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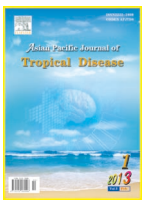

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Acute kidney injury in visceral leishmaniasis: a cohort of 10 patients admitted to a specialized intensive care unit in northeast of Brazil

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PEER REVIEW

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Comments

This is a good cohort study in which the authors found how AKI was important with VL infection as well as other hiding important diseases, AIDS, tuberculosis and leprosy as co-infection. And also they addressed that patients admitted to the ICU with VL should be done a detailed investigation to diagnose possible associated diseases.

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ABSTRACT

Objective: To describe co-infections, clinical manifestations, comorbidities and outcome of patients with visceral leishmaniasis and AKI. **Methods:** This is a case study with ten patients with confirmed diagnosis of VL admitted to the reference ICU of Northeast of Brazil during 6 years, with renal injury. Clinical and laboratory parameters were evaluated in admission, period of hospitalization and outcome. **Results:** This study found 10 patients with VL in a group of 253 patients admitted to the ICU with AKI. The main signs and symptoms presented at admission were weight loss, fever, splenomegaly, jaundice, anorexia, asthenia, bleeding and vomits. The main co-infections were: AIDS, tuberculosis and leprosy. Patients were classified in RIFLE criteria. RIFLE-F patients were younger and had a longer time between onset of symptoms and hospital admission. Death was observed in 60% of cases. The causes of death were septic shock, respiratory insufficiency and multiple organ dysfunction. **Conclusions:** AKI is an important complication in VL. The progression of the disease and their complications can achieve high level of severity, even in the absence of comorbidities or co-infections. The high mortality in this group alerts to the importance of adequate management of these patients.

KEYWORDS

Visceral leishmaniasis, Kala-azar, Intensive care unit, Kidney disease, HIV, Leprosy

1. Introduction

Visceral leishmaniasis (VL) is a public health problem in Brazil and other developing countries. The disease is transmitted by the vector *Lutzomyia longipalpis* and is caused by several species of *Leishmania*. It is a zoonotic disease typically found in tropical areas, which is now found predominantly in urban and peri-urban areas, affecting the cities of medium and large size in Brazil[1,2].

The number of VL confirmed cases from 2004 to 2010 was 3467 in Ceará state, Northeast Brazil[3]. VL can develop serious complications such as acute kidney injury (AKI) that may need intensive care unit (ICU). This disease was responsible for 4.1% of AKI in ICU admissions, and the number of deaths

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was 174 (5%) in a cohort of VL patients in our region[4]. Several authors have described renal pathological changes in VL[5-9]. The main pathophysiological mechanism responsible for renal impairment in VL probably includes the deposition of immune complexes. The most frequent pathologies found are proliferative glomerulonephritis and interstitial nephritis[10]. The development of AKI is an important clinical complication in patients with VL, which appears to increase the mortality rate in this group of patients[10].

The aim of this study is to describe clinical manifestations, laboratory tests, comorbidities and outcome of patients with visceral leishmaniasis and AKI admitted to a reference intensive care unit in Northeast Brazil.

2. Materials and methods

2.1. Study population

This is a case study with ten patients with confirmed diagnosis of VL admitted to the ICU of São José Infectious Diseases Hospital in Fortaleza city, Northeast of Brazil, between January 2004 and December 2009, with renal injury. All patients had clinical and epidemiological data suggestive of VL. Confirmed infection was defined by mielogram and positive serologic K-39. They were selected from a group of 253 patients admitted to the ICU with AKI in this period.

2.2. Clinical and laboratory parameters evaluated

The clinical parameters were age, sex, onset of symptoms to admission, length of hospital stay, admission mean blood pressure, clinical symptoms, causes of hospitalization, medications in use, comorbidities, co-infections, cause of death, dialysis requirement, type of dialysis, number of sessions and days after AKI diagnosis to start dialysis.

