Is Visceral Leishmaniasis Different in Immunocompromised Patients Without Human Immunodeficiency Virus? A Comparative, Multicenter Retrospective Cohort Analysis

José M. Ramos,^{1,2*} Rafael León,^{1,2} Esperanza Merino,^{2,3} Marta Montero,⁴ Asunción Aljibe,⁴ Marino Blanes,⁴ Sergio Reus,^{2,3} Vicente Boix,^{2,3} Miguel Salavert,² and Joaquín Portilla^{1,2,3}

¹Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain; ²Department of Clinical Medicine, Universidad Miguel Hernández de Elche, Campus of San Juan de Alicante, Alicante, Spain; ³Unit of Infectious Diseases, Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain; ⁴Unit of Infectious Diseases and Department of Internal Medicine, Hospital Universitario-Politécnico La Fe, Valencia, Spain

Abstract. Although visceral leishmaniasis (VL) can affect immunocompromised patients, data from the human immunodeficiency virus (HIV) infection context are limited, and the characteristics of VL in other immunosuppression scenarios are not well defined. A retrospective review of all cases of VL in immunocompromised patients from January 1997 to December 2014 in two Spanish hospitals on the Mediterranean coast was performed. We included 18 transplant recipients (kidney: 7, liver: 4, lung: 3, heart: 2, and blood marrow: 2), 12 patients with other causes of immunosuppression (myasthenia gravis: 3 and rheumatoid arthritis: 2), and 73 VL HIV-positive patients. Fever was more common in transplant patients (94.4%) and patients with other types of immunosuppression (100%) than in HIV-positive individuals (73.3%). Hepatomegaly was less common in transplant recipients (27.8%) and patients with other types of immunosuppression (41.7%) compared with HIV-positive patients (69.9%) ($P = 0.01$; $P = 0.001$, respectively). Patients with other types of immunosuppression had a median leukocyte count of $1.5 \times 10^9/L$, significantly lower than HIV-positive patients ($2.5 \times 10^9/L$) ($P = 0.04$). Serology was more commonly positive in nontransplant immunosuppressed individuals (75%) and transplant recipients (78.6%) than in HIV-patients (13.8%) ($P < 0.001$). Antimonial therapy was rarely used in transplant recipients (1.9%) and never in patients with other immunosuppressive conditions, whereas 34.2% of HIV-positive patients received it ($P = 0.05$ and $P = 0.01$, respectively). Mortality was 16.7% in both transplant recipients and patients with other immunosuppressive conditions and 15.1% in HIV-positive patients. The features of VL may be different in immunosuppressed patients, with more fever and less hepatomegaly and leukopenia than in HIV-infected patients.

INTRODUCTION

Visceral leishmaniasis (VL) is a chronic infectious disease caused by a group of protozoan parasites of the genus *Leishmania*. Autochthonous cases remain relatively rare in Europe and are mostly confined to the southern half of the continent, including Spain, where the infection is endemic in most of the Iberian Peninsula and in the Balearic Islands.^{1,2}

Immunosuppression is a risk factor for VL and can also alter disease presentation and treatment response.³ From the mid-1980s to the late 1990s, there was a progressive increase in the number of VL cases detected in Spain, mainly because of the human immunodeficiency virus (HIV) pandemic.^{4,5} *Leishmania* with HIV coinfection has several characteristic features: lower cure rates, higher rates of drug toxicity, and higher relapse and mortality rates when compared with VL in the general population.⁶

In recent decades, there has been a significant increase in the number of immunocompromised patients, mainly fueled by immunosuppressive therapies (anticancer therapy, prophylaxis for transplant rejection, anti-tumor necrosis factor (TNF) drugs, and monoclonal antibodies), expanding the population at risk for VL.⁷

VL has been found in severely immunocompromised patients with T-cell defects, such as transplant recipients; people with leukemia, lymphoma, systemic lupus erythematosus, and AIDS; and patients on corticosteroid or other immunosuppressive therapy.^{3,8–14} Although the clinical features of VL in the setting of HIV infection have been widely described,^{4–6}

there are only a few reports of VL in hematologic or solid organ transplant recipients,^{3,8,9} and even fewer exploring the clinical profile of VL in immunocompromised individuals who are neither transplant recipients nor infected with HIV.^{10–14} At the same time, there are very few reports comparing VL in immunosuppressed individuals versus VL in HIV-infected patients.^{15,16}

The aim of this study is to begin to fill the gaps in knowledge about this population, defining the clinical and epidemiological differences of VL in three groups of immunocompromised patients: transplant recipients, HIV-infected patients, and people with other immunosuppressive conditions.

