Lower trypanosomatids in HIV/AIDS patients

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Although the family Trypanosomatidae includes parasites of plants, insects and vertebrates, only two genera in the family, Leishmania and Trypanosoma, are usually found in humans. Since 1995, however, other monoxenous trypanosomatids have been isolated from several HIV-positive individuals, in whom the parasites cause either visceral or cutaneous lesions. These odd cases are reviewed here. It appears that immunocompromised patients may be vulnerable to infection with trypanosomatids (and other parasites) that either fail to survive or never cause detectable morbidity in the immunocompetent.

The family Trypanosomatidae includes several genera which undergo cyclical development in both vertebrate and invertebrate hosts. Such digenetic parasites include the Leishmania and Trypanosoma species that cause disease in humans and other mammals. The Phytomonas species that parasitise lactiferous plants, the Endotrypanum species that infect two- and three-toed sloths, and the so-called ‘lower trypanosomatids’ — the Blastocrithidia, Crithidia, Herpetomonas and Leptomonas species that are restricted to invertebrate hosts — also belong to the Trypanosomatidae.

Over the last decade, Leishmania and T. cruzi have been found to be causing new types of pathology in immunosuppressed patients, particularly those with HIV co-infection. In HIV-infected patients, for example, the re-activation of T. cruzi infections has been associated with meningo-encephalitis (Rocha et al., 1994; Pacheco et al., 1998a; Silva et al., 1999), gastro-intestinal disease (Ferreira et al., 1997) and cutaneous lesions (Amato et al., 1997; Sartori et al., 1999). In Europe, zymodemes of Lei. infantum that are entirely dermotropic in immunocompetent patients are causing visceral leishmaniasis (VL) in HIV-positive patients (Campino et al., 1994; Jiménez et al., 1995; Gramiccia et al., 1995). Perhaps more surprisingly, some zymodemes of Lei. infantum have only ever been found in cases of Leishmania/HIV co-infection, and not in immunocompetent humans or dogs (Alvar et al., 1997). Although the monoxenous or lower trypanosomatids have never been confirmed as pathogenic in humans, there are several reports of human infection with such parasites. These infections are reviewed below, with particular emphasis on several cases of apparent infection with lower trypanosomatids in those with HIV/AIDS.

HUMAN INFECTIONS CAUSED BY MONOXENOUS TRYpanosomatids

In 1980, McGhee and Cosgrove (1980) described a possible Herpetomonas infection in a woman from Texas. Several years later, flagellate parasites isolated from individuals
in Kenya were found to be more like *Herpetomonas* and *Crithidia* species, in terms of their iso-enzymes or kinetoplast DNA (kDNA), than *Leishmania* species (Githure et al., 1986; Mebrahtu et al., 1992). A case of atypical VL observed in Guinea-Bissau, in a 10-year-old girl who was seropositive for HIV-2 (Sabbatani et al., 1991), was puzzling because VL had never been described in the country (WHO, 1984); Sabbatani et al. (1991) thought the disease was the result of the girl’s infection with a trypanosomatid normally parasitising reptiles.

Dedet et al. (1995) described an HIV-positive patient from Martinique who had a diffuse cutaneous infection with a trypanosomatid. Iso-enzymatic characterization showed that this syndrome was not caused by a known *Leishmania, Sauroleishmania* or *Trypanosoma* species. Although the parasite looked like a lower trypanosomatid, the structure of the kinetoplast, the lack of a cytopharynx and flagellar cysts and the absence of chaomastigote and epimastigote forms indicated that it was not *Blastocrithidia* or *Crithidia*. Dedet and Pratlong (2000) thought that the flagellate was probably a (normally) monoxenous parasite of insects, and possibly a species of *Leptomonas* or *Herpetomonas*. Although the human infection described by Dedet et al. (1995) was thought to be an abnormality resulting from HIV-attributable immunosuppression, the same parasite has recently been isolated from a localized cutaneous lesion on an immunocompetent patient, again on Martinique (Boisseau-Garsaud et al., 2000). The results of DNA sequencing of selected genetic foci indicate that this parasite may represent a novel clade within the genus *Leishmania* (Noyes et al., 2002).

