Visceral leishmaniasis masquerading as tuberculosis in a patient with AIDS

Amitabh Yaduvanshi, Meenakshi Jain, S K Jain, Shyama Jain, Suneet Arora

Summary

We report a case of visceral leishmaniasis presenting as significant lymphadenopathy in a patient with acquired immune deficiency syndrome. The lymphadenopathy was initially suspected to be tubercular in nature on pathological examination. This report highlights the increasing incidence of acquired immune deficiency syndrome and Leishmania co-infection in India, and the importance of demonstrating tubercle bacilli on culture before suggesting a diagnosis of tuberculosis.

Keywords: leishmaniasis; AIDS; tuberculosis

Visceral leishmaniasis (VL) is being increasingly recognized in human immunodeficiency virus / acquired immune deficiency syndrome (HIV/AIDS) patients.[1 2] It occurs in epidemic form in Eastern India. Given the endemicity of VL in this area, physicians can expect to see VL in patients with HIV/AIDS. Resistance to sodium antimony gluconate, the paucity of alternative drugs such as pentamidine and amphotericin B, and woefully inadequate vector control measures in VL, make the situation positively explosive in developing countries. To the best of our knowledge there are only two case reports of HIV and VL co-infection from India, but this is the first report in which the patient presented with predominant lymphadenopathy, with no suspicion of HIV or leishmaniasis.

Case report

A 30-year-old man from Eastern Uttar Pradesh (in the VL belt in India) presented with moderate-grade intermittent fever associated with chills for the last 7 months. He also complained of swelling in the neck, axillary and inguinal regions for the past 6 months, and associated complaints of anorexia, weight loss and malaise. He had no other symptoms. He had undergone surgery for varicose vein removal 8 years earlier, during which he had received multiple units of blood. There was no history of any other high-risk behaviour.

He had been treated for tuberculosis for the past 6 months based on an inguinal lymph node fine needle aspiration cytology (FNAC) diagnosis of granulomatous lymphadenitis, possibly of tubercular nature. The patient was started on antitubercular drugs (rifampicin, isoniazid, ethambutol, pyrazinamide) reduced to two drugs after three months (RH). However there was no improvement in the patient's symptomatology.

Physical examination revealed generalised lymphadenopathy of 2–3 cm in size, firm, non-tender and non-matted. Pallor, cachexia, herpes simplex labialis and oral thrush were present along with a 3-cm hepatomegaly and a 5-cm splenomegaly. The rest of the systemic examination was normal.

Investigation revealed haemoglobin 8.7 g/dl, total leucocyte count 3200/µl with 70% polymorphs and 30% lymphocytes, platelets 99 × 10 g/l, erythrocyte sedimentation rate 75 mm/1st hour. Other investigations were within normal limits. Ultrasonographic examination revealed hepatosplenomegaly with abdominal lymphadenopathy.

A review of the previous FNAC revealed non-caseating granuloma (figure 1); acid-fast bacilli (AFB) staining was not done. At the same time lymph node biopsy from axillary lymph nodes showed non-specific dermatopathic changes. Mantoux test and ELISA for tuberculosis IgG and IgA were within normal limits. Bone marrow aspirations did not reveal any haemoparasites.

ELISA for HIV was positive and later confirmed by Western blot technique. Repeat FNAC from inguinal lymph node revealed numerous intracellular and extracellular amastigote forms of *Leishmania donovani* (LD bodies) (figure 2). The CD4 count (helper/inducer) was 2% and absolute CD4 count was 30/µl.

A final diagnosis of AIDS stage IVC with VL (kala azar) was made. The antitubercular drugs were withdrawn and the patient was started on intramuscular (im) sodium stibogluconate (20 mg/kg body weight/day), continued for 28

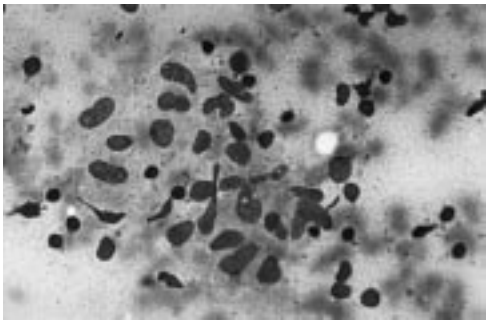

Figure 1 First FNAC smear from inguinal lymph node showing non-caseating epithelioid cell granuloma

