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The case of visceral leishmaniasis in a child with acute lymphoblastic leukemia

Kandaurava S.[1],Kishkurno E.[2], Osvetimskaya Y.[1], Ivanova M.[3], Anisko L.[4]
[1.] *Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk, Belarus*
[2.] *Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus*
[3.] *Belarusian State Medical University, Minsk, Belarus*
[4.] *City Children's Infectious Diseases Clinical Hospital, Minsk, Belarus*

Abstract
Leishmaniasis is a vector-borne protozoal disease caused by protozoa of the genus Leishmania. There are several clinical forms of this disease. The most severe is visceral leishmaniasis, especially in patients with immunodeficiencies. Without early treatmentvisceral leishmaniasis leads to death in 75 - 95% of cases. The clinical picture that immunosuppressed patients can often demonstrate resembles the course of visceral leishmaniasis, which can complicate and delay timely diagnosis and adequate therapeutic measures. This article reviews published data on the problem of leishmaniasis in immunocompromised patients. Also, this article reviews a clinical case of visceral leishmaniasis in a six-year-old patient with acute lymphoblastic leukemia. Treatment of the visceral leishmaniasis in this patient with the first-line therapy (with liposomal amphotericin B) resulted recovery, allowing the patient to undergo a successful stem cell transplant.
Key words: *visceral leishmaniasis, immunocompromised patients, amphotericin B, children.*

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I. Introduction

Leishmaniasis is a transmissible protozoal disease caused by protozoa of the genus *Leishmania.*

Microbiology

The carriers of *Leishmania* are female mosquitoes of the genera *Phlebotomus* (eastern hemisphere) and *Lutzomyia* (western hemisphere). To date, more than 20 species of *Leishmania* are known that can cause disease in humans. As obligate intracellular parasites, Leishmanias multiply in macrophages / monocytes, dendritic cells and neutrophils. There are three main clinical forms of leishmaniasis: cutaneous, mucocutaneous, and visceral. The first two forms are distinguished by local lesions of the skin and / or mucous membranes, while viscerotropic leishmanias (*Leishmania donovani, L. infantum / chagasi*) spread throughout the human body after inoculation, causing a generalized process - visceral leishmaniasis (VL) or kala-azar.

Epidemiology

A species commonly found in East Africa and the Indian subcontinent, *L. donovani*, and a species found in Europe and South America, *L. infantum / chagasi*. Visceral leishmaniasis is characterized by the severity of its course and, without timely treatment, leads to death in 75 - 95% of cases, while cases of spontaneous recovery have been proven [1, 2, 3].

Infection with these protozoa in most cases does not lead to the development of a clinically significant disease, especially in endemic areas, where seropositivity according to *L. donovani* ranges from 7 to 63% [4].

According to the WHO, about one billion people live in countries endemic for leishmaniasis; up to 30,000 cases of VL and up to 1,000,000 cases of CL are registered annually. In 2018, 98 countries and territories remained endemic for leishmaniasis, with over 90% of all global VL cases occurring in Brazil, Somalia, India, Ethiopia, Kenya, Sudan and South Sudan. As for imported VL, in 2018 140 cases were registered in non-endemic countries [5].

Pathogenesis

Leishmanias are able to avoid destruction after phagocytosis and, after transformation into flagellate forms - amastigotes, multiply intracellularly, which leads to the activation and death of macrophages. The organs richest in macrophages (liver and spleen) gradually increase in size, sometimes significantly. Amastigotes hematogenously enter the bone marrow, which leads to inhibition of hematopoiesis, anemia, leukopenia and thrombocytopenia, while increasing the susceptibility of patients to other infectious agents.

Clinical symptoms

The incubation period for VL lasts from 2 weeks to 8 months; in some cases, the clinical picture may appear several years after infection. Prolongation of the incubation period is typical for immunosuppressed patients [6, 7].

The clinical picture of VL is characterized by the following symptoms:

• fever of the wrong type;
• hepatosplenomegaly (the size of the spleen prevails over the size of the liver);
• loss of body weight with the formation of cachexia with the course of the disease;
• lymphadenopathy;
• pancytopenia;
• hypergammaglobulinemia;
• hyperpigmentation of the skin.