In 1991, an intravenous-drug user from Madrid, who was infected with HIV, was found to be suffering from symptoms typical of VL and to be co-infected with a flagellate (Jiménez et al., 1996). Although the result of an IFAT for leishmaniasis was borderline, with a titre of 1/80, the results of iso-enzymatic analyses and of biochemical characterization with specific probes based on genomic or kinetoplast DNA probes indicated that the parasite was not of a *Leishmania* species. The microscopical examination of Giemsa-stained smears of a culture of the parasite revealed only promastigotes, indicating that the parasite was probably not of a *Trypanosoma* species, and its iso-enzyme patterns were not similar to those of *Crithidia fasciculata, Herpetomonas muscarum, Leptomonas ctenocephali, Blastocrithidia spp* or *Sauroleishmania* spp. In cross-hybridization experiments, no kDNA sequence homology was observed between the unknown flagellate and *Leishmania* or several genera of lower trypanosomatids. No infections developed either when *Phlebotomus perniciosus* (or *Lutzomyia longipalpis; unpubl. obs.) were fed experimentally on the flagellate or when laboratory mice or hamsters were inoculated with it. It is hoped that the current sequencing of the parasite’s ribosomal DNA will allow it to be identified more fully (M. I. Jiménez, unpubl. obs.). Jiménez et al. (1996) believed that immunocompromised patients may be vulnerable to disease caused by infection with trypanosomatids that are not generally considered to be pathogenic in humans. Their patient with the unknown flagellate was treated with meglumine antimoniate (Glucantime®; Specia, Paris), remains alive, and has shown no relapse of her leishmaniasis-like symptoms (M. I. Jiménez, unpubl. obs.). Almost all of those with *Leishmania/HIV* co-infection have relapses after treatment for their leishmaniasis (Laguna, 2003).

In Brazil, Pacheco et al. (1998b) described a flagellate, apparently a monoxenous trypanosomatid, in a 35-year-old, HIV-positive man who had presented with the symptoms of VL. As this patient lived in an area where cutaneous leishmaniasis caused by *Lei. braziliensis* was endemic, the clinicians who examined him at first suspected that his disease was the result of the visceralization of *Lei. braziliensis*. This suspicion was supported by a positive result in an immunofluorescence test for leishmaniasis and by
the observation of amastigotes in a smear of bone-marrow aspirate. The results of the iso-
enzymatic characterization of the flagellate, using 12 enzymatic systems, indicated, how-
ever, that the parasite did not belong to the genera Leishmania, Sauroleishmania, Trypano-
soma, Endotrypanum, Phytomonas, Crithidia, Blastocrithidia, Leptomonas or Herpetomonas.
Hybridization analyses, against a panel of many different trypanosomatids, revealed
that the unknown flagellate had kDNA cross-homology only with Leptomonas pulex-
simulans, a parasite of a dog flea. The HIV-attributable depression of the patient’s
immune system may have permitted opportu-
nistic parasitism by this trypanosomatid.

It is perhaps not surprising that (1) indi-
viduals who have become severely immuno-
compromised as the result of HIV infection
are particularly prone to symptomatic
infection with lower trypanosomatids that
are usually considered non-pathogenic; or
(2) the clinical manifestations of such co-
factions resemble those of visceral or
cutaneous leishmaniasis. The presence of
symptomatic infection with lower trypano-
somatids in immunocompetent patients
(Boisseau-Garsaud et al., 2000) is much
more startling.

It is difficult to explain how any human,
whether immunodeficient or immuno-
competent, actually acquires an infection
with a lower trypanosomatid. Invertebrates
usually become infected with lower trypano-
somatids when they ingest parasites excreted
in the faeces of other invertebrates. It
seems possible that humans are also infected
per os. Blastocrithidia gerridis and Crithidia
flexonema, two parasites of water striders
(Gerridae), can survive in water for 48 and
30 h, respectively (Tieszen and Molyneux,
1989). Intravenous-drug users may be
infected when they use syringes that have
been washed in water contaminated with
such flagellates.

As the global incidence of Leishmania/HIV
co-infection increases (Alvar et al., 1997),
clinicians examining HIV-positive patients
who present with the symptoms of leish-
maniasis need to be aware that trypanoso-
matids other than Leishmania may be the
cause.

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