Visceral leishmaniasis in those infected with HIV: clinical aspects and other opportunistic infections

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Cases of visceral leishmaniasis (VL) in HIV-positive individuals have been reported from most areas of the world where the geographical distributions of the two infections overlap. The majority of the co-infected cases that have been recorded, however, live around the Mediterranean basin. In these subjects, the length of the incubation period of VL is presumably very short, particularly in those who have severe immunodepression. At diagnosis, almost all cases of VL/HIV co-infection have been found to have fewer than 200 CD4+ cells/μl blood, and about 50% meet the AIDS-defining criteria during their first episode of VL.

The clinical manifestations of VL in HIV-infected individuals may be similar to those seen in HIV-negative cases; fever, pancytopenia and hepatosplenomegaly, for example, are found in 75% of all the HIV-positive cases. Following the dissemination of the parasites, however, the HIV-positive cases may develop unusual, multi-organ pathology.

Almost all the cases of co-infection are very prone to VL relapses, even after carefully managed antileishmanial treatment. The opportunistic infections that are often seen in HIV-positives frequently develop during VL episodes, the signs and symptoms of the leishmaniasis then confusingly overlapping with those of the other infections.

The clinical presentation and evolution of human visceral leishmaniasis (VL) are the result of a complex interplay between the causative parasite and the host’s immune system, clinical outcome largely being dependent on whether a Th1 response is able to destroy the intracellular parasites that cause the disease (Barcellini et al., 1994; Cacopardo et al., 1996; Preiser et al., 1996; Nigro et al., 1999). Those infected with HIV appear particularly prone to VL, probably because they cannot mount an immune response that is sufficient to kill the parasites or at least to prevent symptomatic leishmaniasis. There are reports of Leishmania/HIV co-infection from most areas of the world where the geographical distributions of the two pathogens overlap. However, the majority of such cases live around the Mediterranean basin, where 3%–7% of those infected with HIV now develop VL.
That, during any VL episode, other, con-
comitant, opportunistic infections are dia-
gnosed in 42%–68% of HIV-positive patients
should not come as a surprise. Most cases of
leishmaniasis in HIV-positives appear when
the patient is seriously immunodepressed and,
as indicated by the marked drop in CD4 +
counts seen during VL in HIV-negatives,
the parasitic disease is itself associated with
depression of the host’s immune system.
The clinical symptoms of leishmaniasis can
often be masked by those of other oppor-
tunistic infections (Altés et al., 1991; Alvar
etal., 1992, 1997; Alvar, 1994; Rosenthal
etal., 1995; Nigro et al., 1996).

CLINICAL FORMS

Although the clinical manifestations of VL
(caused by Leishmania infantum) may be
generally similar whether the case is immuno-
competent or immunodepressed, they are
often much more varied in the immuno-
depressed. Those co-infected with L. infantum
and HIV, for example, may be asymptomatic
or oligosymptomatic (in terms of leish-
maniasis), develop typical, symptomatic VL
(even when the parasites are of a zymodeme
only associated with cutaneous leishmaniasis
in the immunocompetent) or develop a
particularly disseminated form of VL, with
multi-organ pathology (Rosenthal et al.,
1995; Nigro et al., 1996).

The classical, clinical triad of VL — fever,
pancytopenia and hepatomegaly and/or spleno-
egaly — is found in 75% of all HIV-
positive cases. The clinical manifestations
most commonly encountered (Medrano et al.,
1992; Rosenthal et al., 1995; Nigro et al.,
1996; WHO, 1997) are fever (80%–95% of
cases), a constitutional syndrome with
asthenia and weight loss (70%–90%),
(generally moderate) splenomegaly without
hepatomegaly (54%–90%), hepatomegaly
without splenomegaly (34%–85%), hepato-
splenomegaly (68%–73%), adenopathies
(12%–57%), anaemia — which is usually