PATIENTS AND METHODS

Study design. Retrospective multicenter cohort analysis from January 1997 to December 2014 in two Spanish hospitals: Hospital General Universitario de Alicante (HGUA) and Hospital Universitari i Politècnic La Fe (HUPF). HGUA covers a health area including 256,000 inhabitants in the metropolitan city of Alicante; the hospital has all the medical and surgical specialties and is a referral center for part of the province of Alicante in certain surgical (vascular, thoracic, cardiac, and plastic) and medical (clinical hematology and endocrinology) specialties; it also has programs for kidney, liver, and bone marrow transplants. HUPF covers a health area of 356,000 inhabitants in the metropolitan city of Valencia; it has all the medical and surgical specialties and is a referral center for part of the province of Valencia and Valencian community; it has programs for heart, liver, kidney, lung, pancreas, and bone marrow transplants.

Patient characteristics. We use the hospital admissions database set up in compliance with the Spanish surveillance

* Address correspondence to José M. Ramos, Department of Internal Medicine, Hospital General Universitario de Alicante, Pintor Baeza 12, Alicante 03010, Spain. E-mail: jramosrincon@yahoo.es

system register, using the minimum basic data set for hospital discharge. This system uses clinical codes for the Spanish version of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We reviewed all hospital discharges for leishmaniasis (ICD-9-CM: 085.0–085.9) in adults aged more than 14 years reported during the study period.

Inclusion criteria were all patients diagnosed with VL and immunosuppression. Patients were diagnosed with VL if they met one of the following criteria: 1) presence of *Leishmania* amastigotes in the bone marrow Giemsa stain, isolation of promastigotes in the biopsy culture (bone marrow, liver, kidney, spleen, lymph node or mucosa), or *Leishmania* polymerase chain reaction (PCR) positive on bone marrow or solid tissue samples or 2) prolonged fever, positive *Leishmania* serology, and response to specific treatment (N-methylglucamine) or liposomal amphotericin B. Serology was determined by immunofluorescence; a titer of $\geq 1:80$ was considered positive.

Exclusion criteria were immunocompetent patients diagnosed with VL and immunosuppressed patients with VL whose data could not be properly extracted from the clinical chart. Figure 1 shows the flow chart of patients in the study.

We included HIV-infected patients, transplant recipients, and other immunocompromised patients, defined as 1) patients treated with a biological drug whose target is a molecule of the immune system (anti-TNF and anti-CD20); 2) patients on immunosuppressive therapy such as cyclosporine, tacrolimus, methotrexate, everolimus, azathioprine, or mycophenolate; 3) patients with a primary immunosuppressive disease such as primary immunodeficiency or an autoimmune disease; or 4) patients on steroid treatment: prednisone > 10 mg for more than 3 weeks or > 15 mg for 7 days or longer.

Study variables. Study variables were center; age; sex; nationality; date of VL diagnosis; HIV infection; date of HIV diagnosis; CD4 count at HIV diagnosis; CD4 at VL diagnosis; antiretroviral treatment at VL diagnosis; existence, type, and date of transplant; existence, type and date of diagnosis for immunologic disease; administration and type of

immunosuppressive therapy; clinical syndrome in the first episode of leishmaniasis; presence of fever, hepatomegaly, splenomegaly, lymphadenopathy, and/or other organ pathology; coinfection with other pathogens in the first episode of leishmaniasis; hemoglobin; leukocytes; platelets; total protein; gamma globulin; C-reactive protein (CRP); erythrocyte sedimentation rate (ERS); VL diagnostic test; serology; treatment type and duration; response to treatment; relapse; secondary prophylaxis; prophylaxis treatment used in the patients, duration of prophylaxis in days; and VL-related death (posthoc by the researchers).

