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Short Communication

Visceral leishmaniasis and leishmaniasis-HIV coinfection: comparative study

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Abstract

Introduction: This study aimed to draw clinical and epidemiological comparisons between visceral leishmaniasis (VL) and VL associated with human immunodeficiency virus (HIV) infection. **Method:** Retrospective study. **Results:** Of 473 cases of VL, 5.5% were coinfected with HIV. The highest proportion of cases of both VL and VL/HIV were found among men. A higher proportion of VL cases was seen in children aged 0-10 years, whereas coinfection was more common in those aged 18-50 years. **Conclusions:** VL/HIV coinfected patients presented slightly differently to and had a higher mortality rate than those with VL only.

Keywords: AIDS. Visceral leishmaniasis. Human immunodeficiency virus. Coinfection. Recurrence.

Visceral leishmaniasis (VL) and infection with human immunodeficiency virus (HIV) are considered to be of great importance[1]. Visceral leishmaniasis is a zoonosis caused by protozoans of the *Leishmania* genus. In Brazil, it is caused by *Leishmania chagasi*, that is transmitted to humans through the sting of the female phlebotomine insect, *Lutzomia longipalpis*[2]. HIV, a retrovirus, is typically sexually transmitted. After the discovery of conditions that favor HIV dissemination, a change in the disease profile was observed, suggesting a trend toward increased incidence in impoverished and rural areas[3].

The first case of leishmaniasis-HIV coinfection was described in Europe in 1985; cases have subsequently been reported in 35 countries[1]. A significant increase in the number of cases has been observed since the beginning of the 1990s, and a continual increase is predicted due to the geographical overlap of these infections as a result of the urbanization of leishmaniasis and ruralization of HIV infection[4]. It is estimated that 25-70% of adults with VL are coinfected with HIV, prompting some authors to support the inclusion of VL as an opportunistic infection, indicative of acquired immunodeficiency syndrome (AIDS)[5]. Coinfection has particular aspects in terms of clinical presentation, diagnosis, and response to specific treatment; moreover, early diagnosis is essential to reduce both disease severity and mortality[5].

This was a retrospective comparative study of patients with VL and VL/HIV coinfection who were treated at the *Hospital de Doenças Tropicais of Araguaína*, Tocantins, between 2009 and 2014. Cases were selected using the notification register for VL of the Hospital Epidemiological Surveillance Center. This register records all cases that were treated at the hospital, both suspected and confirmed; all confirmed cases of VL were selected. Information was then collected from the patients' charts in the Patient Chart Service. Cases were divided into two groups: Patients with VL only and patients with VL/HIV coinfection. The criterion for VL cure was improvement of symptoms over a follow-up period ofat least six months. We included all confirmed cases of VL that met the following requirements: I). Clinical-laboratory criteria: clinically suspected cases that met at least one of the following criteria: parasite detected on stool parasite testing or by reactive immunofluorescence at a titer of 1:80 or higher, with other differential diagnoses excluded. II). Clinical-epidemiological criteria: clinically suspected cases without laboratory confirmation, coming from an area of known VL transmission, and with a favorable response to therapy.

For cases of VL/HIV coinfection, in addition to the above criteria, patients had to meet the diagnostic criteria for HIV infection, i.e., a positive HIV enzyme-linked immunosorbent assay (ELISA) test result with confirmation of the result by immunofluorescent assay or Western blot.

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All collected data were entered into a Microsoft Excel® 2010 spreadsheet and were analyzed using Stata statistical software, version 13.1 (StataCorp, Texas, USA). The categorical variables were described as absolute and relative frequencies and compared by means of the chi-square test or Fisher's exact test. P-values below 0.05 were considered significant.

Between 2009 and 2014, a total of 473 cases of VL were reported in Araguaína, Tocantins: 447 (93.9%) had VL only and 26 (5.5%) were coinfected with HIV. Most patients were from the State of Tocantins (VL, *n* = 391 and VL/HIV, *n*= 22), with 245 (54.8%) patients with VL and 14 (53.8%) with VL/HIV residing in the City of Araguaína.

