

## **Recurrent American visceral leishmaniasis in a kidney transplant recipient: A case report**

Leishmaniasis visceral americana recidivante en un trasplantado renal:  
reporte de caso

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**Introduction:** American visceral leishmaniasis (AVL) is a neglected tropical disease that causes severe conditions in immunosuppressed patients such as kidney transplant recipients. In these individuals, the infection can be associated with renal graft dysfunction and loss.

**Objective:** To describe the case of a female kidney transplant recipient assisted at the Hospital das Clínicas of Marília Medical School, who died probably as a result of hemodialysis-related complications after graft loss due to treatment toxicity of her underlying disease.

**Clinical case:** A 22-year-old patient, resident in an endemic region of AVL, immunosuppressed due to renal transplantation, who evolved to graft loss after successive relapses, treatment and drug prophylaxis for AVL. With the interruption of immunosuppressive therapy and return to dialysis, amastigote forms were not observed

in a bone marrow aspirate smears. However, after one year, she progressed to death due to a cerebrovascular accident resulting from comorbidities.

**Conclusions:** It is described a rare case of successive relapses of AVL and difficult medical decision due to the therapeutic impasse between the use of immunosuppressive drugs for renal graft maintenance and treatment for the parasitic disease. The parasitological control was observed with the immunosuppression suspension, demonstrating the importance of a competent immune system and the adjuvant of specific drugs for the disease control.

**Keywords:** visceral leishmaniasis; immunosuppression; kidney transplantation; hypertension; dialysis.

## Resumen

**Introducción:** La leishmaniasis visceral americana (LVA) es una enfermedad tropical desatendida causante de cuadros graves en pacientes inmunodeprimidos, tales como los trasplantados renales. En estos individuos, la infección puede asociarse a la disfunción y pérdida del injerto renal.

**Objetivo:** Describir el caso de una paciente con trasplante renal, atendida en el Hospital Clínico de la Facultad de Medicina de Marília, que murió probablemente como resultado de complicaciones por una hemodiálisis después de la pérdida del injerto por toxicidad del tratamiento de su enfermedad.

**Caso clínico:** Paciente de 22 años, residente en una región endémica para LVA, con inmunosupresión debido a trasplante renal, que evolucionó con pérdida del injerto después de sucesivas recidivas, tratamiento y profilaxis medicamentosa contra LVA. Con la interrupción de la terapia inmunosupresora y el retorno a la terapia dialítica, no se observaron formas amastigotes en la muestra de aspirado de médula ósea. Sin embargo, después de un año, evolucionó a muerte por accidente vascular encefálico resultante de comorbilidades.

**Conclusiones:** Se describe un caso raro de sucesivas recidivas de AVL y la toma de decisiones médicas difíciles debido a la disyuntiva terapéutica entre el uso de medicamentos inmunosupresivos para mantener el injerto renal y el tratamiento antiparasitario. El control parasitológico se logró con la suspensión de la inmunosupresión, lo que demuestra la importancia de un sistema inmunocompetente y la adyuvancia de drogas específicas para el control de la enfermedad.

**Palabras clave:** leishmaniasis visceral; inmunosupresión; trasplante de riñón, hipertensión; diálisis.

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## Introduction

American visceral leishmaniasis (AVL) is a neglected tropical disease with a cosmopolitan distribution.<sup>(1)</sup> Brazil, Ethiopia, India, Kenya, Somalia, Sudan and South Sudan represent 94% of the world cases of human visceral leishmaniasis.<sup>(2)</sup> In the Americas, Brazil accounts for 97% of cases, with infected individuals in 22 states of the five Brazilian regions.<sup>(3)</sup>

The Central West region of São Paulo State is considered endemic since 2004, with the first reports of AVL in the Adamantina microregion, spreading to adjacent municipalities through the Comandante João Ribeiro de Barros highway.<sup>(4)</sup>

