CASE REPORT

Visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate

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Summary

Visceral leishmaniasis (VL) is a relatively rare occurrence in rheumatoid arthritis (RA) patients treated with tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) antagonists, corticosteroids and methotrexate, or methotrexate alone. A review of the literature revealed that only one case of VL in an RA patient treated with methotrexate has been previously published. We describe an additional case, that of a 65-year-old female with RA being treated with methotrexate, who presented with fever, abdominal discomfort, splenomegaly and pancytopenia. A diagnosis of VL was ultimately established, after a splenectomy was performed. Because RA is characterized by immune cell dysfunction and dysregulation, which potentially predisposes patients to infection, it is unclear whether this serious opportunistic infection can be solely attributable to the methotrexate, an immunosuppressive medication that also increases the risk of infection.

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Introduction

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause.\textsuperscript{1} It is characterized by immune cell dysfunction and dysregulation, which potentially predisposes patients to infection. As the long-term use of immunosuppressive medication for RA, such as methotrexate, also increases this particular risk, it is unclear whether this increased infectious morbidity and mortality is solely attributable to RA per se or represents sequelae of the immunosuppressive therapy, or a combination thereof. In addition, it is often difficult to differentiate between reactivation of a latent infection induced by immunosuppressive drugs and a recent infection in an immunocompromised patient.

Case report

Herein, we report the case of a 65-year-old Caucasian female, living in a rural area of central Greece, who had been suffering from RA for the past eight years and was being treated with methotrexate. She was admitted to our hospital complaining of fever, night sweats, abdominal discomfort for two weeks, and 10 kg weight loss over three months. On physical examination, her spleen was palpable approximately 20 cm below
the left costal margin; no hepatomegaly, peripheral lymphadenopathy nor skin rashes were detected. She denied any history of travel outside Greece. Laboratory findings were as follows: erythrocyte sedimentation rate (ESR) 98 mm/hour; white blood cell (WBC) count 2.9 × 10^9/l; platelets 114 × 10^9/l; hematocrit (Ht) 29%; lactate dehydrogenase (LDH) 560 IU/L; hypoalbuminemia 2.8 g/dl; and polyclonal hypergammaglobulinemia (chiefly involving IgG). The Mantoux test, Widal—Wright reaction and serology for HIV, hepatitis B and C viruses (HBV, HCV), Epstein—Barr virus (EBV), cytomegalovirus (CMV) and toxoplasma were all negative.

Because of the splenomegal and pancytopenia, a splenectomy was recommended and finally performed. The excised spleen weighted 1120 g and measured 21 × 15 × 5.5 cm. Histological examination displayed a hyperplastic red pulp containing an increased number of macrophages both in the cords and within the vascular sinuses. Numerous reactive plasma cells were also noted (Figure 1). A large proportion of the cortical macrophages were stuffed with ingested parasites morphologically consistent with Leishmania donovani (Figure 2). The white pulp showed follicular hyperplasia and occasional atrophy. Occasional arterioles showed perivascular fibrosis with an 'onion skin' effect. On the basis of pathological features alone, a diagnosis of visceral leishmaniasis (VL) was considered. Subsequently, a bone marrow biopsy revealed abundant Leishmania parasites, and indirect immunofluorescence antibody testing (ELISA) was strongly positive for Leishmania. The patient was treated with liposomal amphotericin-B for a total dose of 21 mg/kg (3 mg/kg per day on days 1—5, day 14 and day 21). Four years later, she is clinically stable with no further clinical or biological symptoms of leishmaniasis detected.

Discussion

Leishmaniasis is caused by a group of obligate intra-macrophage protozoan parasites transmitted to humans by approximately 30 different species of phlebotomine sandflies.3,5 There are three general forms of leishmaniasis [cutaneous leishmaniasis (CL); mucocutaneous leishmaniasis; and visceral leishmaniasis (VL) or kala-azar] and three rare clinical variants of CL [diffuse cutaneous leishmaniasis; leishmaniasis recidivans (recurrent leishmaniasis); and post-kala-azar dermal leishmaniasis].3,4 VL results from infection with Leishmania donovani or Leishmania infantum (Leishmania donovani complex) and is endemic in some parts of South America, Africa, China, India and the Mediterranean basin.3,5

Apart from the aforementioned clinical syndromes, HIV-associated leishmaniasis has been recognized in increasing numbers over the past two decades.5 In addition, malnutrition or impaired immunocompetence (other than that related to HIV) associated with young age, neoplastic diseases, transplantation and immunosuppressive therapy increase the risk of VL manifestation after Leishmania infection.1,5—8 The development of VL in cancer patients has been more frequently reported with hematologic malignancies rather than solid tumors.9 VL in organ transplant recipients has been most commonly associated with renal transplantation.10 VL was formerly a disease of childhood. Clinical VL in older age groups might be attributable to the increased travel of otherwise immunocompromised elderly subjects to endemic regions, or to the increased proportion of Leishmania and HIV co-infected subjects.7,8