Laboratory tests were serum urea and creatinine, total blood count, aspartate amino transaminase (AST), alanine amino transaminase (ALT), maximal serum urea (SU_{max}), serum urea at admission (SU_{adm}) and discharge (SU_{dis}), maximal serum creatinine (SCr_{max}), serum creatinine at admission (SCr_{adm}) and discharge (SCr_{dis}), prothrombin time, total bilirubin, indirect bilirubin, direct bilirubin, serum sodium and potassium, arterial pH, pCO_2, pO_2, HCO_3, and IFO_2.

2.3. Definitions

Acute kidney injury (AKI) was defined according to the RIFLE classification (Risk, Injury, Failure, Loss, and End-stage kidney disease)[12]. Hypotension was defined as mean arterial blood pressure (MAP) <60 mmHg, and therapy with vasoactive medication was initiated when the MAP remained <60 mmHg despite fluid administration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at admission. Lung manifestation was considered if patients present with dyspnea, pulmonary crackles, hemoptysis, or PO_2 < 60 mmHg in arterial blood gas. Oliguria was considered to be present when the urinary volume was < 400 mL/day after adequate fluid replacement. Dialysis was indicated for those patients who remained oliguric after effective hydration, in those cases where uremia was associated with hemorrhagic or severe respiratory failure, in severe cases or refractory metabolic acidosis and severe or refractory hyperkalemia.

2.4. Ethics

The protocol of this study was approved by the Ethical Committee of the Walter Cantídio University Hospital and São José Infectious Diseases Hospital.

Table 1
Clinical characteristics at admission of 10 cases with viscerak leishmaniasis and acute kidney injury.

Case Number	1	2	3	4	5	6	7	8	9	10
Age (Years)	17	49	51	47	34	34	73	36	35	44
Gender	M	M	M	M	M	M	F	M	M	M
Onset of symptoms to admission (day)	90	365	120	60	90	20	40	30	45	60
Length of hospital stay (day)	48	303	38	24	10	33	7	17	85	47
Admission mean blood pressure										
SBP (mmHg)	115	173	120	101	104	127	150	146	138	88
DBP (mmHg)	78	94	70	49	74	77	50	90	87	51
Other Diseases										
AIDS	N	Y	N	Y	N	Y	N	Y	N	N
TB	N	N	N	N	N	Y	N	Y	N	N
Leprosy	N	N	N	N	N	N	Y	N	N	N
Use of mechanical ventilation	N	Y	N	Y	N	Y	Y	Y	Y	N
Oliguria	N	N	Y	Y	Y	Y	Y	N	N	Y
Death	N	N	N	Y	Y	Y	Y	N	Y	Y

M: male; F: female; SBP: Systolic Blood Pressure; DBP: Diastolic blood pressure; TB: Tuberculosis; Y: yes; N: No.

Table 2
Laboratory findings in 24 h of diagnosis of AKI in patients with visceral leishmaniasis.

Case number	1	2	3	4	5	6	7	8	9	10
Laboratory findings										
Cr (mg/dL)	2.1	1.6	5	3.3	1.8	3.6	2	3.5	2	1.8
Ur (mg/dL)	111	75.1	136	165	86	104	88	115	86	89
TGO (IU/L)	100	13.8	422	1220	440	26	107	221	47	406
TGP (IU/L)	100	11.9	167	1350	450	9	35	136	18	55
TAP (s)	–	–	–	31	29.3	–	22.7	–	46	46
Na_+ (mEq/L)	131	144	123	134	127	139	125	121	131	135
K_+ (mEq/L)	3.5	3.8	3.7	4.8	6.6	3.2	4.4	4.8	4.1	3.9
BT (mg/dL)	1.1	1.6	3.8	0.73	13.2	0.8	13.2	10.28	1.37	3.24
BD (mg/dL)	1	0.5	1.1	0.66	12	0.5	11.61	5.88	1.19	3.19
BI (mg/dL)	0.1	1.1	2.7	0.07	1.2	1.3	1.59	4.4	0.18	0.05
Ht (%)	22.8	30,7	23.9	16.4	32.7	26.5	23.9	29.5	23.8	29.1
Hb (g/dL)	7.6	10.5	8	5.6	10.8	8.6	7.6	10.6	7.9	9.7
White blood count (/mm^3)	1 300	4 800	700	2 300	6 800	2 900	2 400	1 200	1 400	14 400
Platelets (/mm^3)	114 000	90 000	37 000	98 000	28 000	16 000	156 000	140 000	94 200	126 000
pH	7.44	7.38	7.37	7.4	7.4	7.33	7.33	7.28	7.33	7.29
pO_2 (mmHg)	98	–	–	59.8	137.9	114	128	108	138.2	75.9
pCO_2 (mmHg)	24.4	47.2	32.3	28	24	30	39	37.5	19.5	24
HCO_3 (mEq/L)	16.2	27.2	18.9	12.3	15.6	15	17	17.6	10.1	11.4
FiO_2 (%)	21%	–	21%	100%	50%	50%	60%	40%	28%	50%