It is estimated that 20% of immunocompetent individuals living in endemic areas will develop clinical manifestations of the disease.<sup>(5)</sup> However, immunosuppressed patients, having human immunodeficiency virus – acquired immunodeficiency syndrome (HIV-AIDS) patients as a prototype, present a 100 to 1000 times greater chance of developing clinically active disease in relation to the general population in the same locations.<sup>(6)</sup>

Considered rare in solid organ transplant (SOT) recipients, AVL may evolve with complications such as disease reactivation and successive relapses, especially in the face of impaired immunological response.<sup>(7)</sup> Most reported cases are the result of kidney transplants, accounting for more than 75% of SOT, and proceeded from southern Europe.<sup>(7)</sup> Therefore, this makes infections in SOT recipients caused by *Leishmania infantum chagasi*, the etiologic agent in the American continent, scarce in the literature.<sup>(7)</sup>

Thus, this report aims to describe a case of a renal transplanted patient, resident in an endemic area and infected by AVL, assisted at the Hospital das Clínicas of Marília Medical School (HC - Famema) who died probably due to complications from haemodialysis after the loss of the renal graft because of the treatment toxicity for this disease.

## Clinical case

A 22-year-old female, caucasian, housewife, graduated from high school, born, and coming from a city in the West of São Paulo State, weighing 44 kg, that underwent a kidney transplantation surgery when she was eighteen years old. She was referred from another service to HC - Famema, on suspicion of visceral leishmaniasis relapse.

Concerning her preceding personal history, the patient was diagnosed at six months of age with congenital cardiopathic interventricular communication, which presented moderate hemodynamic repercussion. Six-year-old electrocardiogram (EKG) suggestive of right ventricular overload. At the age of 16, severe arterial hypertension with target-organ damage was observed in ophthalmological evaluation of the macular scar type with bilaterally perimacular hard exudates, associated with renal functional deficit.

She started hemodialysis at 17-year-old in order to chronic kidney disease secondary to hypertensive nephrosclerosis, receiving after 13 months' kidney transplantation from previously healthy deceased donor, victim of traumatic brain injury, with creatinine of 0.9 mg/dl, 1A1DR compatibility and negative panel for lymphocyte reactivity. It was initiated immunosuppression with methylprednisolone (DEPO-MEDROL®) 500 mg, single dose, intravenous, and maintenance therapeutic with prednisone (METICORTEN®) (0.73 mg/kg/day), orally, once a day in the morning, continuous use; azathioprine (IMURAN®) (1.8 mg/kg/day) orally, once a day in the afternoon, continuous use; and tacrolimus (PROGRAF®) (0.29 mg/kg/day) orally, twice a day, continuous use, with control blood measurements every three months, featuring good evolution with serum creatinine of 0.7 mg/dl and no side effects. In the tenth month after transplantation, she developed diabetes mellitus (DM), starting treatment with oral hypoglycemic agent.

Four years later, the patient presented diarrhea, febrile hepatosplenomegaly, with polyclonal elevation of plasma gamma globulin and negative serology for cytomegalovirus. She was diagnosed with AVL by bone marrow aspirate smear (BMAS) from sternum, in another service, being treated with liposomal amphotericin B (AmBisome®) (LAB). In the same year, she started prenatal care in the first trimester of pregnancy and follow-up in a high-risk prenatal outpatient clinic at "Hospital Materno-Infantil" HCII - Famema. At 12 weeks of gestational age, she had first AVL relapse, with

pancytopenia, splenomegaly and positive BMAS, from sternum bone sample. Then, LAB in scheme 4.8 mg/kg/day, intravenous, for seven days was introduced, with reinforcement in tenth day (total dose of 38.4 mg/kg). No side effects were observed. She started hemodialysis therapy three times a week requiring blood components transfusion. Echocardiography indicated a valvular lesion, a moderate tricuspid regurgitation. She evolved with preeclampsia, with worsening of renal function and fetal death in the twenty-third week by intrauterine anoxia.

Renal biopsy revealed chronic graft nephropathy, interstitial fibrosis and tubular atrophy, segmental and focal secondary glomerulosclerosis 5/20 and global sclerosis 3/20 glomeruli. Due to renal function deterioration and decompensation of DM, insulin therapy and angiotensin-converting-enzyme inhibitor were initiated.