Statistical analysis. Variables were entered directly into the SPSS statistical package, version 22 (SPSS Inc., Chicago, IL) and subsequently analyzed with the same software. We performed a descriptive analysis of the clinical and epidemiological characteristics using absolute and relative frequency counts, tables, and graphs. We described quantitative variables using median and their corresponding measures of variability (interquartile range [IQR]). We tested the normality of the distribution using the Kolmogorov–Smirnov test.

To analyze the differences between groups of patients (immunosuppressed HIV-positive and HIV-negative), we used the chi-squared test or Fisher's exact test for qualitative variables and Mann–Whitney U or Kruskal–Wallis tests for quantitative variables, as needed. A *P* value less than 0.05 was considered significant. To measure the strength of the association, we used the odds ratio (OR) with 95% confidence interval.

Ethics statement. The institutional research ethics committee approved the study protocol of HGUA. All data were anonymized.

RESULTS

Over the course of the study period, 30 immunosuppressed non-HIV patients (12 from HUPF and nine from HGUA) and 73 HIV-positive patients (50 from HGUA and 23 from HUPF) were diagnosed with VL. Of the 30 immunosuppressed non-HIV patients, 18 were transplant recipients (kidney: 7, liver: 4, lung: 3, heart: 2, and bone marrow: 2), and 12 had other causes

FIGURE 1. Flow chart of leishmania visceral patients.

of immunosuppression: myasthenia gravis: 3, rheumatoid arthritis: 2, and others: 7. We present the main epidemiological characteristics in Table 1. All 12 nontransplant, non-HIV immunosuppressed patients were receiving immunosuppressive treatment (steroids: 6, methotrexate: 3, mycophenolate: 2, adalimumab: 2, and tacrolimus and azathioprine: 1 each). One patient had a common variable immunodeficiency (CVID).

Clinical manifestations. Fever was more common in transplant recipients (94.4%) and patients with other immunosuppressive conditions (100%) compared with HIV-positive individuals (73.3%). Hepatomegaly was less common in patients with other immunosuppressive conditions (41.7%) and in transplant recipients (27.8%) than in HIV-positive patients (OR: 0.22, 95% CI: 0.06–0.79, and OR: 0.66, 95% CI: 0.05–0.52, respectively) (Table 2). In immunosuppressed patients (transplant recipients and other causes), fever was more common, and splenomegaly and lymphadenopathy less common, than in HIV-positive patients, but the differences did not reach statistical significance (Table 2).

Coinfections. At VL diagnosis, a coinfection was present in six (33%) transplant recipients, 27 (37%) HIV patients and four patients with other causes of immunosuppression (33%). The most common coinfections were opportunistic infections followed by pyogenic infections. Table 1 shows the coinfections in relation with the type of immunosuppressive condition. There were no significant differences between groups except for pyogenic infections, which were more common in patients with other immunosuppressive

conditions than in HIV-positive patients (25% versus 5.5%; $P = 0.02$).

Laboratory data. Table 2 shows the laboratory data in relation to the type of immunosuppressive condition. Patients with other immunosuppression had a median leukocyte count, platelet count, and ESR significantly lower than HIV-positive patients ($P < 0.05$). The median PCR was significantly higher in patients with other immunosuppression than in HIV-positive patients ($P = 0.02$).

Diagnosis. VL diagnosis was mainly made by bone marrow study, by means of Giemsa, culture, or *Leishmania* PCR in 83.3% of transplant patients, 87.4% of HIV-positive patients, and 91.7% of patients with another immunosuppressive condition (Table 3). The other cases were diagnosed via aspiration of the spleen and biopsy of the other organ. Two transplant recipients (11.1%) and two HIV-positive patients (2.7%) were diagnosed by positive serology and response to treatment (Table 3). In the patients in whom serology was performed, it was positive (immunofluorescence titers ≥ 1 : 80) more commonly in patients with other immunosuppressive conditions (75%) and in transplant recipients (78.6%) compared with HIV-positive patients (13.8%) ($P < 0.001$) (Table 3).

