## Visceral leishmaniasis among immunosuppressed patients with rheumatic diseases

Sirs,

We have read with great interest the review of De Leonardis *et al*. concerning the occurrence of visceral leishmaniasis (VL) in rheumatic patients under anti-tumour necrosis factor (TNF)-α therapy (1). This review has prompted us to report an additional personal case of VL in an immunosuppressed rheumatic patient living in Sardinia (Italy). Concerns about the utility of the screening for latent Leishmania (*L*.) infection and follow-up modalities for rheumatic patients apparently cured from VL are also presented.

A 71-year-old woman who had received a diagnosis of rheumatoid arthritis (RA) 4 years previously and was taking adalimumab (40 mg every other week) and methotrexate (10 mg weekly) was admitted to hospital for fatigue, lethargy, weight loss and fluctuant fever. Concomitantly she presented a recurrent cutaneous pruritic erythematosus/papular rash on the trunk. Physical examination was negative for hepato-splenomegaly and lymphadenopathy. Laboratory tests showed severe pancytopenia, marked elevation of C-reactive protein (28 mg/dl) and erythrocyte sedimentation rate (80 mm/h) and polyclonal hypergammaglobulinemia. Indirect immunoflorescent antibody (IFA) assay for *L*. tested positive and bone marrow biopsy microscopy revealed amastigotes into macrophages and intercellular fluid yielding the diagnosis of VL. Liposomal-encapsuled amphotericin B (AmBisome®) at a conventional dose was started with prompt clinical recovery. Due to high disease activity of RA after careful discussion and evaluation with the patient of the risk/benefits ratio adalimumab was reintroduced and a tight control for *L*. recurrence with polymerase chain reaction (PCR) on peripheral blood sample was planned. At 18 months of follow-up, RA disease activity is low, PCR tested negative and no stigmata of VL relapse have been detected.

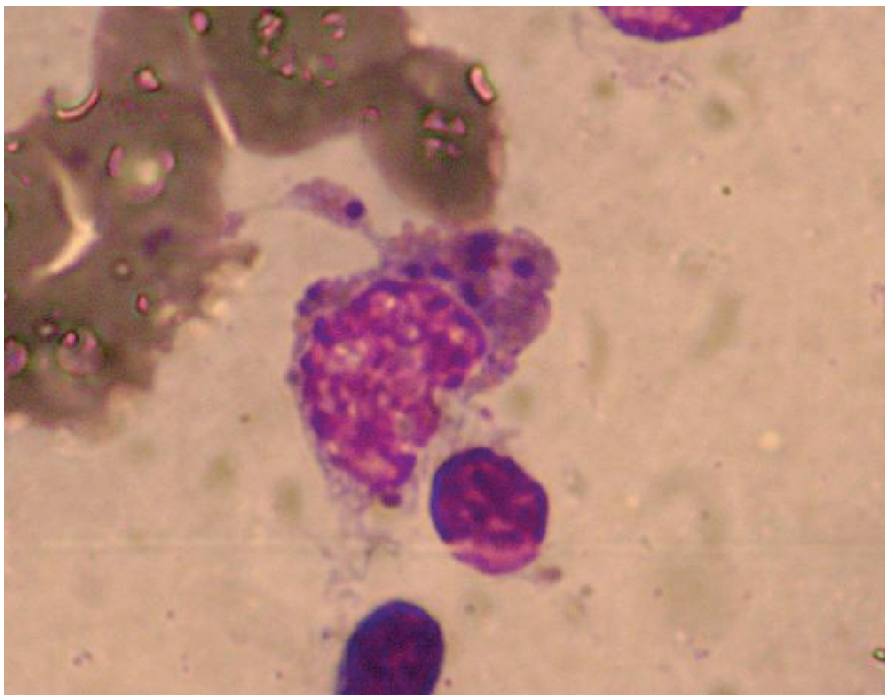

**Fig. 1.** Bone marrow smears showing L. amastigotes engulfed by a monocyte (Giemsa staining, original magnification 100x).

Mediterranean countries are considered to be (hypo)endemic for VL: 1817 cases of VL have been reported in the decade 1993–2003 in Italy (2). A not negligible part of immunocompetent population in the Mediterranean basin shows positive screening tests for latent *L*. infection with an estimated ratio asymptomatic:clinical case of 50:1 in Spain (3). In a survey carried out in 1990 in Sardinia, a positive leishmanin skin test (an intradermal injection of a suspension of killed *L*. promastigotes that measures the delayed type hypersensitivity) rate of 39.3% in the 55–65 years age group of apparently immunocompetent individuals has been reported (4).

Most cases of VL in the Mediterranean basin have emerged as opportunistic infection in HIV positive patients and other immunocompromised individuals. Among high-risk categories for *L*. infection, also rheumatic patients bear a background susceptibility due to impaired host defense mechanisms and long-term use of immunosuppressive drugs. Low-dose corticosteroids and methotrexate treatments have been reported to be variably associated with VL in rheumatic patients (5-7). In an intriguing analysis Xinos *et al*. suggested an higher incidence of VL in rheumatic patients in coincidence with increased anti-TNF-α drugs prescription in the last five years (7).

Moreover, the number of rheumatic patients suffering from *L*. infection should be expected to rise in consideration of the following conditions: 1) anti-TNF-α prescription is going to be extended to patients with moderate disease activity (especially RA patients) and earlier in the course of disease; 2) foreign travels, immigration from areas at high endemicity and global warming process are likely to facilitate the spreading of *L*. into the more temperate areas of the Mediterranean coasts, thus increasing the risk of exposure.

Therefore, an important clinical issue is whether rheumatic patients scheduled for immunosuppression should be routinely screened for latent *L*. infection. In agreement with De Leonardis *et al*. (1), we think that a *systematic* screening is not advisable. Firstly, although an high prevalence of contact with *L*. is typical of our latitudes, the incidence of VL should be considered very low. Secondly, and mostly importantly yet, firm evidences about the need and the modalities of treating immunocompromised patients positive for latent *L*. infection have not been provided so far: experiences coming from the management of *L*. infection in HIV-positive patients do not recommend primary prophylaxis (8). Thus, to date, the best approach seems to be to maintain a high index of suspicion for VL in immunosuppressed rheumatic patients presenting with anarchic fever and pancytopenia, bearing in mind that typical features of VL may be absent or unimpressive and that *L*. infection may mimic a flare of the underlying rheumatic disease (9).

Another point of practical relevance concerns the safety of reintroducing immunosuppressive drugs in rheumatic patients after (apparent) clinical cure. *L*. shares with many other intracellular pathogens the ability of persisting lifelong in the host organism after drug-induced resolution of the acute infection. So that restarting immunosuppression can cause fulminant relapse of infection.

As in immunocompetent subjects, a test of (parasitological) cure (microscopy/culture of bone marrow aspirates) could be performed 1 and 6 months after the interruption of treatment for VL before restarting aggressive immunosuppression. To avoid pain and stress related to invasive techniques, guided by experience gained in the management of relapse in HIV-positive patients, a PCR for *L*. on peripheral blood sample may be a sensitive way of evaluating treatment response (8) and predating VL recurrence.

PCR testing could be also appropriate to predict reactivation in rheumatic patients under immunosuppressive treatment. In the

management of our patient we adopted such an strategy both for the diagnosis of cure and for the evaluation of infection recurrence. To date, studies and/or clinical experience are required to provide evidence to recommend maintenance therapy in rheumatic patients scheduled for restarting immunosuppression soon after clinical cure from VL.

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