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Review

Visceral leishmaniasis in organ transplant recipients: 11 new cases and a review of the literature

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Abstract

Eleven new cases of visceral leishmaniasis (VL) are reported in organ transplant patients in France. The epidemiological, clinical, biological, diagnostic and therapeutic features are reviewed, based on these cases and 46 cases reported in the literature. VL was most commonly associated with renal transplantation (77% of the cases). Most patients were from Southern European countries. The main clinical symptom was fever. Leucopoenia and anaemia were the most frequent haematological disorders. Diagnosis was by direct finding of the parasite in smears of bone marrow (85.2%) or, by positive serology (90.9%). Without antileishmanial treatment, VL in transplant recipients was fatal. Treatment using either antimonials or amphotericine B gave similar cure rates of around 80% of the cases. But toxicity was higher for antimonials. Relapses occurred in 14.3%.

Keywords: Visceral leishmaniasis; Organ transplantation; Immunosuppression; France

1. Introduction

Visceral leishmaniasis (VL) is a parasitic disease occurring in numerous countries, on four continents. The agents responsible are protozoa of the genus *Leishmania*, which are transmitted by the bite of insect vectors, the phlebotomine sandflies. The disease is endemic in its main historical foci (India, China, East-Africa, Central Asia, Mediterranean basin, South America), but it can be occasionally responsible for severe epidemic outbreaks (India, East-Africa). In endemic countries, the number of asymptomatic infections is greater than that of clinically apparent cases [1].

Since 1985, the prevalence of VL has increased significantly in several countries, mainly in Southern Europe, due to immunosuppression associated with HIV infection [2]. Other immunosuppressive states can occasionally lead to the appearance of clinically overt VL in previously asymptomatic patients. The effects of neoplasic diseases and immunological disorders are, often worsened by immunosuppressive drugs, such as corticosteroids, and cytotoxics [3].

In the last 20 years, the increasing frequency of organ transplantations and improvement of the associated immunosuppressive treatments have led to the recognition of several cases of VL complicating organ transplantation.

In the present paper, we report 11 new cases diagnosed between 1992 and 2003 in three academic hospital centres (Centres Hospitaliers Universitaires, CHU) in the South of France.

These cases extend to 57 the number of reported cases. We review the epidemiological, clinical, biological and therapeutic aspects of VL associated with organ transplantation, based on both our 11 cases and cases reported in the literature.

2. Case reports

Eleven cases were diagnosed in the south of France between 1992 and 2003, in the following hospitals: CHU of

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Table 1
Epidemiological data on the cases reported from Montpellier (1–5), Nice (6–7) and Marseille (8–11)

N°	Sex	Age	Transplanted organ	Time* (month)	Immunosuppressor treatment	Sequence of infection	Location of infection
1	F	48	Kidney	16	Azathioprine prednisolone cyclosporine	Post-transplant.	Cévennes
2	F	61	Liver	16	Cyclosporine	Post-transplant.	Provence
3	M	62	Liver	4	Cyclosporine prednisolone	Pre-transplant.	Côte-d'Azur
4	F	38	Kidney	21	Azathioprine	Post-transplant.	Pyrénées-Orientales
5	M	6	Liver	60	Cyclosporine predisone	Post-transplant.	Pyrénées-Orientales
6	M	48	Kidney	80	Azathioprine	Post-transplant.	Côte-d'Azur
7	F	48	Kidney	8	Azathioprine cyclosporine	Post-transplant.	Côte-d'Azur
8	M	67	Kidney	93	Cyclosporine	Post-transplant.	Provence
9	M	58	Kidney	144	Cyclosporine corticoid azathioprine	Post-transplant.	Provence
10	M	53	Kidney	24	Cyclosporine	Post-transplant.	Provence
11	F	62	Kidney	41	Azathioprine corticoid	Post-transplant.	Côte-d'Azur

Marseille (four cases), CHU of Montpellier (five cases) and CHU of Nice (two cases). There were six males and five female patients, with a mean age of 50.1 years (extreme values 6 and 67 years; nine out of 11 were more than 48 years old). Eight had received renal, and three hepatic, transplants (Table 1). All patients came from the Mediterranean region of southern France.

