Clinical Manifestations of Visceral Leishmaniasis (American Visceral Leishmaniasis)

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Abstract

Visceral leishmaniasis (VL) is the most severe form of leishmaniasis. It is endemic in tropical and subtropical countries and responsible for about 50,000 deaths annually. It is characterized by irregular fever, progressive pallor, spleen and liver growth, and consequent increase in abdominal volume, lymphadenopathy, anorexia, and weight loss. Some changes in epidermal structures can be observed such as dry, brittle and depigmented hair, while the eyelashes are long and silky, pale skin, and as the disease progresses may arise petechiae, ecchymosis, hemorrhagic suffusion, and sometimes jaundice. Edema appears very often, mainly in lower limbs. Hematologic changes are manifested by the reduction of all blood cells. Hypoalbuminemia is a frequent finding, while globulin increases. The patient suspected of having the disease is the one who has fever and splenomegaly. It is valuable to the diagnosis of epidemiological data, history of irregular fever, hepatomegaly, splenomegaly, and blood disorders such as pancytopenia and hypoalbuminemia. In the course of the disease, bacterial infections are established, especially in the respiratory tract, sometimes responsible for the death. VL is a consumptive disease that requires specific treatment as early as possible.

Keywords: American visceral leishmaniasis, clinical manifestations

1. Introduction

American visceral leishmaniasis (AVL) is a systemic protozoan infection characterized by fever, malaise, adynamia, and weight loss, besides splenomegaly, hepatomegaly, anemia, leukopenia, pancytopenia, and hypergammaglobulinemia. Later, cachexia, hepatic dysfunction with jaundice, hypoalbuminemia, and edema also arises. If untreated, almost always progresses to death [1].
Visceral leishmaniasis (VL) is the most severe form of leishmaniasis, endemic in tropical and subtropical countries. It is estimated that there are 200,000–400,000 cases of VL each year worldwide, 90% of these cases are from Bangladesh, Brazil, Ethiopia, India, Sudan, and South Sudan [2].

American visceral leishmaniasis is similar to that found in the Mediterranean region regarding the etiologic agent, the animals reservoir, domestic and wild canidae, and the concentration of cases in people under 10 years old [3]. The signs and symptoms are also similar whatever the region the disease is found. Some differences are observed such as blackened skin (India and Sudan) and bulky lymph nodes, mainly in Sudan, whose aspiration is used for diagnosis, while the skin of patients in Americas reminds aged wax and the lymph nodes are little bulky. In the Indian subcontinent, there is no animal reservoir; the disease is transmitted from one individual to another (anthroponosis) through sand flies [3].

In Latin America, VL has been found in at least 12 countries, 90% of the cases are from Brazil [4]. The first case described in Americas dates back to 1913 in a patient from Mato Grosso, diagnosed in Asuncion, Paraguay [5]. In Brazil, the first case of visceral leishmaniasis was a male patient, coming from Aracaju [6].

Nowadays, the disease is described from Mexico to northern Argentina. In Brazil, according to the Ministry of Health, 21 of the 27 Brazilian states have reported autochthonous cases. Until the decade of 90, 92.9% of the cases coming from Brazil were concentrated in the Northeast region, expanding to the North, Midwest, and Southeast regions. In 2011, only 47.8% were from the Northeast region [7]. In the State of Alagoas, located in the central-eastern area of the Northeast region, the disease occurs predominantly in the countryside, affecting mostly children. In recent years, VL has occurred in urban areas of several cities in Brazil.

The disease worried health authorities from the 1990s because of the increased incidence, urbanization, and expansion, a phenomenon observed worldwide. It is believed that some factors favor the expansion such as migration from rural to urban and urban to rural areas, as a result of agro-industrial projects, conflicts between people, and natural phenomena.

The disease can present an acute, subacute, or chronic evolution [8]. Acute leishmaniasis appears most often in children under 2 years old. It is manifested by a severe and continuous high fever and moderate spleen growth, leading to death in 3–4 months [9]. Subacute leishmaniasis last between 6–18 months; patients have persistent fever, progressive splenomegaly, anemia, cachexia, and sometimes diarrhea and bronchitis. The course of VL may be modified by the appearance of opportunistic infections. In other patients, the course is chronic, lasting 2 or more years, interspersed with periods of almost complete recovery; during these periods of apparent cure, splenomegaly is maintained [9].

