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Visceral leishmaniasis mimicking systemic lupus erythematosus: Case series and a systematic literature review

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is an autoimmune disease that may present manifestations that resemble other diseases. Visceral leishmaniasis (VL) is a parasitic infection whose hallmarks may mimic SLE symptoms. Here, we report a case series and evaluate the published, scientific evidence of the relationship between SLE and VL infection.
Methods: To assess original studies reporting cases of VL-infected patients presenting manifestations that are capable of leading to inappropriate suspicions of SLE or mimicking an SLE flare, we performed an extensive search in several scientific databases (MEDLINE, LILACS, SciELO, and Scopus). Two authors independently screened all citations and abstracts identified by the search strategy to identify eligible studies. Secondary references were additionally obtained from the selected articles.
Results: The literature search identified 53 eligible studies, but only 17 articles met our criteria. Among these, 10 lupus patients with VL mimicking an SLE flare and 18 cases of VL leading to unappropriated suspicions of SLE were described. The most common manifestations in patients infected with VL were intermittent fever, pancytopenia, visceromegaly, and increased serum level of acute phase reactants. The most frequent autoantibodies were antinuclear antibodies, rheumatoid factor, and direct Coombs' test.
Conclusion: In endemic areas for VL, the diagnosis of SLE or its exacerbation may be a clinical dilemma. Hepatosplenomegaly or isolated splenomegaly was identified in the majority of the reported cases where VL occurred, leading to unappropriated suspicions of SLE or mimicking an SLE flare. Furthermore, the lack of response to steroids, the normal levels of complement proteins C3 and C4, and the increased level of transaminases suggest a possible infectious origin.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease classically characterized by chronic, multisystemic inflammation of unknown etiology. Many patients alternate between periods of exacerbation (flare) and reduced disease activity [1]. It is characterized by polyclonal activation of B lymphocytes with production of multiple autoantibodies. Physiologically, polyclonal B cell activation occurs in chronic infectious diseases, such as VL. Additionally, patients with SLE (particularly those treated with immunosuppressive drugs) are at an increased risk for infections that can complicate, exacerbate, or mimic their symptoms [2].

Visceral leishmaniasis (VL) is an acute or chronic systemic protozoan infection transmitted to humans by sandflies of the *Phlebotomus* species. Dogs are the main host reservoir. VL is a major public health problem in tropical and subtropical countries. Specifically, it is endemic in 64 countries, and 90% of the world's cases are reported in India, Bangladesh, Nepal, Sudan, and Brazil [3]. In Brazil, VL was originally restricted to rural areas, mainly in the Northeast region of the country, but since the 1980s, the geographical distribution of this disease has expanded with increasing urbanization, reaching virtually all regions, with an average annual incidence rate of two cases per 100,000 inhabitants [4,5]. The disease has a wide clinical spectrum: from asymptomatic infection to an acute or chronic life-threatening condition with fever, hepatosplenomegaly, and pancytopenia.

Therefore, the objective of this study is to describe three cases of VL mimicking the symptoms of SLE and systematically

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review the literature on the relationship between these two conditions.

Case series

Case 1

A 25-year-old woman was admitted to our hospital with a 2-year history of additive and symmetric polyarthritis (mostly in hand and knee joints) with partial improvement with the use of nonsteroidal anti-inflammatory drugs. She reported worsening of joint manifestations associated with daily fever since the time she became pregnant. Hepatosplenomegaly, jaundice, nonerosive arthritis, and positive antinuclear antibody (ANA) 1:80 speckled pattern were reported by another hospital to which she was admitted; at that time, the diagnosis of SLE with hepatic involvement was suggested. Pulse therapy with methylprednisolone (1 g) for 3 days was administered with considerable clinical improvement, and the patient was discharged with prednisone (80 mg/day). Four days after her discharge, she relapsed with fever, polyarthritis, and abdominal pain. She was referred to our hospital and delivered a stillborn fetus at 26 weeks of pregnancy. On examination, she was febrile (39.0°C) with pale mucous membranes, hepatosplenomegaly, and limitation of motion due to diffuse articular pain. The rest of her physical examination was unremarkable. Laboratory tests revealed mild anemia and negative hepatitis B surface antigen, anti-hepatitis C virus antibody, anti-HIV antibody, IgM anti-cytomegalovirus antibody, ANA, anti-double stranded DNA (anti-dsDNA) antibody, anti-Ro antibody, anti-La antibody, anti-Sm antibody, anti-liver kidney microsomes antibody type 1, anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and IgM and IgG anti-cardiolipin antibodies. Cefepime was initiated despite the negative results of blood and urine culture, and prednisone was reduced to 20 mg/day. However, as there was no clinical improvement, her bone marrow was examined; there were amastigote forms inside the phagocytic cells. Amphotericin B deoxycholate was administered for 32 days with considerable clinical and laboratory improvement; she was discharged after treatment and remained asymptomatic on follow-up examination therefore. SLE diagnosis was not confirmed.

