

# Visceral Leishmaniasis in the Mediterranean area

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To the Editor,

We have read with great interest the case report entitled "Visceral Leishmaniasis in a patient with rheumatoid arthritis undergoing treatment with methotrexate: Case report and review of the literature" by Trigkidis et al. (1) and would like to congratulate the authors and add some comments concerning visceral leishmaniasis (VL) that might be of interest of readers.

As described by the authors, VL in patients with rheumatoid arthritis (RA) has been commonly reported when they receive immunosuppressive agents, which are most commonly tumor necrosis factor- $\alpha$  antagonists. What is clearly uncommon is to present VL under methotrexate (MTX) treatment. Trigkidis et al. (1) mentioned that only eight cases of this condition have been reported so far. We would like to highlight that our group reported a similar case that was recently published elsewhere, increasing the number of cases to nine (2). The onset of VL can be silent or full-blown (kala-azar), with its characteristic pentad: prolonged fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. Different from the patient in the report by Trigkidis et al. (1) who presented with a hemoglobin level of 9.0 mg/dL and leukopenia (white blood cell count of  $2.9 \times 10^9/\text{mL}$ ) without thrombocytopenia, our patient presented with the classical Kala-azar pattern, specifically due to the *Leishmania infantum* subtype. As mentioned by Trigkidis et al. (1), most patients are in their 60s and take MTX at a high dose. Similarly, our patient received 15 mg/week of MTX, which is most commonly prescribed in pivotal drug studies for treating RA (3). Another interesting point is that most reported patients are from Southern Europe, mainly Greece; our patient was from Spain, a nearby country. A vast majority of the side effects of MTX have been evaluated because of pharmacogenetic studies that have analyzed SNPs in SLC19A1/RFC1, ABCB1, FPGS and GGH in the most recognized genes, but to date, opportunistic infections have shown no relationship with those polymorphisms (4).

Leishmaniasis is understood to be a set of syndromes caused by infection of the protozoan of the genus *Leishmania*, which is widely present in tropical regions, mostly *L. donovani*, whereas *L. infantum* causes a disease that is endemic in the Mediterranean area, and this subtype was isolated in our patient using a method different from Trigkidis et al. (1) study. A diagnosis can be made using heterogeneous methods, either indirect immunofluorescence, serological test positive polymerase chain reaction test for *Leishmania* spp. or bone marrow biopsy being all patients are treated with liposomal amphotericin B.

We would like to highlight that MTX reduces the cell immune response and inhibits neutrophil chemotaxis and T-cell proliferation; thus, opportunistic infections can arise. Interestingly, all patients with VL described to date received concomitant oral steroids at a low dose, leading to steroids being partially blamed for lower cellular host defense and increased risk of infection (5). The risk of infection in patients with RA is complicated to evaluate as multiple factors such as age, presence of comorbidities, use of biological therapies, and the persistent activity of the disease itself contribute to the risk (5).

Taking these factors into account, doses lower than 7.5 mg/day of prednisone in combination with DMARDs do not represent an excessive risk of infection. However, if doses above 15 mg/day of prednisone are required in combination with DMARDs, the risk of infection is triggered, particularly when the number of co-morbidities increases (6).

To sum up, we are glad to add another case of VL, specifying that in the Mediterranean area, *L. infantum* is the major subtype that infects patient with RA as an opportunistic germ, not predictable with pharmacogenetic analyses to date (2). Moreover, we want to point out that MTX plays a role in the host defense, but we wonder what is the role deserved to the concomitant use of steroids in decreasing cellular host defense and leading to VL among opportunistic infections.



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