

Review Article

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Visceral leishmaniasis in the New World & Africa

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Visceral leishmaniasis in the New World, primarily found in northeastern Brazil, is caused by *Leishmania chagasi*. Compared to India, unusual features of Brazilian disease are the large number of asymptomatic infections versus symptomatic infections, and the apparent change from a zoonotic disease to a partially anthroponotic one. Visceral disease in Africa is caused by *L. donovani* as in India, but disease differs from that in India in being zoonotic rather than anthroponotic, and in the large numbers of patients who acquire post-kala-azar dermal leishmaniasis.

Key words Cure rate - HIV-co-infection - post-kala-azar dermal leishmaniasis - visceral leishmaniasis

Although visceral leishmaniasis (VL) is most prevalent on the Indian subcontinent, it is also an important medical problem in Brazil and in Africa. To briefly summarize some salient features of Indian VL, it is caused by *Leishmania donovani*; anthroponotic; present in all age groups; diagnosed by splenic aspirate or by rK 39 reactivity; increasingly resistant to standard antimonial therapy but very responsive to amphotericin B in all its formulations, miltefosine, and paromomycin; not frequently associated with HIV-co-infection; and infrequently disseminates in the form of post-kala-azar dermal leishmaniasis (PKDL). It is of interest to review these factors such as infective species, parasite reservoir, means of diagnosis, presentation, response to antimalarial chemotherapy, association with HIV-co-infection, and association with PKDL for Brazilian VL and African VL to note differences or similarities to Indian VL.

Visceral leishmaniasis in Brazil

Visceral leishmaniasis in Brazil is typically caused by *L. chagasi*, and was first reported by *E. Chagas* in 1936¹. It is to be noted that not all Brazilian VL is caused by *L. chagasi*. In one study in the state of Bahia, *L. amazonensis* was found in 11 of the 46 cases of visceral disease². Chagas' short report¹ gives a brief summary of the clinical presentation and appearance of the organisms in biopsy specimens, and mentions that 53 per cent of patients are under 6 yr of age. Since Chagas' description, further experience has established that the disease is most endemic in Northeast Brazil, where it is typically a disease of rural areas, particularly poor farming regions³. The rural reservoirs for *L. chagasi* are domestic dogs and wild foxes, and the vector is *Lutzomia longipalpis*.

More recently, peri-urban regions have been affected. In Natal on the Northeast Atlantic coast, disease was first seen on the outskirts of the city when urbanization was in progress, then disappeared as urbanization became completed^{3,4}. In Teresina the capital of Piauí State, and in São Luís the capital of Maranhão State, a large increase in the number of cases in poor peri-urban regions was seen in 1993-1994⁵.

Leishmania kDNA has been found in the blood of some residents of Teresina who were themselves asymptomatic but who lived in the households of patients with active VL⁶. It was unlikely that these were false-positive PCR results, since PCR was carefully performed and there is no chagasic disease or cutaneous leishmaniasis in Teresina which might lead to false-positive PCR reactions. No dogs lived in any of the four households, and it was previously known that sandflies could become infected with *Leishmania* by feeding on the skin of patients with active VL. Considering the data of their investigations and this other evidence, Costa *et al*⁶ hypothesized that humans may be a reservoir for leishmaniasis at least in peri-urban regions.

For all of Brazil, there are 3000-5000 cases per year, with about 4000 cases in recent years. The disease is predominately paediatric. In Natal, the median age of acquisition of disease is 4 yr and, in remarkable concordance with Chagas' observations 70 yr ago, 56 per cent of VL cases were in children aged 5 yr and less³. In Brazil, the parasitological diagnosis is typically made by visualizing the parasites in bone marrow aspirates (not in splenic aspirates). However, ELISA and rK39 serological tests are also in use. Using bone-marrow positive patients as positive controls, both ELISA and rK39 are highly sensitive and specific. In 128 consecutive patients and in 60 persons with other diseases or no disease, the sensitivity and specificity of ELISA was 89 and 98 per cent, and the sensitivity and specificity of rK39 was 90 and 100 per cent respectively⁷.

