

Leishmaniasis among organ transplant recipients

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Leishmaniasis is a rarely reported disease among transplant recipients; however, the number of published cases has quadrupled since the beginning of the 1990s. Most cases have been observed in patients living in countries of the Mediterranean basin. Leishmaniasis is most commonly associated with kidney transplantation (77%), and cases are also recorded among patients undergoing liver, heart, lung, pancreas, and bone marrow transplantation. Visceral leishmaniasis (VL) is the most frequently observed clinical presentation, followed by mucosal leishmaniasis and more rarely cutaneous leishmaniasis. Transplant recipients with VL develop the classic clinical form of the disease, which is a febrile hepatosplenic and pancytopenic syndrome. Immunodepression seems to predispose to development of mucosal leishmaniasis caused by viscerotropic strains. Early diagnosis of VL is crucial for patient therapy and outcome; however, this is frequently overlooked or delayed in transplant patients. Pentavalent antimonials are the most common form of treatment for VL, but have a high incidence of toxicity (34%). Although used in fewer patients, liposomal amphotericin B seems to be better tolerated and should be considered as first-line therapy in transplant recipients.

Introduction

Leishmaniasis, a group of parasitic diseases encompassing cutaneous, mucocutaneous, and visceral manifestations caused by obligate intracellular protozoa of the genus *Leishmania*, are endemic in more than 88 countries.¹ The natural transmission of the parasites is sustained by phlebotomine sandflies of the genus *Phlebotomus* (in the Old World) or *Lutzomyia* (in the New World). However, artificial transmission by means of blood transfusions²⁻⁵ or by needle sharing among intravenous drug addicts is also described.⁶

Visceral leishmaniasis (VL) is caused by the *Leishmania donovani* complex, which includes three species: *Leishmania donovani*, *Leishmania infantum*, and *Leishmania chagasi* (the latter two now being considered identical). These species are distributed in China, the Mediterranean basin, and South America (zoonotic form), in Africa and the middle east (anthropozoonotic form), and in the Indian subcontinent (anthropozoonotic form). In endemic countries, the number of asymptomatic VL infections is greater than the number of clinically apparent VL disease cases, and among immunocompetent people it is estimated that only one in every five or ten develops clinically overt VL.^{7,8} Malnutrition and immunosuppression may reactivate latent leishmania infection and among HIV/AIDS-infected patients the risk of clinical VL is increased by 100–1000 times.⁹ A comparative study of HIV-infected and uninfected Spanish individuals showed that AIDS patients have an incidence of VL that is 418-fold higher than in HIV-negative individuals.¹⁰

Since 1979, when the first report of a renal transplant patient affected by VL appeared in the literature, a steady increase of all forms of leishmaniasis has been observed among transplant recipients (figure 1).¹¹ By contrast, in a review of infections in organ transplant recipients published in 1997, leishmaniasis is not mentioned among the protozoan infectious complications.¹²

Although leishmaniasis is a rare disease among transplant patients, it requires clinical appraisal for

several reasons. For example, the number of organ transplantations performed worldwide is ever growing, as is the frequency of travel to areas endemic for the disease. Furthermore, there is limited knowledge of the disease among clinicians involved in transplant operations.

Epidemiology and risk factors

Up to now, 81 cases of leishmaniasis in transplant patients have been detailed in the published work, either as single case reports^{11,13-61} or as small surveys from a single centre.^{48,62-69} Two cases were reported twice,^{37,49,50,64} and for the purpose of this Review are only considered once, leaving a total of 79 cases. More than two-thirds of these cases were from the Mediterranean basin (figure 2). Additionally, we have identified a further 27 cases that were mentioned in other publications dealing with leishmaniasis or transplantation.^{61,69,70-72} The geographical distribution of leishmaniasis cases among transplant patients is shown in figure 2, which strongly reflects the known areas of endemicity of human leishmaniasis disease and the number and typology of transplantations done. Spain, France, and Italy not only comprise the

