Case Report

A case of pseudorheumatism with submasseteric abscess and HLH in a patient with visceral leishmaniasis: A diagnostic dilemma

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Visceral leishmaniasis (VL) is a vector-borne parasitic disease, caused by Leishmania donovani species complex, predominantly affecting tissue macrophages. It is the second largest cause of parasitic death after malaria and is responsible for an estimated 2–4 lakhs cases per year worldwide¹. The anthroponotic form, L. donovani is prevalent in the Indian subcontinent and East Africa. Eastern states of India, namely Bihar, Jharkhand, Uttar Pradesh and West Bengal are considered as endemic zone, but sporadic cases have been reported from other areas too². Patients with VL usually present with fever, weight loss, splenomegaly, and cytopenias³. Rarely, it can present with atypical manifestations which can lead to delay in diagnosis or misdiagnosis⁴. Seroepidemiological and molecular analyses have shown that progression to VL occurs only in <10% of all leishmania infections, indicating the role of certain risk factors⁵. HIV, malnutrition, old age, neoplastic diseases, transplantation and immunosuppressive therapy increases the risk of acquiring the infection⁶. Because of chronic immunosuppressive disease state, VL can predispose to frequent bacterial infections and sepsis is the most common cause of mortality⁷. We report a classic case of VL from non-endemic zone in India that initially mimicked as a rheumatic disease and was subsequently diagnosed to have hemophagocytic syndrome/hemophagocytic lymphohistiocytosis (HLH) with submasseteric abscess.

Case report

A 25-yr-old female (home maker), from Madhya Pradesh, India, presented at All India Institute of Medical Sciences (AIIMS) Hospital, New Delhi with history of moderate grade continuous fever, arthralgia involving large joints (only four) for six months and swelling over left side of face for one week. The arthralgia (without joint swelling and significant morning stiffness) had developed one month after the fever. There was no significant weight loss, photosensitivity, alopecia, Raynaud’s phenomenon, dry mouth, or bleeding from any sites. Earlier laboratory reports (from outside), showed that patient had pancytopenia with Hb (62 g/l), TLC (1.2 × 10⁹/l), and platelets (68 × 10⁹/l). Rheumatoid factor (RF), antinuclear antibody (ANA) and antidualle stranded DNA antibodies (anti-dsDNAs) were negative, while anticyclic citrullinated peptide (anti-CCP) antibody titre was elevated (50.1 U/ml, normal range <15).

Other laboratory investigations including imaging of brain, spinal fluid analysis, and liver biopsy were also done, but no specific cause of underlying condition could be made. She was documented as a case of adult-onset still’s disease (AOSD) and started on disease modifying antirheumatic drugs (DMARDs) which she took irregularly. Around five months from the onset of fever, the patient developed a swelling in the left side of the face. The swelling started in the area of the left angle of mandible, progressively increased in size, and the patient subsequently developed painful trismus. The patient did not report any previous history of dental problem or local trauma. Since, the initial symptoms of fever and arthralgia were persisting and the patient also had new onset of swelling on the face and she was referred to New Delhi’s AIIMS Hospital for further management.

On examination, she was febrile with tachycardia and tachypnoea. There was a swelling over left side of face extending from the lower border of the zygomatic arch down to the submandibular region, which was 3 × 2 cm in size with signs of inflammation and reduced mouth opening due to trismus. Abdominal examination revealed hepatosplenomegaly.

Haemogram revealed Hb 85 g/dl, TLC 0.6 × 10⁹/l
with absolute neutrophil count of 0.14 × 10⁹/l, and platelets 100 × 10⁹/l. Kidney and liver function tests were normal. Erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH) levels were elevated being 108 mm (in one hour) and 1380 U/dl, respectively. Chest X-ray, ECG and routine urinary examination were normal. An urgent contrast-enhanced computed tomography was done which suggested evolving abscess in the region of left submasseteric space (Fig. 1). The USG abdomen confirmed hepatosplenomegaly without any lymph node enlargement.

The common differential diagnoses considered are outlined in Fig. 2. The main differential diagnoses were rheumatoid arthritis (RA) with Felty’s syndrome, other connective tissue diseases like systemic lupus erythematosus (SLE), HLH, tropical infections like malaria, kala-azar, brucellosis, tuberculosis, enteric fever, viral hepatitis, infective endocarditis, and hematological malignancies.

Further, investigations were planned to discern the cause of her ailment. Blood culture was sterile. Viral markers (HIV, HBV and HCV) and Brucella IgM were negative. Serum ferritin was highly elevated at 6018 ng/ml. Serum triglyceride was 2.24 mmol/l (<2.26 mmol/l). Serology test, rk39 (for Leishmania) was found to be positive. Bone marrow aspirate and biopsy revealed multiple Leishman-donovan (LD) bodies without any atypical cells (Fig. 3). The HScore calculated for the patient was found to be significantly high (217), suggestive of 95.5% certainty of having HLH. On the basis of these investigations, a diagnosis of VL was made along with evolving HLH syndrome and submasseteric abscess. The joint pains seen in this case was attributed to pseudorheumatism and not due to rheumatological disease per se.

For treating the submasseteric abscess, initially broad spectrum intravenous antibiotics were started. The ENT consultation was taken and incision and drainage of the abscess was done under general anesthesia. Culture of the pus grew Pseudomonas aeruginosa and antibiotics were changed accordingly. Patient was also started on liposomal amphotericin-B. It was administered at a dose of 4 mg/kg/day for 1–5 days followed by weekly administration from Days 10 to 31 (total 36 mg/kg). Fever spikes reduced gradually and patient was afebrile by Day 11 of therapy. With improvement of the blood counts as well as the general condition of the patient, she was discharged after 40 days of hospitalization.

