



Case Report

Visceral leishmaniasis in a patient with systemic lupus erythematosus



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ABSTRACT

Visceral leishmaniasis is an infection with an insidious and disabling course caused by parasites of the genus *Leishmania*. In Europe, it is mostly associated with HIV infection. Systemic lupus erythematosus and its treatment are associated with increased risk of infection, neoplastic and concomitant autoimmune disorders. The association of these diseases may go unnoticed.

A 60 year-old Caucasian woman with lupus presented with a one-year history of fever, malaise, weakness and weight loss. The highlights on physical examination were pallor, palpable hepatosplenomegaly and low-grade fever. Blood tests showed pancytopenia, hyperproteinemia with hypoalbuminemia and hypergammaglobulinemia; electrophoresis showed a polyclonal gamma curve. Full-body CT scan revealed massive hepatosplenomegaly. Microbiology investigation was negative for the most common pathogens, including tuberculosis. There were no signs of hematologic malignancy in the bone marrow smear. PCR for *Leishmania infantum* was positive both in blood and bone marrow. The patient was treated with liposomal amphotericin B, and immunosuppression was adjusted. She showed rapid clinical improvement and 6 months later had no signs of disease.

The differential diagnosis in a patient with lupus presenting with fever and multisystemic manifestations includes infectious or neoplastic disorders. The patient lived in an endemic area of *Leishmania*, and typical clinical and analytical changes were all present, making this case highly educational. The case highlights the importance of a patient's epidemiological background and how it can lead to the diagnosis and timely treatment of a rare disease.

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Introduction

Visceral leishmaniasis (VL) is a systemic infection with a worldwide distribution caused by protozoan parasites of the genus *Leishmania*. *Leishmania* spp. are transmitted to human and animal hosts through the bite of female sandflies from the genera

Phlebotomus, in the Old World, and *Lutzomyia*, in the New World [1]. Dogs and other canines, independent of the clinical form of VL, are the main reservoirs of *Leishmania* and represent the major source of contagion for the vector [2].

Human infection occurs when female sandflies hosting the parasite feed on the human host, in order to ingest blood, and directly inoculate the parasite into the bloodstream. The promastigotes, motile forms transmitted by the sandfly, are phagocytized, first by neutrophils and then by macrophages, transform into amastigotes, the nonmotile form – and the one usually present at diagnosis – and multiply within the macrophages, eventually disseminating and infecting the whole reticuloendothelial system [2]. Parasites and infected macrophages can metastasize within the skin and mucosa, bone marrow, lymph nodes, liver and spleen, resulting in skin and mucosal lesions of cutaneous leishmaniasis, progressive enlargement of internal organs and lymph nodes, and suppression of bone marrow. Host control of infection is a complex

Abbreviations: AmB, amphotericin B; ANA, anti-nuclear antibodies; CMV, cytomegalovirus; CT, computerized tomography; dsDNA, double-stranded deoxyribonucleic acid; EBV, Epstein-Barr virus; ENA, anti-extractable nuclear antigens; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; ID, infectious diseases; LAB, liposomal amphotericin B; LDH, lactic dehydrogenase; PCP, primary care physician; PCR, polymerase chain reaction; RNA, ribonucleic acid; SLE, systemic lupus erythematosus; VL, visceral leishmaniasis; WBC, white blood cell count.

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interplay of innate and adaptive immune factors which are incompletely understood [3]. The disease has, therefore, a wide spectrum of clinical manifestations and severity, from asymptomatic infection to acute or chronic and insidious life-threatening condition. The hallmarks are fever, pancytopenia, hepatosplenomegaly, and low albumin with and increased protein count due to hypergammaglobulinemia [2].

Depending on whether or not a reservoir host is present, there are two basic types of epidemiological cycles: zoonotic, generally caused by *Leishmania infantum*, which occurs in the Mediterranean Basin, China, the Middle East, and South America, and anthroponotic, generally caused by *L. donovani*, which is prevalent in East Africa, Bangladesh, India, and Nepal [4]. The latest estimates point to an annual incidence of 200,000–300,000 cases of VL across 98 countries, with more than 90% occurring in the Indian subcontinent, East Africa and Brazil [5]. The overall case-fatality rate is estimated at 10% [5], but can be up to 20–50% in immunocompromised hosts [6,7]. In Europe the species responsible for autochthonous VL is *L. infantum*, with an estimated annual incidence of around 1200–2000 cases, and it is endemic in countries in the Mediterranean basin, especially Italy and Turkey, but also in Portugal [5,8]. In these countries, it is diagnosed almost exclusively in malnourished children and in adults infected with the human immunodeficiency virus (HIV).

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology classically characterized by chronic multi-systemic inflammation. It is characterized by polyclonal activation of B lymphocytes with production of multiple autoantibodies. Many patients alternate between periods of exacerbation (flares) and reduced disease activity. Patients with SLE, due to the disease but also due to treatment with immunosuppressive drugs, are at increased risk for infections that can greatly complicate its course [9]. Some infections, such as VL, can even mimic a flare. Because lupic flares are common, clinical suspicion of VL is usually very low, and the diagnosis may go unnoticed.

