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Case Report

Safe Treatment With Secukinumab in a Patient With Axial Spondyloarthritis and a History of a *Leishmania donovani* Infection

To the Editor:

Infections during treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) are some of the most frequent adverse events in patients with axial spondyloarthritis (axSpA) and with rheumatic diseases in general.

We report a case of a 41-year-old White male with axSpA who developed a *Leishmania donovani* infection while under treatment with adalimumab (ADA). Consequently, we questioned which treatment could be used in this patient to treat their rheumatic disease after the infection had been resolved.

This case report received the ethics board approval from the "Comité de Ética de la Investigación Provincial de Córdoba" (ethics approval number 5699). The patient's written informed consent was obtained to publish this material.

In July 2021, the patient first presented to our department for an outpatient consultation with a history of inflammatory back pain for more than 10 years, morning stiffness, and good response to nonsteroidal antiinflammatory drugs (NSAIDs). He was under treatment with diclofenac 75 mg/day, and his BMI was 38.9 kg/m^2. The C-reactive protein (CRP) was 13.6 mg/L (reference 10 mg/L), HLA-B27 was positive, and the patient had radiographic sacroiliitis grade IV with concomitant lumbar degenerative disc disease. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was 4.1, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 8. Etoricoxib 90 mg/day was prescribed, but 3 weeks later, the patient continued to have nocturnal pain, his ASDAS was 4.4, and his CRP was 14.8 mg/L. Therefore, 40 mg ADA every 2 weeks was proposed. The patient's serology results were negative for hepatitis B, hepatitis C, and HIV. The Mantoux test and chest radiograph were normal.

After 2 weeks of ADA, the patient showed an excellent clinical response, but he started to have headaches, dyspnea, cough, and fever. His coronavirus disease 2019 (COVID-19) test was negative, and the patient was hospitalized because of hypertransaminasemia, leukopenia, thrombopenia, an increased D-dimer level and elevated ferritin level. ADA was suspended upon admission (Figure). Real-time PCR (qPCR) using the kinetoplast DNA as a molecular target in his blood sample revealed the presence of the *L. donovani* complex (without determination of the species), confirming the diagnosis of hemophagocytic lymphohistiocytosis secondary to visceral leishmaniasis. In August 2021, the patient started treatment with intravenous (IV) liposomal amphotericin B 4 mg/kg per week for 10 weeks, and he has continued with IV pentamidin 4 mg/kg every 4 weeks as prophylaxis. In September 2021, after 1 month of treatment with amphotericin B, the PCR for the *L. donovani* complex was negative (Figure).

During the subsequent months after the withdrawal of ADA, the patient showed a progressive worsening of his axSpA, with the development of lumbar and buttock inflammatory pain, worsening of morning stiffness, and development of right coxitis. His CRP was 15.2 mg/mL despite having a negative leishmaniasis PCR (suggesting active axSpA), his ASDAS was 4.8, and his BASDAI was 8.6.

In December 2021, a multidisciplinary meeting of rheumatologists and infectious disease specialists was held to discuss this patient's case and the possibility of initiating a new bDMARD or a targeted synthetic DMARD. Studies of the pathophysiological mechanism of *L. donovani* infection were reviewed to determine an appropriate drug. Briefly, at an early stage of infection, neutrophils can release neutrophil extracellular traps and destroy *L. donovani* promastigotes, but they can also activate infected macrophages and induce parasite control in a reactive oxygen species (ROS)-dependent manner.[1] In addition, interferon-γ and tumor necrosis factor (TNF) act synergistically to promote the activation of macrophages to eliminate parasites by inducing nitric oxide (NO). In fact, in vivo models have demonstrated that mice deficient in soluble TNF suffered from a high parasite

