

REPORT

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Visceral Leishmaniasis with Hemophagocytic Syndrome in a patient infected by SARS-COV2: a case report

Letícia Vitória Lino Sousa¹, Gilnara Fontinelle Barros¹, Inggryd Eduarda Possidônio de Souza Santos², Ana Carolina Silva Rocha², Kamilly Ieda Silva Viegas²

¹Departamento de Clínica Médica, Hospital Universitário, Universidade Federal do Maranhão (UFMA) - São Luís (MA), Brazil

²Curso de Medicina, UFMA - São Luís (MA), Brazil

Corresponding author: Letícia Vitória Lino Sousa - Hospital Universitário, UFMA – Rua Barão de Itapari, 227 – Centro – CEP: 65020-070 - São Luís (MA), Brazil - E-mail: leticiavlsousa@gmail.com

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ABSTRACT

Introduction: Visceral leishmaniasis is a disease that determines a picture of immunosuppression in the patient after contact with infected sandflies. Secondary hemophagocytic syndrome, on the other hand, is an immune-mediated condition that develops after infections, neoplasms, or autoimmune diseases. COVID-19 has infected more than 130 million people and caused more than 2.6 million deaths worldwide. Immunosuppression triggered by COVID-19 can be an aggravating factor for latent infections. **Report:** This article reported the case of a patient, 37 years old, with a previous history of Severe Acute Respiratory Distress Syndrome due to SARS-COV-2, later diagnosed with Hemophagocytic Syndrome Secondary to Visceral Leishmaniasis. **Conclusion:** A SARS-CoV-2 pandemic has revealed cases of co-infection with visceral leishmaniasis, highlighting the need for case reports that contribute to the efficiency of diagnosing and treating patients with comorbidities, aiming for a favorable outcome in the clinical condition of the patients.

Keywords: Leishmaniasis, Visceral; Syndrome; COVID-19; Lymphohistiocytosis hemophagocytic; SARS-CoV-2; coinfection.

INTRODUCTION

Leishmaniasis has an incidence of between 0.7 and 1 million new cases per year. Brazil is one of the countries with the highest number of cases in the world, along with other subtropical countries, according to Wilhelm¹. The disease is transmitted to humans by female phlebotomines infected with protozoa of the genus *Leishmania* when they practice their hematophagous habits². Visceral leishmaniasis can be present clinically as fever, pancytopenia, lymph node enlargement, splenomegaly, or hepatomegaly. This clinical picture occurs after an incubation period of 2 to 6 months and mimics other infectious or malignant diseases³.

Secondary hemophagocytosis, on the other hand, is a rare pathological immune activation syndrome characterized by clinical signs and symptoms of extreme inflammation, which can be primary, of genetic origin, or secondary, caused by an underlying illness⁴.

The novel coronavirus pandemic has highlighted several weaknesses in the Brazilian health system, especially in the diagnosis and treatment of endemic and neglected diseases. It is known that the pathophysiology of Leishmaniasis and COVID-19 infection are distinct, but there are questions about immunosuppression after severe coronavirus infection, leading to dysregulation of the immune system⁵.

This study reports the case of a 37-year-old patient with a previous history of Severe Acute Respiratory Distress Syndrome due to SARS-CoV-2, later diagnosed with Hemophagocytic Syndrome Secondary to Visceral Leishmaniasis, clinically treated with a favorable outcome.

REPORT

MJCC, 37, female, with no history of comorbidities or use of continuous medication, was referred from the Intensive Care Unit of the Women's Hospital. She was diagnosed with COVID-19, confirmed by Polymerase Chain Reaction (PCR positive), in May 2021, and was

admitted to the Intensive Care Unit of a high-complexity hospital due to Severe Acute Respiratory Distress Syndrome.

Presenting a history of flu-like symptoms that began 14 days before hospitalization, MJCC had already used ceftriaxone and clarithromycin for 4 days, as well as Tazocin for 6 days. The patient required mechanical ventilation, was submitted to the pronation protocol, and was treated with broad-spectrum antibiotic therapy and vasoactive drugs.

