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Review article

Kidney involvement in leishmaniasis—a review

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ABSTRACT

Leishmaniasis is an infectious disease caused by protozoa of the genus *Leishmania* transmitted by insects of the genus *Lutzomyia* sp. or *Phlebotomus* sp. The main syndromes are cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis (kala-azar) and post-kala-azar dermal leishmaniasis. This article reviews kidney involvement in cutaneous and visceral leishmaniasis, highlighting the aspects of their pathophysiology, clinical manifestations, histopathological findings, outcome and treatment.

Introduction

Leishmaniasis is an infectious disease caused by protozoa of the genus *Leishmania* transmitted by insects of the genus *Lutzomyia* sp. or *Phlebotomus* sp.[1] There are more than 20 species of leishmanias causing clinical manifestations in humans, and the main syndromes are cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis (kala-azar), and post-kala-azar dermal leishmaniasis.[2] This article reviews kidney involvement in cutaneous and visceral leishmaniasis.

Cutaneous leishmaniasis

Kidney involvement in cutaneous leishmaniasis

There have been few studies showing renal dysfunction in American cutaneous leishmaniasis (ACL), which is, in some cases, associated with the use of specific treatment with pentavalent antimonial drugs.[3,4]

In a recent study performed in our region, a total of 73 patients admitted with ACL were evaluated. Acute kidney injury (AKI) was observed in 17 cases (23.2%), and oliguria was

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seen in one case. Mean value of maximum serum creatinine (SCr) levels during hospital stay was 1.6 ± 0.6 mg/dL. Risk factors for AKI were advanced age, longer time between symptom onset and hospital admission and longer hospital stay. Complete renal function recovery was observed in 11 cases (64.7%) at the time of hospital discharge.[5] This same study found urinary abnormalities, including proteinuria (4.1%), hematuria (4.1%) and leukocyturia (5.4%). Hypokalemia was found in 12.3% of cases.[5] Proteinuria and AKI had been previously reported in other studies.[6,7]

Decreased urinary concentrating ability, with no reduction of glomerular filtration rate (GFR), was demonstrated by Veiga et al.,[8] who studied an animal model of *leishmaniasis* treated with high doses of meglumine antimoniate. This abnormality in urine concentration results from the action of antidiuretic hormone (ADH) and also by a direct action of the drug in tubular cells.[8] High doses of antimonial drugs also cause a reduction in GFR.

ACL is highly prevalent in the state of Ceará, Northeast of Brazil. Low treatment adherence favors the development of the mucocutaneous forms, which requires higher doses of antimonial drugs for longer periods, which, in turn, increases its toxicity even further. A recent study was performed in this region in order to investigate renal abnormalities in patients with ACL. Oliveira et al.[9] studied 37 patients with confirmed diagnosis of ACL, performed urinary concentration and acidification tests and also investigated the expression of urinary exosomes in the urine of these patients.[3] Urinary concentration deficit was found in 77% of cases. The expression of aquaporin was significantly reduced, while NKCC2 was increased, in comparison to that in a control group. Urinary acidification deficit was less frequent (40.5%). The expression of NHE3, H^+-ATPase and pendrin was significantly higher among patients than in controls.[3] In this same cohort, a urinary concentration deficit was shown in 27 cases (77%) before treatment with Glucantime®, while after treatment it was observed in 31 patients (88%) ($p = 0.344$). It is then possible that ACL can cause urinary concentration deficit and specific treatments do not decrease this defect, although it does not cause significant renal function impairment.

Combined defects (concentration and acidification) were seen in 12 patients. Comparing the patients with and without tubular dysfunction, there were no differences regarding age, gender, time of disease, and number of cutaneous lesions. There was no significant abnormality regarding excretion fraction of sodium, potassium, calcium and phosphate. There was a significant difference in serum magnesium concentrations between patients with and without acidification deficit (2.15 ± 0.06 vs. 2.33 ± 0.04, $p = 0.02$). No patient with urinary concentration or acidification deficit had albumin/creatinine ratio >30 mg/g[3].

Other infectious diseases with predominant involvement of skin and nerves, such as leprosy, can also lead to glomerular dysfunction. Oliveira et al.,[9] in a prospective study with 59 patients with leprosy, showed decreased GFR in 50% of cases when considering GFR < 80 mL/min/1.73 m^2, and in 5% when considering GFR < 50 mL/min/1.73 m^2.

Microalbuminuria is a known marker of glomerular dysfunction in diabetes mellitus[10] and also in cardiovascular diseases.[11,12] Microalbuminuria higher than 30 mg/g creatinine was observed in 35% of patients with ACL followed in a health center in the state of Ceará, Brazil, before specific treatment, and in only 8% of patients after treatment,[3] suggesting the presence of incipient glomerular lesion induced by ACL itself, without concomitant GFR decrease.

Urinary exosomes were also found to be altered in ACL.[3] Some studies have shown that aquaporin-2 (AQP2) is excreted in urine in the form of vesicles. Its amount correlates with circulating levels, and is used in studies to investigate body water balance.[13,14] In the cohort of patients with ACL studied by Oliveira et al.,[3] an increased percentage of patients with urine concentration deficit was observed and this was associated with lower expression of AQP2.[3] The increase in the expression of NKCC2 can occur as a compensatory mechanism. Abnormalities in the transporters involved in acid–base regulation were also observed, including an increased expression of NHE3 (proximal tubule), H-ATPase and pendrin (distal tubule) in patients with ACL, which could explain the urinary acidification deficit.[3]

Pentavalent antimonial drugs are rapidly eliminated through the kidneys,[15] so their use should be avoided in patients with renal dysfunction, due to cardiotoxicity and renal function worsening. Urinary concentrating defect has also been described and the heavy metal used in antimonial composition is the main factor responsible for the toxicity.[16] AKI may be due to massive deposition of immune complexes formed after *Leishmania* destruction by antimonial drugs, a phenomenon similar to that of Herxheimer reaction.[17] Sampaio et al.[18] evaluated 11 patients with ACL who received a double dose of antimonials (40 mg Sb^v/kg/day for 30 days), and observed that one patient developed AKI. Eight patients showed a decrease in GFR after 30 days of treatment. They also observed distal and proximal tubular dysfunction, evidenced as a decrease in urinary concentration ability and increased sodium excretion fraction.

Rarely, treatment with meglumine antimoniate can cause AKI due to interstitial nephritis.[16] At low doses and for a short period, pentavalent antimonial shows low renal toxicity. In ACL treatment, however, it is many times necessary to use higher doses of pentavalent antimonial, which increases toxicity.

Visceral leishmaniasis

Visceral leishmaniasis is a chronic, lethal, parasitic disease, caused by the *Leishmania* parasite, an intracellular protozoan. A large spectrum of clinical manifestations accompanies the *Leishmania* attack on reticuloendothelial tissues – liver, spleen, bone marrow, lymph nodes, and the digestive system. Symptoms range from irregular and recurrent fever to pancytopenia, hemorrhagic spells, and liver and spleen enlargement.[19]

Kidney involvement in chronic leishmaniasis is frequent and associated with increased mortality. It is endemic in southern Europe and in tropical and sub-tropical areas of the globe, with a worldwide incidence of approximately 0.5 million cases/year.[20] When untreated, its mortality rate can reach 95%. Among the so-called tropical diseases, kala-azar is one of the WHO's priorities. Endemic in Brazil, its agent is