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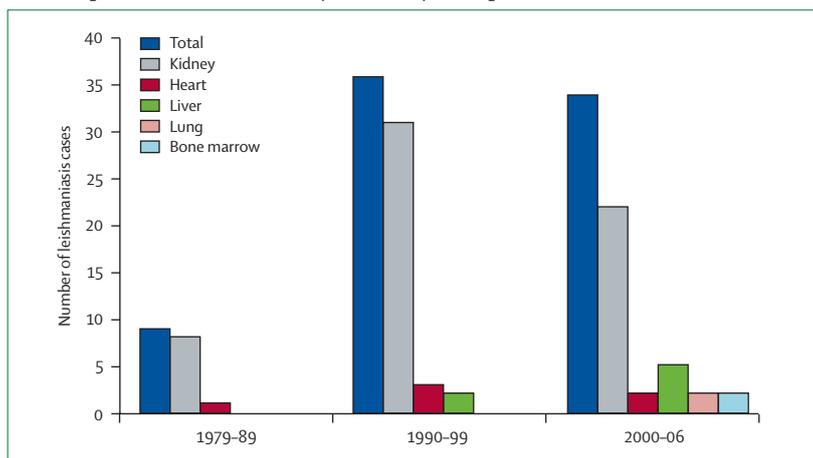


Figure 1: Cases of leishmaniasis among transplant recipients per year of report (1979–2006)

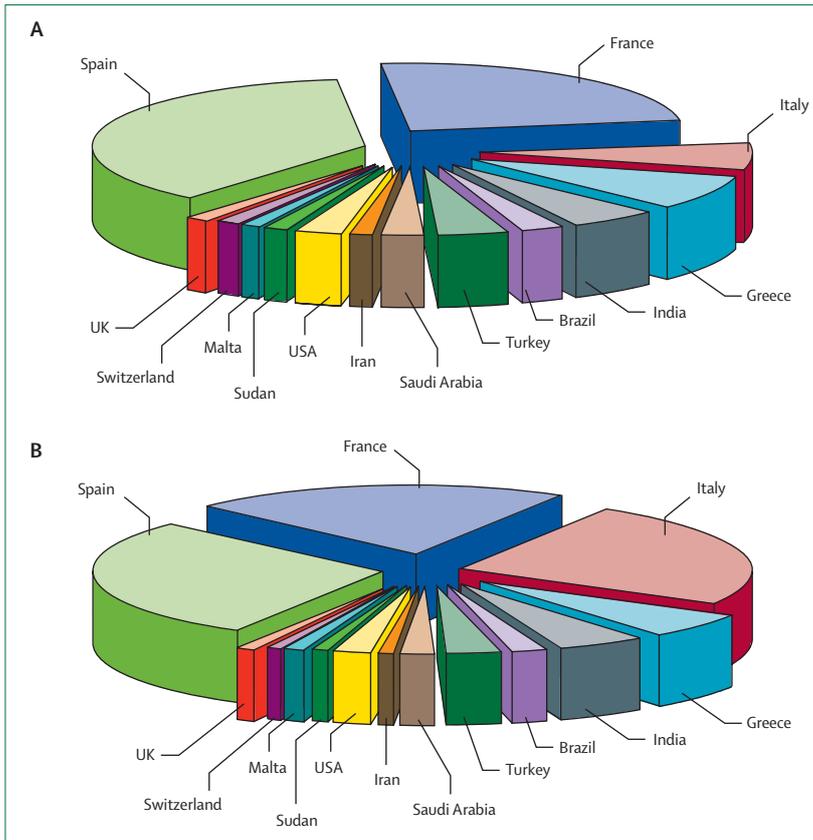


Figure 2: Countries reporting cases of leishmaniasis among transplant recipients according to single case reports (A) and cumulative cases reported (B)

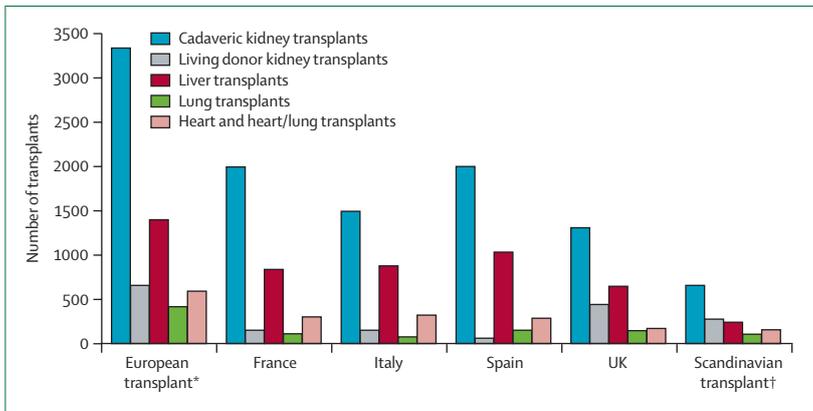


Figure 3: Transplant activity in Europe, 2003
 *European transplant includes Germany, Austria, Belgium, Luxembourg, the Netherlands, and Slovenia.
 †Scandinavian transplant includes Denmark, Norway, Finland, and Sweden.

