

Visceral Leishmaniasis in a patient with rheumatoid arthritis undergoing treatment with methotrexate: Case report and review of the literature

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Abstract

There is growing concern regarding the emergence of visceral leishmaniasis (VL), a disseminated parasitic disease caused by protozoa of the genus *Leishmania*, as an opportunistic infection in immunocompromised patients. This association has been principally studied in the context of human immunodeficiency virus infection, but VL has also been reported in patients undergoing treatment with immunosuppressive medication for various indications. Here a case of VL in a patient with rheumatoid arthritis undergoing treatment with methotrexate and corticosteroid is presented. Despite the rarity of such incidents, physicians should include VL in the differential diagnosis because this infection, if left untreated, is characterized by significant mortality.

Keywords: Visceral leishmaniasis, immunocompromised patients, rheumatoid arthritis, methotrexate, corticosteroids

Introduction

Leishmaniasis is a parasitic infection endemic to tropical and subtropical countries with an estimated annual incidence ranging between 900,000 and 1,500,000 cases (1). It is classified into three primary clinical forms: cutaneous, mucocutaneous, and visceral leishmaniasis (VL); the latter being the most severe and potentially fatal form (2). Its mortality rate ranges between 75% and 95% and is mainly attributed to secondary infections and hemorrhagic complications.

There is accumulating evidence that immunosuppression facilitates the development of clinically overt VL, with most data concerning human immunodeficiency virus (HIV)-infected individuals (2-4). Reports of opportunistic VL in patients with rheumatoid arthritis (RA) undergoing treatment with immunosuppressive agents are fewer (5). We present an additional case of VL in a patient with RA undergoing treatment with methotrexate and methylprednisolone; informed consent was obtained from the patient for presentation of her case.

Case Presentation

A 71-year-old Caucasian woman was admitted to the Internal Medicine Department of Evangelismos General Hospital because of intermittent fever up to 38°C for 1 week as well as fatigue and weight loss during the preceding months. Recent blood examination had revealed anemia [hematocrit (Hct) level, 28%] and hypergammaglobulinemia. The patient also complained of edema and pain in the left lower limb with acute onset.

The patient had a history of RA diagnosed 5 years before and was undergoing treatment with methotrexate (2.5 mg t.i.w. for 3 years) and methylprednisolone (4 mg qd for 3 years) to keep her on remission. She also suffered from well-controlled Parkinson's disease treated with Levodopa and was heterozygote for the V Leiden factor. She reported an incident of deep vein thrombosis 2 years before; however, she was not taking anticoagulants. The patient had not traveled anywhere recently.

Physical examination showed edema and tenderness in the left lower limb and palpable liver and spleen. No active arthritis or joint deformities were detected, and there were no skin rashes or abnormal pigmentation.

Deep vein thrombosis was confirmed with lower limbs venous ultrasonography and was undergoing treatment with low molecular weight heparin.



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Submitted: 3 August 2016

Accepted: 28 September 2016

Available Online Date: 11.04.2017

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Association - Available online at www.eurjrheumatol.org.

Laboratory findings indicated anemia [Hct level, 27.1% and hemoglobin (Hgb) level, 9.0 mg/dL] and leukopenia [white blood cell (WBC) count, $2.9 \times 10^9/\text{mL}$] without thrombocytopenia (platelet count, $161 \times 10^6/\text{mL}$). C-reactive protein level was elevated (7.2 mg/dL). Serum protein electrophoresis showed non-monoclonal hypergammaglobulinemia (IgG level, 6190 mg/dL), while urine protein electrophoresis showed non-monoclonal increase in globulins (alpha-1-globulin, 3.88 mg/dL; beta-2-globulin, 0.24 mg/dL; kappa light chains, 6.9 mg/dL; and lambda light chains, 2.9 mg/dL). Abdominal ultrasonography indicated splenomegaly (width 17.8 cm), hepatomegaly (width 18 cm), and signs of incipient portal hypertension.

During hospitalization the febrile episodes persisted despite empirical treatment with wide spectrum antibiotics (combination of ceftazidime and clindamycin and consequently combination of ceftazidime, teicoplanin, and amikacin). Repeated blood cultures for common bacterial pathogens were negative. Leukopenia and anemia deteriorated (lowest values: WBC count, $1.54 \times 10^9/\text{mL}$; neutrophil count, $0.77 \times 10^9/\text{mL}$; and Hgb level, 7.4 mg/dL) requiring transfusion with 2 units of red cell concentrates.

The diagnosis was established with positive indirect immunofluorescence serological test (titer 1:320) and positive polymerase chain reaction test for *Leishmania spp.* Results from bone marrow biopsy confirmed the diagnosis. Serologic testing for HIV, hepatitis B, and hepatitis C infection was negative.

The patient was treated with liposomal amphotericin B (3 mg/kg of body weight) administered for 5 consequent days and then at the 14th and 21st day. At the last day of treatment, clinical improvement and remission of cytopenia had been achieved.

