Caso clinico

Case report

Visceral leishmaniasis in a psoriatic arthritis patient treated with methotrexate

Leishmaniosi viscerale in un paziente affetto da artrite psoriasica trattato con metotrexate

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Visceral leishmaniasis represents a relatively rare, potentially fatal clinical entity. Here we describe a case of visceral leishmaniasis infection in a 65-year old Greek male with psoriatic arthritis treated with methotrexate, who presented with high grade fever, chills, splenomegaly, pancytopenia and polyclonal hypergammaglobulinaemia.
A diagnosis of visceral leishmaniasis was finally established. Visceral leishmaniasis should be included in the differential diagnosis for infections in patients receiving methotrexate for rheumatic diseases, especially in endemic areas.

INTRODUCTION

Visceral Leishmaniasis (VL) is a life threatening disease, frequently encountered in immunosuppressed patients [1]. Immunosuppressive treatment has been increasingly used for rheumatic diseases; this, in combination with reports of VL in rheumatic patients receiving immunosuppressive treatment, has raised many concerns [2, 3]. The purpose of this report is to describe a case of VL infection in a patient treated with methotrexate for psoriatic arthritis, and to present a brief review on the current literature.

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CASE PRESENTATION

A 65-year old Greek male was admitted to the department of Internal Medicine of the Saint George General Hospital of Chania, Crete, presenting a 3-week history of fever with chills, without any localizing symptoms.
He was diagnosed with psoriatic arthritis 5 years earlier and was treated with methotrexate for approximately 2 years, at a dose of 15 mg per week. His past medical history also included type 2 diabetes and benign prostatic hyperplasia. He was residing in Chania, Crete, an endemic for leishmaniasis area of Greece, had no history of recent travel abroad and reported having pets and domestic animals (dogs, cats, rabbits and chicken). His physical examination revealed a palpable spleen and liver, without peripheral lymphadenopathy.
The hepatosplenomegaly was confirmed with an abdominal ultrasound, which showed an enlarged spleen of 19.3x9.1 cm and a slightly enlarged liver, without any other abnormalities in the rest of the abdomen (Figure 1). Initial laboratory work up revealed pancytopenia (white blood cell count $2{,}22 \times 10^3/\mu l$; red blood cell count $3{,}38 \times 10^6/\mu l$, hematocrit 31%; platelet count $110 \times 10^3/\mu l$), and elevated erythrocyte sedimentation rate [57 mm/h (range: 0-20

mm/h)], C reactive protein [6.1 mg/dl (range: 0-0.5 mg/dl)]) and serum ferritin levels [900 ng/ml (range: 16.4-294 ng/ml)].

The differential diagnosis included infectious, neoplastic, and autoimmune causes of febrile splenomegaly; therefore the patient was admitted for further investigation and methotrexate was interrupted. He underwent a series of additional tests, such as Mantoux test, serology for HIV, hepatitis B and C viruses, Epstein Barr virus, cytomegalovirus and toxoplasma, blood and urine cultures, echocardiogram, tumor markers, immunological blood tests and thyroid function tests which were all negative.

Laboratory tests for rare infectious diseases compatible with the patient's signs and symptoms (including leishmaniasis and other opportunistic infections) were sent to a tertiary care centre (University General Hospital of Heraklion). His serum protein electrophoresis showed polyclonal hypergammaglobulinemia. Computed tomography scan of abdomen and chest were also performed, that confirmed the findings of the ultrasound, but showed no further significant abnormalities.

Over the first week, patient's fever persisted with spikes up to 40.5°C, and his pancytopenia was deteriorating. The differential diagnosis was narrowed down to a few infectious causes (including VL) and lymphoproliferative disorders, which lead us to the decision to perform a bone marrow aspiration/smear and biopsy. The smear revealed several intacellular and extracellular Leishmania parasites (Figures 2 and 3) and the biopsy showed hemophagocytic syndrome, compatible with VL. The diagnosis of VL was reconfirmed when we got the results back from the University Hospital of Heraklion, where our patient tested positive for *Leishmania infantum* in serum IFA test and PCR. He received treatment with liposomal amphotericin B on days 1-5, 14 and 21, with a dose of 3 mg/kg/day.

After the second day of treatment, the patient started to improve clinically with significant fever reduction, gradually leading to a full clinical recovery and restoration of blood exams by the end of the first week. The patient has been on follow-up by our department for 5 months now and no signs of relapse have been noticed.

