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Case Report

Visceral leishmaniasis escaping the diagnosis and withstanding treatment in a case of recurrent pyrexia

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ABSTRACT

Though visceral leishmaniasis (VL) is the leading parasitic infection causing deatharound the world after malaria, it is a less suspected cause of pyrexia of unknown origin (PUO). We present a case of a middle aged man who was diagnosed with VL only months later owing to the stealthily masquerading disease as also to a generally low index of suspicion for it. A 59-year-old from Uttarakhand presented to us with complaint of fever of a few weeks duration. He was found to have a bicytopenia with elevated liver enzymes. Routine imaging studies were non-contributory. Cultures revealed candidemia while tests for viral and other atypical infections were negative. A bone marrow examination (BME) revealed haemophagocytosis. Positron emission tomography–computed tomography (PET-CT) showed mildly FDG avid hepatosplenomegaly. He was treated as a case of candidiasis with secondary hemophagocytic lymphohistiocytosis (HLH) and was discharged. He was readmitted months later with recurring fever. Repeat investigations revealed pancytopenia with marked hepatosplenomegaly. A repeat BME, however, revealed Leishmania donovani (LD) bodies. Patient was treated with liposomal amphotericin B (LAmB) and discharged. Though the patient's symptoms improved soon after, he was again admitted a couple of months later and found to have VL persisting in the BM aspirate. This report underscores the need to extensively evaluate cases of PUO rather than summarily dismissing them as routine. VL is one of the less suspected etiologies despite being the second largest parasitic killer.

Keywords: Visceral leishmaniasis, Kala-azar, PUO, Tropical disease, NTD

INTRODUCTION

A case of long-standing fever with scarce systemic symptoms often runs the risk of getting empirically treated for the more common diseases in the community. Even experienced clinicians, especially in resource poor settings, may sometimes be blinded by such bias. Unfortunately, such a practice eats into the precious time that a disease might afford before turning fatal. We hereby present a case of a middle-aged man who came to us with a fever of many weeks duration. He had received medical attention on multiple occasions prior to his visit to our center. A diagnosis of visceral leishmaniasis (VL) was made only months later much to the chagrin of everyone involved. The delay could be attributed as much to the stealthily masquerading disease as to the generally low index of suspicion for it. Adding to the patient's misfortune, we witnessed a rare disease relapse week after completing treatment with liposomal amphotericin B.

CASE REPORT

A 59-year male, with no comorbidities, hailing from Uttarakhandpresented to us with high grade fever of 1-month duration, which was intermittent in nature, associated with chills and showed no diurnal variation. There was no history of cough, dyspnoea, chest pain, pain abdomen, rashes, joint pains, dysuria, bowel disturbances or weight loss. He was a vegetarian and gave no history of travel or exposure to animals. Patient had multiple

admissions elsewhere and received treatment empirically for typhoid fever as well as scrub typhus but to no respite. He had no relevant past medical or surgical history.

On evaluation, his vital parameters were normal. General and systemic examination did not reveal any abnormality. His haemogram showed leukopenia (2580/µl) and thrombocytopenia (62000/µl). Liver function test (LFT) revealed raised liver enzymes (SGOT: 619 IU/l, SGPT: 362 IU/l, ALP: 939 IU/l, GGT: 213 IU/l) while renal function test (RFT) was grossly normal. Erythrocyte sedimentation rate (ESR) was elevated (33 mm/ first hour). Urine routine and microscopy did not reveal any abnormality. A chest radiograph and an abdominal ultrasound were non-contributory. 2D ECHO revealed no structural or functional valvular abnormality with a normal EF of >60%. Blood culture revealed the growth of *Candida albicans*. Tests for malaria, dengue, scrub typhus as well as Weil-Felix were negative. Markers for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) were also negative. Bone marrow aspiration revealed a reactive marrow with no abnormal cells, however, a prominence of histiocytes with some showing haemophagocytosis was noted. Bone marrow biopsy showed collectionof epithelioid cells with attempted granuloma formation. Fungal and acid-fast bacteria (AFB) staining were negative. Serum ferritin (19964.2 µg/l) and triglycerides (282.8 mg/dl) were raised while fibrinogen level was normal (2.7 g/l). Secondary *haemophagocytic lymphohistiocytosis (*HLH) was suspected and evaluated further. Rheumatoid factor (44 IU/ml, ref range: <20) and anti-CCP (34 U/ml, ref range: <5) were elevated while ANA (IF) and ENA tests were negative. Serum protein electrophoresis showed hypoalbuminemia with polyclonal gamma-globulinemia. A positron emission tomography–computed tomography (PET-CT) was done which revealed no abnormality except mildly FDG-avid hepatosplenomegaly (liver: 21.5 cm, spleen: 11.9 cm) with diffuse uptake in the bone marrow. A final diagnosis of candidemia with sepsis leading to multiorgan dysfunction and secondary HLH was made. The patient was treated with intravenous fluconazole and steroids following which his symptoms improved. He was subsequently discharged and asked to report for follow up.

