



## Case Report

## Immune Restoration Disease Associated with *Leishmania donovani* Infection Following Antiretroviral Therapy for HIV Infection

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Immune restoration disease following antiretroviral therapy for human immunodeficiency virus infection can cause significant morbidity and mortality. We describe the dramatic clinical course of an human immunodeficiency virus-infected patient who developed severe immune restoration disease associated with *Leishmania donovani* infection in a non-endemic area of the world. It highlights the need to consider previous travel history when screening for opportunistic infections before starting antiretroviral therapy, and demonstrates the effectiveness of corticosteroid therapy for life-threatening immune restoration disease.

**KEYWORDS:** HIV, immune restoration disease, *Leishmania*

### Introduction

The aim of treating human immunodeficiency virus (HIV)-infected patients with combination antiretroviral therapy (ART) is to suppress viral replication and restore protective pathogen-specific immune responses. In some patients, this restoration process is dysregulated, and results in

immunopathology that presents clinically as immune restoration disease (IRD).<sup>1</sup> IRD may cause a severe inflammatory illness and is therefore often referred to as immune reconstitution inflammatory syndrome. Risk factors for IRD include severe immunodeficiency (CD4+ T cell count less than  $50 \times 10^6$  cells/L) before starting ART, and the presence of antigens of opportunistic pathogens.<sup>2</sup> We present a case of IRD in which the aberrant immune response was directed against a pathogen that has not previously been associated with IRD.

### Case Report

A 60-year-old man was diagnosed with HIV infection after a prolonged illness. He had experienced progressive malaise, lethargy, and weight loss of 40 kg over 6 months. He presented to hospital after the onset of fever and rigors. Clinical examination revealed several squamous cell carcinomas

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on the scalp that were infected, and hepatosplenomegaly without stigmata of chronic liver disease. He gave a long history of excessive alcohol consumption.

At diagnosis, his CD4+ T cell count was  $55 \times 10^6$  cells/L (11%) and the plasma HIV RNA level was  $>100,000$  copies/mL. Investigations also demonstrated pancytopenia with a normocytic anaemia (haemoglobin, 70 g/L), a lymphocyte count of  $0.52 \times 10^9$ /L, a neutrophil count of  $1.74 \times 10^9$ /L, and a platelet count of  $140 \times 10^9$ /L. This was felt to be a manifestation of the HIV infection. A cholestatic pattern of elevated liver enzymes was detected (total bilirubin, 11  $\mu$ mol/L; alkaline phosphatase, 400 U/L; gamma glutamyl transferase, 220 U/L; alanine aminotransferase, 50 U/L). There was no laboratory evidence of viral hepatitis. A computed tomography scan showed hepatosplenomegaly and multiple small, low-attenuated nodules. A screen for common opportunistic infections revealed only past exposure to *Toxoplasma*, Parvovirus B19, cytomegalovirus, and Epstein-Barr virus.

Combination ART consisting of zidovudine, lamivudine, and efavirenz was commenced, with subsequent clinical improvement. One month after starting ART, his CD4+ T-cell rose to  $100 \times 10^6$  cells/L (27%), and the plasma HIV RNA level dropped to 1,200 copies/mL. Three months after starting ART, he developed a severe anaemia (haemoglobin, 50 g/L). Pure red cell aplasia was demonstrated on bone marrow examination. Zidovudine was felt to be the main cause and ART was ceased. After the haemoglobin level recovered, ART was restarted. Zidovudine was replaced by lopinavir and ritonavir, while lamivudine and efavirenz were not changed. Adverse effects consisting of nausea and diarrhoea on this regimen necessitated replacement of lopinavir and ritonavir by tenofovir.

Five months after starting ART, he became progressively unwell over several weeks, culminating in a further hospital admission. He had developed severe vomiting, lethargy, and become bed-bound. On hospitalisation, he was cachectic, febrile, and severely dehydrated causing haemodynamic compromise. His CD4+ T cell count was  $75 \times 10^6$  cells/L (29%) and the plasma HIV RNA level had further dropped to 562 copies/mL. Inflammatory markers were elevated, with C-reactive protein at 100 mg/L and an erythrocyte sedimentation rate of 130 mm/hour (further risen from 100 mm/hour at the time of HIV diagnosis).

The cause of this febrile illness was not immediately evident from investigations that included an extensive search for opportunistic infections. He was nevertheless covered with antimicrobials that included trimethoprim-sulfamethoxazole, azithromycin, and fluconazole. Pancytopenia developed later (haemoglobin, 80 g/L; lymphocyte count,  $0.2 \times 10^9$ /L; neutrophil count,  $0.9 \times 10^9$ /L; platelet count,  $60 \times 10^9$ /L). The bone marrow aspirate showed normal cells with no evidence of Mycobacteria on culture, and no detection of cytomegalovirus or Parvovirus B19 nucleic acid. Unfortunately, the trephine specimen was insufficient for examination.

