Letter

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Visceral leishmaniasis masquerading as drug-induced pancytopenia in myasthenia gravis

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SUMMARY Visceral leishmaniasis (VL), also known as kala-azar (black fever in Hindi), is a disease primarily caused by *Leishmania donovani*. The most important clinical manifestation of visceral leishmaniasis is fever. Nonspecific laboratory findings of visceral leishmaniasis include anemia, neutropenia, eosinopenia, and thrombocytopenia. Definitive diagnosis of visceral leishmaniasis requires the demonstration of either parasite by smear or tissue by culture (usually bone marrow or spleen). Myasthenia gravis is an autoimmune disease caused by antibodies to acetylcholine receptors in the post-junctional membrane of the neuromuscular junction. It typically presents with fatigable muscle weakness without any sensory or brain involvement. It is usually treated with corticosteroids and immunosuppressants like azathioprine. Here we encountered a confirmed case of myasthenia gravis on azathioprine with pancytopenia. While working up to evaluate pancytopenia, bone marrow examination revealed presence of Donovan bodies and the patient showed good response to liposomal amphotericin-B. In retrospect, a case of myasthenia gravis, who presented with pancytopenia presumably drug-induced, was found to have visceral leishmaniasis.

Keywords Immunosuppression, myasthenia gravis, pancytopenia, visceral leishmaniasis

Visceral leishmaniasis, or kala azar, is an extremely rare condition encountered in the urban population of West Bengal, India. Also, its prevalence is very low among non-HIV-infected patients who are on corticosteroids or other immunosuppressive therapies. There is limited data on the risk factors for developing visceral leishmaniasis in persons on immunosuppressive treatment. Herein we describe a patient of myasthenia gravis on chronic immunosuppressive therapy suspected with azathioprine-induced pancytopenia but eventually diagnosed to have visceral leishmaniasis.

A 62-year-old gentleman, a resident of Kolkata, initially presented to the neurologist with ptosis & limb weakness and was diagnosed to have generalized myasthenia gravis. Repetitive nerve stimulation test was positive. He was started on pyridostigmine (60 mg every 6 hourly) and prednisolone therapy (starting dose 1 mg/kg/day). Subsequently, azathioprine was added as a steroid-sparing agent, and prednisolone dose was tapered to 10 mg/day. After about a year of azathioprine therapy, he developed pancytopenia, but there was no fever or bleeding manifestations, and his myasthenic symptoms were well-controlled. There was no past history of blood transfusion or travel to kala-azar endemic districts. Azathioprine was stopped and bone marrow aspiration and biopsy was performed given the persistent pancytopenia (hemoglobin 6.6 gm/dl, MCV 111 fL, MCH 33.2 pg, total leucocyte count of 2,200/μL with 56% neutrophils, 33% lymphocytes, 11% monocytes, and platelet count 86,000/μL). Clinical examination revealed pallor, mild hepatomegaly (2 cm below costal margin), and moderate splenomegaly (4 cm below costal margin), but there was no peripheral lymphadenopathy, sternal tenderness or skin lesions. Renal and liver function tests, blood glucose, electrolytes, serum ferritin, iron, vitamin B12 and folate levels were normal; viral serology for HIV, HBsAg, anti-HCV were non-reactive. Bone marrow aspiration cytology and biopsy revealed normal trilineage hematopoiesis, adequate marrow storage iron along with numerous intracellular and extracellular Leishman-Donovan (L-D) bodies, thereby confirming the diagnosis of visceral leishmaniasis (Figure 1). The patient was treated with liposomal amphotericin-B (total cumulative dose of 21 mg/kg

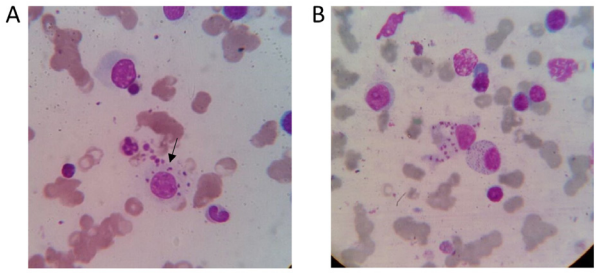

Figure 1. (A) Romanowsky stain showing intracellular LD bodies within macrophage in High power view (40×) (A) and Oil immersion view (100×) (B): marked with arrow.

body weight) and showed complete clinical response. Treatment for myasthenia was subsequently resumed, and he is doing well on follow up.

