Clinical Presentation and Renal Evaluation of Human Visceral Leishmaniasis (Kala-azar): A Retrospective Study of 57 Patients in Brazil

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Visceral leishmaniasis is an endemic disease caused by various species of *Leishmania*. We made a retrospective study of 57 consecutive patients with visceral leishmaniasis in Brazil. Patients with visceral leishmaniasis were identified using the registries of the São José Infectious Diseases Hospital. The sample was divided into two groups: patients with serum creatinine (Scr) <1.3mg/dL and Scr ≥ 1.3mg/dL. We compared these two groups for differences in clinical manifestations and laboratory features. Patients' mean age was 28 ± 18 years old; 74% were male. The main clinical symptoms and signs presented in the initial evaluation were: fever (97%), splenomegaly (96.4%), weight loss (95.5%), pallor (93.6%), cough (89.7%), hepatomegaly (87.2%), asthenia (83.3%), anorexia (82.9%) and vomiting (73.9%). Acute renal failure was found in 15 patients (26.3%) and eight of these patients had ARF before amphotericin B administration. The mean age was higher in the group with Scr ≥ 1.3mg/dL. Death occurred in three cases; all deaths occurred with Scr ≥ 1.3mg/dL. There were no significant differences in the frequencies of the clinical symptoms and signs between the two groups. The laboratory data and demographic characteristics were significantly worse in the Scr ≥ 1.3mg/dL group. Renal dysfunction is an important feature of this disease; it is associated with important morbidity and can increase mortality.

Key-Words: Visceral leishmaniasis, kala-azar, symptoms, acute renal failure.

Visceral leishmaniasis (kala-azar) is an endemic disease in the tropics, subtropics, and southern Europe, affecting one to two million individuals, with approximately 500,000 new cases and 5,000 deaths each year [1-5]. It is a vector-borne disease caused by various species of *Leishmania* [1,6,7]. As a consequence of the intense parasitism of the reticular endothelial system, kala-azar patients present with accentuated anemia, leukopenia and thrombocytopenia, as well as increased plasmatic levels of gamma globulins [2,8].

If untreated, visceral leishmaniasis causes life-threatening disease. Suspicion of infection is therefore of crucial importance to achieve a good outcome. Even in tropical areas, where this disease is endemic, physicians are often baffled by the complexities of leishmaniasis and by the varying clinical presentation [1]. Knowledge of clinical and laboratory features of leishmaniasis can be useful to physicians all around the world, even for those in non-endemic areas, where this disease can be found in travelers returning from endemic regions.

We made a retrospective study of 57 consecutive patients with visceral leishmaniasis (kala-azar) admitted to São José Infectious Diseases Hospital, in Fortaleza, northeast Brazil, from 2005 to 2006.

Material and Methods

Ours was a retrospective study made on 57 consecutive patients with clinical and laboratory diagnosis of visceral leishmaniasis, who had been admitted to the São José Hospital of Infectious Diseases in Fortaleza, Brazil, between November 2005 and March 2006. Diagnosis of kala-azar was based on the identification of *Leishmania* sp. in smears obtained from sternal bone marrow. A standardized case investigation form was used to record demographical, epidemiological, clinical and laboratory data. Patients with previous renal insufficiency, arterial hypertension, diabetes mellitus and other co-morbidities that could affect renal function, were excluded.

The sample was divided into two groups: patients with normal renal function who had serum creatinine levels (Scr) <1.3mg/dL and patients with acute renal failure with Scr≥1.3mg/dL. We compared these two groups to investigate differences in clinical manifestations and laboratory features.

All patients were treated with pentavalent antimonials (Glucantime®) 20 mg/kg daily for 20-40 days; in severe cases, amphotericin B at 7-20 mg/kg total dose was used for up to 20 days. Cases were classified as severe if they had one of the following criteria: age less than six months or above 65 years, jaundice, bleeding (except epistaxis), serious edema, severe malnutrition, serious comorbidities and/or toxemia.

After excluding associated disorders (bacterial infections and/or cancer, for example), patients who had no satisfactorily clinic response after seven days of treatment with Glucantime® were considered refractory and treatment with amphotericin B was initiated with the same original dose.

This study was approved by the Ethics Committee of São José Hospital of Infectious Diseases.

Statistical Analysis

The statistical analysis was performed using the software SPSS 10.0 (SPSS Inc. Chicago, IL, USA) and Epi Info, 6.04b, 2001 (Centers for Disease Control and Prevention, USA). Comparison between two groups were made with the student's

Received on 1 March 2008; revised 28 July 2008.

