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Visceral Leishmaniasis in Children: A Neglected Clinical Entity in Guatemala

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ABSTRACT

Introduction: *Leishmaniasis comprises a group of diseases caused by strict intracellular and unicellular eukaryotic protozoa belonging to the genus Leishmania sp. Clinical syndromes ranging from self-limiting skin ulcers to fatal visceral diseases have also been described.*

Methods: *We describe the clinical, epidemiological, and laboratory characteristics of six children with visceral leishmaniasis evaluated and treated at Roosevelt Hospital, Guatemala City, Guatemala, between 2017-2022.*

Results: *The mean age was 20.8 months. Fever was present in of the 5/6 cases at the time of diagnosis. All patients presented hepatosplenomegaly and hematologic alterations such as leukopenia, anemia, and thrombocytopenia. Diagnostic confirmation was performed in 5/6 patients through direct visualization of amastigotes in the bone marrow, 3/6 by polymerase chain reaction, and 2/6 by detection of rk39 antigen. A total of five patients received treatment with liposomal amphotericin B; only one case was treated with an antimonial, which failed; thus, treatment with liposomal amphotericin B was required. Resolution of hematologic alterations and decrease in splenomegaly were evident in all cases.*

Conclusion: *Guatemala is an endemic country for leishmaniasis in all forms, but visceral leishmaniasis (VL) is rare. The classic presentation of VL in children is fever, hematological changes, and organomegaly. The disease should be considered in children with manifestations originating from endemic countries. A liposomal amphotericin B regimen is currently the recommended treatment.*

Keywords

Visceral, Leishmaniasis, Pediatrics, Children.

Introduction

Leishmaniasis comprises a complex group of diseases caused by protozoa belonging to the genus *Leishmania* sp. They mainly invade the reticuloendothelial system and the bone marrow. Clinical syndromes ranging from self-limiting skin ulcers to fatal visceral diseases have also been described. These are grouped as cutaneous leishmaniasis, mucocutaneous leishmaniasis and visceral leishmaniasis [1]. Visceral leishmaniasis (VL), also known as Kala- azar (Black Fever in Hindi), is a disease caused mainly by two related species: The *Leishmania donovani* complex, which includes *L. donovani and L. infantum (*Synonym *L. chagasi).*

Phlebotomine sand flies of the genus *Lutzomyia* are the main vectors of this disease. Two evolutionary forms of the parasite have been described: amastigotes and metacyclic promastigotes, the latter being the infective form of the vector's biting apparatus [2].

In 2020, the WHO reported nearly 13,000 VL cases [1] Among tropical diseases, leishmaniasis ranks second in mortality; thus, it is considered one of the most neglected diseases, given its strong association with poverty, poor nutritional status, age <5 years, HIV coinfection, and host immunologic factors (Global leishmaniasis surveillance: 2019-2020, a baseline for the 2030 roadmap, 2021) [3].

Children living in the impoverished regions of Central America are at an increased risk of acquiring leishmaniasis. Especially in Guatemala where some regions are populated by mainly Mayan communities, with high levels of poverty and primarily subsistence farming which appear to be highest risk factors for the development of the disease [4]. Cutaneous leishmaniasis (CL) is the most common manifestation of this infection [5]. It is estimated that three million people are at risk of contracting CL in Guatemala [6]. Most cases occur in the northern regions of the country as occupational hazards.

On rare occasions, VL can be caused by species usually associated with cutaneous forms, such as *L. mexicana and L. tropica* [7]. Guatemala, a tropical country located in Central America, is considered endemic for leishmaniasis; however, VL is rare [8].

Here, we describe six pediatric cases of VL acquired in Guatemala. Clinical presentations were similar in their presentation, so we describe one patient to illustrate the main clinical features of children with VL. In addition, a table (Table 1) summarizes key clinical features of all children along with diagnostic test results, treatments and outcomes.

Illustrative Clinical Case

A 19-month-old male patient, originally from Chiquimula in east Guatemala (an endemic focus for VL). was referred to our hospital because of anemia, pallor, and a 10-day history of predominantly nocturnal fever associated with abdominal distension and pancytopenia. Upon physical examination, vital signs were within normal limits, and a grade III/VI systolic murmur was noted along with palpable cervical lymphadenopathies <0.5 cm in size with a palpable liver 5 cm below the right costal margin and palpable spleen 2 cm below the left costal margin.

HIV screening test results were negative. A peripheral blood smear revealed 20% blasts. A bone marrow aspirate/biopsy was performed because of suspected leukemia, but no leukemic cells were noted. A bone biopsy was performed, which revealed large cells suggestive of erythrocytes phagocytized by macrophages. Other tests included *Aspergillus* galactomannan assay, tuberculin skin test, and *Histoplasma capsulatum* antigen assay. All resulted negative.

