Brief report

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Visceral leishmaniasis after orthotopic liver transplantation: impact of persistent splenomegaly

F. F. Horber[1], J. P. Lerut[4], J. Reichen[2], A. Zimmermann[3], P. Jaeger[1], R. Malinverni[1]

[1] Medizinische Universitätspoliklinik, [2] Institut für Klinische Pharmakologie, [3] Institut für Pathologie, and [4] Klinik für Viszeralchirurgie und Transplantation, Inselspital, Freiburgstrasse 3, CH-3010 Bern, Switzerland

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Abstract. Visceral leishmaniasis was observed in a 50-year-old female liver transplant recipient 1 year following transplantation. Signs of active infection were low-grade fever, pancytopenia, persistent splenomegaly, positive cultures for leishmania in liver and bone marrow biopsy specimens, and newly positive leishmania serology. Following sequential therapy with pentavalent antimony and amphotericin B, blood values improved massively, bone marrow cultures became negative, and leishmania serology decreased. Secondary prophylaxis with fluconazole was instituted and the patient remains without signs of active infection 1 year after successful therapy.

Key words: Liver transplantation, leishmaniasis – Leishmaniasis, liver transplantation – Splenomegaly, liver transplantation, leishmaniasis

Infection is a well-recognized complication of immunosuppressive therapy. Various types of protozoal and parasitic infections in transplant patients have occasionally been reported [13]. Visceral leishmaniasis has been observed previously in renal transplant patients, other immunosuppressed subjects, and, more recently, in patients with the acquired immune deficiency syndrome [1, 2, 5, 6, 8–11]. We report for the first time the occurrence of visceral leishmaniasis in a patient who received an orthotopic liver transplant.

Case report

In January 1989, a successful orthotopic liver transplantation (OLT; blood group mismatched A to AB) was performed in a 50-year-old woman with terminal cryptogenic liver cirrhosis, accompanied by positive antinuclear antibodies, refractory ascites, splenomegaly, and severe hypersplenic syndrome. Under triple immunosuppression with cyclosporin A, prednisone, and azathioprine, liver function tests remained within normal limits 3 months after OLT, whereas persistent pancytopenia (hemoglobin 8 g/dl, leukocytes 1.2 10^9/l with 65% granulocytes and platelets 60 10^9/l) and unexplained splenomegaly were observed. Three liver biopsies and one bone marrow aspirate within the first 2 months of OLT showed no evidence of leishmania infection; however, no cultures were performed. In the postoperative course the patient had biopsy-proven cytomegalovirus (CMV) hepatitis, from which she recovered completely after reduction of immunosuppression.

In February 1990 the patient developed temperatures of 37.8°–38.5°C with worsening of general condition and pancytopenia (Table 1). Clinical examination revealed a slightly tender liver and marked splenomegaly. IgM antibodies against CMV again became detectable. To differentiate between rejection and reactivation of CMV hepatitis, a liver biopsy was performed that showed multiple basophilic cytoplasmatic inclusions, suggesting visceral leishmaniasis (Fig. 1). Leishmanial infection was confirmed in a bone marrow aspirate by massive presence of intracellular organisms on Giemsa stain and by culture (performed by Dr. H. Marti at the National Swiss Institute for Tropical Diseases, Basel). Hematological values prior to initiation of therapy with pentavalent antimony (Pentostam) are given in Table 1. With the exception of gamma-glutamyltransferase (68 IU/l, normal < 45), routine liver function tests were within normal limits. Retrospective analysis of stored serum samples revealed that leishmania serology was negative immediately before, but positive (1:1280) 12 months after, OLT. Unfortunately, no serum was kept from the organ donor. However, one heart and two kidney transplant recipients from the same donor remained without clinical signs of leishmanial infection and have, at present, no serum antibodies against leishmania.

