Correspondence

Visceral leishmaniasis during pegylated interferon therapy for chronic hepatitis C: first report

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In their recent article, Puoti et al. [1] offer an accurate analysis of the possible causes and risks of infections in patients with chronic hepatitis C undergoing treatment with pegylated interferons (PEG-IFNs). However, among the causes of infections reported, the authors did not mention visceral leishmaniasis (VL) nor has VL has been previously reported in any other patient treated with IFN or PEG-IFN.

We describe here a case of VL that occurred in a patient with chronic hepatitis C treated with PEG-IFN.

A 36-year-old white Italian male born and living in Sicily, Italy, came to our attention complaining of irregular fever (maximum temperature: 41°C), fatigue and weight loss over 4 weeks. There was a history of intravenous drug abuse. HCV positivity had been documented about a year beforehand and 3 months earlier he had started treatment with PEG-IFN α-2a (180 µg/wk).

On admission, he was febrile (temperature: 39.0°C) and pale with hepatosplenomegaly and oropharyngeal thrush; laboratory examinations showed pancytopenia (haemoglobin 9.4 g/dl, white blood cell count $2.6 \times 10^3/\mu l$ and CD4+ lymphocytopenia (25%, 174/µl). A culture from a pharyngeal swab yielded Candida albicans. Cultures of blood and urine tested negative.

However, although several clinical and epidemiological ‘stigmata’ for HIV infection were present, HIV serology and PCR for HIV-RNA were negative. Based on positive results of serology and peripheral blood PCR for Leishmania, a diagnosis of VL was made and liposomal amphotericin B (3 mg/kg on days 1–5 and 10) was administered. The patient became afebrile 48h after the beginning of specific therapy. Subsequently, red blood cell, white blood cell, platelet, and CD4+ lymphocyte counts gradually came back to normal. PCR for Leishmania performed on day 10 was negative.

IFNs are associated with complex antiviral, immunomodulatory and antiproliferative actions [2]. Neutropenia is a common side effect of IFN therapy. Puoti et al. demonstrated that HCV patients treated with IFN are at a higher risk of developing lower respiratory infections due to IFN-related neutropenia. The use of PEG-IFNs appeared to increase the risk of non-respiratory infections (cellulitis, dental abscesses, parapharyngeal abscess or infections involving other sites independently from neutropenia) [1].

Polyethylene glycol, the molecule covalently attached to α-IFN, accumulates in vitro in focal infections and decreases phagocytic activity of tissue macrophages [3].

Leishmania infection develops in a wide spectrum of clinical findings, ranging from asymptomatic, subclinical and self-resolving infection to progressive VL characterized by fever, splenomegaly and pancytopenia. T-cell-dependent immune response and macrophage activation play a major role during primary infection or reactivation of latent infection [4]. It could be hypothesized that the polyethylene glycol-induced reduction of phagocytic activity may have increased the risk of progression to VL or, alternatively, that the reduction of the T helper cells (described among HIV-infected individuals under treatment with IFN) [5] might be responsible for the disease. It is estimated that in Sicily there is a burden of at least 150 000 HCV-infected patients, one tenth of whom (approximately 1000–1500) are treated annually with IFN. Since VL is
endemic in Sicily as well as in other countries of the Mediterranean basin, physicians should be aware of the possible unmasking of cryptic Leishmania infection by IFN.

References


Response from Massimo Puoti, Sergio Babudieri, Giovanni Rezza, Pierluigi Viale, Maria Giulia Antonini, Ivana Maida, Stefania Rossi, Barbara Zanini, Valeria Putzolu, Luisa Fenu, Chiara Baiguera, Salvatore Sassu, Giampiero Carosi and Maria Stella Mura.

In their letter, Cascio and co-workers report a case of visceral leishmaniasis (VL) occurring in an individual with a history of injection drug use taking pegylated interferon (PEG-IFN) and ribavirin (RBV) as anti-HCV treatment and living in an area endemic for VL. The high prevalence of hepatitis C virus in regions where, not only leishmaniasis, but also tuberculosis (TB) and other infectious diseases caused by intracellular microorganism are endemic, supports a careful evaluation of prolonged febrile episodes in patients using PEG-IFNs. Even if this risk is not considered as a contraindication for anti-HCV treatment, it should be taken into consideration when this treatment is started in such epidemiological settings. Careful environmental considerations should be part of pre-treatment patient counselling and screening for latent TB should be performed in patients at risk of such infections. The incidence of these infections in patients treated with PEG-IFNs in regions with these epidemiological issues should probably be assessed in large Phase IV observational studies and by active Phase IV pharmacovigilance. Lymphocytopenia is not uncommon in patients treated with PEG-IFN and RBV and has been observed in patients with HIV infection even in the absence of a significant decrease in the percentage of CD4 cells [1]. However, in the HAART era, CD4 cell decrease has not been associated with an increased risk of opportunistic infections in HIV-infected individuals [1]. Lymphocytopenia has been associated with an increased risk of infection in an observational study performed predominantly in African Americans [2]; however, there are no data on the changes in lymphocyte subpopulations in HIV-uninfected patients treated with PEG-IFNs and RBV. The severe CD4 depletion observed in this patient could also be the result of leishmaniasis [3], however studies on the change in number and functions of lymphocytes subpopulations in HIV-uninfected patients assuming PEG-IFNs and RBV should be prompted by this interesting case report.

References