After two months of the first relapse, she was referred to our infectology service, as initially mentioned, due to suspicion of new relapse of AVL. The diagnosis was confirmed by BMAS, from sternum, in which frequent free and intracellular amastigote forms of *Leishmania* were observed, and at the same time, the rapid immunochromatographic test for AVL (LSH Ab ECO Teste) was negative. She remained hospitalized for eight days, being treated with LAB 4 mg/kg/day, intravenous, for 7 days and reinforcement on the tenth day (total dose of 32 mg/kg). At this time, secondary prophylaxis was initiated with LAB 4 mg/kg/dose fortnightly, continuously, according to the guidance of the Epidemiological Surveillance Center of São Paulo State.<sup>(8)</sup>

In one month of prophylaxis, ahead the laboratory tests within the normal range, we opted to maintain the LAB 4 mg/kg/day, intravenous, regimen every 21 days. Despite the prophylaxis, she presented the third relapse, being treated with LAB 4 mg/kg/day regimen for 10 days, with reinforcement on 14<sup>th</sup> and 21<sup>th</sup> days (total dose of 48 mg/kg) and adjustment of prophylaxis for LAB 4 mg/kg/day weekly.

After eight months, at fourth relapse episode, we started on LAB 4.4 mg/kg/day for 10 days, prophylactic LAB dose of 4 mg/kg/day weekly, with patient's clinical improvement and no side effects. In a new hospitalization after 4 months, due to fifth episode of AVL relapse, the patient was treated with LAB dose of 5 mg/kg/day for 10 days, but we extend the therapy in a dosing schedule of LAB 1mg/kg/day, totalling 25 days (total dose of 75 mg/kg) and concomitantly introduced antimoniate of N-methyl glucamine (GLUCANTIME®), henceforth pentavalent antimony, 10 mg/kg/day, intravenous, for 20 days. The rapid immunochromatography test remained negative, but numerous amastigote forms were observed in BMAS. Thus, the LAB was suspended due

to drug resistance, and prophylaxis was initiated with pentavalent antimony, 850mg, intravenous, every 14 or 21 days, depending on laboratory tests. In the following fifteen months, she presented two episodes of drug-induced pancreatitis, secondary to pentavalent antimony, with an interval of one year between incidents. Prophylactic treatment was suspended until laboratory tests were normalized and then reintroduced (Table).

**Table** - Haematological, immunological and biochemical parameters in two episodes of acute pancreatitis under treatment with pentavalent antimony

Haematological, Immunological and biochemical parameters (Reference interval)	First episode	Second episode
Hemoglobin (12-16 g/dL)	6.3	9.6
Hematocrit (37-47%)	19.6	27.6
Leukocytes (4,000-11,000 /mm <sup>3</sup> )	1,420	4,690
Band neutrophils (2-4%)	3	0
Segmented neutrophils (36-66%)	64	66
Eosinophil (2-4%)	0	1
Basophils (0-1%)	0	0
Lymphocytes (25-45%)	22	25
Monocytes (2-10%)	11	8
Platelets (150,000-400,000/mm <sup>3</sup> )	70,000	151,000
Creatinine (0.5-1.1 mg/dL)	1.8	2.6
Urea (10-50 mg/dL)	69	145
Creatinine Clearance-Cockcroft-Gault Equation - ( $\geq 120$ mL/min/1,73m <sup>2</sup> )	33.19	22.78
Sodium (136-145 mEq/L)	139	143
Potassium (3.5-5.0 mEq/L)	4.7	-
Phosphate (3.0-4.5 mg/dL)	5.4	-
C-reactive protein ( $\leq 0.8$ mg/dL)	48.1	-
Albumin (3.5-5.5 g/dL)	1.4	-
Amylase (25-125 U/L)	605	474
Lipase (10-40 U/L)	6,869	2,593

After eight months, the patient evolved with drug nephrotoxicity by pentavalent antimony use and consequent loss of kidney graft, which was maintained for 9 years, and then she was submitted to transplantectomy and subsequent interruption of immunosuppressants. Hemodialysis was initiated three times a week and, after another eight months, a new BMAS from sternum was performed, with no *Leishmania* amastigote forms observed,

and a negative rapid immunochromatography test for AVL. She progressed to death by ischemic stroke after nine months of negative results.