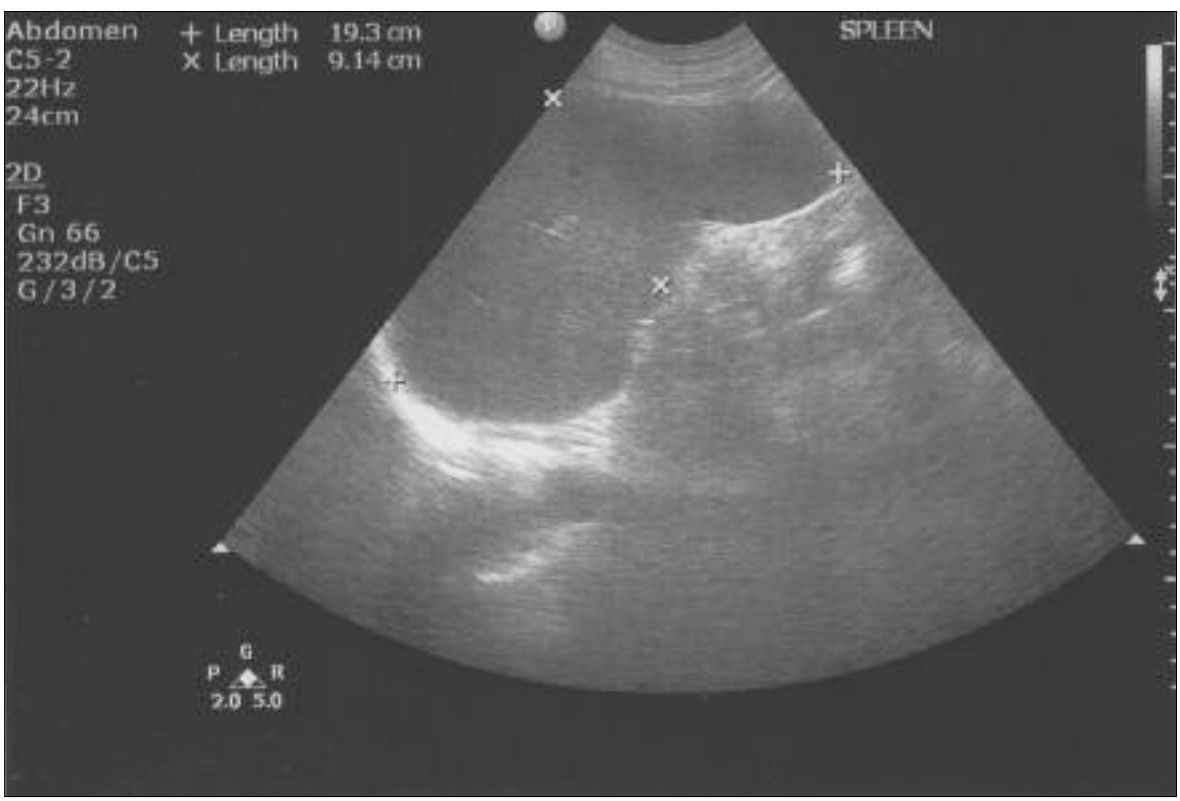

Figure 1 - Abdominal ultrasound showing an enlarged spleen.

DISCUSSION

Approximately 500,000 new VL cases and more than 50,000 deaths are reported every year worldwide [4].
According to the Hellenic Center for Disease Control & Prevention (HCDCP), in Greece approximately 50 new cases of VL are reported per annum. More specifically, in Crete (our patient's place of residence) has been reported the highest incidence.
HCDCP estimates suggest that VL might be underreported in Greece, and also that the parasite could be found in a larger proportion of