The clinical course is usually divided into four periods. Despite the imprecision between them, it is thus considered for being a better way to comprehend in an extended period of observation [10]. They are incubation period, period of start or invasion, period of state, and final period.

The incubation period is difficult to characterize, patients do not know the time of the infecting bite, because often there is no obvious changes. Generally, it is accepted limits between 3–6 months [11].
The initial period is marked by the spread of the parasite, the manifestations appear, sometimes abruptly, sometimes insidious. The patient has fever, loss of appetite, weight loss, pallor, hair loss, bleeding, and apathy [11]. Fever is often the first symptom [12]. Splenomegaly is observed early in the course of the disease, although sometimes it is discreet. The liver also starts to grow. Other manifestations may dominate such as diarrheal attacks, respiratory distress, and seizures, especially in children. The signs and symptoms are unspecific and can be confused with other conditions.

In the state period, signs and symptoms are the same from the initial period, but more intense. Fever may be continuous, irregular, relapsing with remissions of 1 or more weeks and two or more daily peaks [13]. The anemia presented from the onset of the disease is accentuated. The spleen grows at the same rate of the pregnant uterus, which means 4 cm per month [14]; its consistency is firm and sometimes it is painful. The hepatomegaly is common but hardly ever reaches the size of the spleen. The hair is dry, thinned, brittle, depigmented, dull, and falls easily. The skin is dry, rough, and pale, remembering aged wax. The abdomen is large. Edema of the lower limbs and ascites can emerge as well. Even polyadenia and reduced muscle mass are observed. Bleeding becomes frequent. Jaundice, delayed puberty, and amenorrhea can also occur.

The final period is marked by the exacerbation of changes in the state period. Death may be caused by changes resulting from the disease itself or associated infections [10].

The etiological agent of American visceral leishmaniasis (AVL) is the protozoan Leishmania infantum/chagasi. It is transmitted to humans and other animals almost always by the bite of the female sand fly Lutzomyia longipalpis. During blood feeding on infected warm-blooded animals, they suck mainly foxes and dogs and become infective from 15 to 24 h. Since then, every new blood meal, they inoculate promastigotes, which are engulfed by macrophages of the monocytic phagocytic system (MPS) and become amastigotes. Inside the macrophages, the amastigotes are housed in phagosomes that fuse to lysosomes, giving rise to phagolysosomes.

Amastigotes survive and multiply in this environment, resisting to toxic substances such as hydrogen peroxide and hydroxyl radicals [15]. In endemic region, it is known that the interaction between the parasite and its host may result in individuals not infected, infected individuals free of the disease (asymptomatic carrier), and individuals who develop the disease. In a research work, from the total of 88 cases suspected of having the disease, 17 (19.3%) were infected, 24 (27.2%) were infected without the disease, and 47 (53.5%) were sick [16].

It is known that 80–90% of all human infections are asymptomatic or subclinical; these individuals have a competent cell-mediated immunity [17]. Researchers initially linked the illness to malnutrition. It is known that malnutrition weakens the defense mechanism, which predisposes to infectious diseases [18]. In an animal model infected with L. infantum/chagasi, it was found that low protein levels are associated with disease progression and lead to the severe form. It was also observed depletion of leucocytes, monocytes and granulocytes and CD4+ subpopulation. The inability to perform an efficient hematopoiesis influences the host's ability to combat infection [18].
Later, it was observed that there would be other elements involved apart from malnutrition. It is believed that genetic factors act in determinants of susceptibility to illness and how the disease develops. Research shows an interrelationship between environmental and host features [17].

This interaction between the parasite and its host can lead to equilibrium, and the host becomes asymptomatic carrier. It is believed that the clinical expression of disease is linked to susceptibility of the host, genetics of the parasite, and vector-dependent factors [18]. Some individuals are unable to control the spread and multiplication of parasites, developing clinical manifestations of varying severity [18].