Because of fever and granulocytopenia (Table 1), empiric therapy with ticarcillin-clavulanic acid and tobramycin was initiated, together with 850 mg of pentavalent antimony per day; azathioprine was stopped and immunosuppression continued with prednisone and cyclosporin A. Fever subsided after 10 days of treatment and antibiotics were stopped. After 22 days on pentavalent antimony, no intracellular organisms were detected in the bone marrow aspirate. However, the culture remained positive for leishmania and hematological values did not change (Table 1); therefore, the dose of pentavalent antimony was increased to 1200 mg/day [3]. After 20 more days of treatment, granulocyte and reticulocyte counts increased (Table 1), but bone marrow cultures remained positive for leishmania. Concomitantly, significant side effects of antimony therapy developed. Treatment was thus interrupted for 11 days. Antimony treatment was replaced with oral ciprofloxacin (500 mg t. i. d.), which has been reported to be of benefit in an animal model [14]. After

Correspondence to: F. F. Horber

Table 1. Effect of treatment of visceral leishmaniasis with pentavalent antimony, ciprofloxacin, amphotericin B, and fluconazole in a liver transplantation patient. ND, Not done

Day of treatment	0	22	40	52	112	140	180	347
Pentostam (mg/day)	← 850 →	← 1200 →						
Ciprofloxacin (mg/day)			←		1500	→		
Amphotericin B (total mg)						← 1160	→	
Fluconazole (mg/day)							←	150 —
Hematology								
– Hemoglobin (g/dl)	6.6[a]	7.2	6.7	9.0	9.9	9.1	9.2	10.6
– Granulocytes (10^6/l)	260	230	450	1800	890	320	1000	1560
– Thrombocytes (10^9/l)	66	67	69	121	105	77	63	108
Leishmaniasis								
Microscopic								
– Bone marrow aspirate	+ + +	Neg[b]	Neg	Neg	Neg	(+)	Neg	ND
– Liver biopsy	+ + +	ND	ND	Neg	Neg	Neg	ND	ND
Culture (bone marrow)	Pos[c]	Pos	Pos	Pos	Pos	Pos	Neg	ND
Serum antibody titer	1:1280	1:640	1:1280	1:1280	1:1280	1:1280	1:640	1:40

[a] Between day 0 and day 22, 500 ml of blood were substituted
[b] No parasites detectable in bone marrow smear
[c] Culture positive for leishmania after 1 week

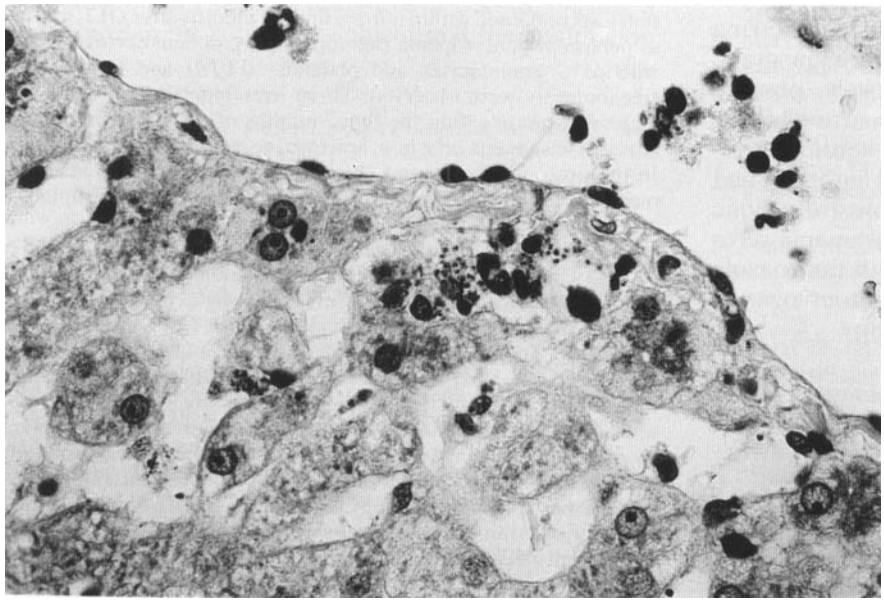

Fig. 1. Liver tissue adjacent to a medium-sized sublobular vein. A group of macrophages visible in the central part of the figure shows numerous small and dense cytoplasmic particles of uniform morphology, typical for leishmania. The small inclusions seen in hepatocytes represent pigment granules. Giemsa stain

8 weeks of ciprofloxacin treatment, the patient felt well and the hematological values remained stable, although granulocyte counts were, again, lower (Table 1). A liver biopsy showed no evidence of leishmania infection, whereas the bone marrow culture remained positive.

