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CASE REPORT

A case of Visceral leishmaniasis in a child on platelet recovery after treatment with filgrastim

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Abstract

Visceral leishmaniasis (VL) is a chronic systemic infectious disease caused by protozoa of the family Trypanosomatidae, genus Leishmania. Death is the outcome in more than 90% of the cases when the disease is left untreated. One of the characteristics of VL is the higher incidence of disease and death in younger children, due to the greater susceptibility to infection and immune disorder observed in this age group. VL is still a neglected disease, with high incidence and high mortality, which calls for substantial improvements in diagnosis and treatment, especially in the pediatric population. There are few drugs available for the treatment of VL. The first choice in Brazil is N-methyl-glucamine antimoniate, known for its toxicity and long treatment protocol. The second option is liposomal amphotericin B or amphotericin B deoxycholate, which produce fewer side effects, although they are prescribed to fewer patients. This report describes the case of a child with symptoms progressing for three months, in addition to pancytopenia, and liver failure, diagnosed and treated with liposomal amphotericin B. Since the patient remained with severe neutropenia, a therapeutic test with filgrastim was performed and led to good platelet recovery. Neutropenia is a characteristic sign of Leishmaniasis, which usually resolves rapidly once treatment has been initiated. Some patients remain with severe neutropenia, and further studies are needed to define the actual benefit of using granulocyte-colony stimulating factor in order to reduce the length of hospital stay.

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INTRODUCTION

Visceral leishmaniasis (VL) is a parasitic disease of great importance to public health worldwide. However, although relevant, it stands as the most neglected tropical disease[1]. Its estimated global incidence is 500,000 new cases and it causes over 50,000 deaths a year. VS is an omnipresent disease in Brazil[2]. It is a notifiable, endemic disease and frequent outbreaks have been reported[3].

Also known as kala-azar, VS is a chronic, infectious, non-contagious, systemic condition that, when left untreated, results in death in over 90% of the cases[3]. It is caused by protozoa of the family Trypanosomatidae, genus Leishmania, and transmission occurs via the bite of hematophagous female sandflies[4].

Infection can cause several clinical manifestations that vary according to the host's immune response. Most cases are asymptomatic or with moderate symptoms such as diarrhea, dry cough, adynamia, low-grade fever, sweating, and mild hepatosplenomegaly, and may or not progress to the classic form of the disease, which includes fever, hepatosplenomegaly with significant splenomegaly, weight loss, cough, diarrhea, pain, and abdominal distension. In its late phase, patients may develop edema and ascites[3,5,6,7].

Diagnosis is based on finding the parasite in the bone marrow, spleen, liver, or lymph nodes; serological tests; molecular biology tests; and polymerase chain reaction. When diagnosis based on laboratory tests is not possible, treatment is based on clinical and epidemiological findings[3,5,7].

The first choice of treatment in Brazil is N-methyl--glucamine antimoniate. The second option is liposomal amphotericin B or amphotericin B deoxycholate[7].

This report describes a case of VL in a pediatric patient diagnosed and treated at a Brazilian university hospital, and the off-label use of filgrastim to resolve severe neutropenia after treatment for VL. Further studies are needed to define precisely in which cases of the disease this medication may be beneficial.

CASE REPORT

Patient E.I.L.A., a female aged 8 years, born in Cacule-BA and residing in São José do Rio Preto-SP, was admitted to the emergency unit on July 14, 2020. The volume of her abdomen had been increasing for three months, and she presented with lethargy, choluria, and weight loss of 5kg during this time period. She did not have fever, vomiting, loss of appetite, or gastrointestinal symptoms. The patient moved from Cacule-BA to São José do Rio Preto-SP in January 2019 and lived in the urban areas of both townships. She reported the presence of several dogs in the neighborhood where she lived (no contact with them), one with an unknown disease.

Abdominal ultrasound examination performed in the emergency unit showed hepatomegaly (right lobe measuring 17.1 cm and left lobe 12.3 cm) and splenomegaly (longitudinal length 20.5cm), portal vein ectasis, and a small amount of free fluid in the cavity. The patient had pancytopenia (hemoglobin 7.7; total leukocytes 1380 with 21% segmented neutrophils, platelets 94,000); AST 700; ALT 271; alkaline phosphatase 400; albumin 1.81; globulin 7.19; total bilirubin 1.75; direct bilirubin 1.62; a positive rapid test for leishmaniasis; and positive IgM and IgG serologies for leishmaniasis. Examination of bone marrow aspirate revealed Leishmania sp. amastigotes.

She was prescribed liposomal amphotericin B 4mg/kg/day for 5 days due to liver failure. After the end of treatment, she was still severely neutropenic (leukocytes 1180 with 10.2% segmented neutrophils). A therapeutic test with filgrastim 5 mcg/kg/day for 2 days was initiated. A complete blood count after the therapeutic test showed the patient was no longer neutropenic (hemoglobin 7.6; leukocytes 2500 with 40% segmented neutrophils; platelets 118,000). She was discharged the following day (07/23/2020) without fever, with pancytopenia and altered liver function, with no complications, and returned to outpatient care with the Infectious Diseases team.