Mediterranean basin countries with the highest prevalence of transplant-associated leishmaniasis disease, but they are also home to the highest number of organ donation and transplantations in Europe (figure 3). Thus, the risk of developing leishmaniasis among transplant recipients is associated with the geographical region in which they and their organ donors reside. However, in several instances, travel to an endemic region following

transplantation has been reported in transplant patients from non-endemic areas with leishmaniasis.^{11,13,23,58}

Three times as many male transplant recipients have leishmaniasis than female recipients (56 men vs 19 women) and the median age is 47.5 years (range 4–70 years). Age of presentation is one of the main differences observed between organ transplant recipients, HIV-positive individuals, and HIV-negative individuals affected by leishmaniasis. HIV-associated VL usually appears in young adults. In the immunocompetent population living in endemic areas, it is most frequent in infants and young children. In organ transplant recipients, older adults are most affected.

Leishmaniasis usually occurs as a late complication after transplantation, with a median delay of 18 months between transplantation and onset of disease. However, this delay varies depending on the transplanted organ—after liver transplantation, for example, median time is 6 months, as opposed to 19 months for kidney transplantation.

Among the 79 cases described in the literature, leishmaniasis is predominantly described with kidney transplantation (61 cases, 77%)^{11,13–23,25,28–38,40,41,43,44,46–49,51,54–56,60–63,65–69} and less commonly with liver (seven cases, 9%),^{26,57,58,65,69} heart (six cases, 8%),^{24,39,42,45,52,65} lung (six cases, 8%),⁵³ and kidney-pancreas (one case) transplantation.²⁷ At present, there is only one report of VL following haematopoietic stem-cell transplantation⁵⁹ and one after bone marrow transplantation.⁶⁷ The absence of prospective studies that have evaluated the incidence of this disease makes it difficult to ascertain whether the higher number of leishmaniasis cases associated with kidney transplantation is caused by the predominance of this particular organ transplant or to other unknown factors.

Among kidney transplant recipients with VL, the immunosuppressive regimens most frequently used include ciclosporin plus azathioprine and steroids (prednisone or methylprednisolone; 53%)^{20,23,24,26,27,30,32–35,37,39,43,44,47,49,53,62,64,66,68,69} and azathioprine plus steroids (32%).^{11,13–18,22,36,40,48,60,68,69} Other regimens are azathioprine alone⁶⁹ or with ciclosporin;⁶⁹ ciclosporin and steroids;²¹ tacrolimus plus mycophenolate mofetil and steroids;⁵⁵ and ciclosporin plus mycophenolate mofetil and steroids.⁴²

Pathogenesis

The cell-mediated immune response largely determines the outcome of leishmania infection, and therefore only a minority of infected individuals develop clinically apparent disease. In the mammalian host, *Leishmania* spp are obligate intracellular pathogens that infect the haematopoietic cells of the monocyte/macrophage lineage, entering these cells by phagocytosis. *Leishmania* spp use sophisticated strategies to subvert normal macrophage function, such as preventing activation of nitric oxide and inhibition of many cytokine-primed macrophage functions. These methods enable the