The clinical picture, which immunosuppressed patients can demonstrate, often, with its atypicality, resembles the course of VL, which can complicate and delay timely diagnosis and correct treatment [8].

The main clinical manifestations caused by *L. donovani* and *L. infantum* are usually indistinguishable, and specific methods are required to identify the species. However, treatment decisions for VL do not usually require species identification as they are based on disease severity, geographic origin and the presence of HIV, immunosuppression, and other co-infections. Among patients with severe immunosuppression, atypical disseminated forms with lesions of the hollow organs of the gastrointestinal tract, liver and lungs have been described [9, 10].

VL is most severe in patients with various immunodeficiencies, including HIV infection, malignant neoplasms, autoimmune diseases, hemoblastosis, and immunosuppression after solid organ transplantation or the use of various chemotherapy regimens, including monoclonal antibodies [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22].

Several cases of VL have been reported after hematopoietic stem cell transplantation [23, 24, 25, 26, 27,28].

The group of non-HIV-associated immunodeficiency states is currently attracting special attention. This group is heterogeneous in composition, but has a common feature - it is the loss of immunological control over latent or newly acquired leishmanias [8].

Diagnostics

The diagnosis of VL is based primarily on epidemic premises, especially in the diagnosis of imported cases of the disease. The doctor's knowledge of the regions endemic for leishmaniasis and of the low-specific clinical picture remains the main thing in the formulation of a presumptive diagnosis. An example is Pakistan, where VL occurs in the northeastern regions of the country and is mainly caused by *L. infantum* [29].

Laboratory confirmation of the diagnosis is based on the identification of Leishmania amastigotes in target cells by examining bone marrow aspirates or spleen punctates. Other diagnostic methods include obtaining a culture of Leishmania in the form of promastigotes using special media, polymerase chain reaction to detect the DNA of the parasite, and serological tests to identify antibodies and antigens. It is advisable to use several diagnostic approaches to increase the likelihood of obtaining a positive result [30].

Treatment and prophylaxis

Treatment of visceral leishmaniasisis carried out with drugs that have antileishmanic activity. Clinical experience in the selection of drugs for the treatment of immunosuppressed and VL patients is fragmented and based on individual clinical cases or case groups.

According to current recommendations, liposomal amphotericin B in a total course dose of 40 mg / kg is the drug of choice for the treatment of VL in recipients of solid organs, patients with malignant neoplasms or other forms of immunosuppression [31,32].

Whenever possible, doses of immunosuppressive drugs are recommended to be reduced in patients with VL during antiparasitic therapy [33].

Alternatively, amphotericin B deoxycholate, pentavalent antimony drugs and miltefosine are used [34,10]. Common amphotericin B deoxycholate is highly antileishmanic but nephrotoxic. Monotherapy with pentavalent antimony drugs (sodium stibogluconate) is no longer a first-line treatment for VL when other less toxic drugs are available. Miltefosine was approved for use in adults by the US Food and Drug Administration (FDA) in March 2014. Pentamidineisetionate was previously a second-line agent, but has rarely been used due to suboptimal efficacy and toxicity (with a particular risk of irreversible insulin-dependent diabetes mellitus) [35].

Secondary prophylaxis is not required for the initial treatment of immunosuppressed patients who are not infected with HIV and who have not had a relapse. Patients with asymptomatic VL require close monitoring but do not require prophylactic treatment or primary prophylaxis.

The optimal secondary prophylaxis regimen has not been determined. Options include amphotericin B, sodium stibogluconate, and pentamidine. One randomized trial demonstrated a lower relapse rate within one year with intermittent administration of the lipid complex of amphotericin B (3 mg / kg every 21 days) compared with no prophylaxis (50% and 78%, respectively) [36]. Reduced relapse rates have also been observed in retrospective prophylaxis trials with monthly sodium stibogluconate (850 mg) or liposomal amphotericin B (200 to 350 mg) [22].