Regarding the sample characteristics (**Table 1**), the age of the groups differed ($p < 0.001$); the average age of those with VL was 17.6 years [standard deviation (SD) 19.2 years] and of those with VL/HIV was 34.4 years (SD 11.3 years). A higher proportion of men than women had VL (60.2% vs. 39.8%) and VL/HIV (80.7% vs. 19.3%). The highest incidence rate of VL was seen in children aged 0-10 years (52.5%), followed by adults aged 18-50 years (31.3%). In the coinfected group, the 18-50-year age group was most affected, with 88.5% of cases. Regarding race, the vast majority of cases (VL and VL/HIV) occurred in people classified as brown. The sample comprised mostly single individuals, followed by married individuals or those in a stable relationship. Overall, the level of education was low. In the VL group, 21.4% of individuals had not completed elementary school and only 6% had completed high school. In the coinfected group, 38.4% of individuals had not completed elementary school, but 11.54% had completed higher education. Regarding place of residence, 88% of individuals lived in an urban area. Among those coinfected, 19 (73.1%) were diagnosed with HIV before being diagnosed with VL, 4 (15.3%) were diagnosed with VL before being diagnosed with HIV, and 3 (11.5%) received these diagnoses concurrently.

The symptomatology observed in each group is described in **Table 2**. In those with VL and with VL/HIV coinfection, fever (97.76% and 92.3%, respectively) and splenomegaly (68.7% and 61.5%, respectively) occurred most commonly. However, a significantly greater proportion of patients in the coinfected group experienced physical weakness ($p = 0.032$) and weight loss ($p = 0.024$), whereas a greater proportion of patients in the VL group presented with pallor (43.2%; $p= 0.001$).

In terms of treatment, 62.4% of all subjects were given glucantime as primary treatment, 99.3% of whom had VL only. Overall, 59% of patients treated with glucantime were cured ($p = 0.013$), with a significant association observed among those with only VL (65.6%, $p < 0.001$). Sixteen (5.4%) patients experienced recurrence ($p = 0.678$); and 2 (0.6%) died of VL ($p = 0.004$). The VL only group had a high rate of individuals transferred out or who did not receive the recommended monitoring (32.7%), which may have produced misleading results (**Table 3**). Initial therapy with amphotericin B deoxycholate and liposomal amphotericin B (53.9% and 34.6%, respectively), was more common in the coinfected group ($p < 0.001$). Of those treated with amphotericin B deoxycholate (14 patients with VL/HIV), only 2 were cured. Seven had a recurrence of VL, 3 died of VL, and 2 did not continue the recommended monitoring. Of the 9 patients who began therapy with liposomal amphotericin B, only 1 was cured; 2 had recurrence, 4 died of VL, and 2 did not continue the recommended monitoring. Two coinfected patients started therapy with glucantime; 1 was transferred and the other had a recurrence of VL and died. The evolution of disease in patients with VL/HIV was unfavorable, with 26.9% of cases resulting in death, compared to the VL group in which 2.2% of cases died ($p < 0.001$).

In the State of Tocantins, VL is considered a serious public health issue. Many factors have contributed to the high incidence of VL since this state was created. Deforestation for profit, animal breeding in back yards (especially chickens and dogs), intense migratory flow, and lack of basic sanitation have all resulted in dissemination of the disease carrier[6]. In recent years, the disease has been concentrated in the central and northern regions of the state[6]. In 2009, Tocantins was the Brazilian state with the second highest rate of VL, and Araguaína has had the highest number of reported cases in Tocantins since 2005: Out of 392 cases of VL reported in 2007, 205 were from Araguaína, that is, 52% of the total[6,7].