Treatment and outcome. Information on treatment was available for 101 of 103 patients (Table 4). Antimonial therapy was never or rarely used in patients with other immunosuppressive conditions (0%) or in transplant recipients (1.9%) compared with HIV-positive patients (34.2%) ($P = 0.01$ and $P = 0.05$, respectively) (Table 4). Treatment changes were made

TABLE 1
Patient characteristics, drugs, and coinfections

	Immunosuppressed patients* (N = 12)	Transplant patients (N = 18)	HIV-infected patients (N = 73)
Sex: n males (%)	10 (83.3)	13 (72.7)	60 (82.2)
Median age in years (IQR)	58 (36.5–70)†	51 (44–57)‡	38 (34–42)
Spanish nationality, n (%)	10 (100)	16 (88.9)	66 (90.74)§
Taking immunosuppressive treatment, n (%)	11 (91.7)	18 (100)	–
Immunosuppressive and antiretroviral drugs at VL diagnosis, n (%)			
Steroids	6 (50.0)	9 (50.0)	–
Methotrexate	3 (25.0)	–	–
Mycophenolate	2 (16.7)	3 (16.7)	–
Adalimumab	2 (16.7)	–	–
Tacrolimus	1 (8.3)	5 (27.8)	–
Azathioprine	1 (8.3)	4 (22.2)	–
Cyclosporine	–	10 (55.5)	–
Everolimus	–	1 (5.5)	–
Antiretroviral treatment	–	–	35 (47.9)
Coinfections at VL diagnosis, n (%)			
Opportunistic infections¶	0	1 (5.5)	13 (17.8)
Pyogenic infections**	3 (25)††	3 (16.7)	4 (5.5)
Herpes virus‡‡	1 (8.3)	2 (11.1)	6 (8.2)
Hepatic virus§§	0 (0)	1 (5.5)	4 (5.5)
Candidiasis	0 (0)	0 (0)	3 (4.1)
Patients with at least one coinfection	4 (33.3)	6 (33.3)	27 (36.9)

HIV = human immunodeficiency virus; IQR = interquartile range; VL = visceral leishmaniasis.

* Immunosuppressive diseases: myasthenia gravis (N = 3), rheumatoid arthritis (N = 2), seronegative spondyloarthritis (N = 1), cyclic neutropenia (N = 1), systemic lupus erythematosus (N = 1), inflammatory bowel disease (N = 1), common variable immunodeficiency (N = 1), hemolytic anemia (N = 1) and idiopathic fibrosis (N = 1).

† $P = 0.01$ (other immunosuppressed patients compared with HIV-positive patients).

‡ $P = 0.005$ (transplant patients compared with HIV-positive patients).

§ Non-Spanish nationality in immunosuppressed patients without HIV infection: Moroccan, English, and Dutch, and in immunosuppressed patients with HIV infection: Colombians (N = 2) and Moroccan, Italian, Russian, and Estonian.

|| Some patients have taken more than one immunosuppressive drug.

¶ *Pneumocystis jirovecii* (N = 7), tuberculosis (N = 6), toxoplasmosis (N = 1).

** Pneumonia (N = 5), *Clostridium difficile* infection (N = 2), endocarditis (N = 1), meningitis (N = 1), cellulitis (N = 1).

†† $P = 0.02$ (other immunosuppressed patients compared with HIV-positive patients).

‡‡ Virus herpes simplex (N = 2), herpes virus type 8 (N = 2), virus varicella zoster (N = 3), cytomegalovirus (N = 2).

§§ Hepatitis C virus (N = 4), hepatitis B virus (N = 1).

||| Some patients had more than one coinfection.

