High visceral leishmaniasis mortality rate in Barra Mansa, a new area of visceral leishmaniasis transmission in the State of Rio de Janeiro, Brazil

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ABSTRACT

Introduction: Nine cases of visceral leishmaniasis occurred recently in Barra Mansa, State of Rio de Janeiro, with a high mortality rate. Methods: We reviewed the medical records of the patients. Results: Eight were male; 7 were adults. Patients who died progressed to death quickly and presented with aggravating factors: systemic steroid therapy before diagnosis, bleeding, severe liver involvement, infection, and/or refusal to receive transfusion. Conclusions: We warn clinicians to be aware of the emergence of visceral leishmaniasis in new areas and to keep in mind the possibility of atypical clinical pictures and aggravating factors, so timely diagnosis can be made and prompt and adequate treatment can be initiated.

Keywords: Visceral leishmaniasis. Lethality. Epidemiology. Therapy.

Visceral leishmaniasis (VL) is an anthropozoonosis caused by protozoa of the genus Leishmania and is transmitted by infected female sand flies during their blood meals. In the New World, the causative agent is Leishmania (Leishmania) chagasi, which is considered to be identical to Leishmania (Leishmania) infantum of the Old World.

In Brazil, VL is endemic mainly in the states of the Northeast Region, but is also prevalent in the North Region, the Southeast Region, with the State of Minas Gerais having the highest prevalence, and the Midwest Region, with a high prevalence in the State of Mato Grosso do Sul. While VL originally affected rural inhabitants of Brazil, urbanization has resulted in the progressive adaptation of the main VL vector, Lutzomyia longipalpis, to the peridomicile,[3,4] feeding predominantly on domestic dogs and chicken,[1,6] but also on synanthropic animals including opossums.[7,9] In the oldest VL endemic areas, most patients are male and/or children.[8] However, in the newer VL affected areas, larger numbers of adults have been diagnosed,[1] and patients present a more severe clinical picture.

In the State of Rio de Janeiro, several cases of VL occurred during the twentieth century; however, the number of autochthonous cases declined between 2000 and 2009. Since 2010, the incidence of human VL has resurfaced in Rio de Janeiro, mainly in the Paraíba do Sul River Valley. We examined the cases of human VL that occurred in Barra Mansa between 2010 and 2013 in order to better understand the behavior of VL in a geographic area where it was previously absent.

Through medical record analysis, we were unable to identify any cases of VL in Barra Mansa before 2010. No autochthonous cases of VL were present in the Brazilian diseases notification system (Sistema de Informação de Agravos de Notificação - SINAN) for Barra Mansa in the preceding decades. We reviewed the medical records of patients who had a diagnosis of VL in the City of Barra Mansa between November 2010 and September 2013. Nine patients were diagnosed with VL by their clinical picture, by parasitological confirmation through direct examination of bone marrow to visualize amastigotes by microscopy, by culture of bone marrow samples in appropriate media (Nicole-Novy-McNeal [NNN] medium with Schneider medium and 10% fetal bovine serum), and/or by positive specific serology (enzyme-linked immunosorbent assay [ELISA], immunochromatographic test with recombinant antigen rK39 [Kalazar Detect®], or immunofluorescence assay [IFA]).

Eight patients were male. Two were children under 5 years of age and 7 were adults. From the 9 cases, 3 patients presented with previous chronic diseases (heart disease and...
renal insufficiency) and 1 patient was addicted to alcohol and marijuana. A total of 4 patients died. The patients who died presented with bleeding, severe liver involvement, respiratory infection, or infection of unclear origin, or had systemic steroid therapy before diagnosis, and/or refused transfusion due to religious beliefs. The first 3 patients did not recover and died of VL. Patients 1 and 2 were diagnosed with VL post-mortem, although patient 2 had suspicion of VL a few weeks before death. Patients 4 to 7 recovered after successful treatment with amphotericin B or meglumine antimoniate; however, all were over the age of 40 years. Patient 8 died as a result of a severe liver dysfunction that was caused by VL. Patient 9, who was 26 years old, recovered after treatment with amphotericin B. Human immunodeficiency virus (HIV) serology was negative in all patients. The characteristics of the 9 patients are shown in Table 1.