At the beginning of the HIV/AIDS epidemic in Brazil, most cases of HIV/AIDS were reported in the large cities of the South and Southeast regions. However, since 2000, there has been a significant increase in the number of cases in medium and large cities located in the North and Center-West regions, a phenomenon known as ruralization. It is believed that, among other factors, awareness of the AIDS epidemic has increased in the North since 2004, and as a result, epidemiological surveillance has been strengthened[6,7]. Between 1980 and 2014, a total of 2,081 cases of AIDS were reported in the State of Tocantins; they were part of a total of 41,036 cases reported in the North[8]. Additionally, Tocantins, especially Araguaína, is a region endemic for VL, so the number of VL/HIV coinfections in this region stands out, as was observed in the present study.

It is also known that VL mainly affects children, especially those younger than 10 years, as they are more exposed to the disease carrier in their home environment and also suffer from nutritional deficits[9,10]. However, both a decreasing trend in the number of VL cases in children and an increasing trend in adults has been seen in recent years; this is one of the factors contributing to the association of the disease with HIV, which still mostly affects young adults[9]. In 2000, the Ministry of Health added to the VL report form a field to indicate HIV infection, which allowed identification of 211 cases of coinfection between January 2000 and September 2004: The prevalence of coinfection was greatest in individuals aged 20-59 years (72%) and among men (69.2%). Other studies have also noted that the majority of coinfections occur in the age group 18-50 years (average age, 38 years) and among men[1,9]. The present study confirms these findings: most cases of coinfection occurred in the age group 18-50 years (88.5%) and among men (80.8%).

The clinical manifestations of coinfected patients do not differ significantly from those of patients diagnosed with VL only. Typical manifestations are fever (80% and 87%, respectively), weight loss (70% and 90%, respectively), hepatomegaly (34%

TABLE 1

Sociodemographic characteristics of the sample of VL and VL/HIV cases reported between 2009 and 2014 in Araguaína, State of Tocantins, Brazil.

Characteristics	VL (n=447)	VL+HIV (n=26)
	n(%)	n(%)
Age group (years)		
0 to 10	235(52.5)	0(0.0)
11 to 17	40(8.9)	0(0.0)
18 to 50	140(31.3)	23(88.4)
> 50	32(7.1)	3(11.5)
Sex		
male	269(60.1)	21(80.7)
female	178(39.8)	5(19.2)
Race		
white	58(12.9)	2(7.6)
brown	382(85.4)	24(92.3)
black	4(0.8)	0(0.0)
indian	1(0.2)	0(0.0)
unknown	2(0.4)	0(0.0)
Marital status		
child	231(51.6)	0(0.0)
married/stable relationship	60(13.4)	7(26.9)
divorced	3(0.6)	3(11.5)
single	135(30.2)	16(61.5)
widowed	7(1.5)	0(0.0)
unknown	11(2.4)	0(0.0)
Level of education		
illiterate	18(4.0)	1(3.8)
Preschool	231(51.6)	0(0.0)
elementary, incomplete	96(21.4)	10(38.4)
elementary, complete	12(2.6)	2(7.6)
high school, incomplete	27(6.0)	3(11.5)
high school, complete	26(5.8)	2(7.6)
higher education, incomplete	1(0.2)	1(3.8)
higher education, complete	3(0.6)	3(11.5)
unknown	33(7.3)	4(15.3)
Place of residence		
rural	51(11.4)	3(11.5)
urban	394(88.1)	23(88.4)
unknown	2(0.4)	0(0.0)
Occupation		
child	231(51.6)	0(0.0)
student	39(8.7)	0(0.0)
employee/self-employed	146(32.6)	21(80.7)
retired	10(2.2)	1(3.8)
housewife	14(3.1)	3(11.5)
unknown	7(1.5)	1(3.8)

VL: visceral leishmaniasis; **HIV/VL**: human immunodeficiency virus/visceral leishmaniasis coinfection.

TABLE 2

Symptomatology of reported cases of VL and VL/HIV between 2009 and 2014 in Araguaína, State of Tocantins, Brazil.