Dr. Celia Pedrosa, the author of this chapter and professor of the Medicine Faculty of Federal University of Alagoas, followed up patients from admission to outcome at the Tropical Diseases Hospital in Maceio, Alagoas/Brazil, a reference Hospital, from 1981 to 1995 [15]. By then, the hospital had the capacity of 80 beds, including general and intensive care, covering a population of 2,514,100. AVL cases were confirmed by clinical history and the identification of the parasite in medullary aspirate. In the cases that parasite was not found, the diagnosis was based on clinical manifestation and favorable response to treatment. The study included 646 patients, 394 (61.0%) were male and 252 (39.0%) were female. The patients’ ages ranged from 6 months to 59 years, with a mean of 8.7 ± 9.4 years and a median of 5.0 years of age. Among male patients, the mean age was 9.8 ± 10.4 years and the median of 6.0 years (minimum 6 months and maximum of 59 years), and among female patients, the average age was 6.8 ± 7.0 years with a median of 4.0 years (minimum of 10 months and a maximum of 37 years). Table 1 shows the distribution of patients by age and sex.

In both genders, the highest percentage of patients consisted of children, peaking between the ages of 1 and 4 years and thereafter decreasing with age.

| Age (years) | Male | Female | Total |
|------------|------|--------|-------|
| <1         | 15   | 10     | 25    |
| 1–5        | 140  | 128    | 268   |
| 5–10       | 103  | 54     | 157   |
| 10–15      | 49   | 31     | 80    |
| 15–20      | 21   | 10     | 31    |
| 20–30      | 38   | 12     | 50    |
| 30–40      | 18   | 7      | 25    |
| ≥40        | 10   | 0      | 10    |
| Total      | 394  | 252    | 646   |

*Table 1.* Patients admitted to the Hospital for Tropical Diseases (Maceió-AL) with American visceral leishmaniasis, distributed by sex and age.
A higher frequency of patients in the younger age groups was observed, especially before the age of five. Similar findings were reported by other researchers [16] who found that 60.9% of the viscerotomies in patients with leishmaniasis were in children under 5 years old. Other researchers [17, 18] found resembling data in Ceará (67%) and Bahia (75%).

The neotropical kala-azar, also known as AVL, is located in an intermediate position between the “Indian,” in which 62% of the cases are in people between 5 and 19 years, and the “Mediterranean” types, in which children under 5 account for 93% of the cases [19]. However, since the emergence of the human immunodeficiency virus (HIV), the use of immunosuppressant in transplanted patients, and chemotherapy, half of European cases are in adults [1].

Male patients have a higher incidence of the disease than female ones, whatever the age. Some researchers attribute this to larger male body area usually discovered [17], and consequently more exposed to the bite of the vectors; however, it is unlikely that only this fact explains the difference. Studies suggest that genetic modulation is linked to sex in the susceptibility to visceral leishmaniasis [20].

The most common clinical manifestation was fever. In the course of the disease, the fever is very variable. In general, the fever is highest early in the disease, with two or more peaks in 24 h. As the disease is established, temperature becomes lower. Some patients, even presenting fever, claim not to feel it.

Among the patients admitted, the duration of the disease was obtained in 622 patients (Table 2). It was observed that 405 (65.1%) of them arrived at the hospital referring 30–179 days of illness. This time is too long for a disease with marked clinical changes such as fever, weight loss, pallor, and increased abdominal volume. Other authors found similar data [21].

Since the onset of the disease, patients always seek medical care. However, even in endemic region, diagnosis is not considered and patients generally receive antimicrobials. By the irregularity of fever itself, patients may spend days or weeks with normal temperature, causing the false impression of cure of another infectious process, believed to be one of the reasons for the difficulty to know the right onset of the symptoms.

| Duration of the disease (days) | Patients | % |
|-------------------------------|----------|---|
| <30                           | 107      | 17.2 |
| 30–90                         | 238      | 38.3 |
| 90–180                        | 167      | 26.8 |
| 180–360                       | 73       | 11.8 |
| ≥360                          | 37       | 5.9  |
| **Total**                     | **622**  | **100.0** |

