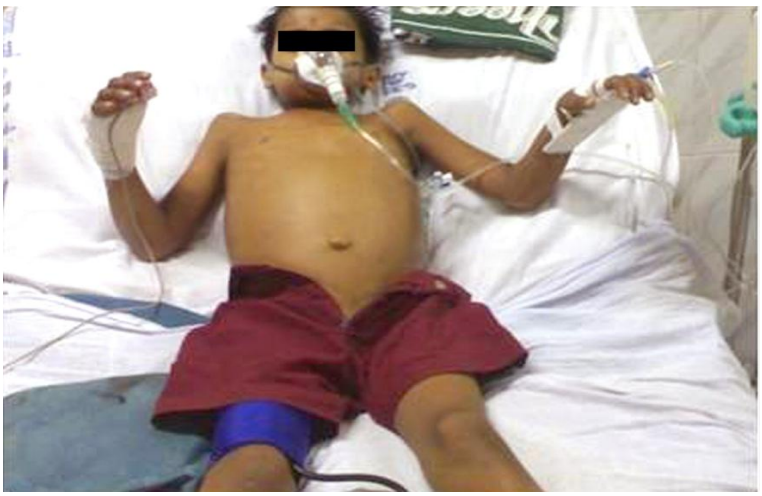


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Figure 4: Macular rash on the trunk.

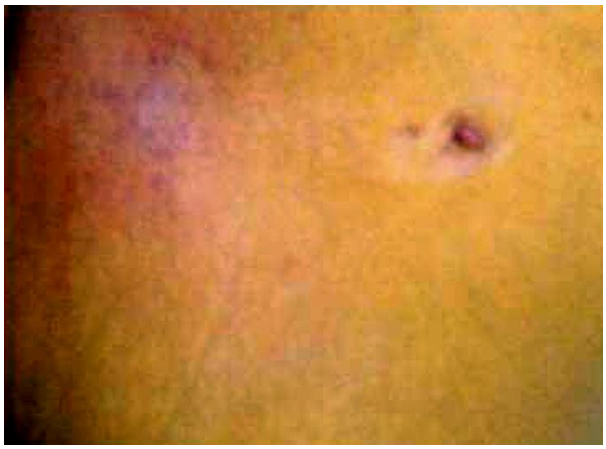
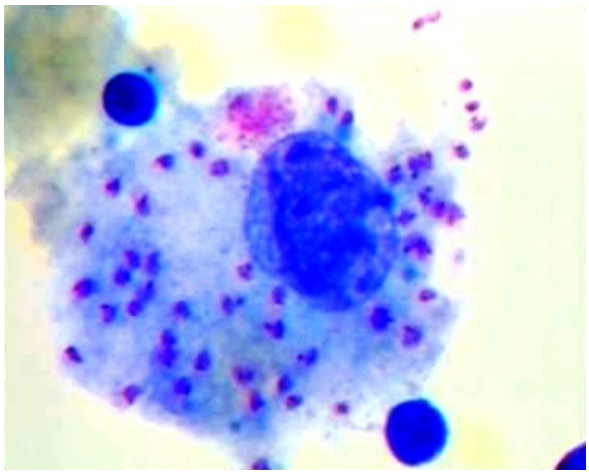


Figure 5: Splenic aspirate showed LD bodies (Giemsa stain, 1000 x).



Peripheral blood smear (PBS) showed LD bodies by Giemsa stain. Patient was HIV negative. The presence of anti-Leishmanial antibodies in the patient's serum was detected by a rapid visual spot test against a patented recombinant antigen (rKE16)('Flow Through, Anti-Leishmanial Spot/Immunodot Test Kit',(Span Diagnostics Ltd, India).

A diagnosis of VL with secondary septicemia was made.He was HIV negative. The patient was treated with Sodium Antimony Stibogluconate, Amphotericin B and antibiotics. Patient responded to the therapy.

DISCUSSION

Leishmaniasis is a disease of the tropics. Approximately 1.5-2 million new cases are added to the pool of 12 million cases world over[13]. Approximately 20000 new cases are reported from central and eastern India from amongst 165 million people residing within a striking distance of Leishmaniasis, claiming over 200 lives per year [13]. It is a grave problem in 33 districts of Bihar, 10 districts of West Bengal, five districts of Jharkhand and four districts of Uttar Pradesh compounded by under-reporting of kala-azar and PKDL[13].Mortality in untreated cases of kala-azar goes upto 90%, which after institutional treatment reduces to 15%; 3.4% in specialized hospitals. The load of subclinical infection in the community is upto 20%[13].A search of literature did not yield any study of Leishmanias in Mumbai, a western urban industrial city host to sizeable migrant population from central and eastern India. We here present two cases with different clinical presentations and suspect that it is under reported from this region.