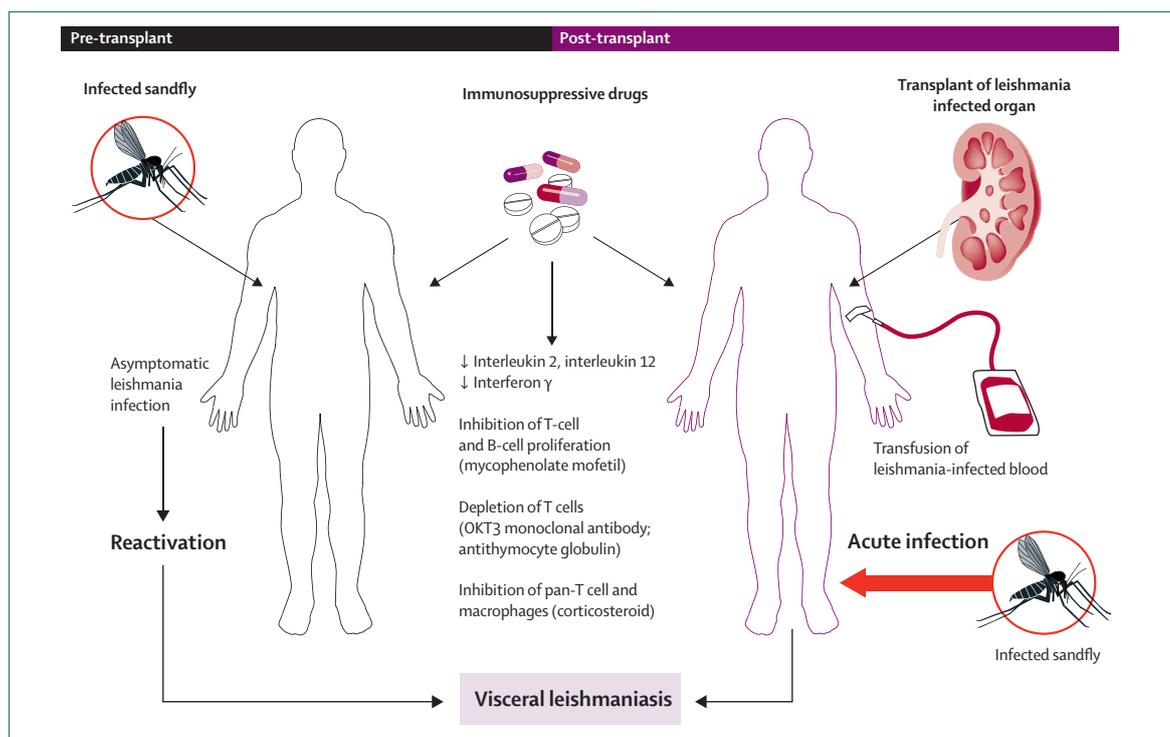


Figure 4: Pathogenetic model of leishmaniasis in transplant patients: reactivation or de novo infection

parasite to escape the innate immune response and to divide within the phagolysosome of the infected macrophage, thereby spreading disease within the host.⁷³ In the murine model of leishmania infection, the immunological pathways responsible for host resistance or susceptibility result from T-helper (Th) 1 and Th2 responses, respectively. In particular, the interleukin-12 driven Th1 response has been widely accepted as promoting protective immunity against all species of *Leishmania*.⁷⁴ However, in HIV-infected patients without fully suppressive ongoing antiretroviral therapy, the decay of CD4+ T lymphocytes is directly linked to an increase in parasite load and dissemination.⁷⁵

The immunosuppressive drugs used in transplant recipients hamper T-cell activation and proliferation, thereby altering defence mechanisms against intracellular microorganisms.^{12,76} For example, ciclosporin forms a complex with the cytoplasmic receptor cyclophilin, which binds to calcineurin. Calcineurin's phosphatase activity is therefore inhibited, preventing the expression of genes such as interleukin 2 and interferon γ that, in turn, promote T-cell activation and proliferation. Azathioprine, a cytotoxic drug, also inhibits T-cell proliferation, whereas corticosteroids inhibit the synthesis of cytokines and suppress cellular immunity. Tacrolimus, a macrolide produced by *Streptomyces tsukubaensis*, acts similarly to ciclosporin by inhibiting the production of interleukin 2 and other cytokines by CD4+ T cells.

In transplant patients, three possible pathogenetic mechanisms may be responsible for the clinical

development of VL. In the first scenario, leishmania infection is acquired ex novo in an immunocompromised recipient with rapid development of clinically overt disease—eg, primary infection (figure 4). This situation is documented in patients who live in leishmania-free areas and have travelled to endemic regions,^{11,13,23,58} but it may also explain cases observed in patients living in endemic countries.⁶⁹ An alternative mechanism is reactivation of a pre-existent, dormant leishmania infection induced by the immunosuppressive drugs. This mechanism has been demonstrated in a liver transplant patient in France with retrospective confirmation of leishmania-positive serology in a stored serum sample collected before transplantation;⁶⁹ in a kidney transplant patient who had lived in an endemic area 22 years before the transplantation;⁶² and finally, in a patient who underwent haemopoietic stem-cell transplantation, demonstrated by retrospective western blot analysis.⁵⁹ The third possible pathogenetic mechanism is iatrogenic acquisition of leishmania infection directly by the transplanted organ or following transfusion of infected blood products. This scenario has been illustrated by a fatal case of visceral leishmaniasis in Macedonia following renal transplantation with a bought kidney from an Indian donor.⁷² Iatrogenic acquisition of leishmania infection was also suspected in a Swiss patient who developed the disease after liver transplantation, lacked antibodies against leishmania in a pre-transplant serum sample, and had not left Switzerland after transplantation.²⁶