Jaundice and hyperbilirubinemia were observed approximately 25 days post-admission. Leptospirosis was suspected, but the assay results were negative. Studies on storage disorders were negative. Absolute neutropenia evolved, and abdominal distension increased. Paleness, respiratory distress, tachycardia, and fever, along with greater abdominal distension with a significantly enlarged spleen (Figure 1). A repeat bone marrow aspirate/biopsy revealed amastigotes (Figure 2). Visceral leishmaniasis was diagnosed, and liposomal amphotericin B treatment was initiated. The polymerase chain reaction was positive for *Leishmania spp*.

Table 1: Clinical Summary of Patients

Patient	Age (Months)	Gender	Clinical Features	HIV Status	Diagnostic Method	Treatment	Outcome	Comments
1	20	M	Fever, pancytopenia, hepatosplenomegaly	NEG	Amastigotes, bone marrow (**Figure 2**)	LAB	Survived	Hospital stay complicated by sepsis due to *Escherichia coli* and perianal abscess
2	8	M		NEG	PCR	LAB	Survived	
3	13	F		NEG	Amastigotes, bonemarrow, PCR	Glucantime: No response. Retreated with LAB	Survived	Protein-caloric malnutrition, chronic diarrhea
4	51	M		NEG	Suspected. No laboratory confirmation	LAB	Survived	Diagnosis based on clinical features and place of residence
5	24	M		NEG	Detection rk39 antigen	LAB	Survived	Moderate malnutrition
6	19	M		NEG	Amastigotesbone marrow, PCR	LAB	Survived	Hyperbilirubinemia, hypergammaglobulinemia

LAB: Liposomal amphotericin B Gender: M, male. F, female NEG: Negative.

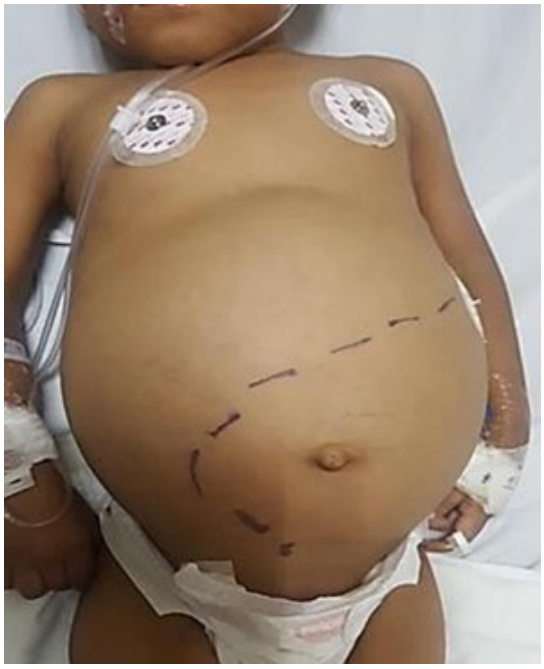

Figure 1: Significant organomegaly.

Clinical improvement and resolution of fever were observed on day 11 of the treatment. By Day 21, pancytopenia had resolved, and the spleen had decreased in size.

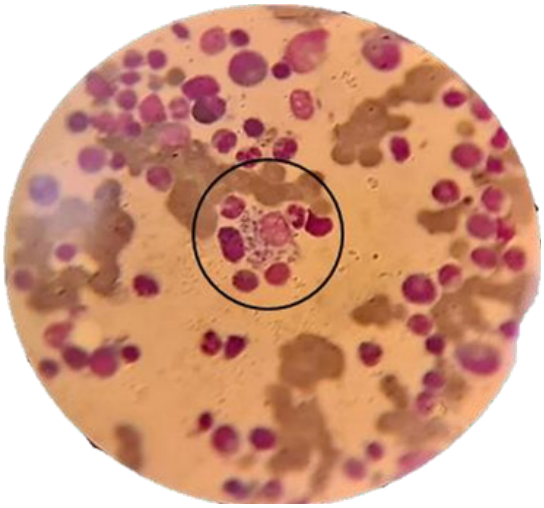

Figure 2: Stain used for bone marrow exam and magnification.

Discussion

Guatemala is a tropical country in Central America. It is considered endemic for leishmaniasis, and its cutaneous form is the most frequent presentation [9]. In 2016, a total of 770 cases of leishmaniasis were reported, of which only one was visceral [9]. It is an occupational disease that mainly affects men aged 15 to 44 years, who due to work-related reasons, access jungle areas where the vector is present, exposing themselves to the vector's bite. The majority of the exposed population lives in rural areas.