### TABLE 1 - Socio-demographic characteristics, clinical features, diagnostic tests, and outcomes of 9 patients from Barra Mansa, State of Rio de Janeiro, Brazil with visceral leishmaniasis that occurred between November 2010 and September 2013.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Clinical picture</th>
<th>Duration of the disease until diagnosis</th>
<th>VL serology</th>
<th>Bone marrow</th>
<th>Aggravating factors</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>2 years 10 months</td>
<td>Typical</td>
<td>2 months</td>
<td>ND (post mortem diagnosis)</td>
<td>A</td>
<td>Steroid therapy, bleeding</td>
<td>Amphotericin B as part of the protocol for febrile neutropenic patients</td>
<td>U</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>37 years</td>
<td>Typical</td>
<td>6 months</td>
<td>ELISA (+), Kalazar Detect®(+),</td>
<td>A</td>
<td>Patient did not accept transfusion; pulmonary infection; severe pancytopenia</td>
<td>None (post mortem diagnosis)</td>
<td>U</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>3 years 10 months</td>
<td>Typical</td>
<td>1 month</td>
<td>IFA 1:160, Kalazar detect®(-)</td>
<td>ND</td>
<td>Infection of unclear origin</td>
<td>Meglumine antimoniate; liposomal amphotericin B, late introduction</td>
<td>U</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>53 years</td>
<td>Typical</td>
<td>3 months</td>
<td>ND</td>
<td>A</td>
<td>No</td>
<td>Meglumine antimoniate</td>
<td>F</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>51 years</td>
<td>Typical</td>
<td>3 months</td>
<td>IFA 1:640, Kalazar Detect®(+)</td>
<td>A</td>
<td>Renal insufficiency</td>
<td>Liposomal amphotericin B</td>
<td>F</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>52 years</td>
<td>Typical</td>
<td>6 months</td>
<td>ND</td>
<td>A</td>
<td>Heart disease</td>
<td>Liposomal amphotericin B</td>
<td>F</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>46 years</td>
<td>Typical</td>
<td>2 months</td>
<td>ND</td>
<td>A</td>
<td>Heart disease; chronic alcoholism and marijuana use</td>
<td>Liposomal amphotericin B</td>
<td>F</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>20 years</td>
<td>Atypical</td>
<td>15 days</td>
<td>IFA 1:160, Kalazar Detect® (+), Direct exam (-) Culture (+)</td>
<td>Severe liver involvement due to VL</td>
<td>None (early death)</td>
<td>U</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>26 years</td>
<td>Typical</td>
<td>4 months</td>
<td>Kalazar Detect® (+)</td>
<td>A</td>
<td>No</td>
<td>Liposomal amphotericin B</td>
<td>F</td>
</tr>
</tbody>
</table>

**VL**: visceral leishmaniasis; **ND**: not performed; **A**: amastigotes in direct exam; **ELISA**: enzyme-linked immunosorbent assay; **Kalazar Detect®**: immunochromatographic test with recombinant antigen rK39; **IFA**: immunofluorescence assay; (+): positive test; (-): negative test; **U**: unfavorable outcome (death); **F**: favorable outcome (recovery).
The delayed diagnosis of the first patients, which occurred in a geographical area where VL was not previously observed, had a negative impact on the management of the cases. The patients with VL that were studied in Barra Mansa presented with unusual epidemiological and clinical characteristics, when compared to the reports of patients in areas where VL is endemic: 77.8% (7 out of 9 cases) of patients were adults, although the oldest patients recovered after therapy. In addition, the duration of the disease until clinical status worsened was short in 3 of the 4 patients who died. Furthermore, none of the patients were HIV-positive. In 1 case, the patient presented with an atypical clinical picture with severe liver involvement due to VL that resulted in premature death before treatment was initiated. The mortality rate of 44.4% (4 out of 9 cases) in Barra Mansa was much higher than the average VL mortality rate in the State of Rio de Janeiro in the preceding years (7.8% between 2000 and 2009).10

It has been reported previously that in areas of Brazil where VL is endemic, several factors are associated with death in VL patients: HIV co-infection, other associated infections, bleeding, jaundice, severe anemia, older age, co-morbidities, cardiotoxicity due to treatment, and use of meglumine antimoniate in patients with co-morbidities11-15. Some of these factors (bleeding, infection, and co-morbidities) were present in our patients; however, the small number of cases included in this study did not allow for statistical analysis regarding lethality. Importantly, co-morbidities were present in 3 out of the 5 patients who recovered after therapy.

To date, there has been no explanation as to why VL patients in Barra Mansa are older. It is possible that this is related to the fact that Barra Mansa was previously not a VL endemic area, resulting in the lack of previous contact of the older population with the parasite. The Epidemiologic Surveillance Services must remain vigilant in identifying VL infection in older patients in areas where VL was previously not present.

The diagnosis, treatment, and surveillance of cases of VL in Barra Mansa have resulted in the development of necessary control actions, including entomological research, active search for VL infected dogs, and euthanasia of seropositive dogs. In addition, VL is now considered in the differential diagnosis of fever, hepatomegaly, jaundice, and splenomegaly in the municipality of Barra Mansa. Between February 2013 and June 2014, some cases of suspected VL were reported; however, the VL diagnosis was subsequently discarded.

Attention must be given to the neglected disease of VL, as it is important to warn clinicians of the resurgence of VL in the State of Rio de Janeiro. It is necessary for clinicians in new areas where VL has spread to be aware that patients with VL may present with an atypical clinical picture, that the disease may rapidly evolve to a disease of much greater severity, and that co-morbidities and aggravating factors may affect the course of VL. The timely diagnosis of VL will allow for prompt and appropriate treatment to be initiated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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5. Oliveira AG, Galati EA, Fernandes CE, Dorval ME, Brazil RP. Epidemiological and clinical characteristics, when compared to the reports of patients in areas where VL is endemic: 77.8% (7 out of 9 cases) of patients were adults, although the oldest patients recovered after therapy. In addition, the duration of the disease until clinical status worsened was short in 3 of the 4 patients who died. Furthermore, none of the patients were HIV-positive. In 1 case, the patient presented with an atypical clinical picture with severe liver involvement due to VL that resulted in premature death before treatment was initiated. The mortality rate of 44.4% (4 out of 9 cases) in Barra Mansa was much higher than the average VL mortality rate in the State of Rio de Janeiro in the preceding years (7.8% between 2000 and 2009).