Ten cases were diagnosed between 4 months and 12 years following transplantation, but in one case a *Leishmania* infection was demonstrated before transplantation. Various classes of immunosuppressive drugs were used, mainly cyclosporine (eight cases) and azathioprine (six cases). Clinically (Table 2), the main symptom indicating VL was fever, either alone (five cases) or associated with splenomegaly (three cases). Liver enlargement was detected in two patients.

Diagnosis was made in all cases by parasite detection, with positive smears from bone marrow (eight cases), blood (one case), liver biopsy (one case) and mucosal lesion (one case). In eight cases, parasites were isolated in culture and identified by isoenzyme analysis as *Leishmania infantum* zymodeme MON-1. Immunological diagnosis was positive in all cases and PCR was positive in seven cases out of eight tested.

Most patients were treated by amphotericin B in various formulations: amphotericin B desoxycholate in glucose suspension (one case) or lipid emulsion (two cases) and liposomal amphotericin B (five cases). Two patients received pentavalent antimony, and one patient had pentavalent antimony and liposomal amphotericin B sequentially. One patient died prior to treatment. The outcome following treatment was favourable in nine patients, with cure in eight patients and relapse in one. A death occurred by toxic hepatitis and pancreatitis following antimonial treatment (Table 2).

3. Literature review

Including the 11 patients described above, 57 cases of VL in transplant recipients have been reported (Table 3) [4–36].

VL was most commonly associated with renal transplantation (44 out of 57 cases, 77.2%). This might be related to the predominance of this kind of organ transplantation. The other transplanted organs were liver (six cases), heart (three), lung (two), bone marrow (one) and kidney plus pancreas (one). All patients were receiving immunosuppressive treatment when VL appeared, but the immunosuppression level was rarely mentioned. In a single case [10] a CD4 level was reported, and was less than 200 per mm^3.

Most patients ($n = 49$) were from the Mediterranean basin: Spain (21 cases) [6–9,12,15,16,19,24,25,28,33,34], southern France (18 cases) [5,14,17,30,36, present paper], Greece (five cases) [26,35], Portugal (two cases) [10,17], Italy (two cases) [21,31] and Malta (one case) [4]. Others were from India (three cases) [13,23,32], Iran (one case) [22] and Saudi-Arabia (two cases) [20,29]. This geographical distribution resembles that of *Leishmania*/HIV co-infection [37].

Male patients predominated (m:f = 36:14, $n = 50$) and their mean age was 33.4 years (range 6–67 years, 75.6% between 31 and 60 years old).

The clinical signs observed in 51 patients were predominantly irregular fever (43 cases, 84.3%), splenomegaly (30 cases, 58.8%), hepatomegaly (14 cases, 27.5%) and weight loss (11 cases, 21.6%).

In 45 patients, for whom blood cell counts were available, leucopoenia was the most frequent abnormality (40 cases, 88.9%), followed by anaemia (35 cases, 77.8%) and thrombocytopoenia (31 cases, 68.9%). In 26 cases (57.8%), pancytopoenia was present.

The diagnosis was made directly by finding parasites in smears of bone marrow (46 of 54 cases), or in liver biopsy in liver transplantation cases (four cases). In single cases, the parasite was present in the buccal mucosa and blood. Serology was positive in 30 (90.9%), negative in three, and not reported in 23 cases. PCR was positive in 10 of the 11 blood samples tested.

The outcome of VL following organ transplantation was good if correctly treated. Four patients did not receive any antileishmanial treatment and did not survive. Of 49 patients who were treated for VL, 39 (79.6%) were cured and 10 died (20.4%). The rates of cure with the two first line antileishmanial drugs were similar: 79.2% for antimonials and 81.8% for amphotericin B. Eight patients who received both antimonials and amphotericin B, were all cured, with the exception of a single patient who received antimonials very late, just before death. Antileishmanial treatment, either by antimoni-