In our group of children, the mean age at presentation was 20.8 months, with a higher incidence in males. The predominance of infants can be explained by their immature immune systems. The principal clinical syndrome is fever associated with hepatomegaly and splenomegaly. In one case there was no fever at the time of diagnosis, and, referring to the literature, fever may be irregular or absent in exceptional cases [1]. Hepatomegaly and splenomegaly were present in 83.3% and 100% of cases respectively. In addition, all patients had anemia and thrombocytopenia requiring transfusion, and 83.3% had leukopenia. None of the patients required intensive care. Other secondary signs and symptoms include respiratory or gastrointestinal symptoms, such as vomiting and diarrhea. In severe cases, malnutrition and edema of the lower limbs may progress to anasarca. Other important signs include hemorrhage (gingival, epistaxis), petechiae, jaundice, and ascites. In these patients, death is usually caused by bacterial infection or bleeding [10]. Up to 50% of the subjects studied had some of these findings. None of the patients died. Clinical manifestations of VL caused by *Leishmania donovani and L. infantum/ chagasi* are usually indistinguishable [11]. These include constant or irregular fever, splenomegaly, hepatomegaly, lymphadenopathy, pallor, severe anemia, leukopenia, thrombocytopenia, and weight loss. Most of the patients were referred to our facility with a clinical suspicion of an oncologic or hemophagocytic syndrome. All the children were HIV-negative.

Diagnosis was confirmed mainly by direct observation of amastigotes in bone marrow smears. In patients 3, 5, and 6, in addition to bone marrow smears, diagnosis was confirmed through polymerase chain reaction and/or rk39 antigen. Molecular detection by PCR was also performed to identify the species, although this was performed for epidemiological purposes [12]. In patients with inconclusive results from histopathology, culture, and/or molecular tests, serological tests such as recombinant kinesin antigen (rk39) can be used, which is useful in ELISA with high sensitivity (92%) and specificity (96%) in immunocompetent patients. Serology was not performed for any of our patients [13].

Previously, antimonials were the drugs of choice for VL, but their longer treatment course requiring hospital stay, potential toxicity, and therapeutic failures have led to the use of liposomal amphotericin B, which can act on the lipid membrane of the protozoan, since its sterol composition is similar to that of fungi and, therefore, allows the formation of complexes with ergosterol precursors and the formation of pores that allow entry to ions and cell destruction. Liposomal amphotericin B was approved by the Food and Drug Administration in 1997 and is the treatment of choice according to the latest IDSA (Infectious Diseases Society of America) 2016 treatment guidelines [10]. Treatment decisions for VL do not require species identification. It can start even in cases without parasitological identification in patients with described clinical symptoms from endemic locations, especially in patients infected with HIV [14]. Therefore, all the patients received liposomal amphotericin B at a cumulative dose of 21 mg/kg. No adverse events were observed. No patient relapses were recorded

during follow-up. Patient 3 was the only patient who was initially treated with antimonial therapy, which resulted in therapeutic failure. When treatment with liposomal amphotericin B was administered, the symptoms resolved, and fever ceased after 72 hours. Response to treatment should be evaluated according to the patient's clinical parameters; in case of patients who do not respond to treatment, other drugs can be considered as an alternative treatment, the dose may be increased, or a longer course may be given [15]. In immunosuppressed patients, prolonged treatment is described with 10 total doses and a cumulative dose of 40 mg/kg [10].

On follow-up, all patients with VL had favorable outcomes, with recovery within 6 months. Fever was the first sign of resolution. Hematological abnormalities may take a few weeks to normalize.

Our case series had some limitations. While Roosevelt Hospital is a major referral center within Guatemala, our experience represents only patients seen at a single institution. It is not possible to precisely calculate the incidence of cases. One of our patients with a classical presentation suggestive of visceral leishmaniasis lacked laboratory confirmation but responded appropriately to therapy.

Conclusion

- Cutaneous leishmaniasis is the most frequently observed clinical form in Guatemala's northern region; however, cases of VL in children occur in the eastern and western areas of the country.
- Clinical suspicion in patients with hepatosplenomegaly residing in endemic areas should be high to avoid a delay in diagnosis. However pentavalent antimony is not recommended.

Ethical Compliance

All procedures performed were in accordance with the ethical standards of the institutional committee.

Author Contributions

All authors contributed to the design and implementation of the research, analysis of the results and to the writing of the manuscript. JJ conceived the original and supervised the project.

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