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Case Report

Visceral leishmaniasis in pregnant women from Rio Grande do Norte, Brazil: A case report and literature review

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Abstract

Visceral leishmaniasis (VL) in pregnant is considered rare. We present the case of a woman with 24 gestational weeks presenting fever, hepatosplenomegaly, pancytopenia, and inversion of albumin/globulin ratio. Anti-rK39 was positive and amastigotes were visualized on myelogram. Treatment with LAmB showed disease improvement. The newborn was born healthy at term, with delivery performed without complications. As VL in pregnancy can progress to death and complications for the mother-fetus binomial, inclusion of VL in the differential diagnosis of patients from endemic areas with compatible clinical picture is mandatory. Treatment with LAmB demonstrates safety and high cure rates in pregnancy.

Keywords: Visceral leishmaniasis. Pregnancy. Liposomal amphotericin B.

INTRODUCTION

Visceral leishmaniasis (VL), also known as kala-azar, is a cosmopolitan zoonosis that mainly affects developing countries. Caused by *Leishmania infantum* and transmitted by *Lutzomyia longipalpis* vector in the Americas, VL is considered endemic in Northeast Brazil. Classic symptoms, after an incubation period with a range from two to six months, are fever, asthenia, weight loss, hepatosplenomegaly, and pancytopenia, and without treatment it can evolve to death[1,2]. Although the transplacental transmission pathway rarely occurs and few reports are found in the literature, VL infection during pregnancy has been associated with congenital transmission and fetal death[1,3]. Therefore, the drug of choice for initial treatment of VL in pregnancy is liposomal amphotericin B, due to its safety profile for both mother and fetus[1].

In this report, we present a VL case in a pregnant woman, discussing the clinical presentation, diagnosis and treatment.

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CASE REPORT

An 18-year-old female patient from Patu (Rio Grande do Norte, Brazil), in her first pregnancy at 24 gestational weeks, reported a two month history of daily high fever, asthenia and headaches. She sought medical attention several times and was treated only with palliatives. She owned two dogs, one of which had recently died of VL. Anti-rK39+ was detected during investigation and therefore she was referred for treatment. On admission, the patient was in a regular general condition, hypoxic (2+/4+), acyanotic, anicteric and febrile (38°C). She presented a globular abdomen, with uterine height 20 cm above the pubic symphysis, and liver and spleen enlargement (6 and 8 cm, respectively), besides lower limb edema. Initial laboratory tests showed 1.91 million erythrocytes/dL, hemoglobin 5.7 g/dL, 3,400 leukocytes/mm^3 (60% neutrophils; 38% lymphocytes), and thrombocytopenia (135,000/mm^3), characterizing pancytopenia. In addition, other tests showed inversion of the albumin/globulin ratio (2.5 and 4.9 g/dL, respectively). Amastigote forms were found on examination of bone marrow aspirate. The patient received hemotherapy support to correct anemia and was treated with liposomal amphotericin B (3 mg/kg/day for seven days), presenting significant clinical and laboratorial improvement. She was discharged three days after the end of treatment and referred for clinical and obstetric

follow-up. The newborn was born healthy at term, with delivery performed without complications. Unfortunately, placental histopathological studies were not performed.

DISCUSSION

Visceral leishmaniasis is a worldwide zoonosis that mainly affects developing countries[4], with an annual incidence estimated at 50,000 to 90,000 cases[5]. VL is an endemic disease in Brazil (reaching the five regions of the country) with outbreaks being frequently reported since the disease is quickly expanding to large centers, presenting different geographic, climatic and social aspects[6]. The average lethality is about 6.9%, and VL is more frequent in children up to 10 years-old (41.9%) and in males (62.8%)[6].

Dogs are the main reservoirs of VL in Brazil and can remain asymptomatically infected or develop a debilitating disease evolving to death[2,4]. A great epidemiological link is established for the patient herein discussed, as she had close contact with infected dogs in an endemic area, with the vectorial route responsible for the transmission of *Leishmania*, due to regurgitation of promastigotes during feed[2]. However, in vertical transmission it may occur either transplacentally during pregnancy (in utero) or, most likely, during labor via blood exchange from the mother to the child[1]. In Italy, a series of five cases of pregnant women was identified, four of which primigravida[2]. All five delivered full terms infants, without complications. Twenty passive transmissions of anti-*Leishmania* antibodies were identified in the newborns, but after a six-month follow up they tested negative. Infants were followed up for 24 months after delivery and no abnormalities were detected, culminating in the hypothesis of vertical transmission of antibodies[7]. Another study describes a 29-year-old pregnant woman from Iran. Mother and fetus died and diagnosis was later confirmed. Necropsy confirmed the presence of numerous Leishman bodies in several tissues of the mother (including the placenta), but not in fetal tissues[8].