The blood count showed the following results: hemoglobin (HB) of 10.30 g/dL, leukocyte count of 16,280, platelets of 193,000, urea of 35, creatinine of 1.27, sodium (Na) of 148, potassium (K) of 4.6 (Table 1). In addition, the following biochemical parameters were assessed: AST (aspartate aminotransferase) of 41, ALT (alanine aminotransferase) of 11, CRP (C-reactive protein) of 18.97, magnesium (Mg) of 2.2, CPK (creatinine phosphokinase) of 299, chlorides of 99, LDH (lactate dehydrogenase) of 1077, ionic calcium of 1.18, albumin of 4, D-dimer of 42,239.23. Analysis of the chest CT scan revealed visual impairment of over 75%. Arterial blood gas values were pH 7.38, Pco₂ 45, Po₂ 69, HCO₃ 25.6, LAC (lactate) 1.11, BE (base excess) 1.6 and F/F (fraction of inspired oxygen/fraction of expired oxygen) 230 (Table 2).

On the seventh day in the ICU, the patient presented edema and hyperemia in her left lower limb, and a Doppler ultrasound of the limb was performed, which showed deep vein thrombosis of the left femoral vein. Full anticoagulation with enoxaparin was started. The patient had no renal or hepatic dysfunction.

The patient was discharged from the intensive care unit after 25 days, using an O₂ catheter and on a weaning program. However, on the first day in the ward, the patient developed a fever, with no focus identified despite extensive propaedeutics and negative blood cultures. Complementary tests showed pancytopenia. The results of the blood count showed the following parameters: hemoglobin (HB) of 9.2 g/dL, hematocrit (HT) of 27.7%, mean

corpuscular volume (MCV) of 93.4 fL, mean corpuscular hemoglobin (MCH) of 30.9 pg, platelet count of 155,000, total leukocyte count of 5,000, with 3,065 neutrophils. In addition, creatinine values of 0.81 mg/dL, potassium (K) of 3.4 mEq/L, sodium (Na) of 132 mEq/L and an erythrocyte sedimentation rate (ESR) of 140 mm/h were recorded.

Complementary tests included a negative transthoracic echocardiogram for infective endocarditis, a BAAR test, and a negative Rapid Molecular Test for Tuberculosis (TRM-TB) for *M. Tuberculosis* and negative serology for the human immunodeficiency virus (HIV) (Table 3).

The patient remained feverish daily, and her general condition and pancytopenia worsened. Inflammatory tests were elevated with increased lactate dehydrogenase, hyperferritinemia, significant hypertriglyceridemia, and negative hemolysis tests. A rapid test for leishmaniasis was requested with a positive result and a myelogram showed hemophagocytosis in the bone marrow. The patient had no history of previous treatment for leishmaniasis. Treatment with liposomal amphotericin B was started for 10 days, with a good response. The patient was discharged from the hospital asymptomatic, with improved tests, and was referred to an outpatient follow-up.

This study was approved by the Research Ethics Committee (CEP) of the University Hospital of the Federal University of Maranhão (HU/UFMA) under Opinion 6.068.956 and CAAE: 66866223.1.0000.5086 by Resolution 466/2012 of the National Health Council.

DISCUSSION

The manifestations of visceral leishmaniasis can take many forms, including fever, pancytopenia, enlarged lymph nodes, splenomegaly, or hepatomegaly. It can also be present as lymphoma or infective endocarditis. This clinical picture usually develops after an incubation

period of 2 to 6 months. Due to this variety of presentations and the incubation period, visceral leishmaniasis can mimic other infectious or malignant diseases³.

The diagnosis of the visceral form of leishmaniasis can be made by PCR of peripheral blood or bone marrow, histopathology, isolation cultures, or molecular detection, the method of choice being the one available to the health team according to the study by Machelart et al.³. In addition, pentavalent antimoniate is the drug indicated as first-line treatment, although combinations can be used for management. Regardless of how the disease is approached if left untreated, it is potentially fatal, according to Aronson et al.⁶.

The potential interaction between visceral leishmaniasis (VL) and COVID-19 regarding possible immunological and epidemiological implications is not yet well established.

However, according to Carvalho et al.⁷, both infections require specific immune responses to control. The production of IFN- γ is crucial in the protective response against *Leishmania* and SARS-CoV-2. Polarization towards a Th1-type immune response is associated with the cure of cutaneous leishmaniasis (CL), while the Th2 response is linked to the progression of visceral leishmaniasis.

In a retrospective study by Bamorovat et al.⁸, it was suggested that patients with cured cutaneous leishmaniasis may have cross-protection against COVID-19. According to the authors, patients with a history of CL and the presence of a scar from the disease had a reduced incidence of morbidity and mortality from COVID-19. This observation raises the possibility that the immune response developed against one infection may confer some degree of protection against the other, but longitudinal studies must be conducted to validate this assumption. However, in the case of Visceral Leishmaniasis, the polarized immune response may make patients more susceptible to COVID-19⁹.