	Transplant recipients	HIV-positive*	HIV-negative†	Total
Fever	59/63 (94%)	267/330 (81%)	177/179 (99%)	503/572 (88%)
Hepatomegaly	23/55 (42%)	254/330 (77%)	154/179 (86%)	431/564 (76%)
Splenomegaly	43/57 (75%)	244/330 (74%)	176/179 (98%)	463/566 (82%)
Weight loss	13/36 (36%)	28/90 (31%)	..	41/126 (33%)
Lymphadenopathy	..	12/240 (5%)	10/121 (8%)	22/361 (6%)
Anaemia (haemoglobin <12 g/dL)	51/59 (86%)	260/294 (88%)	134/158 (85%)	445/511 (87%)
Leucopenia (white blood cells <4000 per µL)	55/59 (93%)	266/294 (90%)	79/158 (50%)	400/511 (78%)
Thrombocytopenia (<150 000 platelets per µL)	50/59 (85%)	231/294 (79%)	126/158 (80%)	407/511 (80%)
Serology (IFAT ≥1/40)	45/49 (92%)	113/237 (48%)	126/135 (93%)	284/421 (67%)
Bone marrow microscopy	59/60 (98%)	282/348 (81%)	128/158 (81%)	469/566 (83%)
Bone marrow culture	23/28 (82%)	105/151 (70%)	39/53 (74%)	167/232 (72%)

..=not reported. IFAT=indirect fluorescent antibody test. *Cumulative analysis of references 10, 72, 78, and 80.
†Cumulative analysis of references 10, 72, 79, and 81. Values show number of patients with clinical feature/total patients tested (%).

Table: Comparative clinical and biological features of visceral leishmaniasis among transplant recipients, HIV-positive patients, and immunocompetent HIV-negative patients

However, iatrogenic transmission is probably the least common mechanism involved in the transplant setting.

Clinical presentation of leishmaniasis in organ transplant recipients

VL is the dominant clinical presentation in 68 patients (86%),^{11,13–28,30–37,41–45,47,49–55,57–59,62–69} one of whom had coexistent cutaneous and ocular lesions.⁶¹ Clinical signs and symptoms of VL in transplant recipients closely resemble those observed in immunocompetent and HIV-positive patients,^{10,71,77–81} as shown in the table. However, diagnosis in transplant recipients can be delayed for several months because of low index of suspicion^{32,36,47,57,64} or misdiagnoses (eg, drug toxicity, which led to azathioprine discontinuation in some cases).^{14,32,34,35,45} The time from onset of symptoms to diagnosis of VL varies from 7 days to as long as 5 months (median 30 days).^{28,30,32,37,43–45,47,59,62,66,68}

Fever is the most common symptom of VL in organ transplant patients, being present in 59 patients (94%). However, splenomegaly is reported less frequently than in immunocompetent (eg, HIV-infected) patients.^{10,71,77}

In the 59 patients for whom blood cell counts were available, leucopenia was the most frequently observed abnormality (93%), followed by anaemia (86%) and thrombocytopenia (85%). The calculated median values of haemoglobin (8.2 g/dL), white blood cells (2200 cells per L) and platelet counts (57 000 per L) are indicative of a long-lasting severe disease.

Diagnosis of VL in transplant recipients can be particularly challenging because the disease is frequently concealed by the presence of concomitant opportunistic infections with similar symptoms. Superimposed or coexistent infections were observed in 20 patients and shown to be the immediate cause of death for seven of

them.^{11,13–15,30,62,65} There are published reports of 12 cases of bacteraemia, sepsis, pneumonia, or urinary tract infection caused by *Streptococcus pneumoniae*,^{11,64} *Pseudomonas aeruginosa*,^{11,14,33,64} *Escherichia coli*,^{28,65} *Enterococcus* spp.,^{13,27} *Branhamella catarrhalis*,³⁰ or *Salmonella* spp.⁵⁵ Additionally, human cytomegalovirus disease is documented in six patients^{21,23,27,28,66} and pulmonary tuberculosis in two.^{27,55}

By contrast, cutaneous leishmaniasis (CL) is rare among organ transplant recipients, with reports of two cases of classic disease,^{24,48} one case of disseminated CL caused by *Leishmania major*,²⁹ one case of nodular disease,⁶¹ and two cases (one of which was a recurrence) of post-kala-azar dermal leishmaniasis (PKDL) caused by *L. infantum*.^{38,65} Notably, in patients with HIV infection, post-transplant disseminated CL and PKDL were caused by *Leishmania* species that are not associated with these cutaneous manifestations in the immunocompetent host.^{82,83}