**DISCUSSION**

Visceral leishmaniasis is an intracellular protozoan disease (caused by *L. donovani* in India and Africa and *L. infantum* in Mediterranean and America) with ende-
ficity in 88 countries worldwide (mainly Bangladesh, Brazil, Ethiopia, India, south Sudan and Sudan). Infection occurs commonly after bite of phlebotomine sandflies; but it may also be transmitted through the blood-borne route, transplacentally, or through solid organ transplantation.

*Leishmania donovani* infection persists in reticuloendothelial system, may be life-long, and with waning host immunity may manifest as mucocutaneous symptoms or visceral involvement. Demonstration of the parasite in the relevant tissues (e.g. bone marrow) using Giemsa or Leishman stains is required for diagnosis of VL. However, serological tests should precede the parasitological tests, namely direct agglutination test and rK39 dipstick test (detects antibodies to a specific 39 amino acid sequence) with sensitivities of 94 and 93%, respectively. These tests have regional variations and remain positive after infection for years, so can not be used to detect re-infection or relapse.

This case was initially diagnosed as RA with possible Felty’s syndrome (neutropenia and splenomegaly). However, Felty’s syndrome, a type of secondary autoimmune neutropenia, occurs in <1% of RA cases, has positive RF in >95% of the cases along with ANA positivity in 47–100% of the cases, and is a diagnosis of exclusion. In the present case, RF was absent and moreover the patient did not show much improvement to DMARDs. It is interesting to note that all serological markers [RA factor (IgM), anti-CCP, ANA, anti-dsDNA, direct coombs, and anticardiolipin IgM] of rheumatic disorders can be positive in *L. donovani* infections due to strong humoral immune response. Any systemic inflammation can cause citrullination of antigenic peptides; therefore, anti-CCP is positive in variety of diseases like RA, SLE, psoriatic arthritis, systemic sclerosis, and chronic infections like HIV, TB, leishmaniasis, leprosy, atypical mycobacteriosis, hepatitis B and C, human T-lymphotropic virus–I (HTLV-I) infection, Chagas disease, infectious mononucleosis, schistosomiasis, yersinia and lyme disease. Anti-CCP reactivity is, therefore, not specific for rheumatoid arthritis. If laboratory uses control wells in ELISA method for defining anti-CCP reactivity, it can differentiate true rheumatism from pseudorheumatic disorders. Pseudorheumatism, a rarely used term in medical science, is defined as joint or muscle symptoms (arthralgia/myalgia) without objective findings and with no apparent underlying causes.

The patient also satisfied the criteria for secondary HLH which is associated with hyper-activation of cytotoxic T-cells, NK-cells, and macrophages. The major pathogenic role of Th-1 cells activation is suggested by the co-existence of HLH and infections which are associated with marked Th-1 cell activation, mainly intracellular organisms such as Epstein-Barr virus, tuberculosis and leishmaniasis. The likelihood of the diagnosis of HLH was very high (95.5%) as per HScore calculated from online software available from the website of the Saint-Antoine Hospital, Paris (http://saintantoine.aphp.fr/score) which predicts probability of HLH in a patient based on multiple factors. In most cases of secondary HLH, treatment of the precipitating factor is paramount as was seen in this case too. The treatment of VL led to resolution of all the symptoms, and steroids or other immunosuppressives were not required. Follow up of the serum ferritin showed gradual reduction and the repeat HScore after three months of therapy returned a significantly low value.

Visceral leishmaniasis is prone to different bacterial infections and sometimes severe sepsis. Bacterial sepsis is also the primary cause (34–75%) of death in VL. Reason for sepsis is multifactorial: pancytopenia, malnourishment, drugs used for associated conditions like methotrexate/steroids, neutrophil/phagocytic dysfunction by *Leishmania* infection, and other unknown factors. They usually present with focal infections like otitis media, pneumonia, urinary tract infections, and skin and soft tissue infections. Submasseteric space infection or abscess has not been reported previously in this context. Surgical drainage of the abscess, either intra-orally or externally is the best approach although needle aspiration may be used as the initial method of treatment. Appropriate treatment of the focus of infection along with treatment of VL is imperative.

Liposomal amphotericin-B (total dose recommended for immunosuppressed patients 40 mg/kg divided on Days 1–5, 10, 17, 24, 31 and 38), which is selectively taken up by the reticuloendothelial cells, provides cure rates up to 100% and have less systemic side-effects unlike conventional ones. Amphotericin-B may inhibit macrophage function, cytokine expression, antigen-induced proliferation of T and B-cells *in vitro*, and the function of cytotoxic T-cells. Therefore, it may have exerted a dual effect on both HLH and leishmaniasis in our patient.

In conclusion, the observations suggest that VL might present with manifestations resembling a rheumatological condition causing diagnostic dilemma. Visceral leishmaniasis can be associated with atypical focus of infections like submasseteric abscess which needs to be addressed with appropriate measures and HLH a known complication of VL, requiring a high index of suspicion. Lastly,
anti-CCP antibodies can be positive in any systemic infections like leishmaniasis; therefore, its control assay for confirmation along with exclusion of alternative diagnoses is important prior to labeling a diagnosis of a rheumatological condition.

Conflict of interest
The authors have no conflicts of interest to declare.

REFERENCES


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