Visceral leishmaniasis: a threat to immunocompromised patients in non-endemic areas?

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ABSTRACT

Visceral leishmaniasis is rare in western Europe, but may be life-threatening in immunocompromised patients. It is therefore important to understand the incidence of the disease in a non-endemic area and its relationship with immunosuppressive conditions. Between 1990 and 2005, 12 patients were diagnosed with leishmaniasis at Basel University Hospital, Switzerland. Eleven presented with visceral symptoms and ten had an underlying immunosuppressive condition. Since increasing numbers of immunosuppressed patients have a history of travel to endemic countries, an association of visceral leishmaniasis with cellular immunosuppression (other than that associated with human immunodeficiency virus) might become more frequent in non-endemic areas.

Keywords Cellular immunodeficiency, immunocompromised patients, immunosuppression, Leishmania spp., non-endemic areas, visceral leishmaniasis

Clin Microbiol Infect 2007; 13: 751–753

The clinical presentation and course of visceral leishmaniasis depend on complex interactions between the parasite and host [1]. Classic symptoms are night sweats, weight loss, hepatosplenomegaly and pancytopenia. Control of infection is achieved via leishmania-specific CD4 T-cells of the TH1 type and the activation of macrophages to kill the intracellular amastigotes [2]. A strong cellular immune response leads to the formation of granulomas with few parasites and an asymptomatic or oligo-symptomatic disease. In cases of malnutrition or immunosuppression, macrophage predominance, lack of granulomas and poly-parasitic disease are seen, with severe symptoms and occasional deleterious clinical outcomes.

Reactivation of leishmaniasis following cellular immunosuppression is a particular diagnostic and therapeutic challenge [3–9]. With an increasing incidence of travel and migration, leishmaniasis might become more frequent in patients with immunosuppressive conditions in non-endemic regions. In order to better understand the incidence of the disease in a non-endemic area, and its relationship with immunosuppressive conditions, the databases of the Division of Infectious Diseases and the Department of Pathology at University Hospital of Basel, Switzerland were searched for documented cases of infection with Leishmania spp. Medical charts and histopathological examinations were also analysed. Twelve patients (eight male and four female), aged 22–71 years (median age 42 years), were diagnosed with leishmaniasis during the period 1990–2005, with 11 patients having a visceral form and one patient having a mucocutaneous form of the disease. Leishmaniasis was confirmed by histology in 11 patients (bone marrow, liver), while serology was the only test performed for one patient. PCR results were available for six cases, with four Leishmania infantum isolates, one Leishmania donovani isolate and one Leishmania braziliensis isolate being identified.

Ten of the 12 patients had an immunosuppressive condition as an underlying disease. Four patients suffered from advanced infection (CD4
cell count <100/mm³) with human immunodeficiency virus; none of these patients was receiving anti-retroviral therapy, and three presented before the introduction of anti-retroviral therapy. Six other patients were receiving immunosuppressive therapy. Of these six patients, two had haematological malignancies; one received fludarabin for non-Hodgkin’s lymphoma, and one was aplastic following high-dose chemotherapy for newly diagnosed acute lymphatic leukaemia. This second patient developed severe intestinal mucositis that necessitated surgical intervention, with a biopsy revealing invasive infection with L. braziliensis. A third patient, with leishmaniasis involving the tongue, underwent a thymectomy with local radiation treatment for malignant thymoma 9 years before the onset of infection. The initial diagnosis of a fourth patient was allopurinol-associated granulomatous hepatitis [10], which was treated with steroids. One month later, a second liver biopsy, performed because of pancytopenia and fever, revealed L. infantum, but with disappearance of granulomas. Reactivation of a latent Leishmania infection was postulated. Diabetes mellitus was the only immunosuppressive condition found in the fifth patient. Finally, the sixth patient had severe acute mononucleosis, diagnosed by positive antibodies (IgM and IgG) to early Epstein–Barr virus antigens. Infection with Leishmania was diagnosed serologically during investigation of persisting fever, weight loss, hepatopathy and pancytopenia, and this patient improved following anti-leishmanial treatment. It is of interest that an association of Epstein–Barr virus infection with Leishmania has not been described previously in the literature, but herpes viruses are known to exacerbate immune impairment in solid-organ transplants, increasing the risk of activation of co-infecting agents [11]. It can be hypothesised that Epstein–Barr virus infection, with its complex immune activation, interacts at the cytokine level with defence strategies against Leishmania.

No clear underlying disease was found in two patients: one patient with histologically diagnosed (bone marrow, liver and spleen) leishmaniasis, who showed recovery following anti-leishmanial treatment, presented several times during the following years with unexplained fever without recurrence or an underlying disease; the other patient had no obvious impairment of immune function, but was aged 80 years and had multiple co-morbidities, e.g., coronary heart disease, localised prostate cancer and severe pneumonia.

All patients had a history of migration from or travel to an endemic area. Seven patients were originally from Mediterranean countries, where dogs are a major reservoir of Leishmania [12]. The five patients from Switzerland and Germany also had a history of travel.

Data concerning outcome were available for all patients. Three patients were treated with intravenous pentamidine, four received meglumine antimoniate, and six were treated with liposomal amphotericin B. Four patients died shortly after the diagnosis and start of treatment for leishmaniasis, demonstrating the severity of infection in the presence of immunosuppression and the high failure rate of antimicrobial therapy in such situations [13]: one died of advanced infection and untreated human immunodeficiency virus infection; a second developed a fatal bleeding complication after splenectomy, with progressive renal failure and nosocomial pneumonia; a third was treated for acute lymphatic leukaemia and developed multi-organ failure; and the fourth died from acute liver failure. In this retrospective analysis, it was impossible to assess the specific outcome regarding leishmaniasis, as all these patients had severe underlying conditions. The eight remaining patients were discharged, but three patients with AIDS died later because of advanced immunosuppression. The patient with leishmaniasis of the tongue presented with a recurrence of the infection after 3 years [14]. Four patients remained well at follow-up.

Before the era of anti-retroviral therapy, AIDS was a common risk-factor for symptomatic visceral leishmaniasis. However, the present analysis identified a significant proportion of patients with less well-known risk-factors, e.g., malignant disorders, high-dose chemotherapy, treatment with radiation and steroids. As such therapies become more frequent, and as current therapies have fewer side-effects, thereby allowing patients to travel to countries in which Leishmania is endemic, an increase in infections with Leishmania in non-endemic countries may be expected. A delay of up to 10 years between exposure and the start of symptoms was found. An immunosuppressive condition was found in ten of the 12 patients analysed, confirming that symptoms of visceral leishmaniasis develop mostly in the presence of cellular immunodeficiency, whereas
a normal immune system is often capable of controlling the infection. As the present analysis selected cases according to the histological diagnosis, the patients comprised a series with severe illness, having been hospitalised for diagnosis and treatment, whereas less ill patients, diagnosed by less invasive methods (e.g., serology, PCR) in an outpatient setting, might have been overlooked. Nevertheless, this analysis yielded clear information: in patients with a history of migration or travel to endemic areas in conjunction with an underlying immunosuppressive condition, the exclusion of *Leishmania* infection should be mandatory in the event of unexplained fever, hepato-splenomegaly and/or cytopenia.

**ACKNOWLEDGEMENTS**

We thank the Stiftung Forschung Infektionskrankheiten Basel for supporting this work.

**REFERENCES**