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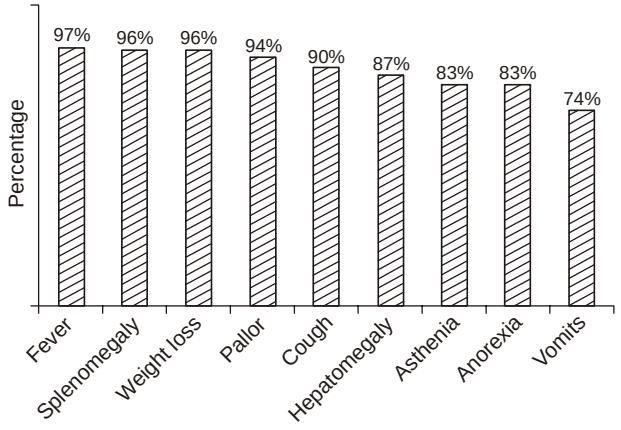
The Brazilian Journal of Infectious Diseases 2008;12(4):329-332.

t test, Fischer's exact test and Mann-Whitney test and the chi square test, when appropriate. P values < 0.05 were considered statistically significant.

Results

Among the 57 patients with confirmed diagnosis of kala-azar, the mean age was 28±18 years and 42 (74%) were male. The average length of hospital stay was 21±12 days, and the duration of treatment was 22±17 days. The main clinical symptoms and signs presented at the initial evaluation were: fever (97%), splenomegaly (96.4%), weight loss (95.5%), pallor (93.6%), cough (89.7%), hepatomegaly (87.2%), asthenia (83.3%), anorexia (82.9%) and vomiting (73.9%) (Figure 1).

Figure 1. Main signs and symptoms at admission of patients with kala-azar.



The main drug used for visceral leishmaniasis treatment in these patients was pentavalent antimonials (96.3%); 11 patients (19%) needed a second drug for treatment and amphotericin B was the choice in 73% of these.

Acute renal failure was found in 15 patients (26.3%). The clinical and laboratory features for patients with Scr <1.3 mg/dL and Scr≥1.3 mg/dL are summarized in Tables 1 and 2. The mean age was higher in the group with Scr≥1.3 mg/dL (p=0.01). All patients in the group with Scr < 1.3 mg/dL were treated with pentavalent antimonials, with no need for second-drug treatment. Eleven patients, all from the group with Scr ≥1.3 mg/dL, needed a second-drug treatment; eight of these patients already had acute renal failure before amphotericin B administration. There were no significant differences in the frequencies of clinical symptoms and signs between the two groups. When we compared laboratory test data, we found significantly greater severity in the group with Scr ≥1.3 mg/dL (Tables 1 and 2). Death occurred in three cases, and all occurred in the group with acute renal failure.

Discussion

Visceral leishmaniasis occurs endemically in 62 countries, with an estimated incidence of approximately 3,500 cases per year in Brazil [5,6,9,10]. All over the world, about 200 million people are at risk [4]. Over 90% of visceral leishmaniasis cases in the world occur in five countries, including Brazil [11]. During recent years, the incidence of this disease has been increasing in urban areas of Brazil [10]. There is a broad range of manifestations. Infection can be asymptomatic or subclinical in many cases [1]. The classic clinical picture of kala-azar includes fever, cachexia, hepato-splenomegaly (splenomegaly usually predominates), pancytopenia (anemia, thrombocytopenia and leucopenia, with neutropenia, marked eosinopenia, and a relative lymphocitosis and monocytosis), and hypergammaglobulinemia (mainly IgG from polyclonal B-cell activation) with hypoalbuminemia [1,5]. Differential diagnosis includes malaria, tropical splenomegaly syndrome, schistosomiasis, cirrhosis with portal hypertension, African trypanosomiasis, military tuberculosis, brucellosis, typhoid fever, bacterial endocarditis, histoplasmosis, malnutrition, lymphoma and leukemia [1].

In our study, there was a predominance of young males, with an average age of 28 years, similar to what has been reported in the literature. The main clinical manifestations among our patients were fever, splenomegaly, weight loss, pallor, cough, hepatomegaly, asthenia, anorexia and vomiting. In recent Brazilian studies of 78 to 530 patients with visceral leishmaniasis, the main signs and symptoms presented were hepatomegaly (77%-100%), pallor (98%), fever (94%-96%), splenomegaly (77%-100%), lymphadenopathy (86%), abdominal volume increase (72%-82%), eyelash growth (74%), dry hair (73%), weight loss (69%-71%), anemia (69%), asthenia (59%-66%), anorexia (38%-61%), cough (30%), hemorrhage manifestations (10%-28%), nausea/vomiting (27%), myalgia (19%), headache (19%), diarrhea (19%), edema (14%-17%) dry skin (12%) and jaundice (6%) [9,12,13]. This demonstrates the large spectrum of clinical manifestations that can be seen in visceral leishmaniasis. It is important to consider kala-azar as a differential diagnosis in every patient with fever of unknown origin [14].

