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Anthony Amoroso, Section Editor

Digestive Bleeding in a Georgian Liver Transplant Recipient

(See page1083 for the Photo Quiz.)

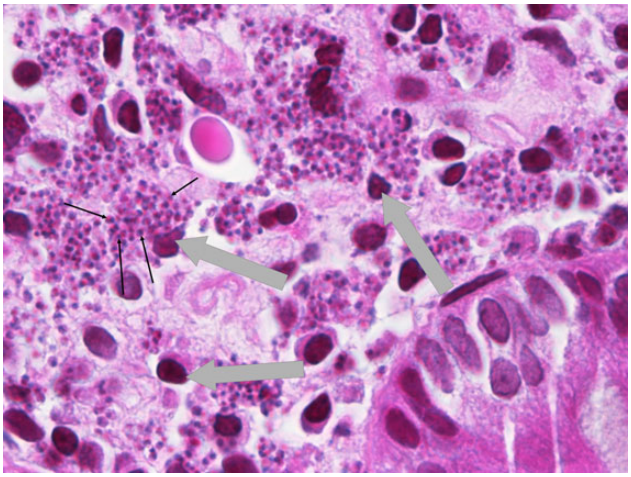

Figure 1. Pathology slide from the cecal biopsy specimen (hematoxylin and eosin staining, magnification ×1000). Although the mucosa of the colon is on the whole preserved, overabundance of the *lamina propria* indicates noticeable local inflammation (3 nuclei are indicated by large gray arrows). Numerous *Leishmania* species amastigotes are clearly visible within the cytoplasm of mononuclear cells (thin black arrows) as oval, small bodies, 1–5 µm long × 1–2 µm wide, with indistinct cytoplasm and 1 single large nucleus. No other causes of bleeding were found by means of microbiological or histological investigations.

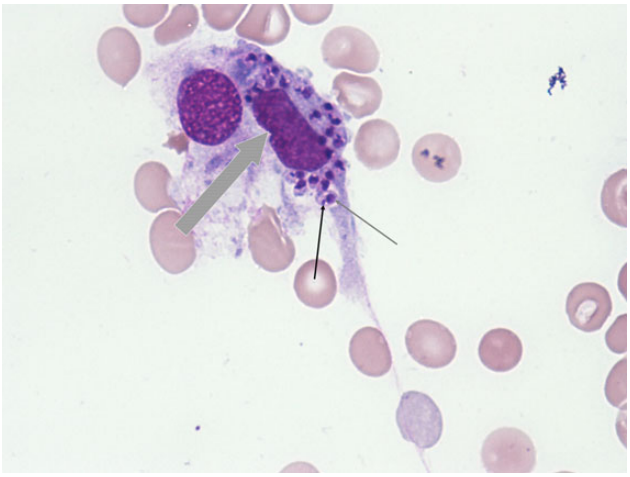

Figure 2. Smear of bone marrow aspirate (May-Grünewald-Giemsa, magnification ×1000). This image shows intracellular amastigotes, although most parasites are generally observed free between mononuclear cells. The nucleus of the parasitized histiocyte is indicated by the large gray arrow. Amastigotes were unambiguously identified by the association of their rod-shaped kinetoplast (thin black arrow) and single nucleus (thin gray arrow).

Diagnosis: Visceral leishmaniasis in a liver transplant recipient.

The pathology slides showed numerous rounded structures, about 5 µm in diameter, inside macrophages (Figure 1). A single stick-like organelle was visible inside some of these structures. These findings are consistent with amastigote forms of *Leishmania* protozoa, also called Leishman–Donovan bodies. The parasites were thereafter identified in smears of bone marrow aspirate (Figure 2), and the serology was positive (*Leishmania*-Spot IF, bioMérieux; *Leishmania* immunoglobulin [IgG] enzyme-linked immunosorbent assay, Novagnost Siemens; and *Leishmania* Western blot IgG, LDBio Diagnostics). *Leishmania* DNA was detected in the blood by polymerase chain reaction (PCR) (primers RV1/RV2), and the species *Leishmania infantum* was identified by sequencing.