Mucocutaneous leishmaniasis is usually caused by New World species of *Leishmania*, but it has occasionally occurred following infection with other species, and has been reported in the Mediterranean basin.⁸⁴ Mucosal leishmaniasis has been described in six of 79 transplant recipients (8%), five of whom were from the Mediterranean basin (France and Italy).^{39,40,46,56,60,69} Clinically, the lesions present either as long-lasting ulcers on the tongue (two patients),^{39,40} palate,⁶⁹ labial commissure⁶⁰ (figure 5), or lip,⁴⁶ or as a diffuse nodular swelling of the gums and palate.⁵⁶ The disease course is usually protracted with a median time of 12 months from onset of symptoms to diagnosis, because the symptoms are usually mistaken for neoplasia.^{56,60} In three cases, leishmania isolation was successful and the following zymodemes were reported: *L. infantum* MON1,⁶⁹ *L. infantum* MON183,⁵⁶ and *L. donovani* MON83.⁴⁰ Interestingly, *L. infantum* MON183 is a zymodeme seen exclusively in immunocompromised HIV-infected patients,⁸¹ reinforcing the assumption that particular zymodemes may be restricted to immunocompromised hosts.

The protracted time interval between transplantation to the appearance of mucosal lesions (median 132 months, range 18–144 months), when the immunosuppressive treatment is generally of lower intensity, may suggest primary infection rather than leishmania reactivation, even if the latter cannot be completely dismissed.

Mucosal leishmaniasis is rarely reported in the Mediterranean basin in immunocompetent patients but immunosuppression appears to be a promoting factor, reflected by the rising number of cases reported in association with HIV/AIDS, lymphoma, and chronic steroid treatment.⁵⁶ However, mucocutaneous leishmaniasis comprises only 0.3% of the 1285 cases of leishmania/HIV co-infection reported in southwestern Europe.⁹

Notably, in two transplant patients with relapsing VL, mucosal localisations to the tongue and the hard palate

were observed.^{65,68} In all post-transplant cases of mucosal leishmaniasis (apart from one³⁷), leishmania serology was positive despite no clear evidence of visceralisation as demonstrated by the absence of parasites in the bone marrow aspirate.

Diagnosis

Bone marrow and spleen aspiration, followed by direct microscopic examination, are the most frequently used diagnostic procedures for confirmation of VL in immunocompetent individuals. Amastigotes appear as round or oval bodies measuring 2–3 μm of length and are found in monocytes and macrophages (figure 6). The splenic aspirate is considered the most valuable method for diagnosis of VL with a sensitivity exceeding 95%, but the high risk of complications associated with the procedure is a matter of concern.

By contrast, in HIV-positive patients the diagnostic yield of bone marrow aspirate is slightly lower with an overall reported sensitivity of 85%,⁹ probably caused by the hypoplastic nature of this location in individuals with advanced disease. In organ transplant recipients, the diagnosis of VL was achieved by direct detection of leishmania amastigotes in bone marrow biopsy samples in 98% of patients (table). In-vitro isolation is less sensitive with a positive result in 82% of cases, allowing the identification of *L infantum* zymodeme MON1 in nine cases. The remaining *Leishmania* spp were identified as *L infantum* (three cases), *L donovani* (one case), and *Leishmania braziliensis* (one case). In three circumstances the parasite was identified after liver biopsy,^{26,31,69} of which two cases were identified exclusively by this technique.^{26,69}

Leishmania serology was found positive in 45 (92%) of 49 transplant recipients, with unexpectedly high titres (median 1/400, range 1/20 to 1/5120). This is in sharp contrast with findings in patients with HIV-associated VL, where diagnostic sensitivity is much lower. The reasons for this discrepancy are still unknown. It is, however, worth noting that the guidelines for the prevention and management of infectious complications of solid organ transplantation, published by the American Society of Transplantation,⁸⁵ state that “serologic tests are often negative in transplantation”. Therefore, based on the results of the current review process, serology should always be used at least as a first-line method of diagnosis in transplant recipients whenever VL is suspected.

Leishmania PCR was positive in 11 out of 12 cases.^{38,49,59,66,69} Notably, in two of these cases, molecular amplification was the only positive method used (both from blood and bone marrow) for establishing the diagnosis; Lachaud⁷⁰ and Gatti⁷¹ and their colleagues confirm the high sensitivity of PCR for the diagnosis of VL in a limited number of patients. In addition to its unrivalled sensitivity, which is already firmly demonstrated in both immunocompetent and HIV-infected patients with VL, PCR offers the advantage of achieving a non-invasive diagnosis of the disease through the use of peripheral blood as template.