Leishmania-HIV co-infection cases have shown an increasing trend across the world; 50-75% of adult cases of VL in Europe are HIV positive. One third of the 45 million people infected by HIV worldwide live in the zones of endemic Leishmania infection. Of the world disease burden for Leishmaniasis, 40-50% i.e. the largest number of kala-azar cases are in India and it has the second-largest i.e. 10% HIV-infected population. The coexistence of VLand HIV on a common ground in countries where both infections are highly endemic,such asIndia, may have serious consequences.Worrisome combination of circumstances is that labourers from the Leishmania endemic

states are migrating to urban areas with high HIV-prevalence. Mathur Preported 5.7% prevalence of HIV sero-positivity in VL patientsin Northern India[14].

The persons who are infected with Leishmania species, with or without symptoms, seem to remain infected and reactivation can occur if cellular immunity diminishes as a resultof HIV. Identifying co-infected persons will be vital, so that appropriate highly active antiretroviral therapy and anti-Leishmanial therapy can be initiated. The skin load of Leishmania species is much higher in HIV-infected persons with aco-infection with HIV and Leishmania.

The endemic VL is mostly seen affecting children aged between 1 and 3 years. In places outside endemic areas, patients are travelers reporting a stay in an area of possible contamination[15]. The diagnosis of VL is easily overlooked in non-endemic regions, even in travelers in India[16].In our study VL was detected in an 8 year old child.

Though, VL is common in India, we have encountered the dermal variety more commonly as the case reported in our study probably acquired infection on a visit to their home town in Bihar where the patient was incompletely treated and presented with PKDL on return to Mumbai.

Over a period of six months, we came across with four cases of PKDL which usually occur after treatment. The lesion in the first caseof PKDL was confusing and with no clear history of kalaazar was confused with tuberculoid leprosy especially as it presented in an area from where kalaazaris not reported. It was only while taking the history that it was revealed that all the patients had recently visited their hometown in Bihar which helped increase clinical suspicion of kalaazar.

Demonstration of amastigotes in macrophages in tissue smears prepared from visceral aspirates in case of VL and scrapings in cases of CL is the best method of investigation[17].The gold standard for the diagnosis is visualization of the amastigotes in splenic aspirate or bone marrow aspirate.Because of its high specificity,in 3 patients, the laboratory diagnosis was made on the basis of Giemsa stained lesion biopsy impression smearsof Skin biopsy, Nodule aspirate, Bone marrow aspirate, and Splenic aspirate.

The standard diagnostic approach at tertiary, secondary, or even primary health levels in areas of endemicity is Microscopy, since sophisticated techniques are currently expensive and out of reach of general population. Parasite species identification and characterization can be done by culture in combination with multilocus enzyme electrophoresis but is time-consuming. “Histopathological examination of fixed lesion biopsies or culture of biopsy triturates and aspirates can also help in the diagnosis”[18].

In areas where Leishmaniasis is endemic serological testing is much more frequently used.The village health workers can be easily trained to use the K39 dipstick test as it is easy to perform.Latex agglutination test (KA tex) is currently being tested in Asia and Africa. Due to high sensitivity and specificity freeze-dried antigen-based direct agglutinationtests and commercially available immunochromatographic dip stick tests have become reference tests in operationalsettings, since they are easy to use and require minimal technological expertise and or laboratory setup.However, serological tests are rarely used in CLdiagnosis because the prevalence of cross-reacting parasites such as *Trypanosomacruzi* leading to a variable specificity;sensitivity can be variable because thenumber of circulating antibodies against CLcausing parasitestends to be low (e.g., if previous chemotherapy has been administered)[18].

Simplicity of use, high sensitivity and specificity makes the Montenegro skin test (MST) useful in CL diagnosis in epidemiological surveys and vaccine studies. Disadvantages of the MST are requirement of culture facilities to produce the MST antigen, suspect sensitivity due to different antigen preparations, and inability to distinguish between past and present infections. Strong Leishmania-specific cell-mediated immunity develops only after successful cure hence MST cannot used for VL diagnosis[18].

PCR-basedassays for main molecular diagnosis, currently constitutes the preferred approachof researchers and health professionals.More promising recent alternative method is Oligochromatography-PCR (OC-PCR)[18].

Pentavalent antimony ($Sb5^{+}$) compounds are the drugs of choice and both patients responded to this treatment. Single infusion of second generation drug Amphotericin B is found successfully helping these patients though resistance was being reported. [2] Amongst other drugs the Indian Kala Azar was found to be successfully treated by Fluconazole, Aminoside (Intramuscular injection) and Mitefosine (Oral Agent) [19].

To summarize, both patients presented here are migrants from endemic areas of Bihar. Though, Mumbai has a large migrant population, we have not encountered a single case over the last decade, literature search did not show of any report of new clinical presentation, investigation, diagnosis and management. Thus, the occurrence of two cases within six months seems to be an indication of reemergence of Leishmania in the sub-continent and raises a query as to the effectiveness of the current control measures being under taken. Leishmaniasis therefore

presents an excellent model for emerging disease in general, and for the generation of the principles governing emergence. These principles shall be equally applicable to all the geographical areas that represent hubs of development worldwide. The model is, however, limited by gaps in our knowledge regarding the reservoirs.

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