The syndrome of asymptomatic infection with visceral *Leishmania* has been particularly studied in Jacobina, a city in Bahia State. In the early 1980s, approximately 2000 persons were surveyed. In this population, the median age of symptomatic VL was 3.2 yr and 78 per cent of VL cases were in children less than 5 yr⁸. In addition to patients with symptoms of VL confirmed by the presence of parasites in the bone

marrow, there were other children who had high levels of anti-leishmania antibodies as defined by ELISA values. In this ELISA test, the mean \pm SD was 0.02 ± 0.01 OD units. Values >0.05 OD units were therefore more than 3 SD above the mean. The number of children with sera giving OD values >0.05 was 6-to-18 times the number of children with confirmed VL. Thus by immunologic measures, the ratio of asymptomatic to symptomatic disease was greater than 6:1.

In another article published at the same time, 86 children with asymptomatic disease were further followed up for the next 5 yr⁹; 20 children with mean initial OD readings of 0.07 were completely asymptomatic except for minimal hepatomegaly or brief diarrhoea; 38 children (mean initial OD = 0.16) were subclinical with mild constitutional symptoms (malaise, diarrhoea, poor play tolerance) as well as intermittent hepatomegaly, 13 children (mean initial OD = 0.13) were initially subclinical but progressed to acute VL over 2-15 months, 15 children (mean initial OD = 0.20) progressed rapidly to acute VL in less than 2 months. Thus neither initial serology nor initial symptoms could distinguish children who remained subclinical and then self-healed from children who progressed slowly or rapidly to classic VL. However, measures of T-cell immunity had some correlation with progression to VL. Lymphocyte stimulation tests with *L. chagasi* antigen showed greater uptake of labeled thymidine in asymptomatic patients (25,286 counts) compared to subclinical patients (15,511 counts) and to children who progressed to VL (4,811 counts)¹⁰.

Other groups of initially asymptomatic patients have had extended follow up. In rural regions of Ceará State, 108 children seroconverted and were followed up for 3 and then 10 yr¹¹⁻¹³. Twelve children developed classic VL in the first 3 yr of observation, and no further patients developed VL in the next 7 yr¹³.

Classic treatment of Brazilian VL is with pentavalent antimony (glucantime). The cure rate is very high, at least 95 per cent. Only 16 of 941 patients (1.7%) treated in Teresina failed antimonials therapy¹⁴, although isolated failure rates of 5 per cent have also been reported¹⁵. Amphotericin B was used as second line therapy¹⁴.

There are several reports exploring the use of chemotherapeutic alternatives to glucantime and

amphotericin B. One alternative form of amphotericin B is amphotericin B cholesterol dispersion -ABCD. When administered at a dose of 2 mg (amphotericin B)/kg/day for 10 days or for 7 days, each of the 10 patients in the 2 cohorts cured¹⁶. When administered at the same daily dose for 5 days, all 10 patients initially responded but one patient relapsed, for a final cure rate of 90 per cent¹⁷. Although the cure rate for merely 1 wk of therapy is outstanding, side effects of fever, sometimes accompanied by increased respirations, were generally seen and required pre-medication with a non steroidal anti inflammatory drug (NSAID)¹⁶. Amphotericin B within liposomes -liposomal amphotericin B - was also studied in Brazil. Surprisingly, more drug was required to cure Brazilian VL than was required in India or in Kenya. In each country, a dose of 2 mg/kg/day was administered on days 1 to 6 and day 10. In Brazil, 8 of 13 cured without relapse (62%) whereas in both Kenya and India, 10 of 10 (100%) cured¹⁸.

The combination of interferon-gamma with glucantime was first reported from Brazil¹⁹. Eight patients who failed antimony alone ('refractory' cases) and 9 patients with previously untreated disease constituted the patient groups. The previous failures received interferon-gamma at a range of doses (from 35 µg/day for 10 days to 500 µg/day for 20 days) in combination with more antimony (20 µg/kg/day for 10 to 60 days). The naïve patients received a more narrow range of doses: interferon gamma from 35 µg/day for 10 days to 125 µg/day for 10 days, and glucantime for 10 to 20 days. Six of 8 patients in the first group, and 8 of 9 patients in the second group, cured¹⁹. In another report, among 22 patients, only 9 of 14 refractory cases and 7 of 8 naïve cases cured²⁰.