Hb: Hemoglobin; Ht: Hematocrit; TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect bilirubin; FiO_2: Inspired fraction of O_2.

Table 3
Renal evaluation during hospitalization in patients with visceral leishmaniasis.

Case number	1	2	3	4	5	6	7	8	9	10
SU adm (mg/dL)	33	29	97	40	30	104	88	115	63	16
SU max (mg/dL)	118	78	180	165	86	137	104	145	95	100
SU dis (mg/dL)	27	75	63	–	86	118	73	89.7	41	100
SCr adm (mg/dL)	0.6	0.7	3.1	1	1	3.6	2	3.5	1.4	0.57
SCr max (mg/dL)	3.2	2.58	7.4	3.3	1.8	4.3	2	5.4	2.32	2.04
SCr dis (mg/dL)	1.2	1.8	3.6	1.2	1.8	1.5	2	0.8	0.9	2.04
Days after diagnosis of AKI	–	–	0	2	1	–	–	–	1	2
Number of dialysis sessions	–	–	21	4	1	–	–	–	7	2

SU: serum urea; SCr: serum creatinine; Adm: admission; Max: maximum; Dis: discharge.

3. Results

This study found 10 (4%) patients with VL in a group of 253 patients admitted to the ICU with AKI in 6 years. The patients mean age was (42.0±14.7) years, with 90% males. The majority (60%) of them were from rural areas. The time between the onset of symptoms and hospital admission ranged from 20 to 365 d (mean 92±100.7 d). The duration of hospital stay ranged from 7 to 303 days (mean 61.2±87.9 d). Epidemiologic data are shown in Table 1.

The main signs and symptoms presented at admission were weight loss (100%), fever (100%), splenomegaly (70%), jaundice (60%), anorexia (60%), asthenia, bleeding and vomits (40%). Pancytopenia occurred in 50% of cases. The mean systolic blood pressure at admission was 126.2±25.9 mmHg and diastolic blood pressure was 72±16.8 mmHg. The main co-infections were: AIDS (40%), tuberculosis (20%) and leprosy (10%). The main comorbidities were diabetes mellitus (20%), systemic arterial hypertension (10%) and respiratory insufficiency (10%). The medications in use were hydration (100%), loop diuretic (50%). vasopressor (40%), angiotensin converting enzyme inhibitors (20%) and sulfa (10%).