All cases of leishmaniasis should be confirmed by demonstration of the parasite. Examination of giemsa-stained slides of relevant tissue is the technique most commonly used to visualize the parasite [1]. Serological assay for IgG antibody to K39, a recombinant leishmanial polypeptide, can also be used for diagnosis of kala-azar [1,4,10]. This has been an efficient criterion in our region.

The disease is treatable. Since 1940, the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate have been the mainstays of leishmanial therapy [1,5,10,11]. In our study, a meglumine antimoniate was the treatment of choice, used in almost all cases. New therapeutic options, including oral drugs, such as miltefosine, are under consideration [4,11].

We compared patients with Scr < 1.3mg/dL with those with higher values. There are few studies of renal function evaluation in visceral leishmaniasis (kala-azar). Glomerular and tubular abnormalities have been described in past studies;

Table 1. Characteristics and clinical manifestations of kala-azar patients with Scr<1.3mg/dL and Scr≥1.3mg/dL.

	Scr<1.3mg/dL (n=42)	Scr≥1.3mg/dL (n=15)	p value
Age, years	24±18	37±14	0.017
Male,%	67	93	0.084
Time of hospitalization, days	19±10	25±15	0.21
Time of treatment, days	12±11	26±17	0.001
Signs and symptoms			
Fever,%	100	92	0.277
Splenomegaly,%	97.6	92.9	0.448
Weight loss,%	96.9	85.7	0.216
Pallor,%	90.9	100	0.544
Cough,%	92.6	83	0.573
Hepatomegaly,%	91.2	76.9	0.326
Asthenia,%	88.2	76.9	0.628
Anorexia,%	87.5	66.7	0.165
Vomits,%	78.6	66.7	0.643
Coagulation disturbs,%	42.8	53.3	0.48
Treatment			
Use of Glucantime,%	100	85	0.072
Use of Amphotericin B,%	0	73	
Mortality, n	0	3	0.71

Student t test and chi square test; data are expressed as mean±SD and percentage (%); p<0.05 was considered significant.

Table 2. Laboratory result comparisons between kala-azar patients with Scr<1.3mg/dL and Scr≥1.3mg/dL.

	Scr<1.3mg/dL (n=42)	Scr≥1.3mg/dL (n=15)	p value
Scr_{Adm}, mg/dL	0.7±0.2	1.7±1,3	0.001
Scr_{Max}, mg/dL	0.7±0.2	3.6±5,2	<0.0001
Ucr_{Max}, mg/dL	32±14	95±64	0.001
K_{Min}, mEq/L	3.8±0.7	3.2±0,8	0.008
pH_{Adm}	7.47±0.013	7.31±0.12	0.060
$HCO3\text{-}_{Adm}$, mEq/L	22±5.7	12±3.3	0.064
$Albumin_{Adm}$, g/dL	2.63±0.86	1.98±0.87	0.095
TGO_{Adm}, UI/L	80±68	447±653	0.003
Alkaline Phospatase $_{Adm}$, UI/L	213±158	520±209	0.54
$Platelets_{Min}$, /mm^3	110,658±78,743	77,000±5,892	0.05

Adm=admission; Max=maximum and Min=minimum; student t test; data are expressed as mean±SD; p<0.05 was considered significant.

they can cause renal dysfunction in some cases [8,15]. Navarro et al. [16] recently described a case of renal amyloidosis secondary to kala-azar in a patient from Spain who developed chronic kidney disease. In a recent study performed by our group, we found a decreased glomerular filtration rate in 14 out of 50 patients with visceral leishmaniasis (28%). This was attributed to fluid loss, volume contraction and immunological glomerular disease. Impairment in urinary concentration and acidification capacity was also found in 68% and 64% of cases, respectively [15]. In our study, the patients with serum creatinine higher than 1.3mg/dL were older and needed treatment for longer periods.

Amphotericin B is a known nephrotoxin; increases in serum urea and creatinine have been reported to occur in over 80% of patients treated with this drug [17,18]. Amphotericin B was used in 11 patients in the group with Scr≥1.3mg/dL; however, eight of these patients had elevated creatinine before anphotericin B administration. Patients from the group with Scr≥1.3mg/dL had lower levels of potassium and higher levels of AST, and they had a tendency to have lower levels of arterial pH, bicarbonate and albumin. All deaths were observed among the group with acute renal failure. Acute renal failure occurs frequently in patients with kala-azar and this often leads to a severe outcome. Further studies are necessary to establish the mechanisms through which kala-azar can lead to renal dysfunction. In summary, renal dysfunction is an important feature of this disease, which is associated with significant morbidity and increased mortality.

Acknowledgements

We are very grateful to the team of physicians, residents, medical students and nurses from the Hospital São José de

Doenças Infecciosas for their assistance with the patients and for their technical support in the development of this research. This research was supported by FUNCAP - Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (Research Council of Ceará State, Brazil).

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