Figure 5: Mucosal leishmaniasis in a kidney transplant recipient; a large ulcer is present on the labial mucosa

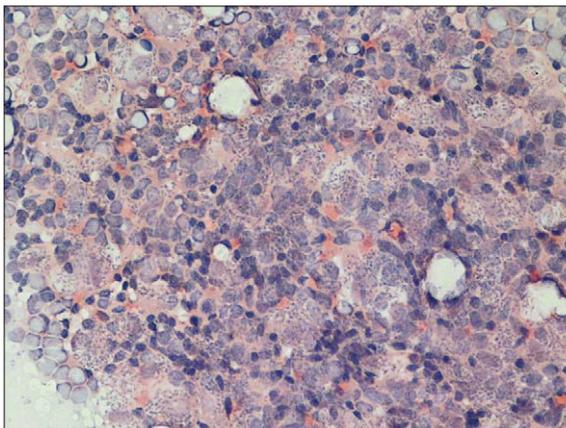


Figure 6: Lymph node showing massive infiltration by amastigotes

Furthermore, quantitative or semiquantitative PCR assays allow the in-vivo measurement of the blood parasite load, which is a useful surrogate marker of disease activity, response to specific therapy, and monitoring of disease recurrence. For these reasons, PCR should be recommended as the method of choice for the diagnosis and follow-up of VL in transplant recipients.

Treatment and outcome

For more than 60 years, pentavalent antimonial compounds (eg, meglumine antimoniate and sodium stibogluconate) given intravenously or intramuscularly for 28 consecutive days have been the treatment of choice for VL.⁸⁶ Pentavalent antimonials have established toxic effects on the heart, liver, pancreas, and kidney. Additionally, possible additive side-effects with immunosuppressive drugs should be considered. For example, azathioprine may cause pancreatitis, reversible hepatitis, rash, and gastrointestinal disturbances, raising the issues of cumulative toxicities. Moreover, antimonials are mainly excreted by the kidney and dose adjustments are recommended when the glomerular filtration rate is lower than 15 mL/min.⁸⁷ In addition to their nephrotoxic

properties, antimonial compounds may increase serum ciclosporin levels by direct substrate competition on the hepatic cytochrome p450.

Several studies have shown that pentavalent antimonials require a preserved cell-mediated immune response for expression of their anti-leishmanial effect *in vivo*, whereas amphotericin B can act directly on the parasite.⁸⁸ The liposomal form of amphotericin B (Ambisome, Gilead) is the first drug that has been approved by the US Food and Drug Administration for the treatment of VL^{89,90} and it has been established as the first-line drug in view of its tolerability and short course of treatment.^{91,92} However, none of the anti-leishmanial drugs are completely safe in organ transplant recipients.

The antifungal agent amphotericin B deoxycholate is active against *Leishmania* species, but has a high incidence of adverse reactions (eg, fever, severe malaise, hypotension, thrombophlebitis, azotaemia, renal tubular damage, hypokalaemia, anaemia, and hepatitis). Thus, this drug is not the best choice in renal transplant recipients because of its nephrotoxicity. Moreover, the drug has a synergistic nephrotoxic effect when used with ciclosporin. A possible alternative is represented by new clinical formulations of the drug with less toxic effects, such as liposomal amphotericin B. In a large study on the use of liposomal amphotericin B in 187 ciclosporin-treated transplant recipients (of whom 20 were kidney recipients), an increase of serum creatinine was observed in 31% of patients with an overall mean increase of 20%.⁹³ Miltefosine is a new oral drug recently registered for the treatment of VL in India and Germany and for CL and VL in Colombia, but, to our knowledge, it has not yet been used in transplant patients.⁹⁴

The 79 transplant patients reviewed here were treated in the majority of cases with pentavalent antimonials (65%)^{13,16–23,26–28,30–35,37,39,41,43,44,49–51,58,64,65,69} and, less frequently, with liposomal amphotericin B (25%),^{37,38,40,45,53,55,57,59,60,64–69} deoxycholate amphotericin B, or other lipid formulations. A few reports advocated successful treatment of VL using ketoconazole plus allopurinol,^{28,41,43} or fluconazole plus allopurinol⁶³ following discontinuation of meglumine antimoniate. However, allopurinol therapy may interact pharmacologically with azathioprine, increasing its concentration and thus its immunosuppressive activity and toxicity.⁹⁵

An initial cure rate of 84% (53 of 63 patients) is observed in transplant recipients affected by VL, a number that is similar to the response rate registered in immunocompetent individuals (range 93–97%), but decidedly higher than that observed among HIV-positive patients with the disease (range 55–66%).

