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CASE REPORT

Hepatology

Visceral leishmaniasis as a rare cause of granulomatous hepatitis

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Abstract

Visceral leishmaniasis (VL) is a potentially fatal infection caused by species of Leishmania. It is characterized by fever, weight loss, anemia, and enlargement of the spleen and liver. Hepatitis due to VL is one of the causes of granulomatous hepatitis rarely described in the literature. It poses a problem of differential diagnosis with other causes, notably infectious and autoimmune. Hence the need for a global clinical, biological, and histological evaluation to orientate this entity, especially in endemic countries like ours. In the present case study, a 2-year 8-month-old boy was diagnosed with VL and treated with meglumine antimoniate; the evolution was marked after 2 months by the persistence of a large liver; laboratory results showed elevated liver functions and anemia. A liver biopsy was performed, and the histological findings confirmed the diagnosis of granulomatous hepatitis.

KEYWORDS

amphotericin B, endemic areas, hepatic cytolysis, leishmania serology

1 | INTRODUCTION

Hepatic granulomatosis (HG) is an anatomo-pathologic feature, rising as a response of the liver to the various antigenic, toxic, and infectious substances with an incidence ranged between 2% and 15%.[1,2] The most frequent etiology has been proved to be infectious, particularly tuberculosis, and sarcoidosis.[2,3] Leishmaniasis, one of the causes of HG, is an infectious disease caused by various strains of the protozoa which is transmitted to humans by sandflies in endemic areas.[4] This disease has been nationally notifiable in Morocco since 1995 and causes significant morbidity with the risk of seasonal epidemic outbreaks.[5] Through our case report, we describe the clinical, biological, histological, and therapeutic modalities of granulomatous hepatitis due to visceral leishmaniasis (VL) which is a rarely described entity in children.

2 | PRESENTATION OF CASE

A 2-year 8-month-old boy was referred to the pediatric gastroenterology department for persistent hepatosplenomegaly with significant hepatic cytolysis after an episode of VL treated with meglumine antimoniate for 30 days 2 months ago in another hospital.

A 2-year 8-month-old boy was referred to the pediatric gastroenterology department due to persistent hepatosplenomegaly and significant hepatic cytolysis following an episode of VL. He had received meglumine antimoniate treatment for 30 days at another hospital 2 months prior. Confirmation of the disease was obtained through a myelogram, which revealed the presence of Leishmania bodies. Additionally, initial cytolytic activity was noted before the commencement of treatment (AST: 650 IU/L, ALT: 730 IU/L). The patient hails from a hyperendemic area,

specifically the province of Tata in southeast Morocco. We did not note any malnutrition or prolonged use of corticosteroids.

Clinically, he had a large spleen palpated at 7 cm below the left costal, the median liver span was 18 cm. On the other hand, we did not notice any fever or general fatigue. Complete blood count revealed hemoglobin 10.7 gr/dL, mean corpuscular volume 84 fl, mean corpuslar hemoglobin picograms per cells, leukocyte 6440 mm^3, and platelet 153,000 mm^3. Other laboratory data was as follows: we noted a significant increase in aminotransferases (aspartate amino transferase [AST]: 839 U/l, alanine amino transferase [ALT]: 904 U/l), gamma-glutamyl transferase (GGT) 88 U/l, prothrombin time of 95%, total bilirubin 5 mg/dL, ammonium 50 µmol/L, albumin 3.9 g/dL. Given this clinical situation and the persistence of hepatic cytolysis, the possibility of leishmanial liver disease resistant to the initial antimony treatment was raised, leading to the decision to carry out a liver biopsy (Figure 1).

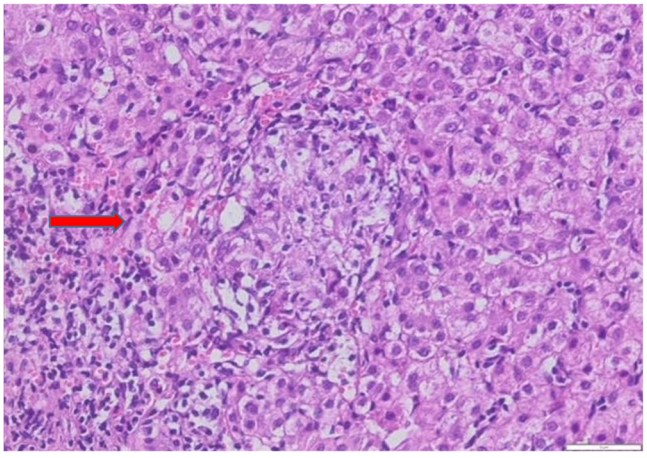

FIGURE 1 Epithelioid granuloma is formed bay aggregates of histiocytes, epithelioid cells admixed with variable inflammatory cells.