INCUBATION PERIOD

Not all immunocompetent subjects who are
infected with the parasites that cause VL
develop symptomatic disease and even those
who do become ill are typically symptom-
free for an incubation period lasting 2–6
months post-infection. The length of the
incubation period in HIV-positive individuals
is unknown but presumably may be very
short, if infection occurs when the host is
severely immunodepressed. Many immuno-
competent individuals who are infected
with leishmanial parasites may carry latent
infections that only develop into VL when
their hosts become immunocompromised.
HIV infection may thus re-activate leish-
manial infections that may have lain dormant
for many months (Kubar et al., 1998). Thus,
in countries where VL is not endemic, cases
of the disease may occur in immigrants,
military personnel or tourists months after
these individuals have visited or lived in a
region where VL is endemic (Jeannel et al.,
1991; Alvar et al., 1996).

HIV STATUS

Most cases of VL recorded in HIV-positive
patients have been diagnosed after HIV-
attributable immunosuppression and disease
have developed. Almost all (77%–90%) of the
cases of VL/HIV co-infection detected have
been found to have fewer than 200 CD4 +
cells/µl blood when their VL was diagnosed
[the rest having 200–500 (7%–22%) or,
more rarely (≤3%), >500 CD4 + cells/µl],
and about one in every two cases (42%–72%)
meets the AIDS-defining criteria before or
during his or her first episode of VL (Altés
etal., 1991; Alvar et al., 1992, 1997; Alvar,
1994; Rosenthal et al., 1995; Nigro et al.,
1996).
marked, with <10 g haemoglobin/dl (49%–100%), leucopenia — which is usually moderate, with <2400 leucocytes/μl (56%–95%), thrombocytopenia — which is generally conspicuous, with <150,000 platelets/μl (52%–93%), and a combination of anaemia, leucopenia and thrombocytopenia (35%–77%). Gastro-intestinal involvement, observed in half of the HIV-positive cases of VL in Sudan (Pesce et al., 1990; Laguna et al., 1994), is also common, amastigotes often occurring in digestive-tract tissue. Some HIV-positive patients undergoing endoscopy for undiagnosed digestive symptoms are found to have leishmanial amastigotes in their gut mucosa (Laguna et al., 1994; Alvar et al., 1997; Rosenthal et al., 2000). Any part of the digestive tract may be invaded. Such infection may be symptomless or associated with oesophageal symptoms, epigastralgia, diarrhoea or rectal discomfort [although these symptoms may be the result of concomitant co-infection with other pathogens, such as cytomegalovirus (CMV) or Candida spp.]. Gastro-intestinal leishmaniasis should be considered in the differential diagnosis of chronic diarrhoea in HIV-positive patients who live in, or have travelled to, countries with endemic leishmaniasis (Borzoni et al., 1991). In reviewing 15 cases of gastro-intestinal leishmaniasis in HIV-positive patients, Laguna et al. (1994) found that all 15 had fewer than 200 CD4 + cells/μl, 12 had been previously diagnosed with AIDS, seven had fever and spleen enlargement, 10 had had their VL diagnosed as the result of gastro-intestinal biopsy, and 13 had gastric symptoms (six had diarrhoea, six had dysphagia and odinophagia, two had abdominal pain, two had epigastralgia, one had intestinal haemorrhage, and one had rectal pain). Although leishmanial amastigotes were found in 90% of samples from the duodenum and 75% of those from the gastric mucosa, the endoscopic observations were quite variable, with six of the cases appearing to have a normal mucosa, three showing erosive gastro-duodenitis, three having a gastric ulcer, and one each having an oesophageal ulcer (associated with CMV), erythematous lesions in the rectal mucosa, and Kaposi’s sarcoma.