After another 2 weeks, granulocyte count decreased further to 230 10^6/l and bone marrow culture still grew leishmania. Thus, therapy with amphotericin B was initiated and continued for 40 days with a total dose of 1160 mg. The culture of bone marrow aspirates 2 and 4 weeks after initiating amphotericin B therapy were negative, indicating eradication of leishmania. As secondary prophylaxis, fluconazole (150 mg/day) was initiated. The patient stayed well thereafter.

Discussion

In Europe, visceral leishmaniasis is endemic in the Mediterranean region. No endemic cases of visceral leishmaniasis have been documented in Switzerland. Since our patient lacked antibodies against leishmania and never left Switzerland after OLT, transmission of infection by the transplanted liver is the most likely explanation. Leishmania multiplies in phagocytic cells and is found principally in the bone marrow, spleen, liver, and lymph nodes. Therefore, it is not surprising that the three patients concomitantly transplanted with the kidneys and the heart from the same donor have not developed infection with leishmania to date. Leishmania can also be transmitted by blood transfusions, although this is quite rare [7]. However, infection through blood transfusion in a nonendemic area and with a very careful selection of donors – as it is performed in Switzerland – is highly unlikely.

Visceral leishmaniasis is a serious threat to the life of patients with severely impaired cell-mediated immunity. In a recent series of 23 immunocompromised subjects [5], 12 patients died despite adequate antiprotozoal therapy,

mostly because of secondary bacterial infections. It is of interest to note that significant side effects were observed in our patient after increasing the daily dose of pentavalent antimony to 20 mg/kg body weight: renal tubular acidosis, bone marrow toxicity, inner ear deafness, and action tremor, as well as ECG changes, side effects that are known to occur after intoxication with other heavy metals [3, 4].

Despite oral therapy with ciprofloxacin [14], the culture of the bone marrow aspirate remained positive for leishmania, indicating a persistent low-grade infection with this parasite. This finding is not surprising in a patient with impaired cell-mediated immunity since the macrophage-monocyte system is predominantly responsible for the elimination of leishmania. Furthermore, even in subjects with no obvious immunosuppression, the failure rate of antimony therapy alone is considerable [2]. Macrophage-stimulating interferon-gamma was not administered to our patient because of the potential risk of transplant rejection [12]. Finally, a 40-day course with intravenous amphotericin B in a total dose of 1160 mg eradicated leishmania, bone marrow cultures were twice negative for this parasite, and hematological values improved massively over the next 5 months. Whether a secondary prophylaxis with an imidazole derivative is necessary and/or effective remains to be investigated [15].

Clinical diagnosis of visceral leishmaniasis in immunocompromised patients is difficult; in fact, the clinical presentation with lymphadenopathy, hepatosplenomegaly, pancytopenia, and fever may be uncommon and clinical signs may be subtle. Splenomegaly after OLT is not uncommon (e.g., as a consequence of pre-OLT liver disease, infections, lymphoproliferative disorders, etc.), and pancytopenia is often attributed to cytotoxic therapy. However, persistent splenomegaly and pancytopenia after successful OLT is very unusual. Infection with leishmania should be suspected in liver transplant patients (even in the absence of relevant travel history) in the presence of persistent splenomegaly after successful transplantation. Some types of infections known to be uncommon outside the endemic regions can be expected to be encountered more frequently with increasing worldwide travel of transplant patients and their potential donors.

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