Discussion

Visceral leishmaniasis is a disseminated parasitic infection caused by obligate intracellular protozoa of the genus *Leishmania*. In the Mediterranean basin, the responsible species is *L. infantum*, whereas in other areas the species *L. donovani* is also involved (2, 6). In most cases, the parasite is transmitted by the bite of infected female sand flies of the genus *Phlebotomus* in the eastern hemisphere and *Lutzomyia* in the western hemisphere. VL due to *L. infantum* follows a zoonotic pattern of transmission because the vectors become infected by biting animal reservoirs, whereas in VL due to *L. donovani*, transmission is typically anthroponotic

(6). Greece, in particular, is considered an endemic region for VL with an estimated annual incidence of 50-80 cases, during the period of 2004-2008 (1).

The pathogen multiplies in the lysosomal organelles of macrophages throughout the reticuloendothelial system. The liver, spleen, and bone marrow are affected, and the disease is characterized by fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia (2). Without treatment, VL has a high mortality rate (75%-95%), mostly because of secondary infections or hemorrhagic complications (6). Various effective medications, such as liposomal amphotericin B, have been developed that has led to cure rates greater than 90% (6).

The competence of infected individuals' immune reactions is a deciding factor in the development and prognosis of VL. HIV and *Leishmania* co-infection increases the risk for developing clinically overt VL by more than 100 times (3). Development of VL in such patients can be attributed to increased susceptibility to primary infection or reactivation of latent parasitic infection (3). HIV-infected patients also exhibit lower cure rates, higher relapse rates, and higher mortality from VL than immunocompetent patients (3). VL has also been reported in immunosuppressed organ transplant recipients, patients with autoimmune disorders undergoing treatment with immune modulating agents, and patients with hematological malignancies (6-10).

There have been several case reports of VL in patients with RA undergoing treatment with immunosuppressive agents; majority of these patients undergo treatment with tumor necrosis factor- α antagonists. Reports in the literature of VL in patients with RA undergoing treatment with methotrexate are few; all of them involve patients residing in or having recently traveled to Southern Europe (8, 9). Only eight cases have been reported of VL in patients with RA undergoing treatment with methotrexate, most of whom were females in their 60's or 70's and who had been taking methotrexate at higher doses than our patient did. It is noteworthy that compared with other cases, our patient underwent treatment with methotrexate at a low dose of (7.5 mg/w). It seems likely that apart from the lymphocyte dysregulation occurring in RA, the addition of methotrexate plus corticosteroids could have accounted for the immunosuppression that characterized our patient. No reports exist that cor-

relate Parkinson's disease and VL nor deep venous thrombosis (DVT) and VL. Therefore, it seems that there is no relationship between VL, Parkinson's disease, or DVT. There is only one report in the medical literature of a patient with VL and Budd-Chiari syndrome, but this patient also had factor V Leiden mutation, similar to our patient (10). The factor V Leiden mutation could account for DVT in our patient as well as in the patient with VL and Budd-Chiari syndrome.

The herein reported case presented differential diagnostic difficulties because more likely diagnoses could be hematological malignancies, including multiple myeloma, methotrexate-induced myelosuppression, Felty's syndrome, or viral infections. Taking into account the significant mortality of VL and the availability of efficient treatment, it is a diagnosis that should not be overlooked, particularly in immunocompromised patients. Notably, our patient was having a dog, an animal well-known to be implicated in the transmission of VL. Therefore, apart from her immunosuppression, there was a dog in her every day environment, which was also suffering from leishmaniasis. Thus, immunosuppression, travel history, and animal contact should always be taken into account when dealing with fever, pancytopenia, and prominent hypergammaglobulinemia.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.V.; Design - E.K.; Supervision - E.K.; Data Collection and/or Processing - E.G.; Literature Search - K.T.; E.G.; Writing Manuscript - K.T.; Critical Review - N.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. 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: e35671. [CrossRef]
2. McGwire BS, Satoskar AR. Leishmaniasis: clinical syndromes and treatment. *QJM* 2014; 107: 7-14. [CrossRef]
3. Ezra N, Ochoa MT, Craft N. Human immunodeficiency virus and leishmaniasis. *J Glob Infect Dis* 2010; 2: 248-57. [CrossRef]

4. Ready PD. Epidemiology of visceral leishmaniasis. *Clin Epidemiol* 2014; 6: 147-54. [\[CrossRef\]](#)
5. Saporito L, Giammanco GM, De Grazia S, Colomba C. Visceral leishmaniasis: host-parasite interactions and clinical presentation in the immunocompetent and in the immunocompromised host. *Int J Infect Dis* 2013; 17: e572-6. [\[CrossRef\]](#)
6. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. *Lancet Infect Dis* 2008; 8: 191-9. [\[CrossRef\]](#)
7. Van Griensven J, Carrillo E, Lopez-Velez A, Lynen L, Moreno J. Leishmaniasis in immunosuppressed individuals. *Clin Microbiol Infect* 2014; 20: 286-99. [\[CrossRef\]](#)
8. Venizelos I, Tatsiou Z, Papathomas TG, Orazi A. Visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate. *Int J Infect Dis* 2009; 13: e169-72. [\[CrossRef\]](#)
9. Karagiannidis GS, Mantzourani M, Meletis J, Anastasopoulou AN, Vaiopoulos GA. Visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate. *J Clin Rheumatol* 2012; 18: 59. [\[CrossRef\]](#)
10. Gürkan E, Unsal C, Başlamışli F, Arslan D. Budd-Chiari syndrome associated with visceral leishmaniasis and factor V Leiden mutation. *J Thromb Thrombolysis* 2004; 18: 205-7. [\[CrossRef\]](#)