In HIV-positive patients with VL, leishmanial infection of the respiratory tract is not uncommon. In their anatomo-pathological study, Rosenthal et al. (1991) found Leishmania amastigotes in the alveoli and pulmonary septa of most cases (76.8%) of Leishmania/HIV co-infection. Pulmonary clinical manifestations were, however, less frequent. Leishmanial parasites in the respiratory tract are only usually detected when HIV-positive patients with cough and fever are undergoing diagnostic fibrobronchoscopy and are subjected to broncho–alveolar lavage. In some co-infected patients with respiratory symptoms and pleural effusion, histological examination of the serous bloody fluid in the pleural space has revealed amastigotes within histiocytes. Pneumonitis, associated with pleural effusion and mediastinal adenopathies in the absence of bone-marrow involvement, and pulmonary involvement detected at autopsy have also been reported among the co-infected cases (Rosenthal et al., 1991; González-Anglada et al., 1994).

Bissuel et al. (1994) described a case of multi-organ dissemination detected at autopsy, with amastigote colonisation of the liver, spleen, bone marrow, lymph nodes, digestive tract, skin, adrenal glands, and myocardium.

In the countries that lie around the Mediterranean basin, the visceral dissemination of an initial cutaneous lesion is uncommon in immunocompetent subjects. In a manner reminiscent of post-kala-azar dermal leishmaniasis, up to 15% of HIV-positive patients from this region who have been treated for VL present, some time later, with cutaneous lesions from which Leishmania parasites can be isolated. As amastigotes occur in the healthy skin of immunocompetent patients infected with L. donovani, it is perhaps not surprising that cutaneous lesions develop in immunocompromised HIV-positives who have had VL (Yebra et al., 1988; Bettini et al., 1990; Belda Mira et al., 1994; Berhe et al., 1995). Antileishmanial treatment
generally leads to clinical cure of immunocompetent cases of VL, although it may not kill every parasite (Aragort de Rossell et al., 1992). Almost all HIV-positive cases with VL, however, suffer VL relapses, even after carefully managed antileishmanial treatment (Russo et al., 1996; Laguna et al., 1999). Such relapses, which usually occur 1–8 months post-treatment, may be symptomatic or symptomless, but are detectable as spleen and liver enlargement, progressive pancytopenia, and amastigotes in the peripheral blood, lymph-nodes and skin; widespread dissemination of the parasite and the absence of fever are typical of the severely immunodeficient cases (Russo et al., 1996; Laguna et al., 1999).

Re-activation of arthritis, which is known to occur sometimes as the result of other parasitic infections, has recently been attributed to *Leishmania* infection, in an AIDS case, for the first time (Perello-Roso et al., 1996).

Survival of the cases of VL/HIV co-infection does not seem to be significantly related to the clinical or parasitological course of the VL but to the progression of the HIV infection. Deaths occur more frequently and rapidly among AIDS patients with VL than among the other cases of co-infection, and the survival of AIDS patients appears similar for those with and without VL (Alvar, 1994; Nigro et al., 1996, 1999; Russo et al., 1996; WHO, 1997).

**OPPORTUNISTIC INFECTIONS**

As mentioned above, other opportunistic infections frequently develop during VL episodes in HIV-infected patients. The most common of these infections — oro-oesophageal candidiasis, tuberculosis, infections with the *Mycobacterium avium* complex, and *Pneumocystis carinii* pneumonia — are, not surprisingly, also those most commonly observed in patients with AIDS who live in southern Europe (Medrano et al., 1992; Rosenthal et al., 1995; Nigro et al., 1996).

To some extent, the spectrum of concomitant opportunistic infections varies with geographical region. Such geographical variability seems to be a consequence of regional differences in the overall prevalence of each infection and in the effectiveness of local treatments. The more widespread use of highly active antiretroviral therapies and prophylaxis against certain opportunistic diseases will probably result in significant changes in the geographical distributions and regional incidences of the infections that co-exist with VL/HIV.

