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CO-INFECTION OF CYTOMEGALOVIRUS AND LEISHMANIA WITHOUT SPLENOMEGALY RESULTING IN IMMUNOSUPPRESSION IN AN HIV-NEGATIVE PATIENT

Inder Preet Singh Bhatia[1], Siddharth Tripathi[1], Amulyajit Singh[2], Jayaraj Hasvi[3], Amit Rajan[4], Dahake Vandana Tukaram[4]

[1] Department of Internal Medicine, 167 Military Hospital, Pathankot, India
[2] Department of Radiodiagnosis, Premier Gastroenterology Institute PGI, Jalandhar, India
[3] Department of Internal Medicine, Military Hospital, Bareilly, India
[4] Department of Lab Sciences and Pathology, 167 Military Hospital, Pathankot, India

Corresponding author's e-mail: dr.inder0219@gmail.com

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ABSTRACT

Background: Leishmaniasis is caused by the parasite *Leishmania donovani* and transmitted by the bite of the sand fly vector Phlebotomus. This disease is endemic in the Bihar region of India. There are three common forms of the disease – cutaneous, mucosal and visceral leishmaniasis. The most common presentation of this disease is prolonged unexplained fever with hepatosplenomegaly.

Case description: We report an unusual case of pyrexia of unknown origin (PUO) in a patient who was extensively worked up for PUO. She was found to have low CD4 counts even though serial samples were negative for HIV. Workup for PUO revealed a positive result for cytomegalovirus (CMV) IgM and polymerase chain reaction (PCR), fundoscopy suggestive of CMV retinitis and bone marrow biopsy suggestive of visceral leishmaniasis. Interestingly, there was no evidence of hepatosplenomegaly. She was diagnosed as a case of CMV infection and visceral leishmaniasis resulting in immunosuppression and was managed with parenteral ganciclovir followed by oral valganciclovir and amphotericin respectively. She had a dramatic response to the treatment and was discharged after two months of in hospital management.

Conclusion: Co-infection of CMV and Leishmania in an immunocompromised patient with HIV-negative status without hepatosplenomegaly posed a diagnostic dilemma and is a rare presentation. This report shows the importance of diagnosis of this co-infectious state, which upon management with ganciclovir and amphotericin lead to resolution of symptoms and pancytopenia. Clinicians should be aware of the unusual presentation to avoid missing the diagnosis of this potentially life-threatening treatable condition.

KEYWORDS

Visceral leishmaniasis, pancytopenia, CMV, AVRT, liposomal amphotericin, ganciclovir, valganciclovir

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LEARNING POINTS

- Visceral leishmaniasis without splenomegaly is a rare presentation.
- Other aetiologies for low CD4 counts in an HIV-negative patient such as cytomegalovirus (CMV) should be considered.
- Co-infection of CMV and Leishmania resulting in immunosuppression in an HIV-negative patient is rare and poses a diagnostic dilemma.

INTRODUCTION

Leishmaniasis is caused by the parasite *Leishmania donovani*, which is transmitted by the bite of the sand fly vector Phlebotomus. This disease is endemic in the Bihar region of India. There are three common forms of the disease – cutaneous, mucosal and visceral leishmaniasis (VL). The most common presentation of this disease is prolonged unexplained fever with hepatosplenomegaly, especially in HIV patients. However, very rarely, VL can present without splenomegaly. In an HIV-negative patient, other aetiologies such as chronic illness or cytomegalovirus (CMV) infection can cause an immunocompromised status.

CASE DESCRIPTION

A 55-year-old female, resident of Bihar, Bhojpuri by ethnicity, a farmer by profession with a known case of primary hypertension, presented with a history of fever of five months duration. Her symptoms had begun when she developed an intermittent fever. It was followed by decreased appetite, unquantified weight loss and multiple episodes of vomiting.

There was no history of pain in the abdomen, decreased urine output, gastrointestinal bleed, chest pain, breathlessness, cough, haemoptysis, oral ulcerations, hair loss, photosensitivity or rashes. On examination, she was cachectic with a BMI of 17.9 kg/m^2. Her vitals included a pulse of 110/minute, blood pressure of 108/90 mmHg on admission, temperature of 37.8°C, respiratory rate of 18 per minute and oxygen saturation of 97% at room air. Pallor was present. There was no evidence of icterus, clubbing, lymphadenopathy or oedema. The rest of the general and systemic examination was normal, without any evidence of hepatosplenomegaly.