We observed elevated total protein levels (hyperproteinemia) at 81 g/l. Kidney function tests were normal, and HIV serology was negative. The rest of the biological assessment was strictly normal. Ultrasonography (us) of the abdomen showed an enlarged liver with regular contours, the spleen was enlarged and infiltrated with small diffuse hypoechoic lesions. Bone marrow aspiration was normal and leishmania serology, using the indirect immunofluorescence method, demonstrated a significant rise in antibody titers at 20.72 U. A liver biopsy was performed and reported an epithelioid granuloma which contains histiocyte cells (Figure 1).

Therapeutically, the child received treatment with liposomal amphotericin B at a dose of 3 mg/kg for 10 days. The progression was characterized by a reduction in the size of the spleen and liver, accompanied by a significant decrease in aminotransferases. The follow-up examination revealed an AST level of 62 IU/L and ALT of 64 IU/L 7 days after discontinuation of amphotericin B treatment (Figure 2).

3 | DISCUSSION

VL, also known as kala-azar, is fatal if left untreated in over 95% of cases. Most cases occur in Brazil, East Africa, and India. The World Health Organization estimates that 50,000–90,000 new cases of VL occur worldwide each year.[5]

Since 1995, Morocco has made reporting this disease mandatory, leading to a considerable impact on morbidity, including the risk of seasonal epidemic outbreaks. In the country, Leishmania infantum is responsible for both cutaneous and VL, particularly in the mountainous regions of Rif and pre-Rif, characterized by a humid and subhumid climate. Conversely, Leishmania tropica and Leishmania major contribute to cutaneous leishmaniasis, with the former prevalent in

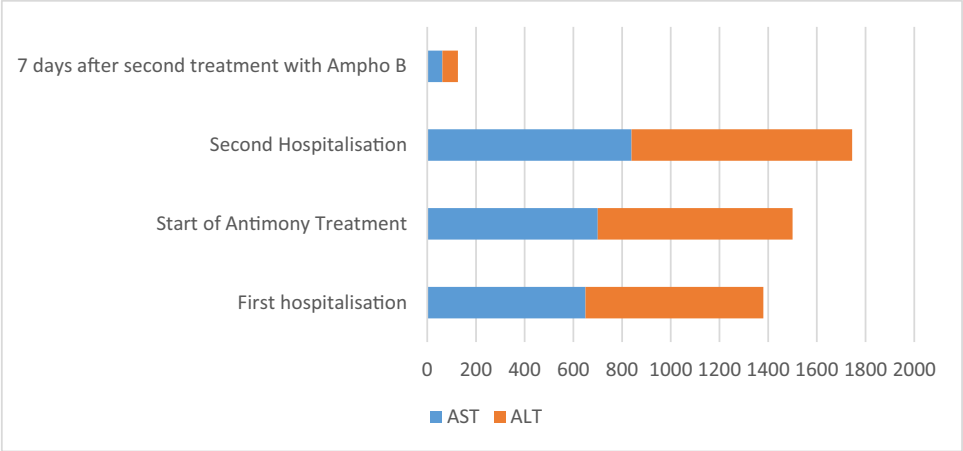

FIGURE 2 Evolution kinetics of transaminases. ALT, alanine amino transferase; AST, aspartate amino transferase.

the western slope of the Atlas range, featuring a semi-arid climate, and the latter in the southern and southeastern slope of the Atlas range, known for their arid climate. The period of activity of sandflies is mainly between May and September during spring and summer. Surveillance methods are therefore accentuated during these periods of high risk of infection. Between 2001 and 2020, nearly 2287 Moroccan children were affected by VL, nearly 98% of the total infected population, compared to 47 people over 15 years old. Of the 2124 children, 1890 are under 5 years of age. Children aged 0–5 years are the age group most affected by the disease, accounting for 81% of cases, followed by children aged 5–14 years, where there are 397 cases, or 17% of the infected population.[5]