**CLINICAL DIFFERENTIAL DIAGNOSIS**

In general, as discussed above, the clinical and biological features of VL in HIV-infected patients closely resemble those of VL in immunocompetent hosts. Most HIV-negative cases present with the classical triad, of fever, liver and/or spleen enlargement and pancytopenia, but atypical clinical manifestations, such as the occurrence of fever only or the complete absence of all three components of the triad, have also been described. As the signs and symptoms of VL are non-specific, overlapping with those of many possible infections in HIV-infected patients, bedside diagnosis may be difficult (Medrano et al., 1992; Belda Mira et al., 1994; Rosenthal et al., 1995; WHO, 1997). Several diseases induce fever, liver and/or spleen enlargement and cytopenia in patients infected with HIV, and VL may be easily confused with, for example, tuberculosis, infections with the *M. avium* complex, or lymphoma. Other, less common diseases to be considered are disseminated CMV infection, toxoplasmosis of the central nervous system, *Salmonella* bacteraemia, *P. carinii* pneumonia, extrapulmonary cryptococcosis and bacillary angiomatosis, all of which may occur in HIV-negative patients, with or without VL (Medrano et al., 1992; Rosenthal et al., 1995; Nigro et al., 1996).
Infection with HIV itself should be included in the differential diagnosis, since it is associated with fever and haematological abnormalities, particularly in its more advanced stages. Isolated cytopenias may also occur as a consequence of therapies employed against HIV or associated conditions. Zidovudine therapy, for example, is a common cause of anaemia, and ganciclovir, foscarnet sulfa derivatives (used to treat toxoplasmosis or P. carinii infections) and pentamidine may all cause myelosuppression and cytopenia (Valencia et al., 1990). Leishmaniasis should be considered in the differential diagnosis of fever of uncertain origin (FUO) in patients infected with HIV (Albrecht, 1998). In two Spanish surveys, VL accounted for 14%–20% of all HIV-infected patients with FUO, representing the second most frequent diagnosis (Altés et al., 1991; Bissuel et al., 1994).

The extra-haematopoietic dissemination of leishmanial parasites, which occurs in 16%–34% of HIV-infected cases of VL, is frequently discovered only by accident, as all of the clinical indicators of leishmanial infection have been swamped by those of other opportunistic infections (Alvar et al., 1997; Rosenthal et al., 2000).

In the cases of gastro-intestinal leishmaniasis, the dysphagia, odinophagia, abdominal pain, diarrhoea and intestinal haemorrhages caused by the parasites need to be distinguished from the symptoms of other infections. The oesophageal symptoms of disseminated VL, for example, need to be distinguished from other causes of oesophagitis in HIV-infected patients, such as infection with Candida spp, CMV or herpes simplex virus. The lower gastro-intestinal involvement of Leishmania is difficult to distinguish from intestinal infections with other parasites (e.g. Cryptosporidium, Isospora, Giardia, Entamoeba and microsporidia), CMV or mycobacteria (e.g. M. avium-intracellulare, M. tuberculosis) (Pesce et al., 1990; Borzoni et al., 1991; Laguna et al., 1994). The contribution made by pleuropulmonary leishmaniasis to the pulmonary symptoms of those co-infected with HIV is a matter of some controversy, since this form of leishmaniasis rarely occurs in the absence of other pulmonary opportunistic diseases, such as P. carinii pneumonia, pulmonary tuberculosis or CMV pneumonitis. However, VL should be included in the differential diagnosis of exudative pleural effusion and lesions of the larynx (Rosenthal et al., 1991; González-Anglada et al., 1994).

Finally, HIV patients can develop cutaneous leishmaniasis, with many parasites found throughout skin that looks normal or abnormal or in diffuse papules. Mucocutaneous forms of leishmaniasis have also been described. Such cases need to be distinguished from other skin complications of HIV infection, such as Kaposi’s sarcoma, herpes simplex and zoster infections, and bacillary angiomatosis (Yebra et al., 1988; Bettini et al., 1990; Belda Mira et al., 1994; Berhe et al., 1995).

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