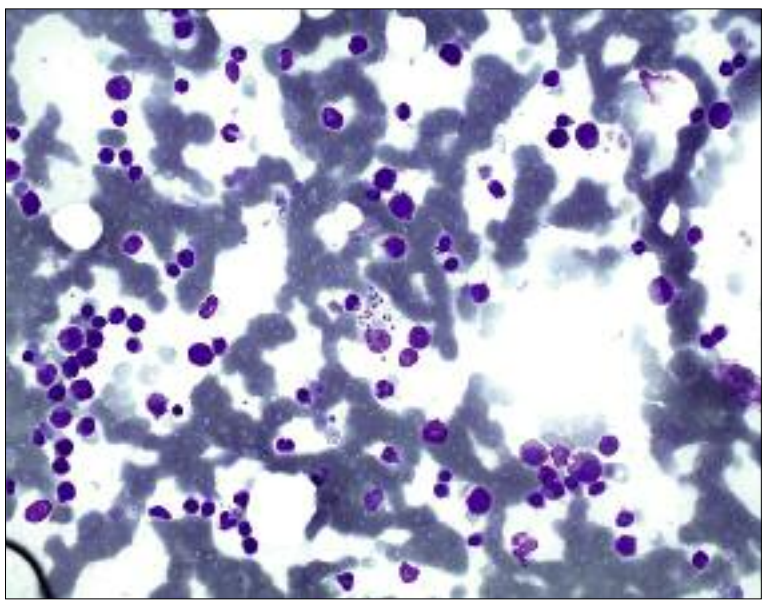

Figure 2 - Bone marrow smear showing extracellular Leishmania parasites.

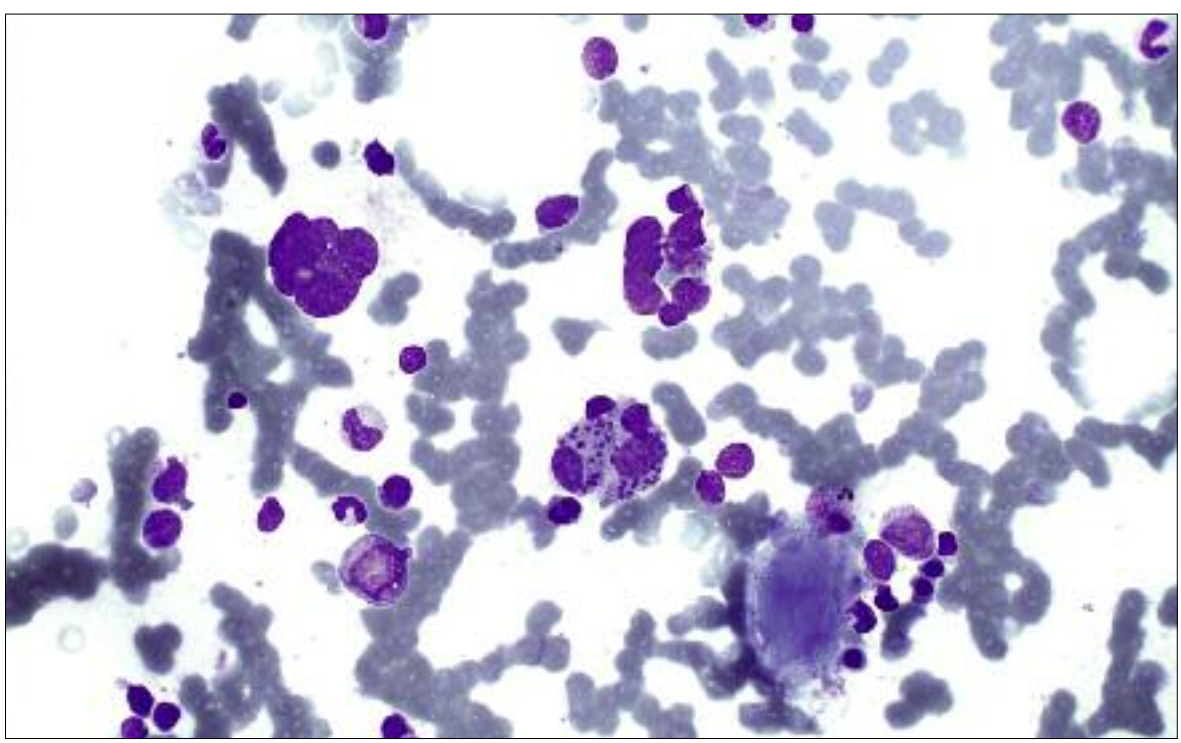

Figure 3 - Bone marrow smear showing intracellular Leishmania parasites aspiration