	VL (*n*=447)	VL+HIV (*n*=26)	
Symptom	n(%)	n(%)	*p*-value
Fever	437(97.7)	24(92.3)	0.137* **
Physical weakness	180(40.2)	16(61.5)	0.032* **
Swelling	20(4.4)	2(7.6)	0.344* **
Weight loss	175(39.1)	16(61.5)	0.024* **
Cough and/or diarrhea	150(33.5)	11(42.3)	0.360* **
Pallor	193(43.1)	3(11.5)	0.001* **
Enlarged spleen	307(68.6)	16(61.5)	0.447* **
Enlarged liver	249(55.7)	14(53.8)	0.853* **
Jaundice	34(7.6)	1(3.8)	0.410* **

VL: visceral leishmaniasis; **HIV/VL**: human immunodeficiency virus/visceral leishmaniasis coinfection. *Fisher's exact test. **Chi-square test.

TABLE 3

Initial therapy and prognosis of VL and VL/HIV cases reported between 2009 and 2014 in Araguaína, State of Tocantins, Brazil.

	VL (*n*=447)	VL/HIV (*n*= 26)	*P*
	n(%)	n(%)	
Initial therapy			
amphotericin B deoxycholate	97(21.7)	14(53.8)	<0.001
liposomal amphotericin B	37(8.2)	9(34.6)	<0.001
glucantime	293(65.5)	2(7.6)	<0.001
pentamidine	2(0.4)	0(0.0)	0.893
unknown	18(4.0)	1(3.8)	-
Evolution			
cure	254(56.8)	4(15.3)	<0.001
recurrence	26(5.8)	9(34.6)	<0.001
death by VL	10(2.2)	7(26.9)	<0.001
death by other causes	3(0.6)	4(15.3)	-
transfer/no monitoring	146(32.6)	5(19.2)	-

VL: visceral leishmaniasis; **HIV/VL**: human immunodeficiency virus/visceral leishmaniasis coinfection.

and 85%, respectively), and splenomegaly (59% and 90%, respectively), although some specific differences have been noted in coinfected patients: minor hepatosplenomegaly, fever, and splenomegaly occur less frequently, and acute gastrointestinal symptoms occur more frequently[11]. In the present study, some differences were observed in the presenting symptoms: Physical weakness and weight loss were more common in patients with VL/HIV coinfection than in patients with VL only; however, this is a consumptive condition that may be confused with symptoms of HIV-infection/AIDS.

As of 2011, there was no consensus regarding the treatment of patients with VL/HIV coinfection; they received the same treatment as patients with VL only, with pentavalent antimonials being the preferred drugs[6,12]. In subsequent years, some studies showed better results with the amphotericin B than with pentavalent antimonials. This led the Ministry of Health to change the preferred drug from a pentavalent antimonial to amphotericin B deoxycholate in 2011, and then to liposomal amphotericin B in 2015[13]. Long-term cohort studies have shown high recurrence rates of VL in patients coinfected with HIV,

even with the use of liposomal amphotericin B[14,15]. The present study also showed high rates of recurrence and death, both in patients treated with amphotericin B deoxycholate and those treated with liposomal amphotericin B.

Mortality is reported to be significantly higher in coinfected patients than in patients with VL only[14]. This was also shown in the present study, in which 26.9% of coinfected patients and 2.2% of patients without coinfection died. Many studies have shown that low levels of CD4+ T-lymphocytes at the time of VL diagnosis, absence of immune reconstitution after treatment, and previous recurrence are associated with increased rates of recurrence and death. Recurrence functions as an indicator of poor prognosis, and some authors believe that the chance (risk) of dying from VL is eight times higher in patients with recurrence than in HIV-infected individuals who have undergone VL treatment before[14,15].

Therefore, it is worthwhile to draw the attention of healthcare professionals, especially those who work in areas where VL is endemic, to the occurrence of VL/HIV coinfection, considering the high number of cases as HIV spreads to small and medium-sized cities like Araguaína, Tocantins. The present study confirms the need to have all patients with suspected or confirmed VL tested for HIV; to include VL in the differential diagnosis of pathologies involving HIV-infected patients; and to implement secondary prophylaxis in patients who have had VL, to prevent recurrence and poor prognosis.

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Conflict of interest

The authors declare that there is no conflict of interest.

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