Case 2

A 27-year-old woman was admitted to our hospital reporting a history of intermittent fever for approximately 12 months without proper investigation. At 30 days before admission, she reported persistent fever associated with profuse dry coughing, low back pain, abdominal pain, asthenia, and arthralgia. She had been under treatment for SLE (prednisone 10 mg/day), which had been diagnosed approximately 6 years prior; at that time, she had presented with cutaneous involvement (malar rash and photosensitive rash in the chest), renal involvement (nephritic proteinuria, hematuria, and cellular casts), hematological involvement (anemia, leukopenia, and lymphopenia), articular involvement (arthritis and Jaccoud's arthropathy), hypocomplementemia, positive ANA (1:320), positive anti-Ro, and positive anti-dsDNA. Her previous history also included infectious endocarditis in the mitral valve (diagnosed 5 years prior) with proper treatment and osteomyelitis in the right lower limb (diagnosed 4 years prior) treated with antibiotics and surgery. On examination, she presented with fever (38.5°C), blood pressure of 100 × 70 mmHg, tachycardia, pale mucous membranes, cushingoid appearance, butterfly-shaped malar rash, and painless mouth ulcers without palpable lymph nodes. There was a systolic murmur in the mitral and the tricuspid areas; abdominal examination revealed diffuse abdominal distension and splenomegaly. The rest of the physical examination was unremarkable. On admission, her laboratory results were as follows: hemoglobin, 11.0 g/dL; white blood cell count, 3570/mm^3; platelet count, 80,000/mm^3; ionized calcium, 1.09 mmol/L; creatinine, 0.4 mg/dL; aspartate transaminase, 348 mg/dL; alanine transaminase, 99 mg/dL; alkaline phosphatase, 468 mg/dL; and γ-glutamyltransferase, 777 mg/dL. Bone marrow aspiration was normal. By transthoracic echocardiogram, there was moderate mitral regurgitation, mild tricuspid regurgitation, and preserved systolic and diastolic function. Crystalline penicillin, oxacillin, and amikacin were initiated despite the negative results of blood and urine culture and the absence of valve vegetation. The patient developed respiratory discomfort and worsening cough; by chest radiography and tomography, there was left lung consolidation and bilateral exudative pleural effusion, which was drained. Later, she presented worsening thrombocytopenia with moderate epistaxis and hematemesis, which was treated with a platelet transfusion and proton-pump inhibitor. As the patient's clinical condition was not improving, despite the use of broader-spectrum antimicrobial agents (at that time, meropenem, teicoplanin, fluconazole, and polymyxin B), pulse therapy with methylprednisolone (1 g) was administered for 3 days with partial improvement. However, as there was no full clinical improvement, a new bone marrow study with biopsy was performed; however, the patient's clinical condition rapidly deteriorated with refractory disseminated intravascular coagulation and septic shock. Unfortunately, despite intensive care treatment, she died. Postmortem examination of the bone marrow biopsy demonstrated amastigote forms of *Leishmania donovani*.

Case 3

An 18-year-old woman was admitted to our hospital with a 5-month history of fever, almost daily and mainly in the mornings without chills or drenching sweats. She had been under treatment for SLE, which had been diagnosed approximately 1 year prior; at that time, she had presented with cutaneous involvement (malar rash and photosensitive rash in the chest and the arms), renal involvement (nephrotic syndrome), positive ANA (1:1280), low-grade fever, and axillar and cervical lymphadenopathy. With this initial diagnosis, she started prednisone and mycophenolate mofetil (2 g/day). Because she became pregnant, mycophenolate was interrupted and prednisone was maintained, and she was referred to an obstetrician. The patient evolved with miscarriage 30 days later, and uterine curettage was performed. Thereafter, she developed a febrile condition (without other signs or symptoms) and was treated with ciprofloxacin plus metronidazole for 14 days without improvement. She had no other relevant past medical history and no alcohol intake, smoking, or drug abuse. On examination, she presented with fever (39.5°C), blood pressure of 120 × 80 mmHg (using captopril 50 mg/day), tachycardia, pale mucous membranes, cushingoid appearance, mild butterfly-shaped malar rash, and mild bilateral leg edema. The rest of the physical examination was unremarkable. On admission, her laboratory results were as follows: hemoglobin, 8.2 g/dL; white blood cell count, 2320/mm^3; platelet count, 80,600/mm^3; creatinine, 0.8 mg/dL; erythrocyte sedimentation rate (ESR), 34 mm/h; C-reactive protein (CRP), 3.2 mg/dL; C3, 52 mg/dL; C4, 4 mg/dL; positive anti-dsDNA, 1:320; and 24-h proteinuria, 2440 mg. By abdominal ultrasonography, there was splenomegaly (15.2 cm) and gall bladder stones without cholecystitis signs. She had negative serologic tests for HIV and viral hepatitis and a positive recombinant K39 antigen (rK39) strip test. A bone marrow examination was performed, which revealed amastigotes inside phagocytic