TABLE 2
Clinical manifestation and laboratory data

	Immunosuppressed patients	Transplant patients	HIV-infected patients
Signs and symptoms, n/N (%)			
Fever	12/12 (100)*	17/18 (94.4)	55/73 (73.3)
Hepatomegaly	5/12 (41.7)†	5/18 (27.8)‡	51/73 (69.9)
Splenomegaly	6/12 (50)	9/18 (50)	49/73 (67.1)
Lymph nodes	1/12 (8.3)	1/18 (5.6)	13/73 (17.8)
Laboratory parameters, median (IQR)			
Hemoglobin (g/L)	9.6 (8.6–10.3) N = 12	9.5 (8.7–10.4) N = 17	9.0 (7.8–10.2) N = 70
Leukocytes ($\times 10^9$ /L)	1.5 (1.2–2.8)§ N = 11	2.6 (1.7–6.4) N = 17	2.5 (1.6–3.7) N = 71
Platelets ($\times 10^9$ /L)	62 (32–89)§ N = 11	86 (52–101) N = 17	83 (60–121) N = 71
Proteins (g/dL)	7.2 (5.0–8.4) N = 10	7.3 (5.6–7.8) N = 11	7.5 (6.5–8.5) N = 60
Gamma globulins (g/dL)	2.1 (0.4–3.3) N = 7	2.8 (2.3–4.7) N = 5	3.0 (1.8–3.7) N = 49
C-reactive protein (mg/dL)	6.4 (3.8–14.6) N = 9	5.8 (2.4–15.2) N = 10	2.9 (1.5–7.8) N = 59
Erythrocyte sedimentation rate (mm/h)	59 (42–62) N = 9	71 (54–81) N = 4	83 (59–105) N = 51
CD4 count/ μ L at diagnosis	–	–	56 (26–125) N = 73

HIV = human immunodeficiency virus; IQR = interquartile range; n = total positive response; N = total sample for which the variable was available.

*P = 0.006 (other immunosuppressed patients compared with HIV-positive patients).

†P = 0.01 (other immunosuppressed patients compared with HIV-positive patients); odds ratio: 0.22 (95% confidence intervals: 0.06–0.79).

‡P = 0.001 (transplant patients compared with HIV-positive patients); odds ratio: 0.66 (95% confidence intervals: 0.05–0.52).

§P = 0.04 (other immunosuppressed patients compared with HIV-positive patients).

||P = 0.02 (other immunosuppressed patients compared with HIV-positive patients).

in 11.3% of HIV-positive patients, 11.1% of transplant recipients and never in patients with other immunosuppressive conditions. The main cause for changing treatment was toxicity. Twenty-seven patients relapsed of which 21 were on prophylactic treatment. VL relapse occurred in 16.7% of patients with other immunosuppressive conditions, 27.8% of transplant recipients, and 32.8% of HIV-positive patients. The median number of relapses was lower in patients with other immunosuppressive conditions (1.0) and transplant recipients (1.3) compared with HIV-positive patients (2.6), but without statistical significance. Most of the relapses were treated with amphotericin B liposomal; in the particular case of a patient who had been treated and maintained on prophylaxis with liposomal amphotericin B, after a second relapse was treated with N-methyl-glucamine, maintaining prophylaxis with that drug with good response.

From 101 patients, 62 received secondary prophylaxis. Transplant recipients (33.3%) and patients with other

immunosuppressive conditions (41.7%) used less secondary prophylaxis compared with HIV-positive patients (77.3%) (OR: 0.14; 95% CI: 0.05–0.44; OR: 0.20; 95% CI: 0.06–0.74, respectively) (Table 4). From 62 patients with secondary prophylaxis, 40 received with liposomal amphotericin B, 21 N-methyl-glucamine, and 1 pentamidine.

Sixteen patients died between 4 and 57 days, 15 after the initial diagnosis, and one during a relapse of the disease. Mortality was similar in all three groups. Median time from diagnosis to death was shorter in patients with other immunosuppressive conditions and in transplant recipients than in HIV-positive patients but without significance. Table 5 summarizes data on cause of death.

DISCUSSION

This study provides an 18-year review of clinical manifestations and outcomes for VL in immunocompromised patients,

TABLE 3
Leishmania serology and diagnosis test of visceral leishmaniasis (VL)

	Immuno-suppressed patients	Transplant patients	HIV-positive patients
<i>Leishmania</i> serology, n/N (%)			
Performed	8/12 (66.7)	14/18 (77.8)	58/73 (79.5)
Negative, < 1/80 by IF	2/8 (25)*	3/14 (21.4)*	50/58 (86.2)
Positive, $\geq$ 1/80 by IF	6/8 (75)	11/14 (78.6)	8/58 (13.8)
Diagnosis of VL, n/N (%)			
Bone marrow aspiration	11/12 (91.7)	15/18 (83.3)	64/73 (87.4)
Tissue biopsy	0/12 (0)	1/18 (5.6)†	4/73 (5.5)‡
Spleen aspiration	1/12 (8.3)	0/18 (0)	3/73 (4.1)
Serology and response to treatment	0/12 (0)	2/18 (11.1)	2/73 (2.7)

HIV = human immunodeficiency virus; IF = immunofluorescence; n = total positive response; N = total sample for which the variable was available.