Leishmaniasis refers to a diverse spectrum of clinical syndrome caused by infection with a protozoan parasite of genus *Leishmania* acquired by the bite of a sandfly (*1*). The most common presentation of visceral leishmaniasis is the abrupt onset of moderate to high-grade fever associated with rigors and chills. Skin gradually develops dark discoloration due to hyperpigmentation (*2*). Except in the Indian subcontinent and Africa, where all age groups are affected, it is a disease of infants and small children.

The number of leishmaniasis cases associated with immunosuppression has increased regularly over the past 20 years. Immunosuppression related to human immunodeficiency virus (HIV) infection, immunosuppressive treatment, organ transplantation, and neoplastic diseases increases the risk for *Leishmania*-infected people to develop visceral illness (*3,4*). Immunosuppression is one of the most substantial risk factors for overt clinical disease, and can also alter disease presentation and treatment response. Although immunosuppression has been mainly observed in HIV-infected patients, non-HIV related immunosuppressive conditions are becoming increasingly prevalent globally, mainly because of better medical care of patients with chronic illnesses and the therapeutic use of immunosuppressive drugs. Visceral leishmaniasis has also been reportedly associated with the use of various immunosuppressive drugs, such as azathioprine, methotrexate, steroids, cyclosporine, and cyclophosphamide (5).

The fact that immunosuppressive conditions pose a real challenge in visceral leishmaniasis endemic regions is illustrated by a *Leishmania* community outbreak in Madrid (*6*). Among the 446 cases detected between July 2009 and December 2012, 15.2% (n = 68) had immunosuppressive conditions, mostly non-HIV-related. Overall, 31.3% of visceral leishmaniasis cases and 6.3% of CL cases were diagnosed in immunosuppressed individuals.

Visceral leishmaniasis is a potentially fatal infection in immunocompromised hosts, and current therapies have failed to eradicate *L. donovani* from infected tissue (*7*). In such conditions, unusual forms of leishmaniasis can develop and foster the risk of a fatal diagnostic delay and of a poor response to therapy (*8*).

Our patient did not give any history of travel to endemic areas with distribution of sand-fly vectors. He did not have fever or skin pigmentation as the initial presentation; neither was he associated with any immunosuppressive condition. He presented with pancytopenia while being treated for myasthenia with oral corticosteroids and azathioprine as a steroid-sparing agent. Though pancytopenia is a crucial feature and occurs early in the course of visceral leishmaniasis, it was not considered as a presenting feature in the index case because of the absence of fever and epidemiological factors. Rather a bone marrow aspiration and biopsy was contemplated which clinched the diagnosis of leishmaniasis and definitive treatment was offered.

Silvia et al. had reported a case where prolonged steroid use was likely to be associated to the clinical severity of the disease (*9*). In the female patient affected by myasthenia, the relapses, the clinical spread to the gastrointestinal tract, and the severe T lymphocyte defects were all factors likely to be related to the sustained impairment of the immune response.

Nevertheless, unusual presentations of leishmaniasis have to be suspected as a differential diagnosis in patients with immunosuppressive conditions other than HIV infection. In such patients, the occurrence of lymphopenia, anemia, pancytopenia or hypergammaglobulinemia even in the absence of fever or a positive travel history, particularly in kala azar-endemic countries should alert clinicians to include leishmaniasis in their differential diagnosis.

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