Case

A retired 60 year-old Caucasian female with SLE was admitted to the Rheumatology Department in our hospital with persistent low-grade fever, night sweats, malaise, weakness and weight loss. She had no neurologic, respiratory, gastrointestinal or urinary symptoms, and no cutaneous lesions or joint pain, although she had a sensation of abdominal fullness. The symptoms had started approximately one year earlier, had shown progressive worsening, and she had lost 30 kg (approximately 1/3 of her previous body weight). During that time she was seen by her primary care physician (PCP) on several occasions and had several consultations with her rheumatologist. The investigation performed had been negative for common pathogens associated with chronic febrile illnesses, such as tuberculosis and brucellosis, and progression of immunosuppression had not stalled the symptoms. The patient had been treated for presumptive tuberculosis for 6 months, having shown no signs of improvement.

The patient had been diagnosed with SLE in her late 20s, had consultations with a rheumatologist in our hospital since 2003, and was being treated with a daily dose of 5 mg prednisolone and a weekly 10 mg dose of methotrexate. She also had diabetes mellitus and hypertension, both being treated by her PCP. Her SLE had been deemed controlled until these symptoms started, and she had no past history of confirmed tuberculosis or any chronic febrile infection. An HIV screening performed by her PCP had been negative. She had no past surgeries and no family history of cancer. The patient lived in a farm, in a town located in the region of the Douro river basin, in the north of the country. She had no history of smoking or of any drug use.

On admission, the only abnormalities were a low-grade fever (37.5 °C), marked pallor and a palpable, non-tender hepatosplenomegaly. Her blood pressure was 105/63 mmHg, heart and respiratory rates were 84/min and 18/min, respectively. There were no abnormalities on cardiac or lung auscultation, no rash, and her neurologic examination was unremarkable. A careful examination revealed no swelling, redness or pain of any joint.

Preliminary analytical study revealed pancytopenia, with a hemoglobin of 8.0 g/dL, white blood cell count (WBC) of 3020/mm³, and platelet count of 98,000/mm³, erythrocyte sedimentation rate (ESR) of 116 mm/h, lactic dehydrogenase (LDH) of 2331 U/L, low serum albumin (18 g/L) with increased total proteins (90 g/L). Hepatic aminotransferases were slightly elevated, bilirubin, blood urea nitrogen and creatinine were normal. Blood was also collected for culture of bacteria, mycobacteria and fungi, and for serologic study. Chest X-ray showed no opacities, nodules or effusions; abdominal ultrasound revealed massive hepatosplenomegaly, with a liver and spleen of 35 cm and 16 cm, respectively. The first diagnostic hypothesis was a hematologic malignancy, although subacute infections such as brucellosis or tuberculosis were also considered. A differential protein analysis with electrophoresis, antibody search, and full body computerized tomography (CT) scan were performed. A Hematology consultation was requested.

The patient had marked hypergammaglobulinemia, with a total gamma globulin count of 7580 mg/L, and a polyclonal gamma curve was seen on electrophoresis; gamma globulin differential was normal. There was no complement consumption, anti-nuclear antibodies (ANA), anti-extractable nuclear antigens (ENA), and anti-double stranded DNA (anti-dsDNA) antibodies were negative. Full-body CT confirmed the hepatomegaly and homogeneous splenomegaly, but did not show any other relevant abnormalities. Serial blood cultures for bacteria, mycobacteria and fungi were persistently negative. The serologic study revealed multiple positive IgG and IgM for *Coxiella burnetti*, *Mycoplasma pneumoniae* and for *Rickettsia conorii*. IgM for Epstein–Barr virus (EBV), cytomegalovirus (CMV) and parvovirus B-19 were negative. Blood and bone marrow cultures for bacteria and fungi were negative. Bone marrow aspirate and biopsy were performed and sent for histologic and microbiologic study (culture for bacteria and mycobacteria). The patient and the preliminary results of the marrow smear were seen by an experienced hematologist who considered the patient had no consistent signs of hematologic malignancy. Amoxicillin/clavulanate and ciprofloxacin were empirically administered, but showed to be ineffective.

On day 18 of admission, an infectious diseases (ID) consultation was requested. The clinical history and the physical examination were those previously described, but the patient revealed for the first time that she lived next to livestock and that her husband was a sports hunter, had a pack of dogs, and one had died recently of an undiagnosed consumptive disease. The hypothesis of visceral leishmaniasis was considered: the patient had an appropriate background, prolonged fever and constitutional symptoms, pancytopenia, and increased protein count with low albumin and hypergammaglobulinemia. The multiple positive antibodies were interpreted as resulting from increased gamma globulin production. Polymerase chain reaction (PCR) for *L. infantum* was positive both in the blood and in the bone marrow.

The patient was transferred to the ID Department and was treated with liposomal amphotericin B (AmB), in a dosing of 3 mg/kg. She received one daily dose during the first 5 days, another one on day 10, and then once weekly until she completed 10 doses. A prolonged regimen was chosen due to her long standing immunosuppression, long duration of disease, and overall poor clinical condition. She was discharged on day 29 of admission (10 days after being transferred to the ID department), after completing her sixth

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