One of the Many Faces of Immune Reconstitution Inflammatory Syndrome
(See pages 764–5 for the Photo Quiz)

Figure 1. Bone marrow smear showing a monocyte with multiple intracellular Leishmania microorganisms. Within the Leishman-Donovan bodies (arrow), 2 separate ultrastructures can be distinguished, the nucleus and kinetoplast (hematoxylin and eosin stain; original magnification, ×1000).

Diagnosis: visceral leishmaniasis.

Hematoxylin-eosin and Giemsa staining revealed many histiocytes and an abundant presence of intracellular microorganisms (figure 1). On light microscopic investigation, typical Leishman-Donovan bodies were recognized. These represent the Leishmania parasite’s amastigote intracellular stage, characterized by an ovoid, nonflagellated form with a discernable nucleus and adjacent kinetoplast (mitochondrial DNA) [1]. Electron microscopic investigation of a renal tissue specimen revealed Leishmania parasites with a clearly visible ultrastructure of intracellular organelles (i.e., nucleus, kinetoplast, and intracellular flagellum) (figures 2 and 3). Direct agglutination testing revealed high Leishmania antibody titers (1:51,200), and species analysis by PCR had results that were positive for Leishmania donovani infantum complex. A diagnosis of visceral leishmaniasis, complicated by renal insufficiency, was made.

One question remained to be answered: when and where was our patient infected? The incubation period, as described in the literature, extends from a few weeks to several months or years [2]. Additional data on the patient’s travel history was obtained, with specific inquiries regarding areas in which Leishmania infection is endemic, but only revealed a trip to Ibiza, Spain, in 1996 (10 years before this presentation). The prevalence of leishmaniasis is high in the Mediterranean region, including in Ibiza, which is a Spanish island in the Mediterranean Sea. The patient’s medical history was negative for other risk factors for transmission, such as blood transfusion or injection drug use.

Immune reconstitution inflammatory syndrome in HIV-infected individuals with a long period of latent infection and the onset of clinical manifestations after initiation of HAART is a well-known clinical entity [3]. The conversion of asymptomatic Leishmania infection to symptomatic disease in this context has been described sporadically [4, 5]. Frozen serum samples obtained before HAART initiation were tested and were also found to be positive for Leishmania species (direct agglutination test titer, 1:12,800), supporting the hypothesis of a long period of latent infection in our patient. Although these antibody titers seem to be low, compared with those normally seen in Leishmania infection, it has been shown that antibody
titers in HIV-infected patients are lower than those in non-HIV-infected individuals [6].

The *Leishmania* parasite is an obligatory intracellular organism with a natural reservoir in dogs, rodents, and, for several species, humans. Transmission to human hosts is achieved mainly through the bite of a female sandfly of the genera *Phlebotomus* or *Lutzomyia*. After injection of the parasite into the dermal layer, the parasite is phagocytized by the macrophage-monocyte system. Depending on the causative species, *Leishmania* infection can present in a cutaneous, mucosal, or visceral form. Approximately 21 *Leishmania* species that are pathogenic to humans have been identified, each with its own area of endemicity. The most serious clinical form, visceral leishmaniasis, is caused by the *L. donovani infantum* (*chagasi*) species [1, 2].

We treated our patient with liposomal amphotericin B (1.5 mg/kg/day, with the dosage adjusted to renal clearance) for 21 days, during which period renal and bone marrow function

**Figure 2.** Electron microscopic view of renal tissue revealing part of a glomerulus. Clearly visible in the upper section of this figure is a podocyte with its foot processes (arrow 1) spread out on the basement membrane. The greater part of this figure displays a capillary loop filled with monocytes invaded by *Leishmania* parasites (arrow 2).

**Figure 3.** Electron microscopic view of a *Leishmania* parasite. The ultrastructure can be distinguished, with an oval-shaped nucleus (arrow 1), a kinetoplast (arrow 2), and an internal flagellum (arrow 3).
improved. Repeated gastric and bone marrow biopsy specimens were negative for *Leishmania* species, but duodenal specimens still revealed the parasite. After additional higher-dose liposomal amphotericin B (3 mg/kg/day for 7 days), duodenal biopsy specimens were free from *Leishmania* species. Because of high relapse rates among individuals with HIV and visceral leishmaniasis coinfection, our patient continued to receive liposomal amphotericin B (3 mg/kg every 3 weeks) as secondary antileishmanial prophylaxis until his CD4+ cell count was >350 cells/mm³, as suggested in the literature [7, 8]. While the patient was still receiving maintenance therapy, a relapse occurred 15 months after initiation of treatment, when the patient’s CD4+ cell count was 430 cells/mm³. Treatment with high-dose liposomal amphotericin B was resumed for 17 days (the duration of treatment was the patient’s decision; a 21-day course was intended), and the patient thereafter received prophylactic sodium stibogluconate (20 mg/kg/week). Six months later, the patient had a CD4+ cell count of 410 cells/mm³, had experienced no relapse, and was in relatively good health. To our knowledge, this is the first documented case of an HIV-infected patient with *Leishmania* parasites detected in renal tissue while alive.

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