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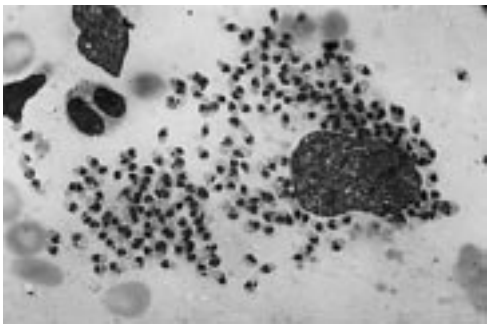

Figure 2 Second FNAC smear from inguinal lymph node showing LD bodies

days. The patient responded well to the treatment and showed an improvement in general condition; his lymph nodes had regressed appreciably by the end of therapy. He was discharged on prophylaxis for tuberculosis and *Pneumocystis carinii*. Repeat lymph node FNAC and bone marrow aspiration did not reveal any LD bodies after 3 months. His fever had completely subsided and there was marked regression of splenomegaly. He was continued on im sodium stibogluconate, once a month, for prophylaxis against relapse of VL.

Discussion

The case has certain unique features. It is the third case of HIV/VL co-infection reported from India. The patient had lymphadenopathy as the predominant presentation, which is uncommon in Indian VL, and the lymphadenopathy had previously been misdiagnosed as tubercular in origin.

Tuberculosis is highly prevalent in India and is a common cause of lymphadenopathy. Due to lack of resources, the patient is usually started on antitubercular drugs on the basis of the cytohistological appearance, without resorting to AFB staining or culture. This strategy is generally helpful, as other granulomatous diseases are uncommon in India. However, lymphadenopathy and granuloma formation are rarely seen in VL. In response to the initial infection there is a migration of histiocytes into the lymph nodes, resulting in the formation of non-caseating granuloma. These granulomas may sometimes be thought to be tubercular in origin due to the paucity of LD bodies in the early stages, as happened in our patient. There is then reactivation of this latent infection when the patient is stressed or immunocompromised in any way. At this stage the granuloma and histocytes are disrupted and numerous LD bodies are seen on cytology or histology, as was the case in our patient whose repeat FNAC showed numerous LD bodies.

In a recent WHO communication, 692 retrospective cases of HIV/VL co-infection were reported; 97.3% of these cases originated from Southern Europe.[1 2] However, this is only the third case of HIV/VL co-infection reported from India.[3 4] The possible reasons for the scarcity of cases from India are, firstly, that the seropositivity of HIV in India is restricted to the urban areas while VL has a predominantly rural and suburban distribution. A study from Bihar, the state with the highest incidence of VL, did not report a single HIV-positive sample from 4567 sera samples obtained from high-risk individuals, showing the low prevalence of HIV infection in rural and semi-urban societies.[5] Secondly, in a developing country like India, other virulent infections are present in the environment (eg, tuberculosis, bacterial pneumonias, etc) and patients suffering from HIV infection usually die from such infections before they are immunocompromised enough to succumb to opportunistic infections like VL.

However, all this may change in the near future, with rapid liberalisation and economic growth, there has been a greater intermixing of populations from urban and rural areas, and due to better medical care and awareness, patients with HIV/AIDS are surviving longer. Thus India is on the verge of breaking through into the circle of developed countries and it will be facing unique health problems common both to underdeveloped and developed countries in the coming decades.

There is a sharp reduction in mean survival (13 months) in patients with Leishmania/HIV co-infection compared to other AIDS patients. There are also reports of frequent severe VL caused by Leishmania strains with lower or no virulence in HIV-negative individuals, and it has been suggested that LV should be included among the AIDS-defining diseases.[1 2] The WHO has recommended treatment with