## Discussion

Renal transplantation constitutes the majority fraction within SOT and presents the highest absolute records of parasitosis resulting from immunosuppression.<sup>(7)</sup> In this context, it is imperative to consider AVL in the face of fever of unknown origin or pancytopenia as a differential diagnosis of natural or endemic patients, submitted to SOT. In these individuals the infection is highly associated with dysfunction and accelerated loss of the renal graft, and consequently, decreased survival rate of these patients.<sup>(8,9)</sup>

The therapy in renal transplants with AVL is a difficult decision, since there is no highly safe drug treatment for these individuals, however, it is considered that LAB is superior in terms of efficacy and safety profile in relation to pentavalent antimony.<sup>(10,11)</sup> Some studies have reported the use of LAB for the treatment of AVL in renal transplants, ranging from 85 to 100% cure, 10% relapse and 15% mortality.<sup>(12,13)</sup> The action mechanism of this drug involves direct injury to *Leishmania*'s cell membrane, differently from antimonials, which does not have a well-elucidated mechanism of action, but acts in adjuvant to a functioning cellular immune response, with limitations on SOT.<sup>(10)</sup>

However, the five relapses suggested therapeutic failure and secondary prevention with the same drug, despite the prospective study by *Lauchaud et al.*,<sup>(14)</sup> in which there was no relationship between relapse in immunosuppressed by HIV and *in vitro* resistance of parasites to the drug.

Thus, due to refractoriness, the introduction of antimony pentavalent was necessary, although this drug has a well-established causal relationship with drug-induced pancreatitis and renal injury, as observed in this patient.<sup>(15)</sup> According to *Antinori et al.*,<sup>(10)</sup> this drug presents toxicity around 34% in organs such as heart, liver, kidneys and high pancreatitis rate (20%), besides an additive adverse effect when associated with immunosuppressants used in TOS.

It is noteworthy that in the years in which the relapse occurred, serological tests were negative, despite the presence of numerous amastigote forms observed in BMAS. False-negative results of antibody detection by serological tests are frequent in immunosuppressed individuals, since some types of test display less than 50%

sensitivity.<sup>(16)</sup> According to the American Society of Transplants, serological tests are generally negative in these patients, probably due to severe T and B cell dysfunction.<sup>(17)</sup> As a consequence of the continuous aggressions of parasitic and drug character, there was loss of the renal graft and return to hemodialysis. Despite the negativity of the BMAS, for AVL, in a possible remission of the disease, the risks of hemodialysis, which promotes thromboembolic events and mortality, such as chronic renal disease itself and other comorbidities, were superimposed on the clinical outcome.<sup>(18)</sup> The patient then evolves with an ischemic stroke, in an even more reserved prognosis, and death in the following months.

### Conclusion

This report describes a rare case of successive relapses of AVL and difficult medical decision due to the therapeutic impasse between the use of immunosuppressive drugs for renal graft maintenance and treatment for this disease. The condition that is normally responsive to the available drug protocols, has undergone refractoriness even with individualization of treatment, optimization of doses and *off-label* drug combinations. It is not described similar refractory in scientific literature or even such therapeutic schemes applied in this case. Initially, we opted for the maintenance of immunosuppression, however, the nephrotoxicity of antiparasitic drugs, administered simultaneously with immunosuppressants, culminated in the loss of the renal graft. The parasitological control was observed with the immunosuppression suspension, demonstrating the importance of a competent immune system in the adjuvant of specific drugs, although of direct action to the parasite in the search for curative treatment of the disease.

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#### **Conflict of interest**

None of the authors has a conflict of interest.

#### **Authors contribution**

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