the population, without causing the disease (latent infection) [5].
Visceral leishmaniasis is mainly caused by *Leishmania donovani* and *L. infantum*, with the latter being associated geographically with the Mediterranean and the Balkans [6]. *L.infantum* transmission is considered zoonotic, with the main reservoir being the domestic dog.
Clinical disease due to *L. infantum*, which is the species detected in our patient, tends to occur in children less than 10 years of age and immunosuppressed adults [6, 7].
The number of latent infection cases in endemic areas proves the ability of the host immune system to control Leishmania [8]. The risk of VL manifestation after Leishmania infection depends on the species and the host nutritional status and immune competence.
Impaired immunocompetence is the reason that VL has been associated with young age, HIV infection, hematologic malignancies, transplantation and immunosuppressive treatment [4, 6, 7].
The reported cases of VL in patients receiving immunosuppressive treatment for rheumatic diseases, in combination with the increasing use of these drugs, have raised many concerns. The past decade, there have been 32 reported cases of VL in patients receiving anti-TNF treatment for rheumatic diseases [2].
To the best of our knowledge, only 7 reports have been made for VL patients under treatment with only methotrexate for rheumatic diseases (8 including ours).
Six of them refer to patients receiving methotrexate for rheumatoid arthritis (RA) and the other one does not clarify that [9-14]. The fact that our patient did not suffer from RA is of some importance.
Some researchers suggest that RA itself sets the patient in immune incompetence, therefore setting him at increased risk for developing VL [11, 12]. Immunosuppressive treatment was stopped in the majority of the reported cases once they were diagnosed and all responded well to anti-leishmanial therapy [2, 9-14]. A number of unanswered issues arise from these reports, such as recommencing immunosuppressive treatment after VL or pretreatment screening before initiating immunosuppression.
Given the difficulty of achieving definitive treatment of leishmaniasis infection, there is, at least theoretically, risk of relapse if immunosuppressive treatment, biological or not, is recommenced after leishmaniasis infection [15-16].
Among the reported cases, only a small number of patients recommenced treatment, with 3 cases of relapse being reported [2]. In fact, in one reported case of a rheumatoid arthritis patient receiving biological treatment (adalimumab, a TNFα inhibitor) along with methotrexate, methotrexate was recommenced after VL, perhaps considered as a safer choice [3]. In our case, methotrexate alone was the only risk factor for VL manifestation.
The ratio of asymptomatic leishmania infection (latent) to VL clinical manifestation is substantially high, especially in Europe, with estimates in some countries up to 50:1 [4]. Many researchers have discussed the need for pretreatment screening in endemic areas before introducing immunosuppressive treatment, although primary prophylaxis is not indicated by current data [15].
Interestingly enough, our patient stated, during his medical interview, owning a dog that was euthanized because of canine leishmaniasis about a decade before.
This, combined with residing in an endemic region, makes the assumption that our patient was a case of latent infection reactivation, a lot more possible.
Given the small number of cases, it is not safe to come to any conclusions on the aforementioned issues; there is need for large scale prospective research to address them.
Another interesting fact is that our patient fulfilled 5 out of 8 diagnostic criteria for Hemophagocytic Syndrome (HS) (fever, splenomegaly, pancytopenia, hemophagocytosis in bone marrow, elevated serum ferritin), enough to establish the diagnosis of HS, according to HLH-2004 diagnostic protocol [17]. HS is a rare condition, especially in adults, and the early recognition of VL as the underlying condition is of great importance, because treatment guidelines for HS include immunochemotherapy, which can result in dramatic deterioration in the case of VL [18]. VL-associated HS responds well to anti-leishmanial therapy, as it did in our case.

CONCLUSIONS

The increasing use of immunosuppressive treatment should be expected to increase the incidence of VL in endemic countries. VL can oc-

cur not only in patients receiving biological treatment, but also in those treated with methotrexate alone. Physicians must have a higher index of suspicion for VL in patients receiving immunosuppressive treatment, that present with febrile splenomegaly, especially in endemic areas.

Informed Consent
Written informed consent was obtained from the patient's next of kin for publication of this manuscript and accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

Competing interests
We declare that we have no competing interests.

Keywords: Visceral leishmaniasis, psoriatic arthritis, methotrexate

SUMMARY

Visceral leishmaniasis, in Greece, represents a relatively rare, potentially fatal clinical entity. Here we describe a case of visceral leishmaniasis infection in a 65-year old Greek male with psoriatic arthritis treated with methotrexate, who presented with high grade fever, chills, splenomegaly, pancytopenia and polyclonal hypergammaglobulinaemia. A diagnosis of visceral leishmaniasis was finally established. Visceral leishmaniasis should be included in the differential diagnosis for infections in patients receiving methotrexate for rheumatic diseases, especially in endemic areas.

