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Case Report

A Challenging Case of Visceral Leishmaniasis in a Transplant Recipient

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ABSTRACT

Visceral leishmaniasis is a rare disease in Western countries. We present the case of a 72-year-old male recipient of a related live donor renal transplant 41 years earlier and a past medical history of visceral leishmaniasis, who presented with progressive malaise, diarrhea, weight loss and darkening of skin, 11 months after the first episode. The main finding on blood work was severe hyponatremia and pancytopenia. He was diagnosed with relapsing visceral leishmaniasis and treated with liposomal amphotericin B (L-AmB), reduction of immunosuppressive therapy and supportive therapy. Throughout treatment he had worsening bradycardia and hyponatremia accompanied with liver failure and acute congestive heart failure. The patient survived the leishmaniasis episode but had sequels of chronic liver disease and chronic heart failure. The authors report the case due to its clinical challenge and due to the fact that data on how to treat immunodeficient patients with relapsing leishmaniasis is scarce.

Introduction

Visceral leishmaniasis is a rare disease in Western countries. This zoonosis, caused by protozoan parasite is transmitted to humans by sandflies. Clinical manifestations vary according to parasitic species, virulence and host factors. Asymptomatic or subclinical infection is most common in immunocompetent individuals, but the parasite can persist in the reticuloendothelial system lifelong and reactivate if immunosuppression occurs. Timely diagnosis is essential for cure but may be hindered due to the long incubation period, insidious progression and the unspecific clinical features. Hyponatremia, pancytopenia and hypoalbuminemia are considered bad prognostics factors of visceral leishmaniasis as they often represent late stages of disease [1]. Treatment with both antileishmanial therapy and supportive therapy is warranted. In Europe the preferred agent is liposomal amphotericin B, which is considered to be the drug with the highest efficacy and best safety profile. Immunocompromised patients, especially those with deficient T cell responses, are known to have atypical manifestations, more disseminated visceral involvement and suboptimal response to therapy [2, 3]. Data on how to treat immunodeficient patients with refractory leishmaniasis is scarce.

Case Presentation

We present the case of a 72-year-old male recipient of a related live donor renal transplant 41 years earlier with a regular follow up at our Nephrology clinic every 3 months. The patient had good renal function (creatinine 1.0 mg/dL; GFR CKD-EPI 2009 75 ml/min/1.73m2) with no signs of proteinuria. The patient had had an episode of visceral leishmaniasis in August 2017 diagnosed by the presence of *Leishmania* amastigotes on bone marrow aspirate. At the time the patient had mild complaints of fatigue and laboratory investigation had revealed moderate anemia with hypersplenism. The patient was treated with liposomal amphotericin B regimen as recommended by FDA with 3 mg/kg on days 1 to 5 and on days 14 and 21, for a total dose of 21 mg/kg.

During that hospitalization he responded well to therapy with complete resolution of clinical and analytical abnormalities; however, no molecular test or biopsy was taken to confirm cure. Due to this episode and remaining signs of incipient liver fibrosis after leishmaniasis resolution, regular transplant-associated immunosuppressive therapy was switched from azathioprine to tacrolimus for target levels of 4-6 ng/ml and maintain prednisolone 5 mg/day. Concurrently the patient was known to have chronic heart disease with mitral regurgitation,

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hypercholesterolemia and hypothyroidism for which he was chronically medicated with simvastatin 20 mg/day, pantoprazol 40 mg/day, irbesartan 75 mg/day and levothyroxine 0.025 mg/day.

On regular consultation, May 2018, the patient complained of malaise, but denied any other complaints such as loss of appetite or intestinal disturbances. On blood work he had slight hyponatremia (134 mmol/l), without any other alteration, which included liver function tests. Endoscopic study was normal. Echocardiography documented a left atrial dilatation (54 ml) with slightly reduced ejection fraction (50%) and moderate mitral regurgitation, which was considered stable considering his last echocardiography. At this time an expectant attitude was warranted.

On July 2018, the patient presented to outpatient clinic complaining of 2-week long watery diarrhea and progressive loss of balance associated with muscle weakness over the last week. On physical examination, the patient was noticed to have lost 7 kg of body weight comparing to the last consultation, was normotensive, normocardiac and afebrile, his skin had darkened but mucosas were pale, dehydrated, and abdominal palpation was notable for non-painful hepatosplenomegaly with no sign of ascites. Blood work at this time had multiple abnormalities (Table 1), mainly severe hyponatremia, pancytopenia and abnormal liver function tests. As can be seen on (Table 1), inflammatory parameters were slightly elevated and renal function remained normal. The patient was hospitalized and started on isotonic saline infusion for slow correction of hyponatremia, which was assumed to be progressive over at least a week.