The classic manifestations of VL include fever, splenomegaly, hepatomegaly, generalized lymphadenopathy, pallor, and weight loss. Other signs and symptoms include respiratory problems or gastrointestinal disturbances such as vomiting and diarrhea; in severe cases there is malnutrition and lower limb edema, which may progress to anasarca. Other important signs are bleeding from the nose or mouth, jaundice, and fluid buildup in the abdomen. In these patients, death is usually determined by bacterial infection or bleeding.[4,6] The clinical diagnosis of VL is difficult, because it has a similar presentation to common infections like typhoid fever, tuberculosis, brucellosis, and malaria as well as some hematologic malignancies.[4]

Diagnosis of the infection depends on identification of amastigotes in tissues. Serologic examination (enzyme immunoassay [EIA], direct agglutination, IFAT) is also useful in immunocompetent individuals.[7] Radiological investigations such as abdominal ultrasound sonography (US) and computed tomography (CT) may reveal enlargement of spleen and liver. Liver biopsy can demonstrate the Leishmania amastigotes inside the reticuloendothelial cells. Splenic tissue is rich in amastigotes allowing a rapid and sensitive diagnosis. Although spleen biopsy is a highly sensitive method for diagnosis, it is not widely used because of the risk of hemorrhage. In addition, infection of the bone marrow may be pronounced, usually resulting in anemia, leucopenia, and sometimes thrombocytopenia or even pancytopenia. The protozoon is isolated in bone marrow biopsy in 90% of the cases.[6]

Although it is known that granulomatous hepatitis can appear in the patients with VL, there have been a few reports about the combination of the VL and HG.[8] Liver enlargement (hepatomegaly) is a common symptom in VL patients; 30%–100% of parasitologically confirmed VL patients have liver enlargement in addition, the biochemical markers of hepatocellular damage, AST and ALT, are elevated in the blood of these patients. In addition, it has been reported that liver failure can be a direct cause of death in VL patients. As hepatomegaly is the most common finding in the liver of VL patients, elucidating the mechanism by which this occurs will be a good start to understanding the various influences that parasites have on the liver, including potentially portal hypertension and hepatocyte necrosis. However, there are currently a limited number of articles in the literature detailing histological changes in the liver of human patients, reporting Kupffer cell and hepatocyte hyperplasia or hepatocyte fat change.[9–11]

Although experimental models of VL are useful for studying protective responses to Leishmania infection, they have received less attention as a tool for studying the immunopathology of VL. Despite the fact that liver abnormalities are features of chronic disease in human VL patients,[12] much research has focused not on the experimental reproduction of these manifestations of chronic VL, but rather on granuloma-mediated protective immunity in the liver during the first 4–8 weeks of experimental infection.[13,14] It has been shown in mice that hepatic resistance to infection by *Leishmania donovani* is associated with the development of granulomas, in which various lymphoid and nonlymphoid populations accumulate. Although previous studies have identified B cells in liver granulomas and functional studies in B cell-deficient mice have suggested a role for B cells in the control of experimental VL, little is known about the behavior of B cells in the granuloma microenvironment.[15]

In our case, the diagnosis of HG was confirmed by histological analysis but was mainly guided by the patient's recently treated history of VL and also by an elevated serum aminotransferase level on admission exceeding 10 times normal.

The diagnostic difficulty of this entity lies in the elimination of differential diagnoses, in particular infectious and autoimmune aetiologias that can take the same clinical and biological picture. In our case, we were oriented towards the diagnosis of a liver damage due to VL, as the patient had been hospitalized 2 months earlier for LV treatment, but the evolution was marked by the persistence of a large liver and significant cytolysis.

There are different strategies for the treatment of VL depending on disease presentations, patient's age, geographic region, and systematic therapy side effects. Treatment with liposomal amphotericin B is less toxic, it is demonstrated that it is effective as first-choice treatment of VL caused by *Leishmania infantum* in children.[16] It has been used successfully to treat VL patients unresponsive to standard drugs.[4] It yielded very satisfactory results in our patient.

4 | CONCLUSION

VL is one of the infections that causes different abnormalities in every system, including intraabdominal solid organs. In the case of GH, as in our patient,

VL must be a part of differential diagnosis, especially in endemic regions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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