*P < 0.001 (other immunocompromised patients and transplant patients compared with HIV-positive patients).

† lymph node (N = 1).

‡ lymph node (N = 2), stomach (N = 1), colon (N = 1).

TABLE 4

Treatment and outcome in immunocompromised patients, organ transplant recipients and HIV-infected patients with visceral leishmaniasis

	Immunosuppressed patients	Transplant patients	HIV-positive patients
Treatment use, <i>n/N</i> (%)			
N-methyl-glucamine	0/12 (0)*	2/18 (1.9)†	25/73 (34.2)
Liposomal amphotericin B	12/12 (100)	16/18 (88.9)	48/73 (65.8)
Changed treatment, <i>n/N</i> (%)	0/12 (0)	2/18 (11.1)	8/71 (11.3)
Reason for changing treatment, <i>n</i> (%)			
Toxicity	—	2 (100)	7 (87.7)
Failure	—	—	1 (12.3)
Relapse, <i>n/N</i> (%)	2/12 (16.7)	5/18 (27.8)	20/61 (32.8)
<i>n</i> relapses, median (IQR)	1.5 (1.0–2.0)	1.0 (1.0–1.5)	2 (1.0–3.5)
Prophylaxis secondary, <i>n/N</i> (%)	5/12 (41.7)‡	6/18 (33.3)§	51/71 (77.3)
Drugs use, prophylaxis secondary, <i>n/N</i> (%)			
Liposomal amphotericin B	5/5 (100)	5/6 (83.3)	28/51 (54.9)
N-methyl-glucamine	—	1/6 (16.7)	20/51 (39.2)
Amphotericin B	—	—	2/51 (3.9)
Pentamidine	—	—	1/51 (2.0)
VL-related death, <i>n/N</i> (%)	2/12 (16.7)	3/18 (16.7)	11/73 (15.1)
Days until death, median (IQR)	8 (7.0–9.0)	4 (4.0–36.0)	23 (12.5–57)

HIV = human immunodeficiency virus; IQR = interquartile range; *n* = total positive response; *N* = total sample for which the variable was available; VL = visceral leishmaniasis.* *P* = 0.05.† *P* = 0.01 (other immunosuppressed patients and transplant patients compared with HIV-positive patients).‡ *P* = 0.01.§ *P* < 0.001 (other immunosuppressed patients and transplant patients compared with HIV-positive patients).

both HIV-infected and immunosuppressed due to other causes. Although VL is well described in HIV infection, few studies have focused on the epidemiology and risk factors associated with the disease in transplant recipients,^{3,8,9} who make up three of every five cases of VL in immunocompromised patients without an HIV infection. Likewise, just two case series^{14,15} and a few case reports are available on VL in patients with other immunosuppressive conditions.^{10–13} In our study, the profile of immunosuppressed, non-HIV patients was a nontransplanted patient receiving immunosuppressive drugs. Only one patient had a primary immunodeficiency, a CVID. Although hematological neoplasms such as lymphoma and leukemia are well-known conditions that facilitate VL,^{14,15,17} no cases were present in our series.

When VL affects immunocompromised hosts, current therapies frequently fail to eradicate *Leishmania* from infected tissue.¹⁴ In our study, some patients received immunosuppressive drugs that reduced Th1 immune response, inducing

the production of IFN- γ and IL-2 in response to leishmanial antigens.¹⁸ Other drugs that predispose to VL are anti-TNF agents, which have been linked to opportunistic infections by intracellular pathogens.¹⁹ There have been several reports of such cases since 2004,^{10,12,19} and in our series, two patients were receiving anti-TNF agents (adalimumab). However, the main drugs used in both the nontransplant and transplant recipient groups were steroids. Glucocorticoids affect the effector, suppressor, and cytotoxic T-cell functions through the blockade of cytokine expression,^{7,20} resulting in an increased susceptibility to infections, particularly intracellular microbes such as *Leishmania* species.²¹ High-dose steroids have also been independently tied to VL in both transplant patients^{22,23} and nontransplant patients.^{13,24} Other important immunosuppressive drugs are methotrexate and mycophenolate in patients with autoimmune diseases, and methotrexate for rheumatoid arthritis has also been associated with VL,^{25,26} as in two cases of our series.