His condition further deteriorated with the development of encephalopathy. This coincided with a rise in liver enzymes that was of a predominantly cholestatic pattern (total bilirubin, 70  $\mu$ mol/L; alkaline phosphatase, 1,000 U/L; gamma glutamyl transferase, 300 U/L; alanine aminotransferase, 180 U/L). Again, no laboratory evidence of viral hepatitis was identified. Computed tomography scanning showed persisting hepatomegaly and further splenic enlargement to a length of 20 cm (from 16 cm). A liver biopsy was performed and showed multiple granulomas containing intracellular organisms. There were also other contributing factors to his deterioration. He was found to have hypercalcaemia that was likely caused by the granulomas, with suppressed serum parathyroid hormone and 25-dihydroxyvitamin D levels. Hyponatraemia, with sodium level dropping to 122 mmol/L, was also detected. Inappropriate antidiuretic hormone secretion syndrome was supported by a low plasma osmolality and relatively high urinary sodium concentration and osmolality.

Upon ascertaining that he had lived in Cyprus several years earlier, infections with organisms that cause granulomatous inflammation, and are prevalent in that region, were considered. Serum antibodies against *Leishmania donovani* were detected in high titre as evidence of visceral leishmaniasis. Retrospective testing of stored serum taken at the time of HIV diagnosis returned a negative result.

A diagnosis of severe IRD associated with *L. donovani* infection was made. ART was ceased and corticosteroid therapy was commenced because of the severity of the illness (methylprednisolone 125 mg/day for 2 days, then prednisolone 1 mg/kg/day that was eventually ceased 6 months later). Liposomal amphotericin B therapy was also commenced (AmBisome 150 mg/day for the first

week, then 200 mg every 3 weeks for the remainder of a 3-month course of therapy). The patient showed a dramatic improvement in his inflammatory symptoms and was able to be discharged home 1 week later. The liver enzyme abnormalities, hepatosplenomegaly and hepatosplenic nodules resolved over a longer period of time.

ART (abacavir, lamivudine, and efavirenz) was restarted 2 months after discharge from hospital. This regimen was well-tolerated and 6 months later the plasma HIV RNA level was <40 copies/mL and the CD4+ T-cell count was  $200 \times 10^6$  cells/L (19%).

## Discussion

This may be the first known reported case of *L. donovani* IRD after initiation of ART for HIV infection. At the time of writing, only two other cases of *Leishmania* sp. IRD have been reported in association with visceral leishmaniasis.<sup>3</sup> Of particular interest is the occurrence of IRD associated with *Leishmania* sp. infection outside of a *Leishmania*-endemic region. The patient had previously lived in Cyprus, but it has only recently been recognised that the MON-37 strains of *L. donovani* affects humans and dogs in that country.<sup>4</sup> We were unable to investigate the subspecies of the *Leishmania* species in this patient.

It is probable that this patient had visceral leishmaniasis that contributed to the abnormal clinical and laboratory findings when he first presented with HIV infection, but this condition was not considered because these abnormalities could be attributed to other causes and he presented outside of a *Leishmania*-endemic region. At that stage of his HIV infection, severe immunodeficiency had resulted in a negative serum antibody assay for *Leishmania* sp. infection when this was undertaken retrospectively. However, antibodies to *L. donovani* were detected at the time of the severe febrile illness. The high titre of these antibodies, and his subsequent response to treatment that included *Leishmania* eradication therapy, are suggestive of the restoration of a pathogen-specific

immune response rather than a non-specific polyclonal response. In the absence of species confirmation by polymerase chain reaction detection, or negative serology against other species of *Leishmania*, the authors concede that infection with other *Leishmania* species cannot be excluded.

This antibody response, taken together with the clinical presentation and decreased plasma HIV RNA level, satisfy the provisional diagnostic criteria for IRD proposed by French et al.<sup>2</sup> The extremely severe inflammatory illness in this patient responded rapidly and dramatically to corticosteroid therapy and ART cessation, which is another characteristic of IRD. Eventual eradication of the *L. donovani* infection led to the slower resolution of his other clinical and laboratory abnormalities.

This case demonstrates the importance of identifying and treating opportunistic infections before starting ART, if possible. With hindsight, more rigorous consideration of this patient's travel history might have led to an earlier diagnosis of visceral leishmaniasis. Non-antibody based investigations, such as liver biopsy and polymerase chain reaction detection, could then have proved useful in identifying the organism, thus allowing eradication of the Leishmaniasis before commencing ART. Our case also demonstrates the effectiveness of corticosteroid therapy in patients with severe inflammation complicating IRD.

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