The pathogenesis of the disease is a mixture of the direct effects of the organism on infected cells and the host response to the infectious process.3 Interestingly, disease expression largely depends on the species of the infecting parasite, whereas the course of infection is based on the host-specific cell-mediated immune response.4 In experimental leishmaniasis, two distinct subsets of T-helper cells are crucial in inducing susceptibility or resistance to infection. T-helper type 1 (Th1) cells produce IL-2, interferon-γ, tumor necrosis factor (TNF)-α and TNF-β, and enhance cell-mediated immune responses by activating macrophages to phagocytize and kill intracellular amastigotes. In addition, IL-12 exerts its effect by inducing naïve T cells to differentiate into Th1 cells and by inducing both T cells and natural killer cells to produce interferon-γ. Th2 cells, which secrete IL-4, IL-5 and IL-10, inhibit some cell-mediated immune responses. Of importance, IL-10 has pleiotropic, primarily deactivating effects on target cells, including antagonizing dendritic cell functions and rendering macrophages unre-
sensitive to activation signals. In VL patients, the inability to control Leishmania donovani infection is associated not only with an inadequate T-cell response (due to a Th1 defect or Th2 dominance per se) to leishmanial antigens, but also with concomitant production of IL-10, which might be triggered as a potential homeostatic mechanism in order to limit immune-mediated pathology.11,12

Experimental evidence, based on the mouse model, strongly supports a potential role for IL-10, as a mediator of splenic pathology in VL. Although the spleen is an initial site for the generation of cell-mediated immune responses, it ultimately becomes a site of parasite persistence with the associated immunopathology, encompassing splenomegaly and a breakdown in tissue architecture. In particular, the pathology is mediated by the direct loss of specific cell populations (follicular dendritic cell networks, marginal zone macrophages, gp38+ stromal cells) and an array of changes to the local tissue microenvironment that ultimately result in fatality due to the immunocompromised status of the host.13 Of note, in VL, the white pulp becomes disorganized and reduced in size (follicular atrophy), whereas the red pulp becomes hyperplastic with heavily infected macrophages demonstrated in multiple and unusual locations.

By contrast, reactive follicular hyperplasia is almost always observed in untreated RA and Felty’s syndrome (a complication of RA).14,15 Hyperplastic germinal centers, along with an increase in the red pulp (expanded red pulp sinuses and cords with a prominent macrophage population), constitute the structural basis for the observed splenomegaly in Felty’s syndrome.15,16 With regard to splenomegaly in uncomplicated RA, this represents a common, extra-articular feature of the disease. It is observed, upon manual palpation, isotope scanning or abdominal ultrasonography, in 5–10% up to 58% of patients with RA, while rendering them at risk of experiencing spontaneous splenic rupture.17 Of interest, an enlarged spleen in such cases might be attributed to a mechanism similar to that in Felty’s syndrome, in which there is an excessive margination of granulocytes caused by antibodies to these cells, complement activation or binding of immune complexes, suggesting that these patients might be in an early stage of Felty’s syndrome.1,15,16

VL is a relatively rare event in RA patients treated with TNF-α antagonists; only four reports have been described (two treated with adalimumab, one treated with infliximab, one treated with etanercept). TNF-α blockade results in deactivation of T and B lymphocytes, and macrophages necessary for ingestion and killing of Leishmania pathogens.17–21 VL is also rare in RA patients treated with corticosteroids/methotrexate; only two cases have been reported.22 Glucocorticoids affect the effector, suppressor and cytotoxic T-cell functions through the blockade of cytokine expression, whereas methotrexate appears to decrease antigen-stimulated T-cell proliferation, neutrophil chemotaxis and superoxide generation, as well as T-cell release of TNF-α and interferon-γ, in patients with RA.6,17 Finally, to our knowledge, there are only two case reports of VL in RA patients treated with methotrexate (including the one described herein).7

With the increasing use of anti-TNFα therapy, the risk of an increasing incidence of VL in leishmaniasis endemic countries, such as those in the Mediterranean, is to be expected and anticipated. However, because of the low incidence of Mediterranean VL, it seems difficult to propose a systematic screening for leishmaniasis in all patients treated with immunobiologicals. Another point of clinical importance concerns those patients returning from an endemic area with clinical signs and symptoms characteristic of VL. As untreated VL is fatal, clinicians should consider the diagnosis more rapidly in order to ensure that pertinent laboratory evaluation is employed and appropriate treatment is administered.

The clinical picture of our VL case was typically characterized by fever, weight loss, splenomegaly and pancytopenia. The diagnosis relied on the splenic pathology, detection of parasites in the bone marrow biopsy and indirect immunofluorescence antibody testing. Although splenectomy was recommended to relieve abdominal discomfort, ameliorate hypersplenism, and pre-empt a splenic rupture and subsequent life-threatening hemorrhage, it was retrospectively unnecessary.

Conflict of interest: No conflict of interest to declare.

References


