IDCases 2 (2015) 102–105

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case Report

Visceral leishmaniasis in a patient with systemic lupus erythematosus

André Filipe Santos Silva [a,c,*], João Paulo Branco Calheiros Figueiredo Dias [a,c], João Miguel Neves Gonçalves Santos Nuak [a,c], Francisca Rocha Aguiar [b], José António Araújo Pinto [b], António Carlos Eugénio Megre Sarmento [a,c]

[a] Infectious Diseases Department, São João Hospital Center, Alameda Hernâni Monteiro, Estrada da Circunvalação, 4200-019 Oporto, Portugal
[b] Rheumatology Department, São João Hospital Center, Alameda Hernâni Monteiro, Estrada da Circunvalação, 4200-019 Oporto, Portugal
[c] Faculty of Medicine of the University of Oporto, Alameda Hernâni Monteiro, Estrada da Circunvalação, 4200-019 Oporto, Portugal

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 22 September 2015
Accepted 22 September 2015

Keywords:
Visceral leishmaniasis
Systemic lupus erythematosus
Fever

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.

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 *Lutzomiya*, 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.

* Corresponding author at: Avenida Fernão de Magalhães 3454, 7° centro, 4350-163 Oporto, Portugal. Tel.: +351 916271966; fax: +351 916271966.
E-mail address: afss.md@gmail.com (A.F. Santos Silva).

http://dx.doi.org/10.1016/j.idcr.2015.09.006

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 autochthone 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 multisystemic 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/mm^3, and platelet count of 98,000/mm^3, 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

dose of AmB. She showed great improvement, sustained normal body temperature once she started treatment, and recovered some of the analytical anomalies. The patient completed therapy in our department's ambulatory clinic. A histologic review of the bone marrow biopsy showed histiocytes infected with amastigotes, confirming our diagnosis, without any signs of primary hematologic disease.

Six months later, on her second appointment after discharge, the patient was completely asymptomatic, had recovered 10 kg, and had an overall normal physical examination. Hemoglobin rose to 11.7 g/dL, WBC to 7340/mm^3, platelet count to 164,000/mm^3, total serum protein was 81 g/L, serum albumin rose to 34 g/L and globulin count decreased to 5460 mg/L; abdominal ultrasound no longer showed signs of organ enlargement.

Discussion

The case presented here is the first ever reported case of VL in a lupus patient in Portugal and, based on a very recent review and case series by Santana et al. [6] and on our own investigation, the 14th described so far in medical literature.

Early recognition of infection in SLE is important as misdiagnosis and inadequate treatment (such as augmenting immunosuppression) may lead to disastrous consequences. With VL that can be very difficult, because it is very rare and clinical and laboratory features may mimic a lupic flare. Some important differences which may help distinguish between a lupic flare and VL can be highlighted: almost all patients with VL have splenomegaly, with or without hepatic enlargement, while those are rare findings in SLE flares; on the other hand, aggravated arthralgia or arthritis is very common in flares, but not common symptoms of VL. In lupus flares the serum complement levels C3 and C4 are usually decreased and anti-dsDNA antibodies increased [6,10].

Clinical suspicion, however, comes with the knowledge of a disease's epidemiology and clinical presentation. While there are some endemic foci of leishmaniasis in Portugal, overall incidence is at 15 cases per year [5]. But even within the country, most areas have never had a reported case of VL, while others – such as the one where our patient hailed from – have an incidence rate of 8/100,000 inhabitants a year [8]. As for the classic manifestations of VL, our patient manifested all of the typical hallmarks – fever, malaise, weight loss, pancytopenia, hepatosplenomegaly, and hyperproteinemia with hypoalbuminemia and hypergammaglobulinemia – which, without making it a unique case, make it perhaps the most illustrative, paradigmatic and educational of the few ever reported in SLE patients. A Chinese woman described in 1983 by Wallis and Clark [11], the first ever reported similar case, had all the same features as our patient, but the epidemiological link to a specific canine reservoir was more evident in our patient. The other 12 cases have different combinations of typical findings, but not all of them [6,12–15].

Confirmative diagnosis is usually made by observing histiocytes infected with amastigotes in microscopy of bone marrow smears or biopsy, hepatic biopsy or splenic aspirate – classically named Leishman-Donovan bodies [16]. Histology microscopy is more sensitive than smear observation, but due to its technical characteristics, it may delay the diagnosis. There are other laboratory tests that may lead to a quicker confirmation of diagnosis: culture using triple-N media, detection of antibodies using recombinant k-39 antigen, and detection of DNA through PCR [17,18]. The serologic tests have the further advantage of being used for monitoring [18], but they have mostly been tested with *L. donovani* and *L. chagasi*, not with *L. infantum*, the existing species in southern Europe [5]. Both the serologic assay and culture media are unavailable at our hospital and preliminary observation of marrow smear had been negative. The patient was very ill and a timely diagnosis was essential. PCR targets the DNA of the kinetoplast or ribosomal RNA genes, it can be performed in peripheral blood or in the bone marrow tissue, and studies show it can have an increased sensitivity for microbiologic diagnosis [17] as well as faster results, since it only takes a few hours to perform.

There are a number of therapies for VL and current World Health Organization treatment advice varies by global region [19]. This is partially explained by parasite susceptibility. In many developing countries, however, where most of the cases are reported, the cost of treatment is the greatest challenge. Pentavalent antimony was considered the mainstay of therapy in VL for decades. However, the precise mechanism of action of this agent is unknown; it has multiple toxicities and is increasingly failing due to development of parasite resistance. Furthermore, the emergence of drug-resistant strains is rapidly increasing worldwide and these treatments fail to induce a sterile cure because they do not eliminate persistent parasites from the host [2,16]. A critical challenge is related to widespread resistance to pentavalent antimony, especially some areas in India, where it can go up to 60%.