Patient was readmitted 5 months later with high grade, continuous fever of 5 days duration. A repeat workup revealed pancytopenia with normal RFT and LFT. Ultrasonography revealed a hepatosplenomegaly (liver: 17.3 cm, spleen: 15 cm). Cultures along with tests for typical and atypical agents were all negative. Autoimmune workup was negative for rheumatoid arthritis this time though cANCA was positive (23.9 AU/ml, ref range: <18). Hyperferritinemia (2623 µg/l) and hypertriglyceridemia (301 mg/dl) were noted. Repeat bone marrow aspiration revealed presence of numerous extracellular and intracellular LD bodies with significant increase in histiocytes showing haemophagocytosis suggestive of *HLH* secondary to VL. Leishmania IgG antibody against rK-39 was positive but IgM was negative. Patient was given intravenous liposomal amphotericin B (total dose of 21 mg/kg given on days 1-5, 14 and 21) and steroids. In due course of hospitalization, patient improved and he was again discharged with advice for follow up. Unfortunately, patient again developed fever a couple of months later. This time, the tests revealed thrombocytopenia and a deranged LFT while blood culture revealed *E. coli* and *Pseudomonas* sepsis. Ultrasonography revealed hepatosplenomegaly. Once more, while IgG antibodies against rK-39 was positive, IgM was negative. Nevertheless, bone marrow aspiration was repeated which again showed LD bodies. Amphotericin B was restarted and, this time, continued for a prolonged duration. The patient improved and was discharged on request. Sadly, he developed a cardiovascular arrest few weeks later and succumbed to it.

DISCUSSION

A case of prolonged fever with no localising symptoms and signs usually warrants a battery of tests. Atypical infections including tick-borne diseases, malignancies and autoimmune disorders are the usual suspects in such cases. In this instance, our initial tests revealed nothing except for *Candidemia*. A subsequent bone marrow examination showed features suggestive of haemophagocytosis but, unfortunately, did not find any evidence of VL the first time. Evaluation for HLH returned elevated markers for rheumatoid arthritis while awhole body PET-CT revealed no abnormality except for mildly FDG-avid hepatosplenomegaly with diffuse bone marrow infiltration. After being treated with IV fluconazole and steroids, the patient's symptoms improved. He remained asymptomatic for the next 5 months only to be admitted again, this time with a widespread disease. A diagnosis of VL was made on the basis of serology (rK-39 IgG positive only) and bone marrow examination. The symptoms improved after receiving liposomal amphotericin B (a total dose of 21 mg/kg) but, as a rare occurrence and adding to the misfortune that he had already faced, our case developed a disease relapse a couple of months later.

Leishmaniasis is a prime example of a group of infections with the sobriquet 'neglected tropical diseases'. Itis less commonly suspected in patients who are not from the eastern parts of the country. The causative agent is the intracellular protozoa belonging to genus *Leishmania*. The vector for these parasites is the female phlebotomine sandfly and humans are the primary host. There are two forms of the parasite, the motile extracellular promastigote form is seen in the sandfly while the non-motile intracellular amastigote form is seen in the humans. There are three varieties of the disease, cutaneous, mucocutaneous and visceral. While the cutaneous type is the most common, it is the VL (kala azar) which poses a major health problem because of the high fatality associated with it. VL is the second largest parasitic killer in the world, only next to malaria.[1] Worldwide, approximately 20,000 people die annually. The Indian subcontinent contributes maximally to this disease burden

with most of the cases clustered in the middle and lower Gangetic plains.

VL usually presents after few weeks to months of incubation period. Symptoms are generally constitutional with a high grade fever often being the lone complaint. As the disease usually affects the spleen and the liver, splenomegaly and hepatomegaly are the common examination findings. Anaemia is another frequent feature. The chronic immunosuppressive state with this disease causes a predisposition for other infections frequently leading to septicaemia. In fact, the most common reason for mortality in VL is sepsis.[2] Microscopic demonstration of the amastigote forms from organ needle aspirates is the gold standard for diagnosis of VL. Diagnostic sensitivity is highest for aspirates from spleen (95-98%) but, because of the fear of splenic haemorrhage, bone marrow examination (sensitivity of 53-85%) is often preferred.[3-5] Culture or PCR testing of aspirate material are not performed in clinical laboratories. Detecting antibodies against recombinant K39 (rK-39), an epitope present on amastigote forms, has become the most popular serological test because of its high sensitivity that is comparable to the invasive tests.[5] Globally, pentavalent antimony (sodium stibogluconate) was the mainstay of treatment for VL for many years. But a protracted regimen and a rapidly developing resistance has now led to liposomal amphotericin B becoming the preferred first line therapy. The treatment failure rate is miniscule (<5%) and the luxury of shortened regimens has further made it the popular choice.

Retrospectively, there was little else that we could have done except for not having a low threshold of suspicion for VL. The absence of marked splenomegaly and the failure of bone marrow aspirate to reveal VL were two important influencers that led us away from the diagnosis. VL was not considered to be a disease of significance in high altitude areas till recent past. But, of late, there have been many reports of this disease from previously non-endemic regions of Uttarakhand, Himachal Pradesh, and Jammu and Kashmir.[6-9] Now, VL is reportedly the most common cause of bone marrow infections in the northern Himalayan region.[10] Our patient had evidence of septicaemia (fungal and bacterial) at different times during his prolonged disease course which seemed to be valid explanations for his fever spikes. Another pitfall that is commonly encountered in cases of VL is the fact that it mimics various autoimmune diseases greatly. A strong humoral immune response in chronic infections like leishmaniasis and tuberculosis would mean that all serological markers of autoimmune disorders (including ANA, RF, anti-CCP, ANCAs and APLA) can be positive.[11,12] Lastly, we would like to state that a bone marrow aspirate negative for leishmaniasis should not be considered as irrefutable evidence. Although they may still be preferred as a diagnostic procedure, bone marrow examinations are not as sensitive as splenic aspirates and maybe falsely negative in many cases like ours.

CONCLUSION

VL is one of the less suspected etiologies of PUO despite being the second largest parasitic killer. We also wish to highlight the rare occurrences of missing out on VL despite a BME and treatment failure with LAmB. Lastly, we note that it is not uncommon for PUO cases to show falsely elevated autoimmune markers and such reports should be taken with a pinch of salt.

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