Learning points

- clinicians in developing countries should be aware of co-infection of HIV and VL
- VL can rarely present as lymphadenopathy
- the initial response to leishmanial infection may be in the form of non-caseating granuloma formation
- caseating/non-caseating granulomas should be stained for AFB before a diagnosis of tuberculosis is made, and the diagnosis should be revised if the patient does not show clinical improvement after 3 months of anti-tubercular therapy
- non-specific dermatopathic changes in lymph-node biopsy are also features of AIDS-related lymphadenopathy
- a higher incidence of HIV/VL co-infection has been reported in patients with AIDS, manifesting as opportunistic infection
- patients with AIDS and leishmaniasis have a sharp decline in mean survival as compared to non-leishmania infected patients
- WHO recomends sodium stibogluconate (20 mg/kg/day for 28 days) as first-line therapy in HIV/VL co-infection, but such patients are often resistant to first-line therapy
- pentamidine, amphotericin B, and combined stibogluconate and allopurinol are second-line therapies
- amphotericin B lipid complexes (AmBisome) have been found to be more effective and less toxic in immunocompromised VL patients
- pentavalent antimony given once a month is effective in prevention of relapses

sodium stibogluconate (20 mg/kg/day for 28 days) as first-line therapy. Pentamidine at a dose of 4 mg/kg on alternate days for 3–4 weeks, sodium stibogluconate and allopurinol (10 mg/kg/day), and amphotericin B (0.5 mg/kg/day for 14–21 days) have been used as second-line drugs in HIV/VL co-infected patients,[6] but have been associated with relapse, unresponsiveness and low efficacy. More recently, amphotericin B lipid complexes (AmBisome) have been found to be more effective and less toxic in immunocompromised VL patients.[6] Pentavalent antimony given once a month was effective in prevention of relapse in HIV-infected leishmania patients after initial cure.[7]

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Fatal phenytoin hypersensitivity syndrome

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Summary
The phenytoin (hydantoin) hypersensitivity syndrome is rare but potentially fatal. Often, as in this case, it presents with non-specific symptoms and signs, requiring a high degree of clinical suspicion for diagnosis.

Keywords: phenytoin; hydantoin; hypersensitivity.

Phenytoin (diphenylhydantoin) is an aromatic ring compound which is metabolised in the liver by hydroxylation of one of its phenyl groups and then excreted in the urine and bile as a glucuronide conjugate. It was first introduced as an anticonvulsant in 1938. Dose-dependent side-effects (neurological impairment, gingival hyperplasia and megaloblastic anaemia) soon became apparent but an idiosyncratic hypersensitivity syndrome to phenytoin (and other hydantoins) was first described in 1959.[1]

We report a case of unrecognised, fatal, phenytoin hypersensitivity syndrome with characteristic pathological changes in the heart, liver, skin and lymph nodes at autopsy.

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Case report

The patient was an 85-year-old AfroCaribbean woman who was admitted following collapse at home, with drowsiness, fever, rigors and a pruritic rash. Her medical history included a hysterectomy, ischaemic heart disease, type II diabetes mellitus and paraphrenia. One month prior to admission she was diagnosed as having complex partial seizures and was commenced on phenytoin 300 mg at night. Her other medications included metformin 500 mg bid, tolbutamide 500 mg bid, nifedipine 10 mg bid and risperidone 1 mg od. She was a non-smoker and had stopped taking alcohol since the onset of the fits.

On examination she was unwell and confused with a temperature of 38°C, regular pulse rate of 90 beats/min and a blood pressure of 120/70 mmHg. She had a generalised maculopapular erythaematous rash, marked neck stiffness but no photophobia or focal neurological signs. She had a systolic murmur at the apex. Her chest auscultation was normal. Abdominal examination was unremarkable.

The initial working differential diagnoses were septicaemia, a drug reaction, or possible food allergy (the patient was allergic to salmon and she had consumed some one day prior to admission).

The results of initial investigations are presented in box 1, the most notable abnormal findings were a raised blood eosinophil count and C-reactive protein; a markedly elevated creatine kinase; and grossly deranged liver function tests. Skin biopsy was not performed.

She was treated empirically with intravenous antibiotics, corticosteroids and antihistamines. All her usual medication apart from the phenytoin was discontinued over a period of 3 days. Phenytoin was completely stopped on day seven and benzodiazepines were used to control any seizures. Unfortunately she developed renal, hepatic and cardiac failures and generalised skin desquamation. She deteriorated rapidly and died 12 days after admission.

At post-mortem examination there was florid desquamation of the entire skin surface. Internal examination revealed heavy lungs (right 520 g, left 420 g) , a large, yellow liver (1640 g), a slightly enlarged spleen (140 g) and widespread soft, fleshy lymphadenopathy (up