The main laboratory tests in the first 24 hours after AKI diagnosis were Ht 25.9%±4.7% (16.4%-32.7%), Hb 8.6±1.6 g/dL (5.6-10.8 g/dL), white blood count 3 820±4160/mm^3 (700-14 400/mm^3), platelets count 89920±48.233.8/mm^3 (16 000-156 000/mm^3), AST 300.3±364.6 IU/L (13.8-1220 IU/L), ALT 233.1±413, 9 IU/L (9-1350 IU/L), total bilirubin 4.9±5.2 IU/L (0.73-13.2 IU/L), direct bilirubin 3.7±4.6 IU/L (0.5-12 IU/L), prothrombin time 28.6±12.2 seconds (14.8-46 seconds), serum urea 105.5±27.6 mg/dL (75.1-165 mg/dL), serum creatinine 2.7±1.1 mg/dL (1.5-5 mg/dL), K^+ 4.3 ±0,9 m Eq/L (3.2-6.6 mEq/L), Na^+ 131±7.2 mEq/L (121-144 mEa/L), as summarized in Table 2. The arterial blood gas analysis showed arterial pH 7.3±0.05 (7.28-7.44), HCO_3 15.3±4.9 mEq/L (10.1-27.2 mEq/L), pCO_2 30.6±8.5 mmHg (19.5-47.2 mmHg), pO_2 104.5±32.4 mmHg (51.4-138.2 mmHg). Mechanical ventilation was used in 70% of cases.

AKI was observed in 9 patients according to the RIFLE

criteria. Patients were classified as Injury (22.2%) and Failure (77.8%). Oliguria was observed in 6 cases (66.6%) and 5/6 oliguric died. Dialysis was carried out in half of the patients with AKI and the modality used was intermittent hemodialysis in all cases. It was started in 1.2±0.8 d (range 0-2 d) after AKI diagnosis. The number of dialysis sessions was 7±8.1 d (range 1-21 d). Death was observed in 60% of cases. The causes of death were septic shock (84%), respiratory insufficiency and multiple organ dysfunction (16%).

4. Discussion

This is the first study to investigate AKI in patients with VL admitted in a specializated intensive care unit. Human VL is an endemic parasitic infection in Brazil that has reemerged, especially in peri-urban areas. Renal involvement is considered rare, presenting as hematuria, proteinuria, or renal function impairment[5]. Prospective and cross-sectional studies showed AKI (considered as the levels of serum creatinine above 1.3 mg/dL) in 11% to 33.9% of patients with confirmed VL[10,13,14].

AKI was more frequent in male patients in the present study. This is in accordance with previous study[15]. The analysis of signs and symptoms showed that high frequency of jaundice, weight loss, anorexia, splenomegaly, hepatomegaly and fever, which are commons signs and symptoms in VL[16-20].

This study found that 4 of the 10 patients admitted in the ICU had HIV co-infection. Two of these were had pulmonary tuberculosis. The association between VL and HIV is common and it may have increased the severity of the patients` clinical condition and the patient become more prone to diseases such as tuberculosis[21]. The diagnosis of VL in patients with HIV infection is difficult, because the occurrence of hepatosplenomegaly, fever, and skin lesions, which are the main manifestations of VL and this manifestation can be seen in many opportunistic infections as histoplasmosis, miliar tuberculosis, and other infections that are common in our region[21-23]. Thus, the difficulty in giving a diagnosis delays treatment for VL. This can increase the damage caused by renal disease. The AKI is a frequent complication that occurs in 10 to 30% of patients with AIDS[24-26]. Common causes of AKI in these patients include use of antiretroviral drugs, volume depletion and sepsis[27].

One patient had also leprosy associated with VL and AKI. Leprosy can cause different types of renal abnormalities. Glomeruli injury has been described in histology findings in leprosy patients, progressive mesangial glomerulonephritis being the most common lesion[28-31]. Many other kinds of glomerulonephritis have also been described[30,32-34]. The incidence of glomerulonephritis has been reported to range from 6% to 50% in leprosy patients[41]. Amyloidosis, the incidence of which ranges from 2% to 55%, is attributed to chronic granolomatous reactions caused by *Mycobacterium leprae*[42], and it is manifested mainly by significant proteinuria[44]. It may progress to chronic renal failure, which is one of the causes of death in leprosy[43,44]. This makes call attention since the presence of several diseases that cause kidney damage associated to AKI has a poor prognosis and is a risk factor for death[4,5]. Half of the patients studied did not have co-infections. Sixty percent of these died. This poor prognosis should be avoided. This result also leads to concern with patients apparently not so serious, who are already without co-morbidities. Therefore special attention is required with this type of patient admitted to the ICU, especially in ICU hospital of infectious diseases.