An oral treatment, WR 6026 (sitamaquine) for 28 days, has been studied in Brazil²¹. Dose of 1 mg/kg/day and 1.5 mg/kg/day were ineffective, and 2 mg/kg/day showed attractive efficacy. However, 2.5 mg/kg/day was both ineffective and caused kidney toxicity, and thus the drug was not further pursued.

HIV is well known in Brazil, with 260,000 cases being reported between 1980 and 2002²². One might think that there would be a large number of patients with combined HIV-*L. chagasi* infection. Interestingly, relatively few Brazilian cases have been

reported, even from regions where the overall incidences of HIV and *Leishmania* infection are both relatively high. By 2002, only about 90 cases of co-infection were reported, with 37 per cent being VL and the rest being cutaneous leishmaniasis (CL) or mucosal²².

PKDL: L. chagasi can be cultured from the skin of clinically normal patients, and rarely from a case of simple cutaneous disease². Classic PKDL due to *L. chagasi* seems not to have been seen in Brazil, although a few cases are stated to have been caused by *L. amazonensis* in association with visceral disease due to that organism².

Visceral leishmaniasis in Africa

The aetiologic agent of VL in Africa, as in India, is *L. donovani*. Yet there are several aspects of African disease worth commenting upon: the epidemic in Sudan, PKDL in Sudan, HIV disease in Ethiopia, and treatment studies in Kenya.

Sudan

Sudanese VL has been known since 1904 to be endemic along the Blue Nile where it enters Ethiopia and its tributaries²³. Beginning in 1988, large numbers of Nuer tribe members from the Bentiu area in the Upper Nile were recognized as being infected after migrating to other towns including Khartoum for treatment. Because Bentiu was not previously thought to be endemic for *L. donovani*, it was assumed that migration to and from endemic regions led to the Nuer infections²⁴. In addition to the classic features of kala-azar, unusual features seen in the epidemic in western Sudan were neurologic features such as peripheral neuropathy with foot drop and nerve deafness²⁵.

To better understand the disease in Sudan, a longitudinal study in the endemic region in Eastern Sudan was undertaken. Between 1991 and 1993, the village of Um-Salala with 1430 inhabitants was surveyed. In these two years, a total of 92 kala-azar cases were diagnosed, with mean age 6.6 yr, but many of these were retrospectively identified on the basis of clinical symptoms²⁶. There were 30 new cases, with mean age 8.6 yr, that were parasitologically confirmed in these two years. In comparison, there were 11 persons who converted both in terms of serology and skin test to *Leishmania* antigen, and

may be regarded as persons with subclinical infection²⁶.

Some of the most noteworthy clinical features of the Sudanese experience are the occurrence and natural history of post-kala-azar dermal leishmaniasis. In the small studies in Um-Salala, PKDL developed in about 60 per cent persons with kala-azar^{26,27}. From the total experience in the Sudan, the clinical definitions that proved useful are²⁸: Grade 1: scattered maculopapular or nodular rash, primarily on the face; Grade 2: dense maculopapular or nodular rash covering most of the face, and also on the chest/back/upper arms/legs, and more dense proximally than distally; and Grade 3: maculopapular or nodular rash covering most parts of the body, including hands and feet, and lip and palate. Crusting, ulceration, and scaling lesions may be seen.

In spite of the name, PKDL can begin almost simultaneously with kala-azar, and the interval between kala-azar and PKDL was 0.5 to 13 months²⁹ among 134 patients in eastern Sudan. With this time interval, the mean age of acquisition of PKDL is of necessity close to the mean age of acquisition of kala-azar itself. The shorter the interval between VL and PKDL, the more severe the cutaneous symptoms. For example, with an interval of 2 to 8 wk, 23 of 81 patients (28%) had grade 3 disease, but with an interval of 9-18 wk, 6 of 42 patients (14%) had grade 3 disease. Self healing was the rule in Sudan. Of the 134 cases, 113 (84%) healed spontaneously, apparently within 12 months, and there was no correlation of spontaneous healing with severity grade. Treatment is recommended for patients who do not heal within 1 yr, or for patients who initially present with mucosal lesions. Stibogluconate at 20 mg/kg/day is recommended, but 30 days appears not to be sufficiently long²⁸.