Table 1: Blood work on the day the patient was hospitalized.

Parameter	Result	Reference Value
Hemoglobin	10.7	13.0 - 17.0 g/dL
White blood cell count	2.4	4.0-10.0 x 10^3/µL
Platelet count	88	150 - 400 x 10^3/µL
Sodium	115	136 - 145 mmol/L
Potassium	4.5	3.6 - 5.0 mmol/L
Chloride	83	98 - 107 mmol/L
Albumin	2.5	3.5 - 5.0 g/dL
Bilirubin	1.5	0.2 - 1.3 mg/dL
Gamma-glutamyltransferase	236	15 - 73 U/L
Alkaline Phosphatase	207	38 - 126 U/L
Aspartate Transaminase	71	17 - 59 U/L
Prothrombin time	18.5	13 - 15
Activated partial thromboplastin time	56.5	28 - 40
Creatinine	1.2	0.5 - 1.2 mg/dL
Urea	42	19 - 43 mg/dL
C- Reactive Protein	46	< 10 mg/L
Procalcitonin	0.41	< 0.1 g/dL
Sedimentation Rate	24	< 10mm

During the first days of hospitalization he was noticed to be febrile, which he had always denied. Blood, urinary and fecal cultures were consecutively negative. Ultrasound of the upper abdomen confirmed severe hepatomegaly with irregular edges and a non-homogeneous hyperechoic structure, as well as thin hepatic veins with a flat Doppler waveform. The portal vein diameter was 1.6 cm (normal ≤ 1.2 cm). Homogeneous splenomegaly was also noticed with a 15 cm diameter. Computer tomography revealed no lymphadenopathies and confirmed hepatosplenomegaly seen on echography.

Investigations and Differential Diagnosis

Due to the patient's past medical history of visceral leishmaniasis 11 months earlier, relapse of this disease was suspected. Due to the thrombocytopenia, instead of a biopsy procedure, molecular DNA-amplification assay on peripheral blood was preferred, which confirmed *Leishmania infantum* presence. Autoimmune markers and serologic markers for other infectious agents (hepatitis A, B and C; HIV; *Brucella*; parvovirus B19; *Coxiella*; cytomegalovirus) were ordered and had negative results. Considering the patient's transplant history, age and race another diagnosis that should be considered is post transplantation lymphoproliferative disorder. Despite the gastro-intestinal tract being the most commonly involved site in renal transplant recipients, it usually does not course with acute diarrhea and it doesn´t cause darkening of skin.

Treatment and Outcomes

Considering it was a severe relapse after standard liposomal amphotericin B (L-AmB) treatment, the medical team opted for prolonged therapy to allow for larger doses of L-AmB to be delivered without risking so much nephrotoxicity, especially considering the patient was a renal transplant recipient. The selected regimen was 4 mg/kg on days 1 to 7 and on days 10, 17, 24, 31 and 38, for a cumulative dose of 44 mg/kg. For each amphotericin administration, the patient received pre-medication with paracetamol 1g IV and hydrocortisone 100 mg IV. Simultaneously, transplant-associated immunosuppressive therapy was reduced to target levels of tacrolimus between 3 to 4 ng/ml and prednisolone 2.5 mg/day.

Table 2: Blood work on the 9th day of hospitalization (1 week after starting L-AmB treatment).

Parameter	Result	Reference Value
Hemoglobin	11.5	13.0 - 17.0 g/dL
White blood cell count	4.1	4.0-10.0 x 10^3/µL
Platelet count	196	150 - 400 x 10^3/µL
Sodium	136	136 - 145 mmol/L
Potassium	4.1	3.6 - 5.0 mmol/L
Chloride	98	98 - 107 mmol/L
Albumin	3.3	3.5 - 5.0 g/dL
Bilirubin	1.2	0.2 - 1.3 mg/dL
Gamma-glutamyltransferase	295	15 - 73 U/L
Alkaline Phosphatase	237	38 - 126 U/L
Aspartate Transaminase	51	17 - 59 U/L
Creatinine	1.2	0.5 - 1.2 mg/dL
Urea	41	19 - 43 mg/dL
C- Reactive Protein	19	< 10 mg/L

The patient was started on L-AmB on the 3rd day of hospitalization. Over the first week of treatment the patient frankly improved with resolution of most complaints like diarrhea, anorexia and loss of balance.