In normal pregnancies, changes in the immune response with decreased cellular immunity and a proportional increase in humoral immunity are expected. On the face of suppression of cell-mediated immune mechanisms, there is an increasing risk of infections by certain parasitic agents (such as *Leishmania*, whose specific immunity is dependent on the predominant cellular response). However, although the immunological evidence demonstrates that the risk of VL during pregnancy may be greater, no specific epidemiological data support this hypothesis[7].

Clinical manifestations of VL during pregnancy match with those observed in non-pregnant individuals. Classical manifestations of VL (such as fever, severe weight loss, asthenia, and hemorrhage) are present, and the later symptom is often confused with pregnancy-related hemorrhagic conditions[4]. Hepatosplenomegaly is another frequent finding. However, in pregnant women the detection of visceral enlargement can be compromised due to uterine growth[9]. In advanced stages, hypoalbuminemia can lead to edema and ascites, as well as to secondary infections[1]. In the case presented herein, there were both liver and spleen enlargement, in addition to prolonged fever.

The basis for establishing diagnosis of VL is the epidemiological data produced by laboratory tests. Hematological tests usually identify anemia, leucopenia, relative lymphocytosis, and thrombocytopenia. When comparing these alterations with those expected within the physiology of pregnancy, there is a synergism between anemia and thrombocytopenia, which are alterations already expected in a normal pregnant woman. However, while VL induces leucopenia, pregnancy shows a tendency to leukocytosis by increasing neutrophil granulocytes in a compensatory mechanism[10]. Another typical laboratory alteration present in VL is a strong inversion of the albumin/globulin ratio, which consists in an unexpected alteration in normal pregnancy since there is a decrease in cellular and humoral immunities, not justifying an increase in globulin production[10].

The gold standard for parasitological diagnosis of VL is the identification of amastigotes in splenic aspirate. In pregnancy, sternal bone marrow is preferred over others sites. Among the serological methods, the anti-rK39 immunochromatographic test shows good sensitivity and specificity, and can be used for early diagnosis of leishmaniasis. Yet, it is not suited as a tool to detect relapses or cure control, since it remains positive for months to years, even after effective treatment[2]. In the case being presented, the association of epidemiological data, clinical manifestations, compatible laboratory tests, and myelogram findings, established the diagnosis.

Treatment during pregnancy is intended to both treat the pregnant women and prevent transmission to the fetuses. Treatment is imperative and should not be postponed due to the risk of miscarriage, prematurity or fetal infection[7]. Liposomal amphotericin B (LAmB) is the drug of choice because of its higher safety profile and effectiveness when compared to pentavalent antimonials or amphotericin B deoxycholate, which presents a higher risk of nephrotoxicity. No case of vertical transmission of VL nor any abnormality in the fetus was reported after liposomal amphotericin B treatment[1,3]. However, pentavalent antimonials can cross the placental barrier and, in theory, cause mental retardation. The use of LAmB offers the additional advantage of a short-term treatment and provides a rapid improvement in clinical and laboratory parameters[7]. The main disadvantage of this drug is its high cost, which explains the preference for antimonials in developing countries, in spite of the secondary expenses related to prolonged hospitalization, emergence of resistance, therapeutic failures and adverse effects such as abortion and preterm labor in pregnant women. In a retrospective analysis Mueller et al. reviewed 39 cases of pregnant women suffering from VL in Eastern Sudan between 2004 and 2005, 23 of whom were treated with sodium stibogluconate, 12 with LAmB and 4 with both drugs. The most striking feature was that there were 13 (57%) spontaneous abortions in the sodium stibogluconate monotherapy group and none in the other two groups. All spontaneous abortions occurred in the first two quarters[1].

The criteria for cure are essentially clinical, with disappearance of the fever, gradual reduction of hepatosplenomegaly, improvement of hematological parameters and weight gain.

In this situation, parasitological control is dispensable. The resurgence of eosinophils is a sign of good prognosis. Serological tests have little use because they later become normal[11]. Follow-up should be made for 12 months after treatment, and the patient is considered cured if he remains clinically stable in this period.

The prevention and control of leishmaniasis require a combination of intervention strategies, since the transmission occurs in a complex biological system involving the human host, the parasite, the vector, and the reservoir[5]. Some measures of individual protection should be stimulated, such as the use of fine mesh on mosquito nets, the use of screens on doors and windows, and the use of repellents[11].

We are facing an endemic and neglected disease that, although rare in pregnancy, should be included in the differential diagnosis of all physicians who encounter women presenting signs and symptoms compatible with VL, especially prolonged fever in endemic areas. Thus, the recognition of signs and symptoms and early treatment are essential for survival and reduction of vertical transmission risk in pregnant women with VL. Currently, LAmB is the drug of choice for treatment due to its high cure rate and safety profile, but further studies and discussions are still needed in the scientific-academic scope, to better pathophysiologically elucidate VL and its effects in pregnancy.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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