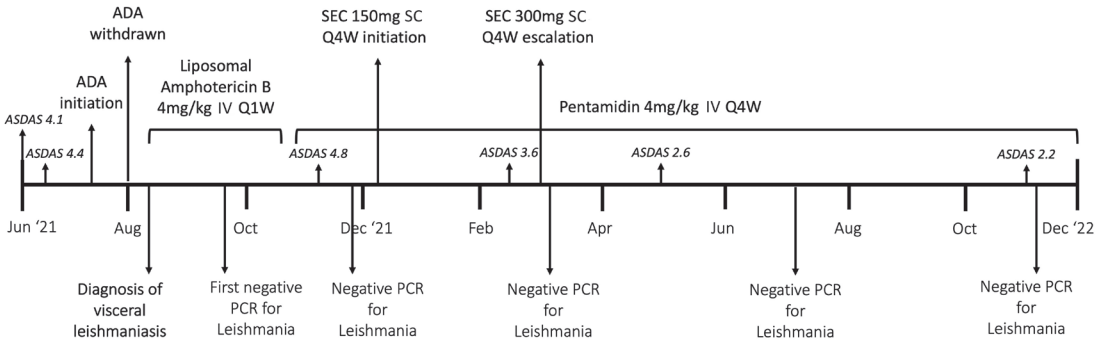

Figure. Chronogram of the patient from July 2021 (date of axSpA diagnosis) to December 2022. ADA: adalimumab; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; IV: intravenous; Q1W: once a week; Q4W: every 4 weeks; SC: subcutaneous; SEC: secukinumab.

burden and fatal disease.[2,3] Monocytes are recruited from the blood and produce ROS to kill *L donovani* promastigotes parasites. Monocytes also differentiate into dendritic cells (DCs), migrate to the lymph nodes, and promote the differentiation of Th1 cells by producing interleukin 12 (IL-12).[1] Th1 cells then migrate and eliminate the parasites by inducing NO production.

According to the literature review, most cases of leishmaniasis that were reported in patients with rheumatic diseases were under treatment with TNF blockers. Only 1 case of leishmaniasis has been reported in a male patient with psoriatic arthritis who was under treatment with anti–IL-17 (secukinumab [SEC]), but he continued with this same drug after the resolution of the infection.[4] Thus, based on the pathways of *L. donovani* promastigotes infection and the literature review, we considered SEC (an inhibitor of IL-17) as a potential treatment in this patient.

SEC was started in December 2021 using a subcutaneous (SC) dose of 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. At the beginning of the treatment, the PCR for the *L. donovani* complex was negative, and the CD4+ T cell and CD8+ T cell levels were in normal ranges in this patient. After 3 months of treatment, the patient noticed a partial improvement (ASDAS 3.6, BASDAI 5.9, CRP 14.1 mg/L), including that of nocturnal pain and stiffness. The SEC dose was escalated to 300 mg SC every 4 weeks, and the patient then had a complete response after 2 months (ASDAS 2.6, BASDAI 3.9, CRP 8.3 mg/L). The PCR results for *L. donovani* promastigotes and CD4+ T cell and CD8+ T cell levels were monitored every 3 to 4 months by infectious disease specialists (Figure).

After 1 year of treatment with SEC (December 2022), no relapses of leishmaniasis had occurred, and the patient's rheumatic disease was reasonably under control, with slight fluctuations in his axial pain that could be partially explained by his existing mechanical lesions.

Pentamidine is suggested in patients with HIV with visceral leishmaniasis coinfection, particularly in those with CD4 counts < 200 cells/μL. Our patient was HIV negative, and his CD4+ T cell count was normal, but we decided to initiate secondary prophylaxis with pentamidine, because he would be treated with immunosuppressant drugs and no specific guidelines have been developed for the management of patients with this diagnostic profile. In addition, the selection of pentamidine as prophylaxis instead of amphotericin B was based on our prior experience with the drug's efficacy and safety in HIV-positive patients treated at our hospital. Further, the pentamidine dosage schedule of 1 infusion every 4 weeks was considered more comfortable for the patient.

In addition, whether serologic screening for latent *L. donovani* infection before bDMARD initiation is needed in a specific population is unclear. Although southern Spain is one of the regions with the highest prevalence of leishmaniasis (incidence of 0.70-0.88 new cases per 100,000 inhabitants), the incidence is too low to warrant the evaluation of latent infection in patients who will start a bDMARD. Thus, routine screening for seroconversion in these patients is not recommended.

In summary, treatment with SEC could be a safe and effective treatment in patients with axSpA and a history of *L. donovani* complex infection.

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The authors declare no conflicts of interest relevant to this article.
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DATA AVAILABILITY

Data are available upon reasonable request. All data relevant to the study are included in the article.

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