TABLE 5

Causes of death in immunocompromised patients, organ transplant recipients and HIV-infected patients with visceral leishmaniasis

Age	Sex	Immunosuppressive condition	Time from diagnosis of immune-compromise (years)	Time from diagnosis to death (days)	No. relapses before death	Cause of death
32	Male	HIV infection	1	27	0	<i>Pneumocystis</i> pneumonia
34	Male	HIV infection	11	51	0	Pulmonary tuberculosis
38	Female	HIV infection	11	13	0	Pulmonary tuberculosis
37	Male	HIV infection	6	39	0	Gastrointestinal hemorrhage
33	Male	HIV infection	17	16	0	<i>Pneumocystis</i> pneumonia
37	Male	HIV infection	0.4	75	0	<i>Mycobacterium avium</i> intracellulare disseminated infection
35	Male	HIV infection	0.1	12	0	Pneumococcal pneumonia
42	Female	HIV infection	12	689	1	<i>Escherichia coli</i> bacteremia
40	Female	HIV infection	17	2	0	Hemoperitoneum post liver biopsy
43	Male	HIV infection	10	19	0	<i>Pneumocystis</i> pneumonia
51	Female	HIV infection	7	9	0	<i>Pneumocystis</i> pneumonia
68	Male	Heart transplant	14	36	0	Nosocomial pneumonia
59	Female	Liver transplant	0.1	4	0	Cytomegalovirus colitis
21	Male	Bone marrow transplant	10	4	0	Methicillin sensitive <i>S. aureus</i> bacteremia
58	Male	Idiopathic pulmonary fibrosis	5	9	0	Nosocomial pneumonia
58	Male	Rheumatoid arthritis	10	7	0	Nosocomial pneumonia

HIV = human immunodeficiency virus.

In consonance with previous reports,^{8,9,22} we found that among transplant recipients, VL is predominantly described in renal transplant. Although this is probably attributable to the higher number of kidney transplants, some authors have suggested that renal insufficiency and hemodialysis may be factors that contribute to the increased risk.²⁷

The outcome of VL is determined by the Th1 immune response against leishmanial antigens,¹⁴ and this response—and hence the clinical features—may vary according to different causes of immunosuppression. In our study, fever was less common in immunocompromised patients without HIV compared with those with HIV. Fernández-Guerrero et al.¹⁵ compared clinical features and VL prognosis in immunocompromised patients with and without acquired immune deficiency syndrome (AIDS) (12 and eight patients, respectively), finding no significant difference; however, their sample was small and the risk of a type II error was high.

The differences we found in splenomegaly and enlargement of lymphatic nodes did not reach statistical significance; however, Pintado et al.¹⁶ also noted that HIV-infected patients were less prone to developing an enlarged spleen than HIV-negative individuals.

Bacterial infections are a well-known complication of VL. Other coinfections in HIV-infected patients are also common.^{4,14–16,28,29} We found at least one coinfection in one of every four cases of VL, with similar prevalence in transplant recipients and HIV patients. After grouping different coinfections, pyogenic and other bacterial infections were more common in immunosuppressed individuals.

Fernández-Guerrero et al.¹⁵ did not find significant differences in hematological data (leukopenia, anemia, thrombocytopenia) or elevations of liver enzymes in patients with or without AIDS. We found a lower number of leukocytes in patients with other immunosuppressive conditions, probably because of drugs that produce leukopenia. Non-HIV patients had a lower ESR than HIV-positive patients, as previously noted; this is likely because HIV patients have multiple exogenous insults that can condition a higher ESR^{16,28} and because non-HIV patients receive immunosuppressive drugs that reduce the ESR.²² CRP was higher in non-HIV patients with VL (though without statistical significance); this may be because the acute process that induces a CRP response from the liver is mediated by interleukin 6.²⁹

The most widely used diagnostic method was bone marrow aspiration microscopy, as in other series.^{14–16,22} Serology is minimally invasive and can be used for diagnosis; however, it cannot distinguish between prior exposure and active infection and may have a cross-reaction with other protozoa.³⁰ In our study, serology was more commonly positive in immunocompromised (non-HIV) patients. Fernández-Guerrero et al.¹⁵ also observed that serology was more useful in non-HIV immunosuppressed patients than in those who were HIV-positive.