In Europe, liposomal formulations of AmB (LAB) are recommended as first-line treatment. Compared to deoxycholate formulations ("classical" AmB), LAB has a more favorable safety profile and seems to increase anti-leishmanial activity, improving effectiveness [20]. It is used against several severe fungal infections which have become much more common in our daily practice, giving us extensive knowledge of its side effects. There was no adverse events with treatment in our patient and, as described in literature [16], the patient became afebrile and asymptomatic within the first week. SLE patients are immunosuppressed both by the underlying disease and immunosuppressive drugs. Our patient was on daily prednisolone and, until she was admitted, had been on methotrexate for several years. The disease was thought to have at least one year of duration, based on the beginning of symptoms, and had taken quite a toll on the patient. Because of all those reasons, we chose the recommended regimen with LAB for immunocompromised patients [19].

The differential diagnosis in a patient with systemic lupus erythematosus presenting fever and multisystemic manifestations is often difficult but must always include infectious or neoplastic disorders. The patient lived in an endemic focus of *Leishmania*, and typical clinical and analytical changes were all present, making this case highly educational. It also highlights the importance of a patient's epidemiological background and how it can lead to the diagnosis and timely treatment of a rare and deadly disease. The authors hope it will be able to help guide clinicians who may face a similar situation.

Conflict of interest

None declared.

Acknowledgements

The authors would like to acknowledge the contribution of Dr. Fátima Ferreira, hematologist, and Dr. Joana Sobrinho-Simões, head of the Molecular Biology unit of the Pathology Department, for the study and unraveling of this case. The first author would also like to acknowledge Dr. Alcina Ferreira's guidance.

References

[1] Dujardin JC, Campino L, Canavate C, Dedet JP, Gradoni L, Soteriadou K, et al. Spread of vector-borne diseases and neglect of Leishmaniasis, Europe. Emerg Infect Dis 2008;14(7):1013–8.
[2] McGwire BS, Satoskar AR. Leishmaniasis: clinical syndromes and treatment. QJM 2014;107(1):7–14.

[3] Liese J, Schleicher U, Bogdan C. The innate immune response against Leishmania parasites. Immunobiology 2008;213(3–4):377–87.
[4] Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 2004;27(5):305–18.
[5] Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS ONE 2012;7(5):e35671.
[6] Santana IU, Dias B, Nunes EA, Rocha FA, Silva Jr FS, Santiago MB. Visceral leishmaniasis mimicking systemic lupus erythematosus: case series and a systematic literature review. Semin Arthrit Rheum 2015;44(6):658–65.
[7] Alvar J, Aparicio P, Aseffa A, Den Boer M, Canavate C, Dedet JP, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clin Microbiol Rev 2008;21(2):334–59. table of contents.
[8] Campino L, Maia C. Epidemiology of leishmaniases in Portugal. Acta Med Portuguesa 2010;23(5):859–64.
[9] Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthrit Rheum 1996;25(5):318–36.
[10] Doria A, Canova M, Tonon M, Zen M, Rampudda E, Bassi N, et al. Infections as triggers and complications of systemic lupus erythematosus. Autoimmun Rev 2008;8(1):24–8.
[11] Wallis PJ, Clark CJ. Visceral leishmaniasis complicating systemic lupus erythematosus. Ann Rheum Dis 1983;42(2):201–2.
[12] Moore J, Brown K. Sun, sangria and sandflies: Leishmaniasis in an immunosuppressed patient returning from Spain. Travel Med Infect Dis 2013;11(2):119–22.
[13] Ravelli A, Viola S, De Benedetti F, Magni Manzoni S, Martini A. Visceral leishmaniasis as a cause of unexplained fever and cytopenia in systemic lupus erythematosus. Acta Paediatr 2002;91(2):246–7.
[14] Braun J, Sieper J, Schulte KL, Thiel E, Janitschke K. Visceral leishmaniasis mimicking a flare of systemic lupus erythematosus. Clin Rheumatol 1991;10(4):445–8.
[15] Fernandez-Guerrero ML, Aguado JM, Buzon L, Barros C, Montalban C, Martin T, et al. Visceral leishmaniasis in immunocompromised hosts. Am J Med 1987;83(6):1098–102.
[16] Herwaldt BL. Leishmaniasis. Lancet 1999;354(9185):1191–9.
[17] Antinori S, Calattini S, Longhi E, Bestetti G, Piolini R, Magni C, et al. Clinical use of polymerase chain reaction performed on peripheral blood and bone marrow samples for the diagnosis and monitoring of visceral leishmaniasis in HIV-infected and HIV-uninfected patients: a single-center, 8-year experience in Italy and review of the literature. Clin Infect Dis 2007;44(12):1602–10.
[18] Srivastava P, Dayama A, Mehrotra S, Sundar S. Diagnosis of visceral leishmaniasis. Trans R Soc Trop Med Hyg 2011;105(1):1–6.
[19] World Health Organization. Control of the leishmaniases. World Health Organization technical report series no. 949; 2010;p. xii–i, 1–186, back cover.
[20] Singh N, Kumar M, Singh RK. Leishmaniasis: current status of available drugs and new potential drug targets. Asian Pac J Trop Med 2012;5(6):485–97.