Given the large numbers of patients in the Sudanese epidemic, several treatment trials for VL have been performed under field conditions^{30,31}. In one study³⁰, patients were randomized between stibogluconate at 20 mg/kg/day for 30 days, or stibogluconate (20 mg/kg/day) in combination with aminosidine (15 mg/kg/day) for 17 days. The treatments were comparable in that 5 of 67 died in the stibogluconate group and 3 of 67 died in the

stibogluconate-plus-aminosidine group. In a larger stibogluconate experience summarized in a later report³¹, the death rate was 336 of 3076 (11%).

Ethiopia

Ethiopia has sizeable numbers of patients co-infected with HIV and *L. donovani*. A study of branded vs generic sodium stibogluconate offers an opportunity to recognize the differential response of these two patient populations to treatment, as well as a comparison of the response to branded vs generic drug³². Approximately 200 kala-azar patients were randomized between the two formulations of stibogluconate. The dose was 20 mg/kg/day, with no upper limit on daily dose, intramuscularly for 30 days. Mean entrance characteristics were spleen size of approximately 10 cm below the left costal margin and haemoglobin values of approximately 7.2 g/dl. In terms of outcomes, the final cure rate for generic stibogluconate was 74 per cent, higher but not significantly higher than the final cure rate for branded stibogluconate 62 per cent. However, the cure rate for HIV positive patients was 44 per cent, a value significantly lower than the value for HIV negative patients 92 per cent. The main reason for this difference was that nine HIV positive patients died during treatment, compared to only four HIV negative patients.

It is of interest that general comparability of this generic stibogluconate to branded stibogluconate was also seen in two other African studies. In Kenya, the comparative cure rates were 83 per cent for generic stibogluconate and 96 per cent for branded stibogluconate³³. In Sudan, the cure rates were 96 per cent for generic stibogluconate vs 91 per cent for branded stibogluconate³⁴. Thus the comparability of one Indian formulation of stibogluconate to branded stibogluconate, first shown by Sundar *et al* in India, was well confirmed in several large studies in Africa.

Kenya

Visceral leishmaniasis has long been studied at the Kenyan Medical Research Center in Nairobi. Although the volume of VL in Kenya is not large, initial advances with many of present chemotherapeutic agents were made at the Kenyan Medical Research Center and are worth reviewing here.

Pentavalent antimony: The presently recommended daily dose is 20 mg/kg/day. A crucial study showing that 20 mg/kg/day was more effective than 10 mg/kg/day was reported by Anabwani *et al* from Kenya³⁵. Patients were either children or adults, administered 20 mg/kg/day or 10 mg/kg/day for a maximum of 4 wk. The difference between the cured rate in children administered 20 mg/kg/day (100%) and children administered 10 mg/kg/day (60%) was one of the driving forces leading to the presently recommended daily dose.

Aminosidine (paromomycin): The first clinical efficacy trial of paromomycin for VL was performed by Chungue *et al* at the Kabernet District Hospital in Kenya³⁶. In the 19 evaluable patients administered aminosidine (~15 mg/kg/day for a maximum of 20 days), 15 cured (79%). Although this cure rate is not high, only 6 of 11 (54%) patients administered standard antimony cured by the same criteria.

WR 6026: The first clinical efficacy study with this oral agent was performed in Kenya³⁷. Eight patients received 1 mg/kg/day for 4 wk; 4 were cured, and the other 4 showed 1 - 2 log declines in the number of parasites. This response was much more impressive than the response in Brazil (0 of 4 cured)³⁷ with the same dose.

Conclusion

Visceral leishmaniasis in the New World and Africa differs from that in India in certain ways. VL in Brazil is due to *L. chagasi*, and classically is a rural zoonotic disease although now peri-urban presumably anthroponotic disease is being seen. An interesting feature is the large predominance of asymptomatic or paucisymptomatic patients compared to those who progress to VL itself. Brazilian VL is still very sensitive to antimonial treatment. The epidemic of VL in Sudan has led to a large number of investigations, and in the course of these it was recognized that PKDL in Sudan was very different from PKDL in India. In spite of the infecting species being the same, *L. donovani*, PKDL in Sudan occurs in approximately half of VL cases, can be almost contemporary with the visceral infection, and generally does not need to be treated because it self-cures within a year. All these features are different from what is described for Indian PKDL. In Africa, VL remains sensitive to antimonials, except in the case of patients co-infected with HIV as seen in Ethiopia.

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