HIV-infected patients were mainly treated with antimonial drugs, but this is only because most cases of VL in HIV-infected patients were treated earlier in the study period. More recently, most patients receive liposomal amphotericin B.

VL relapse is common in HIV infection,^{2,4,16} although in this setting it is not possible to definitively differentiate relapse from reinfection (*Leishmania* can be transmitted by syringe sharing). In our series, the relapse rate was 16.7% in

immunocompromised patients and 32.7% in patients with HIV. This difference is not statistically significant, but we suspect that relapse could be underdiagnosed in HIV infection because of follow-up problems. Although relapse seems less common in immunocompromised patients and in transplant recipients, it does occur; so, as with HIV patients, it is necessary to closely monitor patients, especially during the first year after diagnosis. Although secondary VL prophylaxis is well established in HIV infection,³¹ there is no consensus with regard to its benefit in other populations or to the drug of choice. In our study, immunosuppressed patients received secondary prophylaxis less frequently than HIV patients. Mortality in immunocompromised patients was about 15%, regardless of HIV condition. This figure is clearly higher than in nonimmunocompromised patients.^{1,2}

Our study has several limitations. First, it is a retrospective study, and not every variable is available for all the patients. The study period was also very long, and follow-up of some patients has been irregular. Moreover, case management across different hospitals and over the course of the study period was not standardized; in addition, this period has also seen improvements in diagnostic techniques and treatment options, as reported by Clemente.²² And finally, that only univariate analysis was conducted because of small numbers. Despite these limitations, to the best of our knowledge, this study is the largest series of VL cases in immunocompromised patients and allows us to draw some conclusions: 1) in endemic zones, VL continue to be a complication of immunosuppression; 2) in immunodepressed patients, the disease can be atypical, less hepatomegaly, and atypical localizations; 3) high-dose steroids are the main drug associated with VL in endemic areas; 4) non-HIV immunosuppressed patients differed from HIV immunosuppressed patients for most parameter analyzed: fever, hepatomegaly, white blood count, serology, and antimonial therapy (perhaps an artifact of the time period during which these patients were seen) but not the mortality 5) serology can be useful for VL diagnosis in immunocompromised non-HIV patients. In endemic areas, providers of medical care to immunodepressed patients need to be aware of the risk of VL and its specific clinical features in immunocompromised patients.

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Authors' addresses: José M. Ramos and Rafael León, Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain, and Department of Clinical Medicine, Universidad Miguel Hernández de Elche, Campus of San Juan de Alicante, Alicante, Spain, E-mails: jramosrincon@yahoo.es and leonr86@hotmail.com. Esperanza Merino, Sergio Reus, and Vicente Boix, Department of Clinical Medicine, Universidad Miguel Hernández de Elche, Campus of San Juan de Alicante, Alicante, Spain, and Unit of Infectious Diseases, Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain, E-mails: merinoluc@gmail.com, reus_ser@gva.es, and boix_vic@gva.es. Marta Montero, Asunción Aljibe, and Marino Blanes, Unit of Infectious Diseases and Department of Internal Medicine, Hospital Universitario-Politécnico La Fe, Valencia, Spain, E-mails: martamontero72@gmail.com, asun.aljibe@gmail.com, and blanesmarino@gmail.com. Miguel Salavert, Department of Clinical Medicine, Universidad Miguel Hernández de Elche, Campus of San Juan de Alicante, Alicante, Spain, E-mail: salavert_mig@gva.es.

Joaquín Portilla, Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain, Department of Clinical Medicine, Universidad Miguel Hernández de Elche, Campus of San Juan de Alicante, Alicante, Spain, and Unit of Infectious Diseases, Department of Internal Medicine, Hospital General Universitario de Alicante, Alicante, Spain, E-mail: portilla_joa@gva.es.

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