Investigations revealed a haemoglobin level of 8.7 gm/dl, a total leucocyte count of 16,800 cells/mm^3 with neutrophilic leucocytosis; a left shift was seen with toxic granules; there were toxic vacuoles and a platelet count of 80,000/mm^3. The erythrocyte sedimentation rate was 105 mm/hour, and the rest of the biochemical parameters were normal. Arterial blood gases revealed metabolic acidosis with raised lactate. An ECG and chest-X ray were normal; a peripheral blood smear was negative for malaria. Dengue serology was negative. The patient underwent contrast-enhanced computed tomography of the chest, abdomen and pelvis, which showed normal study and no hepatosplenomegaly.

She was initially managed with empirical parenteral antibiotics (meropenem 1 g every eight hours, metronidazole 500 mg every eight hours and clarithromycin 500 mg every twelve hours).

On day five of admission, she developed atrioventricular re-entrant tachycardia (AVRT), for which she was managed with carotid massage, then with adenosine. She had another episode of AVRT after 72 hours, which was reverted to sinus rhythm with adenosine, and was started on β-blockers. For both the instances, there was no evidence of dyselectrolemia, and a thyroid function test and 2D echocardiography were also normal. The patient was extensively examined and tested for pyrexia of unknown origin (PUO). She was negative for HbsAg/Anti HCV/HIV (by ELISA test)/VDRL test. She was found to have low cluster of differentiation 4 (CD4) count (279/µl); however, serial blood samples were negative for HIV and an HIV viral load was not detected. Opportunistic infection workup was negative for toxoplasma, rubella, herpes and pneumocystis; Mantoux test was negative. Saline-induced sputum samples were negative for both mycobacterium tuberculosis and non-tuberculous mycobacterium by the polymerase chain reaction (PCR) method. Sputum samples were negative for Ziehl–Neelsen/Gram/Giemsa stain. PCR for rickettsia, scrub typhus and leptospirosis were negative, and the Weil-Felix reaction was normal. She was found to have ANA 2+ cytoplasmic; however, anti-dsDNA, anti-Smith antibodies and antibodies against other extractable nuclear antigens were not raised, and complement levels were also found to be normal. 1,25-dihydroxy vitamin D3 and angiotensin-converting enzyme levels were normal, and serial urine and blood cultures were negative. Her thyroid function test and rheumatoid factor were within normal limits.

There was no resolution of fever and neutrophilic leucocytosis after nine days of antibiotics. Antibiotics were modified to piperacillin/tazobactam 4.5 g every six hours and teicoplanin 400 mg every 24 hours.

The patient developed pancytopenia (TLC 2,040 cells/mm3, platelet count of 10,000 on peripheral blood smear) during hospitalisation. Considering there was no improvement in symptoms, she underwent bone marrow studies, the findings of which were suggestive of VL *(Fig. 1)*. She was also found to be positive for CMV IgM/PCR. She underwent fundoscopy which was suggestive of CMV retinitis and was managed as a case of VL and CMV infection. Treatment was with liposomal amphotericin (5 mg/kg body weight daily for 10 days) and parenteral ganciclovir (5 mg/kg body weight twice a day for 21 days) followed by maintenance doses of oral valganciclovir.

Post management with amphotericin and ganciclovir she became afebrile, had improved appetite and resolution of pancytopenia, and there was no recurrence of fever. She was discharged on antihypertensive and valganciclovir. At one, three and six months she remained stable, with no recurrence of fever. Serial investigations showed no recurrence of pancytopenia. At six months, her CD4 counts were also restored to within normal limits.

DISCUSSION

Visceral leishmaniasis (VL), also known as kala-azar, is an infection of reticuloendothelial system. It is caused by the parasite *Leishmania donovani* and transmitted by the bite of sand fly vector Phlebotomus. The most common presentation is unexplained fever, unintentional weight loss, decreased appetite, hepatosplenomegaly and anaemia. It is potentially a fatal condition in 95% of cases if it goes undiagnosed and untreated. According to a WHO report published in 2023, 50,000 to 90,000 cases are reported worldwide annually. India accounts for 18–20% of VL cases. It is endemic in four states of India: Bihar, Jharkhand, West Bengal and Uttar Pradesh. VL is diagnosed based on clinical grounds and a serological test, and is confirmed on aspirate from the lymph node, bone marrow or spleen.