He remained normotensive, was now afebrile and had put on 1.5 kg of body weight from admission, with no signs of peripheral edema. On the 9th day of hospitalization (on the day of the 7th consecutive-day infusion of L-AmB), the patient was not anymore on saline infusions, nor anti-hypertensive medication nor diuretics; and his blood work showed improvement of hyponatremia and pancytopenia, with maintenance of normal renal function, but slight worsening of liver function tests (Table 2).

On the second week of treatment patient status worsened significantly complaining of severe fatigue, anorexia and marked limitation on ordinary activities. The patient had gradually developed severe bradycardia, followed by progressive development of peripheral edema, ascites and hypotension. On blood work hyponatremia showed a steep decline and a hyponatremia directed study along with cardiac and liver re-evaluation was prompted. Relevant results from hyponatremia-directed studies can be seen in (Table 3). Despite low serum osmolarity, urine osmolality was too high for the severity of hyponatremia indicating an impaired water excretion status. As renal function remained stable and fractional excretion of sodium was low, a status of impaired effective arterial blood volume was presumed.

Table 3: Hyponatremia-directed study.

Parameter	Result	Reference Value
Plasma osmolarity	272	285 - 295 mOsm/dL
Urine osmolarity	141	100 mOsm/kg
Plasma Sodium	107	136 - 145 mmol/L
Plasma Potassium	4.9	3.6 - 5.0 mmol/L
Urinary Sodium Fractional excretion ratio	<1%	<1%
Plasma Chloride	83	98 - 107 mmol/L
TSH	1.36	0.4 - 4.0mU/L

Echocardiography showed aggravated bi-atrial dilation (Left atrium 86 ml) and further reduced ejection fraction (42%), maintaining moderate mitral insufficiency. 24-hour electrocardiographic monitoring revealed atrial fibrillation with variable ventricular frequency between 37 and 67 bpm and frequent polymorphic ventricular extra systoles with periods of bigeminism and trigenimism, but no pauses > 2 seconds. These findings were consistent with acute congestive heart failure and the case was presented to the Cardiology team that considered that volume overload could have caused cardiac decompensation and triggered atrial fibrillation secondary to atrial dilation, therefore supportive measures towards cardiac failure with IV diuretics should be taken first.

Other causes for heart failure decompensation were discussed namely liver cirrhosis and the potential hepatotoxicity or cardiotoxicity of L-AmB therapy contributing to this multisystem worsening. Liver function tests had been worsening since the beginning of therapy, though in a very discreet fashion, without jaundice nor abdominal pain. The patient had developed ascites; however portal vein diameter had changed only slightly (1.6 to 1.8 cm). Although no conclusion could be reached at this point, it was decided the patient should remain on a cardiac monitor for the remnant therapy time and as long as larger intervals between amphotericin B doses were used, it should be safe to continue treatment.

Supportive therapy towards cardiac failure was optimized with IV diuretics and over the next 2 weeks the patient improved from his fatigue and anorexia, thought he maintained considerable symptoms on ordinary daily activities. On physical examination, his body weight remained stable, his blood pressure normalized, peripheral edemas disappeared as did signs of ascites, but he remained slightly bradycardiac. Blood work showed normalization of serum sodium and stabilization of liver function tests. Bradycardia was noticed to improve towards the end of time intervals between amphotericin infusions. The patient completed the 38 day scheduled regimen of L-AmB therapy and 24 hours after the last L-Amb infusion was discharged on the following medication: tacrolimus 0.5 mg/day, prednisolone 2.5 mg/day, pantoprazol 40 mg/day, ramipril 2.5 mg/day, furosemide 40 mg/day, levothyroxine 0.025 mg/day and iron. At this time, the patient was asymptomatic, normotensive, slightly bradycardiac (HR 55-60 bpm) with no signs of peripheral edema.

The patient was reevaluated 2 weeks after discharge as an outpatient. He had recovered from most blood work abnormalities (Table 4) and had mostly complains attributable to heart failure, with marked limitations on ordinary daily life activities. On physical examination he was euvolemic, normotensive, had slight bradycardia (HR 56 bpm) and had put on 5 kg since the beginning of *Leishmania* directed therapy. The patient maintained good renal function with no proteinuria and on target levels of tacrolimus. Molecular testing by PCR for *Leishmania infantum* was repeated and results were negative.

Table 4: Blood work on consultation 2 weeks after discharge.