In the present study, high mortality rate (60%) was observed. Oliveira et al. performed a study with patients not hospitalized in ICU with VL and found a mortality rate of AKI patients 30.2% versus 4.7% in non-AKI[11]. The high value of 60% was due to the severity of the patients in ICU. They had VL, AKI and several comorbidities. In ICU study performed by our group, the mortality rate was 66.6%, and the main cause of death was septic shock (88%)[4]. These findings are similar to those in the present study. Schrier et al. showed that sepsis associated with AKI was responsible to 70% of mortality in hospitalized patients as compared with to 45% mortality among patients with AKI alone[45]. Four patients who died were classified RIFLE-F and just one were RIFLE-I. This evidences that RIFLE-F patients had a higher mortality, which is in accordance to literature. Oliguria was observed in 66% of cases, and it was associated with an even higher mortality (83%).

RIFLE-F patients were younger and had lower blood pressure, longer time between onset of symptoms and hospital admission. Half of them had metabolic acidosis. The mechanical ventilation was used to help in reversal of respiratory insufficiency. This information is confirmed by Daher *et al*[4]. Their findings support the view that oliguria, metabolic acidosis, sepsis, hypovolaemia, use of vasopressors, mechanical ventilation were factors associated with death[4,46].

In conclusion, AKI is an important complication in LV. The progression of the disease and their complications can achieve high level of severity, even in the absence of comorbidities or co-infections. The high mortality in this group alerts to the importance of early diagnosis and adequate management of these patients. Moreover, it is necessary that patients admitted to the ICU with VL have a detailed investigation to diagnose possible associated diseases. This may allow proper treatment and achieve a better prognosis.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Visceral leishmaniasis (VL) is a public health problem in Brazil and other developing countries. Visceral Leishmaniasis (VL) can cause serious complications such as acute kidney injury (AKI) that may need intensive care unit (ICU). The aim of this study is to describe co-infections, clinical manifestations, comorbidities and outcome of patients with visceral leishmaniasis and AKI.

Research frontiers

This study found 10 patients with VL in a group of 253 patients admitted to the ICU with AKI. The main co-infections were: AIDS, tuberculosis and leprosy.

Related reports

Oliveira et al. performed a study with patients not hospitalized in ICU with VL and found a mortality rate of AKI patients 30.2% versus 4.7% in non-AKI. The high value of 60% was due to the severity of the patients in ICU. They had VL, AKI and several comorbidities. In ICU study performed by our group, the mortality rate was 66.6%, and the main cause of death was septic shock (88%). These findings are similar to those in the present study. This evidences that RIFLE-F patients had a higher mortality, which is in accordance to literature. This information is confirmed by Daher *et al*. Their findings support the view that oliguria, metabolic acidosis, sepsis, hypovolaemia, use of vasopressors,mechanical ventilation were factors associated with death.In conclusion, AKI is an important complication in VL.

Innovations & breakthroughs

AKI is an important complication in VL. This study found 10 (4%) patients with VL in a group of 253 patients admitted to the ICU with AKI in 6 years. The main co-infections were: AIDS (40%), tuberculosis (20%) and leprosy (10%). The main comorbidities were diabetes mellitus (20%), systemic arterial hypertension (10%) and respiratory insufficiency (10%).

Applications

The progression of the disease and their complications can achieve high level of severity, even in the absence of comorbidities or co-infections. The high mortality in this group alerts to the importance of early diagnosis and adequate management of these patients. Moreover, it is necessary that patients admitted to the ICU with VL have a detailed investigation to diagnose possible associated diseases. This may allow proper treatment and achieve a better prognosis.

Peer review

This is a good cohort study in which the authors found how AKI was important with VL infection as well as other hiding important diseases, AIDS, tuberculosis and leprosy as co-infection. And also they addressed that patients admitted to the ICU with VL should be done a detailed investigation to diagnose possible associated diseases.

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