*Table 2.* Duration of the disease in 622 patients with American visceral leishmaniasis admitted to the Tropical Diseases Hospital, in Maceió-AL.
The clinical manifestations most often found in the admission include hepatomegaly, splenomegaly, fever, and pallor. Hepatomegaly’s predominance over splenomegaly draws attention, and this fact stems from a patient who inadvertently has been splenectomized. The sum of the clinical manifestations exceeds 100% because most of the patients had simultaneously more than one clinical manifestation (Table 3).

| Clinical manifestations | Number of patients | %  |
|-------------------------|--------------------|----|
| Hepatomegaly            | 633                | 98.0|
| Splenomegaly            | 632                | 97.8|
| Fever                   | 628                | 97.7|
| Pallor                  | 533                | 82.5|
| Increased lymph nodes   | 500                | 77.5|
| Increased abdominal volume | 463            | 71.7|
| Weight loss             | 462                | 71.5|
| Long eyelashes          | 454                | 70.3|
| Dry hair                | 450                | 69.7|
| Asthenia                | 447                | 69.2|
| Anorexia                | 416                | 64.4|
| lower limbs edema       | 151                | 23.3|
| Cough                   | 104                | 16.2|
| Diarrhea                | 102                | 14.4|
| Abdominal pain          | 80                 | 12.4|
| Bleeding                | 67                 | 10.4|
| Jaundice                | 90                 | 13.9|

Table 3. Clinical manifestations most often observed in patients with American visceral leishmaniasis admitted to the Hospital for Tropical Diseases in Maceió-AL.

Irregular fever, generally high, and pallor were relevant, associated with increased abdominal volume, led patients to seek medical attention. On admission, the contrast between the hair and the eyelashes drew attention, because while the hair was depigmented, dry and dull lashes were long and silky. A Brazilian researcher studied clinical and laboratory features of kala-azar and also found patients with dry, brittle, depigmented hair, and long eyelashes [22]. According to this author, lower hyperthermia is common when the disease has a long duration, observation confirmed by us. However, other manifestations such as jaundice and edema, also observed in our study, did not maintain relation with the duration of illness.

Some researchers have noted that patients with jaundice had worse prognosis [21]. To other authors, not only jaundice, but also the low age, marked pallor, creatinine elevation, and presence of amastigotes in bone marrow aspirate are factors associated with poor outcome [23].
However, in our study, we found no association between low age, presence of parasites in the bone marrow, and poor prognosis.

The spleen has firm consistency, not painful on palpation, except in some cases. Since it is a good parameter for estimating the duration of the disease and response to treatment, it must be carefully examined and its features registered on medical records. Always measure the spleen and liver size with a tape, describe the location of measurement, or use the Hackett scale.

Liver has firm consistency too, sometimes painful on palpation. Its size as well as the spleen accompanied the duration of the disease; liver is always a little lower than spleen (Table 4), but after the institution of specific therapy, liver regression occurred more slowly.

| Duration of the disease (days) | Number of patients | Size of the liver (cm) |
|-------------------------------|--------------------|-----------------------|
|                              |                    | Mean ± standard deviation | Minimum | Maximum |
| <30                           | 105                | 4.2 ± 1.8              | 0.0      | 9.0      |
| 30–90                         | 221                | 4.7 ± 2.2              | 0.0      | 12.0     |
| 90–180                        | 163                | 5.6 ± 2.5              | 0.0      | 14.0     |
| 180–360                       | 68                 | 5.8 ± 3.3              | 0.0      | 16.0     |
| ≥360                          | 36                 | 7.3 ± 3.6              | 2.0      | 20.0     |

Table 4. Size of the liver in hospital admission for the duration of the disease in 593 patients.