The largest clinical trial for secondary prevention included 74 patients with HIV-VL coinfection in Ethiopia on antiretroviral therapy (ART) who received monthly infusions of pentamidineisethionate (4 mg / kg). The probability of 12-month disease-free survival was 71% with prophylaxis, which compares favorably with historical controls [37].

We present our own clinical case of visceral leishmaniasis in a patient with hematological cancer (acute lymphoblastic leukemia).

Patient *Sh*., Age: 6 years, weight: 57 kg, a resident of Karachi (Pakistan). She was admitted to the Belarusian Research Center for Pediatric Oncology, Hematology and Immunology on January 2020 for the treatment of recurrence of acute lymphoblastic leukemia (ALL). Clinical diagnosis upon admission "Acute lymphoblastic leukemia. Relapse II. Morbid obesity, mixed genesis. Transient hypocorticism. Secondary hydrocephalus ".

From the anamnesis - she first fell ill with acute lymphoblastic leukemia in April 2016. In November 2019, she developed excessive appetite, weight gain (18 kg per month), joint pains, and a significant decrease in motor activity. In January 2020, magnetic resonance imaging of the brain (MRI GM) was performed, where non-occlusive hydrocephalus was detected. On January 17, based on the results of a study of bone marrow and cerebrospinal fluid punctures, a late combined (bone marrow + central nervous system) relapse of II leukemia was diagnosed. On January 17, 2020, a special treatment for the recurrence of leukemia (dexamethasone, vincristine, cytosar) was started. A week later, she was transferred to the intensive care unit (ICU) in a very serious condition with a diagnosis of "Sepsis. Septic shock ", where she received antibacterial and antifungal therapy (meropenem, vancomycin, colistin, amphotericin B). On February 1, 2020, she was transported to Belarus, to the Belarusian Research Center for Pediatric Oncology, Hematology and Immunology. Immediate admission to the ICU according to the severity of the condition, which was due to the underlying disease (ALL, relapse II), the state after chemotherapy, cytopenic syndrome (in the CBC: leukocytes (L) - $2x10^9$ / L, the absolute number of neutrophils (ANC) - $22x10^6$ / L, platelets (Tr) - $18x10^9$ / L), sepsis (clinically, without obtaining a positive blood culture), internal hydrocephalus, obesity of the 3-rd degree. On examination, attention was drawn to hepatosplenomegaly (liver +6 cm, spleen +4 cm from under the costal margin), persistent febrile fever. According to the results of CT-scan of the abdominal organs from March 2, 2020, the liver exited from under the edge of the costal arch by 6 cm, the structure was homogeneous during native scanning; the spleen came out from under the edge of the costal arch by 4 cm, its parenchyma was homogeneous, Fig. 1.

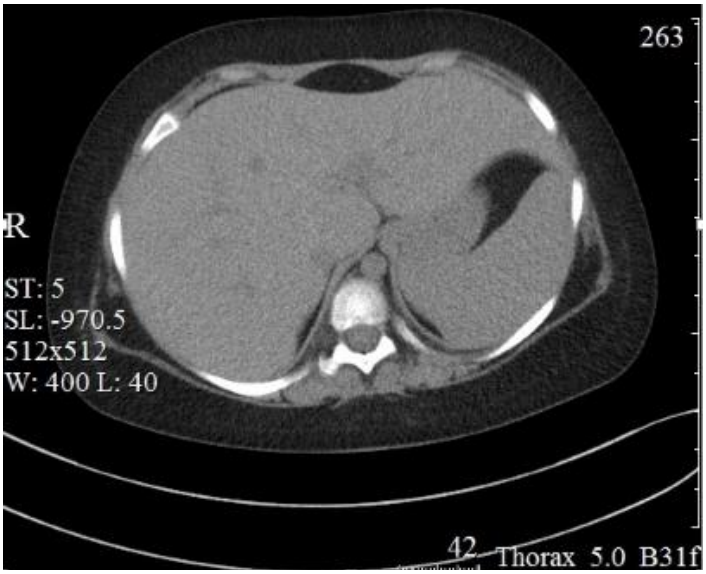

Fig. 1. – CT-scan of the abdominal organs from March 2, 2020

Antibacterial therapy (colistin, meropenem, linezolid) and empiric antifungal therapy with the lipid form of amphotericin B were continued. Due to the lack of laboratory confirmed data on the presence of a fungal infection, the lipid form of amphotericin B after 4 days of use was changed to voriconazole for the antifungal prophylaxis.