DISCUSSION

Different species of the protozoan from the genus Leishmania may cause the disease. *Leishmania donovani* is the main pathogen linked to leishmaniasis in Africa and Asia, while *Leishmania infantum* (known as *Leishmania chagasi* in South America) plays the same role in Europe, North Africa, and Latin America[3]. At first, VL was described as a rural endemic disease. However, since the 1980s, cases have been reported in urban areas as well. It is currently described as a zoonosis that affects humans when they are involved in the parasite transmission cycle. The domestic dog is the main reservoir of the pathogen[1,8]. The sandfly Lutzomyia longipalpis is the vector of greater epidemiological importance in the study of VL[8].

Young children are at significantly higher risk when they contract the disease. Immunity develops with age, and the incidence of disease and death by VL in young children has been associated with the greater susceptibility to infection and poor immune status observed in individuals in this age group[7].

The strategies laid out by the Brazilian Ministry of Health to control the disease have not decreased the number of cases and deaths by VL. Between 2003 and 2012, the average annual number of cases was 3,565 and incidence was 1.9 per 100,000 inhabitants. In the same time period, average lethality was 6.9%[3]. From 1994 to 2002, the Brazilian Ministry of Health counted 48,455 cases, 66% in the Brazilian Northeast[9]. Untreated individuals, malnourished

children, persons with HIV infection and on immunosuppressive drugs are at risk of higher lethality[7].

A wide array of symptoms may occur with VL. Malnutrition is an extremely important factor, since it develops with disease progression. In oligosymptomatic cases involving fever associated with persistent cough, diarrhea for more than three weeks, and mild hepatosplenomegaly, diagnosis may be hampered due to confusion with other infectious processes[9]. The disease may develop insidiously or manifest abruptly with signs of severe involvement, as in our patient's case. The main immediate elements associated with patient death include infection, hemorrhage, severe anemia, young age, and malnutrition[7].

Regarding diagnostic laboratory tests, according to the World Health Organization (WHO), anemia occurs in 98% of the patients with VL in Brazil. This multifactorial condition may originate from bone marrow dysfunction, splenic sequestration, hemolysis, hemorrhage, and iron deficiency. Leukopenia and neutropenia occur due to hypersplenism, in addition to bone marrow hypoplasia or depression and hemophagocytosis. Signs of pancytopenia are completed with thrombocytopenia, a predictor of severe hemorrhage and one of the main causes of patient death[7].

Serological tests used for diagnosis include indirect immunofluorescence, direct agglutination, and ELISA test kits. Molecular biology, polymerase chain reaction, and rapid diagnostic tests are also used. However, diagnostic tests have different levels of sensitivity and specificity, and cost is an element that must be considered in clinical practice[3,5,7]. Microscopy is the gold standard due to high specificity. Amastigotes can be viewed in lymph node, bone marrow, and spleen tissue smears[10].

Few classes of drugs are available for treatment in Brazil. Pentavalent antimonials were introduced in the country in the late 1940s. Amphotericin B deoxycholate was introduced only in the 1980s, followed by lipid formulations such as liposomal amphotericin B, with high efficacy and low toxicity[11,12]. N-methyl-glucamine antimoniate is the treatment recommended by the WHO. Amphotericin B deoxycholate is used as second-line therapy. In cases of severe disease, it is the drug of choice. Finally, liposomal amphotericin B is used in patients with kidney or liver failure, sepsis, or severe comorbidities[9].

Although drug therapy saves a lot of lives, some patients may present resistance to medication and relapse after therapy, which leads to worse outcomes. In addition, patients with VL have a limited number of drugs available to them. There are only three treatment options, and although antimonials have significant toxicity; they have been the mainstay of treatment for decades[9].

Our patient had severe neutropenia even after treatment. Therefore, the medical team chose to start her on off-label filgrastim. Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) that acts on hematopoietic progenitor cells capable of forming neutrophils and stimulating their proliferation and differentiation.[10] The medication is used primarily in patients with transient bone marrow failure after chemotherapy[13]. It is also used in certain cases of neutropenia caused by severe congenital neutropenia, cyclic neutropenia, or AIDS. Filgrastim is not indicated for all types of neutropenia, since most resolve despite treatment[14]. In VL, filgrastim is indicated for patients with severe neutropenia, infectious complications, and no response to initial therapy[15]. There are no specific studies on the reduction of length of hospitalization for patients with severe neutropenia alone after treatment for VL. Treatment prescribed by our team successfully decreased the time for which the patient had severe neutropenia, which allowed her to be discharged as her condition stabilized.

Prompt diagnosis of VL is extremely important to reduce morbidity and mortality, which are still high in our country, especially among children. VL has been primarily neglected due to the scarcity of new drugs to treat patients with the disease. Further studies are needed to evaluate the benefits brought by filgrastim in reducing the length of hospitalization in patients with severe neutropenia after VL treatment and to assess the impact of decreases in patient morbidity upon the public healthcare system.

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