During the follow-up, the duration of the disease compared to spleen size measured at hospital admission (Table 5) was observed. The average size of the spleen does not correspond to what is expected of its size for this duration of illness. Since fever becomes continuous later, patients believe this illness is recent. Investigating important data, such as fever and relating them with celebrating days, you get more accurate information about disease’s duration.

| Duration of the disease (days) | Number of patients | Size of the spleen (cm) |
|-------------------------------|--------------------|-------------------------|
|                              |                    | Mean ± standard deviation | Minimum | Maximum |
| <30                           | 102                | 7.2 ± 3.3               | 0.0      | 16.0     |
| 30–90                         | 220                | 8.6 ± 4.0               | 0.0      | 33.0     |
| 90–180                        | 159                | 9.8 ± 3.6               | 0.0      | 20.0     |
| 180–360                       | 66                 | 10.3 ± 4.2              | 0.0      | 20.0     |
| ≥360                          | 36                 | 12.4 ± 3.8              | 3.0      | 20.0     |

Table 5. Size of the spleen in hospital admission for the duration of the disease in 583 patients.
The normal spleen is rarely palpated, located on the left upper quadrant of the gastric fundus and the diaphragm. In VL, spleen growth takes place since the beginning of the disease. Ancient authors compare its growth to the gravid uterus [24]. Based on this knowledge, for those patients who do not remember since when they were sick, it is possible to estimate the duration of the disease by spleen size. Disease duration is an important factor because the prognosis is directly related to the time they are sick [25].

Liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measured at the time of admission in 444 patients, showed values above normality (>40 units/l) in 169 (38.1%) and 258 (58.1%) patients, respectively (Table 6). Liver enzymes that were abnormal at the time of admission hold no relation to the duration of the disease. Otherwise, for other researchers, the aminotransferase was more pronounced in cases diagnosed late [26].

| Enzymes  | No of patients (%) | Mean ± standard deviation (units/l) | Maximum-minimum (units/l) |
|----------|--------------------|-----------------------------------|--------------------------|
| ALT ≤ 40 | 275 (62.0)         | 19.5 ± 11.2                       | 2.0–40.0                 |
| ALT > 40 | 169 (38.0)         | 145.5 ± 210.1                     | 41.0–1750.0              |
| AST ≤ 40 | 186 (41.9)         | 23.6 ± 10.2                       | 3.0–40.0                 |
| AST > 40 | 258 (58.1)         | 126.9 ± 174.5                     | 41.0–1530.0              |

a ALT, alanine aminotransferase; AST, aspartate aminotransferase.
b Normal values ≤ 40 units/l.

Table 6. Liver enzymes measured in 444 patients at hospital admission.

After treatment, liver enzymes returned to normal, except in four patients who died with liver failure. Histopathologic findings suggested toxic hepatitis.

Associated infections were diagnosed at admission in 134 (20.7%) patients. Airway infections, especially pneumonia, were most often found. Children under 5 years old were the most affected by associated infections, 104 (60.8%) cases.

During the period they were hospitalized for treatment, 258 patients developed some type of infection; the most frequent was pneumonia, which affected 126 (48.8%) subjects. Regardless of the grievance, the higher incidence of infections acquired during hospitalization occurred in children under 5 years old with 229 (61.4%) occurrences.

In our observation, associated infections were not related to the duration of the disease, but they affected mortality.

In 554 patients, we performed blood tests at hospital admission. The count of red cells ranged from 1.03 to 4.55 million red cells/mm$^3$, with an average of 2,762,000 ± 620,307 red cells/mm$^3$, while in 603 patients white blood cell (WBC) counts ranged from 600 to 15,600 leukocytes/mm$^3$ with an average of 4174 ± 2127 leukocytes/mm$^3$. In differential counting, the absolute number of lymphocytes ranged from 102 to 11,100 lymphocytes/mm$^3$ with a mean of 2339 ± 1422 lymphocytes/mm$^3$. Platelets counted in 279 patients ranged from 1000 to 732,600 platelets/mm$^3$,.
with an average of 140,020 ± 103,049 platelets/mm³. Except the leukocytes, all these averages are below normal values. Using analysis of variance, it was observed that except the medium of leukocytes and lymphocytes, which were significantly higher in patients younger than 30 days of illness, all other results showed no significance regarding disease duration (Table 7).