RIASSUNTO

La leishmaniosi viscerale, in Grecia, costituisce un'entità clinica relativamente rara, potenzialmente letale. Descriviamo un caso di leishmaniosi viscerale osservata in un uomo di nazionalità greca, di 65 anni, affetto da artrite psoriasica e trattato con metotrexate, che presentava febbre elevata, brividi, splenomegalia, pancitopenia e ipergammaglobulinemia policlonale. É stata posta diagnosi di leishmaniosi viscerale. Questa patologia deve essere sempre considerata nella diagnosi differenziale delle infezioni che possono manifestarsi nei pazienti che assumono metotrexate per il trattamento delle malattie reumatiche, soprattutto se residenti in aree endemiche.

REFERENCES

[1] Bagalas V., Kioumis I., Argyropoulou P., Patakas D. Visceral leishmaniasis infection in a patient with rheumatoid arthritis treated with etanercept. *Clin. Rheumatol.* 26, 1344-1345, 2007.
[2] Guedes-Barbosa L.S., Pereira da Costa I., Fernandes V., Henrique da Mota L.M., de Menezes I., Aaron Scheinberg M. Leishmaniasis during anti-tumor necrosis factor therapy: report of 4 cases and review of the literature (additional 28 cases). *Semin. Arthritis Rheum.* 43, 152-157, 2013.
[3] Berry C.E., Tsai J., Tierney A., Pickles R. Visceral leishmaniasis in a patient taking adalimumab for rheumatoid arthritis. *Med. J. Aust.* 198, 331-333, 2013.
[4] Chappuis F., Sundar S., Hailu A., et al. Visceral Leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat. Rev. Microbiol*. 5, 873-882, 2007.
[5] HCDCP. Epidemiological data of leishmaniasis in Greece (2005-2009) 2011. Retrieved from kelpno.gr/Portals/0/Αρχεία/Διαβιβαστές/leismaniasi.pdf
[6] World Health Organization. Control of the Leishmaniasis: report of the WHO Expert Committee Meeting, Geneva. March 22-26, 2010. *WHO Technical Report Series*. 949, 1, 2010.
[7] Dye C., Williams B.G. Malnutrition, age and the risk of parasitic disease: visceral leishmaniasis revisited. *Proc. Biol. Sci*. 254, 33-39, 1993.
[8] Badaro R., Jones T.C., Carvalho E.M., et al. New perspectives on a subclinical form of visceral leishmaniasis. *J. Infect. Dis.* 154, 1003-1011, 1986.
[9] Harms G., Schönian G., Feldmeier H. Leishmaniasis in Germany. *Emerg. Infect Dis*. 9, 872-875, 2003.
[10] Venizelos I., Tatsiou Z., Papathomas T.G., Orazi A. Visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate. *Int. J. Infect. Dis.* 13, 169-172, 2009.

[11] Karagiannidis G.S., Mantzourani M., Meletis J., Anastasopoulou A.N., Vaiopoulos G.A. Visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate. *J. Clin. Rheumatol*. 18, 1, 59, 2012.
[12] Garcia Olid B., Guirao Arrabal E., Alcala Diaz J.F., Fernández de la Puebla R.Á. Visceral leishmaniasis in two patients treated with methotrexate for rheumatoid arthritis. *Enferm. Infecc. Microbiol. Clin*. 30, 52, 2012.
[13] Toqeer M., Rahman N., Whitehead M.W., Lockwood D. Visceral leishmaniasis in immunosuppressed Caucasian patient. *BMJ Case Rep.* pii: bcr1120115199, 2012.
[14] Guirao-Arrabal E., García-Olid B., Muñoz-López C., Fernández de la Puebla-Giménez R.A. Comment on "visceral leishmaniasis in a rheumatoid arthritis patient treated with methotrexate". *J. Clin. Rheumatol*. 19, 165, 2013.
[15] de Rossell R.A., de Duran R.J., Rossell O., Rodríguez A.M. Is leishmaniasis ever cured? *Trans. R. Soc. Trop. Med. Hyg.* 86. 251-253, 1992.
[16] Badaro R., Jones T.C., Carvalho E.M. New perspectives on a subclinical form of visceral leishmaniasis. *J. Infect. Dis*. 154, 1003-1011, 1986.
[17] Henter J.I., Horne A., Aricó M., et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr. Blood Cancer.* 48, 124-131, 2007.
[18] Saitis A., Gatselis N.K., Dalekos G.N. Leishmaniasis-associated hemophagocytic syndrome revisited: not an uncommon clinical presentation of leishmaniasis. *J. Med. Cases.* 3, 315-318, 2012.