Parameter	Result	Reference Value
Hemoglobin	11.3	13.0 - 17.0 g/dL
White blood cell count	5.1	4.0-10.0 x 10^3/μL
Platelet count	260	150 - 400 x 10^3/μL
Sodium	136	136 - 145 mmol/L
Potassium	4.3	3.6 - 5.0 mmol/L
Chloride	103	98 - 107 mmol/L
Albumin	3.5	3.5 - 5.0 g/dL
Bilirubin	1.1	0.2 - 1.3 mg/dL
Gamma-glutamyltransferase	244	15 - 73 U/L
Alkaline Phosphatase	199	38 - 126 U/L
Aspartate Transaminase	46	17 - 59 U/L
Creatinine	1.1	0.5 - 1.2 mg/dL
Urea	44	19 - 43 mg/dL

The patient was sent for Cardiology and Gastroenterology evaluation. The repeat 24-hour electrocardiography study revealed the patient maintained atrial fibrillation with variable ventricular frequency between 45 and 92 bpm and very frequent polymorphic ventricular extrasystoles with bigeminism and trigeminism; and echocardiography showed the patient maintained equivalent reduced ejection fraction (41%) with bi-atrial dilation and the same degree of mitral insufficiency. Three months after leishmaniasis treatment, the patient maintains Cardiology follow up and has a functional status as classified by NYHA as class III. The patient also maintains Hepatology follow up for his chronic liver failure. Though liver function tests normalized within 3 months of follow-up, he maintains signs on echography consistent with cirrhosis and he has been considered a Child class A score on cirrhosis severity.

Discussion

Portugal is known to be, among other Mediterranean countries, an endemic region for *Leishmania infantum*. Sandflies, the vectors of this zoonosis, are endemic of Mediterranean basin, but not robust like mosquitoes and are unlikely to disperse intercontinentally. The major reservoirs of leishmaniasis are canines, and reservoir control through dog vaccination could be the tool to eradicate the disease. In Mediterranean countries, visceral leishmaniasis mainly affects immunocompromised patients such as HIV patients and patients on long term therapy with corticosteroid therapy, as solid organ transplantation recipients. The major concern issues nowadays with this disease in such populations are its atypical clinical manifestations, suboptimal responses to treatment and high mortality rates.

Hematologic disturbances, hyponatremia and hepatosplenomegaly are frequently the first recognized manifestation of disease in immunocompromised hosts, as earlier symptoms are often very unspecific. These signs are considered late markers of disease. A study by Daher *et al*., identified hyponatremia, hypoalbuminemia and thrombocytopenia in visceral leishmaniasis as bad prognostic factors for survival, mostly because these signs represent late stages of disease with high parasitic loads and organ involvement. Hyponatremia associated with leishmaniasis is often multifactorial mostly associated to dehydration from intestinal losses, hypergammaglobulinemia due to high parasitic loads and renal failure.

Parasitological demonstration in bone marrow aspirate or splenic aspirates remains the Gold standard technique for VL diagnosis. Serologic testing has the advantage of being non-invasive and cheaper than molecular testing, however these tests must not be used to diagnose relapses as these remain positive for several months to years after cure. Molecular testing by polymerase chain reaction- amplification assay (PCR) in peripheral blood is non-invasive, sensitive and highly specific for primary diagnosis, however *Leishmania* DNA can persist in reticuloendothelial system lifelong and it is a major handicap for diagnosing relapsing disease.

When bone marrow or splenic aspirates cannot be retrieved safely, diagnosis should rely on clinical manifestations, coupled with epidemiological and laboratory data. Real time PCR (also known as quantitative PCR) could be the answer to such difficult cases, but it is not available yet for clinical use in Portugal. The diagnosis of relapsing visceral leishmaniasis in our case report was based on epidemiological data (his previous diagnosis of VL), his clinical picture and consistent laboratory data; which included exclusion of several other disorders and *Leishmania infantum* molecular testing by PCR amplification assay in peripheral blood [4, 5].

The drug of choice for treatment of VL in immunocompromised hosts in Europe and USA is liposomal amphotericin B. Exact treatment scheme for VL has not been established in Europe. FDA approved 2 different regimens for immunocompetent and immunocompromised individuals. The FDA-approved regimen for immunocompetent patients consists of 3 mg per kg daily, by IV infusion, on days 1-5, 14, and 21 (total dose of 21 mg/kg) and for immunosuppressed patients consists of 4 mg per kg daily on days 1-5, 10, 17, 24, 31, and 38 (total dose of 40 mg/kg) [6]. Regarding treatment of VL relapses, Infectious Diseases Society of America (IDSA) guidelines were published in 2017, according to which non-HIV immunocompetent hosts with VL relapse can, typically be managed by retreatment using L-AmB at the same or a higher total dose. Secondary prophylaxis is indicated for HIV-coinfected patients only. For other non-HIV immunosuppressed patients with VL relapse, reduction of immunosuppression, especially corticosteroid therapy, and close monitoring is strongly advised [7].