| Duration of the disease (days) | Hm a (×10⁹/mm³) | Ht b (%) | Hb c (g/dl) | Platelets (×10⁹/mm³) | Leukocytes (mm³) | Lymphocytes (×10⁹/mm³) |
|-------------------------------|-----------------|----------|-------------|----------------------|------------------|------------------------|
| <30                           | 2.770 ± 697     | 23.6 ± 6.4 | 7.2 ± 2.2 | 1.35 ± 0.78         | 4.872 ± 2.186   | 2.7 ± 1.6               |
| 30–90                         | 2.683 ± 633     | 23.0 ± 5.5 | 7.0 ± 1.8  | 1.36 ± 0.11         | 4.168 ± 2.183  | 2.2 ± 1.4               |
| 90–180                        | 2.784 ± 599     | 24.0 ± 5.5 | 7.4 ± 1.8  | 1.39 ± 0.99         | 3.962 ± 2.001  | 2.2 ± 1.2               |
| 180–360                       | 2.797 ± 635     | 24.0 ± 6.0 | 7.4 ± 2.0  | 1.68 ± 0.12         | 3.763 ± 2.190  | 2.0 ± 1.3               |
| ≥360                          | 2.988 ± 453     | 26.1 ± 4.1 | 8.1 ± 1.5  | 1.40 ± 0.88         | 3.955 ± 2.141  | 1.9 ± 1.2               |
| p d                           | 0.155           | 0.062     | 0.061      | 0.0653               | 0.004*          | 0.004*                  |

a Red cells.
b Hematocrit.
c Hemoglobin.
d Comparison of the means (variance analysis, g.l. = 4).

* C.I.: 95%: significant differences (p < 0.05).

Table 7. Blood test data (mean ± standard deviation) of patients at admission according to the duration of the disease.

Our patients had varying degrees of anemia associated with leukopenia and thrombocytopenia. Anemia seems to occur when the spleen becomes palpable and progresses with its gradual increase; this opinion is shared by others [27, 28]. Anemia is one of the most remarkable manifestations of visceral leishmaniasis, and the pathogenesis of this anemia, caused in part by the destruction of red blood cells, is multifactorial (splenic phagocytosis of opsonized erythrocytes, hemodilution, and increased destruction of normal red blood cells by hypersplenism) [3]. In addition, there is a bone marrow failure to replenish red blood cells removed from the circulation, which can be attributed to poor nutrition and infection extension.

There are several hypotheses proposed to explain the pathogenesis of anemia in visceral leishmaniasis. Some pointed to the increased blood volume, while others argue that autoimmune mechanisms are responsible for the decreased survival of red blood cells. Their destruction occurs intensely in the spleen. Others emphasize that the reduced erythrocyte survival and iron deficiency are more common in children under 3 years [29, 30].

For others, the severity of hematological changes depends on the duration of the disease and the spleen size, hypersplenism primarily responsible for these changes. The pancytopenia and thrombocytopenia reflect an extended illness, before the diagnosis is made [31].

In 450 patients in which the temperature was measured during the course of treatment, 25 (5.6%) cases showed no fever when treatment was initiated. In 330 (73.3%) cases, the temperature normalization occurred until day 7 after initiation of therapy. In 56 (12.4%), temperature normalized between the 8th and 14th day, and in 39 (8.7%), from 15th to 21st day.
In 630 patients who started treatment, 109 (16.8%) received incomplete treatment (62 because they died and 47 because they left before the treatment was completed) and 521 (80.6%) received full treatment. There was a death after completion of therapy. Five patients (0.7%) had a new treatment cycle.

Regardless of the duration of the disease, there was a decrease in the average size of liver and spleen after treatment. The percentage reduction of these organs at the end of treatment was higher in patients with less disease duration (Table 8). The analysis of variance showed that the spleen reduction percentage was higher in patients with less disease duration. However, considering the liver, this difference was not observed.

| Duration of the disease | Spleen | | Liver | |
|-------------------------|--------|----|--------|----|
| Number of patients      | % of reduction | Number of patients | % of reduction |
| <30                     | 73     | 70.75 | 60     | 58.73 |
| 30–90                   | 157    | 60.03 | 1248   | 55.41 |
| 90–180                  | 115    | 53.50 | 86     | 46.17 |
| 180–360                 | 49     | 54.37 | 42     | 45.64 |
| ≥360                    | 23     | 52.47 | 16     | 46.61 |

* 100 – (mean of the viscera in the end of the treatment \times 100).
Note: mean of the viscera before treatment.