Our patient presented with a history of intermittent fever, unintentional weight loss and decreased appetite. Examination and evaluation revealed no hepatosplenomegaly; splenomegaly is usually present in almost all cases of VL. Leishmaniasis was not suspected initially, as there was no organomegaly on examination and imaging. The patient was extensively evaluated for PUO and was found to have low CD4 counts. However, serial samples for HIV were negative. The patient was initially managed with parenteral antibiotics but showed no clinical response to initial management. She developed pancytopenia during hospitalisation and underwent bone marrow aspirate and biopsy, which revealed VL. She was also found to be positive for CMV IgM/PCR, with fundoscopy suggestive of CMV retinitis. She was diagnosed with a case of CMV infection and VL. The possibility of secondary haemophagocytic lymphohistiocytosis was also considered in background of pancytopenia, prolonged fever, CMV infection but absence of splenomegaly, normal fibrinogen and triglyceride levels, no evidence of haemophagocytosis in bone marrow biopsy ruled out the possibility of haemophagocytic lymphohistiocytosis[1].

The immunocompromised state could be attributed to CMV infection, as CMV is known to cause immunomodulation and immunosuppression[2]. In our case, a prolonged immunocompromised state secondary to CMV infection could have led to VL. The absence of organomegaly could be because of the prolonged immunocompromised state. The patient was managed with liposomal amphotericin (5 mg/kg body weight) for 10 days, considering her immunocompromised status. Liposomal amphotericin was preferred over other lines of treatment, considering its high efficacy and increasing resistance to other agents in endemic areas[3]. The patient was observed for adverse effects of liposomal amphotericin B such as dyselectrolemia, nephrotoxicity and anaphylaxis[4]. For the CMV infection, she was managed with parenteral ganciclovir (5 mg/ kg body weight twice a day for 21 days) followed by oral valganciclovir[5]. She became afebrile after 14 days and there was resolution of the pancytopenia. She was continued on oral valganciclovir, and it was discontinued at three months as the CD4 count showed an improving trend. At six months post-discharge, the patient remained asymptomatic and there was no evidence of immunosuppression.

As per a PUBMED search, very limited cases of co-infection of CMV and VL have been reported and these cases have been reported in organ transplant recipients[6,7]. No such case has been reported where primary infection of CMV occurring in an immunocompetent patient leads to immunosuppression and subsequently to opportunistic infection with Leishmania.

CONCLUSION

Co-infection of CMV and Leishmania in an immunocompromised patient with HIV-negative status without hepatosplenomegaly is a rare presentation. This

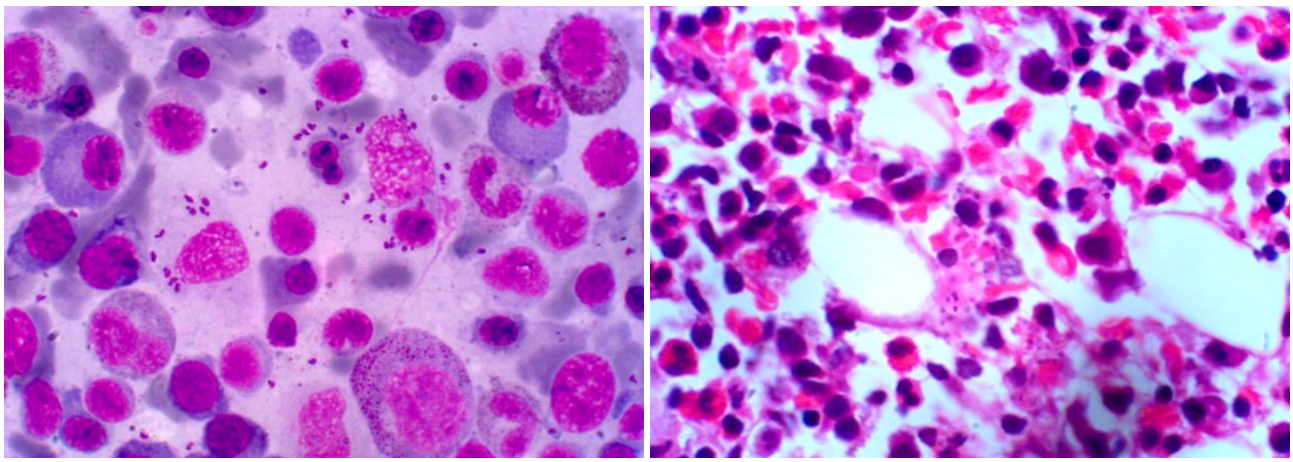


Figure 1. The image on the left side is bone marrow aspirate, and the one on the right is bone marrow biopsy. In both, Leishmania donovani cells can be observed intracellularly as well as extracellularly.

report shows the importance of diagnosis of this co-infections state which, upon management with ganciclovir and amphotericin, led to resolution of symptoms and pancytopenia. Clinicians should be aware of the unusual presentation to avoid missing the diagnosis of this potentially life-threatening but treatable condition. Clinical suspicion of VL should be kept in mind even in patients without splenomegaly presenting in an endemic zone.

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