This case report was a challenge due to the development of acute congestive heart failure and recurrent severe hyponatremia after initial clinical improvement with directed therapy with L-AmB. Initial hyponatremia responded to saline infusion indicating it was most probable secondary to the watery diarrhea the patient reported. Recurrent hyponatremia occurred after worsening of liver function tests and was accompanied by *de novo* atrial fibrillation and a clinical picture of acute congestive heart failure. The study conducted towards hyponatremia and physical examination findings are consistent with hyponatremia being secondary to impaired water excretion possibly due to inappropriately high ADH production, for which both liver failure and heart failure are potential contributors. Though volume overload could have triggered atrial dilation and lead to atrial fibrillation, the timeline was reversed, bradycardia was followed by marked volume overload and its accompanying hyponatremia. The cardiac dysfunction our patient developed a week after starting therapy with L-AmB was a major clinical challenge that is not often observed in visceral leishmaniasis case reports. Three main possible explanations were considered: cardiac dysfunction secondary to aggravated liver dysfunction, cardiac involvement by the parasite itself or cardiotoxicity secondary to L-AmB.

Visceral leishmaniasis causes morphological and functional disturbances in the liver. Focal fibrosis rather than cirrhosis occurs, however in prolonged visceral leishmaniasis cirrhosis can occur and it is usually irreversible [8]. The liver and the heart have a bi-directional relationship in the sense that the dysfunction of one organ can promote or aggravate the other. Moller *et al*. reviewed the liver as a cause of heart disease and the concept of cirrhotic cardiomyopathy which basically relates to the inability of the heart, in patients with cirrhosis, to meet its demands reflecting as a chronotropic incompetence with systolic and diastolic dysfunction, especially when subjected to additional strain (physical or pharmacological) [9]. Our patient could possibly have 2 reasons for additional strain on this compromised liver-heart complex: L-AmB therapy, which has been linked to hepatotoxicity in both functional and histological studies and systemic infection itself that further contributes to the hyperdynamic state [10, 11].

In the case reported advanced liver disease was present on admission, though clinically silent; however liver function tests showed worsening after L-AmB therapy and the patient developed ascites later in the course of disease together with a clinical picture of congestive heart failure, after a significant cumulative dose of L-AmB therapy had been delivered. For such reason hepatotoxicity could not be disregarded as a plausible cause for additional strain on this disturbed liver-heart axis. L-AmB hepatotoxicity is a relatively common side-effect of such therapy, usually dose-dependent and manifesting with mild cholestatic enzyme rise in the first week after starting therapy and reversible soon after stopping treatment. Our patient cholestatic profile of liver enzymes

started declining after discharge and normalized after 3 months, which is consistent with our theory.

Other possible explanations for the cardiac manifestations our patient had could be cardiac involvement by the parasite itself or cardiotoxicity secondary to L-AmB. Cardiac involvement has been reported associated to severe cases of VL in exceptional case reports [12, 13]. These cases were associated to pericardial effusions, which could not be exactly attributable to the parasite itself but to a consequence of the disease manifestations such as hypoalbuminemia or anemia. Cardiotoxicity to amphotericin B could be another possible differential diagnosis for the cardiac manifestations, however the few reported cases so far have been described as a reversible adverse effect that improves after drug suspension [14, 15]. Our patient initial echocardiography could have overestimated ejection fraction in the presence of mitral insufficiency, however the burden of the severe infection with irreversible liver damage probably lead to the development of features of cirrhotic cardiomyopathy superimposed on the valvular heart failure the patient had, explaining why his cardiac functional status did not improve despite being cured from the parasitic infection.

Learning Points

i. Timely diagnosis is essential for cure of visceral leishmaniasis but may be hindered due to the long incubation period, insidious progression and the unspecific clinical features.
ii. Irreversible chronic liver failure can be a consequence of late diagnosis and severe visceral leishmaniasis.
iii. Treatment of choice in immunocompromised hosts is liposomal amphotericin B, however their response to treatment may be different. The exact treatment regimen for recurrences in this population has not been established.
iv. Secondary prophylaxis in non-HIV infected patients is not recommended after recurrent visceral leishmaniasis, but reduction of immunosuppressive therapy and close monitoring is advised.

Consent

The patient has given informed consent for the publication of this manuscript as well as for all investigations and treatments described in the case report.

Competing Interests

None.

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