In the case report by Pikoulas et al.¹⁰, the authors hypothesize that COVID-19 may have triggered the reactivation of previously asymptomatic leishmaniasis in the case presented. The

immune response against SARS-CoV-2 involves a repolarization towards Th1, characterized by the production of IFN- γ , which is a critical component of the protective response against viral infections. However, more specialized studies are needed to understand the immunological mechanism behind these cascades.

This study is necessary since this scenario is in line with a broader pattern observed in several infectious diseases, where COVID-19 has been associated with the reactivation of chronic and latent infections caused by viruses such as VZV, EBV, CMV, HSV, HHV6, and HBV, as well as protozoa and fungi¹⁰.

On the other hand, hemophagocytic syndrome can be triggered by a variety of etiological agents, including viruses and protozoa. As described by Paul and Singh¹¹ in a case report recorded in 2020 in Iran, a child diagnosed with hemophagocytic syndrome due to COVID-19 was diagnosed with visceral leishmaniasis due to findings such as splenomegaly and pancytopenia. The authors point out that in a normal situation, the symptoms would have led to a clinical diagnosis of leishmaniasis. However, the presence of COVID-19 infection led to confusion.

Secondary hemophagocytosis is a disease that rarely affects immunocompetent people, so a previous diagnosis is mandatory for the establishment of the disease, which is usually neoplasia, autoimmune diseases, and infection⁴.

The hemophagocytic syndrome has no pathognomonic clinical picture, and its most typical findings are fever, hepatosplenomegaly, cytopenia, extremely high ferritin levels, and involvement of internal organs. Thus, clinical manifestations and laboratory characteristics are common between leishmaniasis and secondary hemophagocytosis, which makes it difficult to define the clinical pictures³.

The treatment of secondary hemophagocytic syndrome should take place regardless of the management of the previous condition. The use of immunomodulators and

immunosuppressants, cytostatics, T-cell antibodies, and cytokines aims to suppress hypercytokinemia and eliminate activated and infected cells¹².

Therefore, according to the study by Pereira et al.¹³, it is necessary to characterize the clinical picture, evolution, treatment, and sequelae resulting from SARS-CoV-2 co-infections and other endemic diseases to give continuity to the measures that have been adopted for decades in the control of neglected parasites.

In cases of co-infection of Leishmania and COVID-19, Miguel et al.¹⁴ and Carvalho et al.⁷, point out that COVID-19 may be aggravated due to ineffective immune control against viral infections in patients with visceral leishmaniasis¹⁵.

Conclusion

The SARS-COV-2 pandemic revealed cases of co-infection with visceral leishmaniasis, highlighting the need for case reports such as this one, which greatly contributes to the efficiency of diagnosis and treatment of patients with comorbidities since there was a response to the initial treatment and the patient evolved with a favorable outcome.

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Table 1: Admission laboratory tests

Parameter	Value
Hemoglobin (HB)	10.30 g/dL
Leukocytes	16.280
Platelets	193.000
Urea	35
Creatine	1.27
Sodium (Na)	148
Potassium (K)	4.6
AST (aspartate aminotransferase)	41
ALT (alanine aminotransferase)	11
CRP (C-reactive protein)	18.97
Magnesium (Mg)	2.2
CPK (creatine phosphokinase)	299
Chlorides	99
Lactate dehydrogenase (LDH)	1077
Ionic calcium	1.18
Albumin	4
D-dimer	42,239.23

Table 2: Complementary Examinations

Parameters	Value
Chest tomography	Commitment <75%
Arterial blood gas	
pH	7.38
PCO ₂ (Partial pressure of carbon dioxide)	45
PO ₂ (Partial pressure of oxygen)	69
HCO ₃ ⁻ (Bicarbonate)	25.6
Lactate (LAC)	1.11
Base Excess (BE)	1.6
F/F (Fraction of Inspired Oxygen/Fraction of Expired Oxygen)	230

Table 3: Complementary propaedeutics in the investigation of febrile conditions after discharge from the ICU.

Examination	Results
Transthoracic echocardiography	Negative for infective endocarditis
BAAR (Alcohol-Acid Resistant Bacillus) test and TRM-TB (Rapid Molecular Test for Tuberculosis)	Negative for M. Tuberculosis
HIV serology	Negative
Rapid test for leishmaniasis	Positive
Myelogram	Evidence of hemophagocytosis in bone marrow