14 (34%) of 41 transplant recipients had adverse effects after treatment with pentavalent antimonials (acute pancreatitis [20%],^{13,18,28,30,36,37,41,43,64} combined fatal toxic hepatitis and pancreatitis,⁶⁹ palindromic arthropathy,¹⁸ anasarca and oliguria,³⁵ renal tubular acidosis, bone

marrow toxicity and electrocardiographic changes,²⁶ agranulocytosis,³⁴ and neurological alterations⁴⁹). Antimonials had to be discontinued in nine cases out of 41 (22%) because of severe toxicities. Similarly, in HIV-positive patients with VL receiving meglumine antimoniate, hyperamylasaemia was observed in 16% of cases, and the drug had to be interrupted because of any adverse event in 19% of cases.¹⁰

Liposomal amphotericin B used at doses of 3 or 4 mg/kg per day with different schedules (eg, 15–21 days or 5 days plus one more dose a week apart) showed a favourable safety profile with a transient increase of serum creatinine reported in only two of 21 patients. Despite the absence of clinical controlled studies regarding the treatment of VL in the transplant setting, the use of liposomal amphotericin B seems more advisable than pentavalent antimonials because of its lower toxicity, shorter time spent in hospital, and ease of administration.

Left untreated, VL is generally a fatal disease with death being caused by intercurrent infections or bleeding. The outcome depends on early diagnosis and treatment: in the 68 transplant patients with VL reviewed here, death occurred in 15 cases (22%)—five of these patients had not received any anti-leishmanial treatment because diagnosis was obtained post-mortem.^{11,15,65,69}

The follow-up of transplant patients is documented in a limited number of reports and generally covers a period of less than 24 months,^{32,35,36,41,43–53,55,57,58,64} with only few reports covering a more prolonged period of post-therapeutic observation.^{66,69}

15 patients (24%) had relapse of VL, and five (8%) had multiple recrudescences of the disease (two to five relapses).^{31,50,65,68} Relapses occurred as early as 1 month⁴⁷ or as late as 5 years after the first attack of VL.⁶⁵ In patients living in leishmania-endemic areas, it may be difficult to determine whether clinical relapses of VL are caused by reactivation of the same parasite strain or by multiple reinfection episodes, particularly when the relapse occurs after a protracted period of time from the initial episode.

A high relapse rate (46–60%) is seen in HIV-infected patients with VL. Prophylactic administration of antimonials,⁹⁶ liposomal amphotericin B,⁹⁷ or itraconazole⁹⁸ is an effective strategy to reduce the relapse rates of VL in HIV-infected patients. By contrast, among transplant recipients, VL has a high rate of initial cure and a lower rate of recurrences.

Secondary anti-leishmanial prophylaxis has been reported in three transplant patients using different approaches: weekly liposomal amphotericin B,⁵⁷ daily fluconazole,²⁶ and monthly meglumine antimoniate followed by liposomal amphotericin B.⁶⁵ One case in the literature had a 10-year follow-up without secondary prophylaxis and without occurrence of relapse.⁶⁹ Thus far, the limited use of secondary prophylaxis among transplant recipients with VL precludes any conclusive suggestion on this topic.

Search strategy and selection criteria

Data for this Review were identified by searches of Medline and PubMed using a combination of search terms including "leishmaniasis", "transplantation", "transplant", "visceral leishmaniasis", "cutaneous leishmaniasis", and "mucosal leishmaniasis". We also included references from relevant key articles and from our own files. English, Spanish, French, and Italian language papers were considered. The final search date was December, 2006.

CL was successfully treated with antimonials in two cases^{24,29} and oral itraconazole⁴⁸ in another, and both cases of PKDL were successfully treated with liposomal amphotericin B.^{38,65}

Conclusions

VL should be considered in the differential diagnosis of fever and/or pancytopenia occurring after organ transplantation in patients who reside or travel to areas where the disease is endemic. VL may be caused by ex-novo sandfly transmission, reactivation of latent infection, or transmission via an infected allograft or blood transfusion.

Conflicts of interest

We declare that we have no conflicts of interest.

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