Table 8. Percentage reduction in the average size of the spleen and liver after treatment.

Among the patients who progressed to death, 44 (57.9%) were male and 32 (42.1%) were female. Forty-six of them died during the first or second weeks of treatment. The clinical manifestations most often related to death were bleeding, edema (anasarca and ascites), and pneumonia. In the third and fourth weeks, 17 deaths were registered, with a predominance of pneumonia as a probable cause of death.

Table 9 shows the distribution of deaths by age, including those 13 individuals who died before treatment was started, while Table 10 shows the distribution of deaths by disease duration. There was no statistically significant difference in the percentage of deaths in relation to age ($\chi^2 = 13.64, p = 0.058, g.1. = 6$). However, since $p$-value is close to convention (0.05), some different interpretation may be important, like the high mortality rates in patients under 1 year old (33.3%). There was no statistical significance regarding disease duration ($\chi^2 = 0.51, p = 0.973, g.1. = 4$).

According to observations of Brazilian researchers, the deaths occur by the delay in starting the treatment or lack of response to it. Advanced case can present worsening in the first days of treatment, resulting from Herxheimer reaction. In these patients, death occurs mostly by bacterial complications or bleeding [25]. In a survey of medical records at the “Hospital das Clinicas,” in São Paulo (Brazil), about 13% of deaths in 162 patients with visceral leishmaniasis was found and the main causes were pneumonia and sepsis [32].
We did not observe an association between disease duration and the number of deaths, as some claim. According to a study conducted by these authors, the death was more frequent in cases with longer disease duration \[18–23, 25–31, 33, 34\]. Our mortality data are consistent with a study conducted in Sudan which found 12\% of deaths \[35\].

The World Health Organization \[36\] considered as a factor that worsens prognosis the late start of treatment, especially for younger children as well as associated infections. However, in our study we found no relationship between disease duration or age and mortality. Our data, regarding the causes of death, are comparable to other Brazilian researchers who have found bacterial infections in 59\% of their patients; the respiratory tract was the most involved with 48\% of the cases. These infections had no relation to the duration of the disease \[37\].

It is likely that the progress of visceral leishmaniasis, favorable or not, depends on the agent and the genetic constitution of the host, and therefore of the ability of the body in defending itself.

### Table 9. Distribution of deaths by age in 616 patients admitted at the Tropical Diseases Hospital “Constança de Góes Monteiro”.

| Age (years) | Number of deaths/Total number of patients (%) |
|------------|---------------------------------------------|
| <1         | 8/24 (33.3)                                 |
| 1–5        | 34/256 (13.3)                               |
| 5–10       | 18/149 (12.1)                               |
| 10–15      | 7/79 (8.9)                                  |
| 15–20      | 2/28 (7.1)                                  |
| 20–30      | 4/47 (8.5)                                  |
| 30–40      | 3/22 (13.6)                                 |
| ≥40        | 0/10 (0.0)                                  |
| **Total**  | **76/616 (12.3)**                           |

### Table 10. Distribution of deaths according to the duration of the disease.

| Duration of the disease (days) | Number of deaths/total number of patients (%) |
|--------------------------------|---------------------------------------------|
| <30                           | 11/102 (10.8)                               |
| 30–90                         | 25/225 (11.1)                               |
| 90–180                        | 20/157 (12.7)                               |
| 180–360                       | 7/71 (9.9)                                  |
| ≥360                          | 4/36 (11.1)                                 |
| **Total**                     | **67/591 (11.3)**                           |
Continuing observation over the years allows us to conclude that the duration of the disease is correlated to the size of the liver and spleen, the temperature, the number of leukocytes and lymphocytes at hospital admission, and spleen size at the end of treatment. However, associated infections and complications are not influenced by disease duration, as well as the normalization of temperature after the start of specific therapy. Finally, we find that death is not associated with age, sex, positive medullary puncture, or disease duration. We also observed that at the end of treatment, there is no full recovery, but considerable improvement in all clinical and laboratory parameters.

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