Leishmaniasis is an anthropozoonotic parasitosis transmitted by sandfly bites. About 30 *Leishmania* species have been described, but only 2, *L. infantum* and *Leishmania donovani*, have been found to cause visceral leishmaniasis (VL); the other species are limited to the cutaneous or mucosal diseases. Asymptomatic VL is 6–7 times more frequent than symptomatic VL [1]. VL is endemic in East Africa, India, Central Asia, the Amazonian forest, and the Mediterranean basin. Although less well known, VL is also endemic in Georgia. The first report of VL in this country was in 1913, and about 2500 local cases of VL were recorded between 1928 and 2008. The frequency appears to have been increasing since 1996, especially in and around Tbilisi (with 5–10 new cases per 10 000 inhabitants in 2008).

In cases of VL, bone marrow, liver, and the spleen are the most commonly infected organs, and this typically results in cytopenia and organomegaly. However, amastigotes may disseminate through all tissues in cases of severe immunosuppression [2]. The digestive tract may be invaded as in our patient. Most

cases of disseminated VL have involved human immunodeficiency virus (HIV)-infected subjects, but new populations at risk of disseminated VL have recently emerged, including solid organ transplant patients. About 100 such cases have been reported [3]: Spain, France, Greece, Italy, and Portugal are countries with the highest incidence, and are all in southern Europe. Because kidney transplant is the most frequent solid organ transplant, a large proportion (77%) of these VL cases involve kidney recipients [3]. As in our patient, the origin of leishmanial infection in transplant recipients is frequently unclear; one possibility—which is mainly observed in endemic areas—is that the recipient may already have been infected with *Leishmania* before transplant, and the infection subsequently reactivated [4]. By contrast, it is more unlikely that the transplanted organ directly infects the recipient, although serological tests should systematically be performed for screening undiagnosed leishmaniasis in donors from endemic areas [5]. Last, the recipient may also be infected by a sandfly bite after his transplant, especially during the summer months in temperate countries such as Georgia [6]. Irrespective of the cause, the immunosuppressive regimen usually reveals belatedly the clinical signs (between a few months to several years after the transplant, with a median delay of 18 months) [3]. The first and major symptom is the onset of fever. Splenomegaly and hepatomegaly are less frequent than in immunocompetent subjects. Although the diagnosis can be confirmed by smears of bone marrow aspirate and/or histology, serology is generally informative in transplant recipients (as in our case, positive in >90% of cases), unlike in HIV-infected subjects (<50%) [7]. PCR is also valuable both for diagnosis and, applied to sequential blood samples, follow-up [8, 9].

The evolution of VL in transplant recipients is always fatal without specific treatment [7]. Consequently, numerous drugs have been assessed for the treatment of VL. Currently, liposomal amphotericin B is the standard treatment in developed countries, because the alternative pentavalent antimonies are associated with severe toxicity, which sometimes results in toxic hepatitis and pancreatitis, and other alternative drugs (eg, miltefosine, paromomycin) are not available everywhere [10]. Our patient received 6 doses of liposomal amphotericin B at 3 mg/kg over 6 days. The digestive bleeding definitively disappeared, and a substantial normalization of the anemia (to 11.2 g/L) was observed after 3 months. Even in cases receiving appropriate antileishmanial therapy, special vigilance is required because of the possibility of further relapse, especially in immunocompromised patients: 58 episodes of recurrence were reported among 21 transplant recipients with VL [11]. Rigorous follow-up for a long period is therefore recommended. Either liposomal amphotericin B, pentamidine, or pentavalent antimonies are proposed for individuals with heavy immunosuppression (eg, HIV infection) until immunity has been restored [12, 13]. However, we did not administer any secondary prophylaxis to our patient, because his white blood cell count was normal at that time. Furthermore, there is no official guideline for solid organ transplants [5, 12], and VL has usually a low rate of recurrences in such a context [3]. Nonetheless, our patient relapsed 1 year later, because we found evidence of location of amastigotes in the liver.

Notes

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