On February 3, 2020, a diagnostic bone marrow puncture was performed. According to myelogram data, leukemia remission was confirmed. The patient's condition remained grave with a slow deterioration due to the sluggish course of sepsis and the progression of multiple organ dysfunction. Hepatosplenomegaly persisted, periodically there was vomiting, growing in dynamics: icterus of the skin, signs of liver failure, acute renal injury, hemodynamic instability. In a blood test, there was an increase in total bilirubin up to 127 μmol / L due to the direct fraction, CRP up to 32 mg / dL, in a general blood test, a decrease in the L level to $0.2x10^9$ / L, thrombocytopenia. Microbiological studies of sterile (blood) and potentially sterile loci did not reveal the growth of pathogenic microorganisms. They had a negative result of the study of non-sterile loci in order to identify the carriage of multi-resistant flora. According to the ultrasound of the abdominal organs, the dynamics of the increase in the liver remained + 6-6.5 cm, spleen + 3.5 cm, kidneys + 3.5-4 cm; pronounced diffuse changes in the liver parenchyma (the structure is diffusely heterogeneous, without obvious foci; the walls of the hepatic vessels, bile ducts are compacted). According to liver elastometry, the result could correspond to the F2-3 stage of fibrosis on the METAVIR scale. A revision of antibacterial, antifungal therapy was carried out taking into account clinical and laboratory data and in order to reduce the nephro- and hepatotoxicity of drugs. On February 11, 2020, she was consulted by an infectious disease doctor, taking into account the history data (the patient lived in an area endemic for leishmaniasis), it was recommended to conduct a bone marrow study for leishmaniasis. Bone marrow smears from March 2, 2020 (as well as previously performed in Pakistan in January 2020) were sent for parasitoscopy to the Minsk City Center for Hygiene and Epidemiology; where amastigous forms of Leishmania were found, Fig. 2.

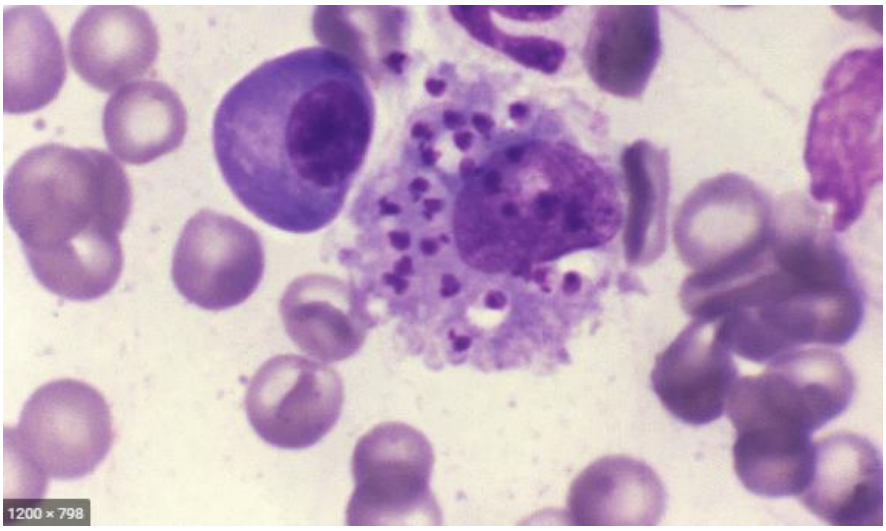

Fig. 2. –leishmaniasis in the bone marrow (amastigotes)

February 17, 2020, taking into account the presence of epidemic prerequisites in the patient (the patient is a citizen of Pakistan), the presence of a nonspecific symptom complex: prolonged intermittent fever, hepatosplenomegaly; and identification of amastigotes leishmanias in the bone marrow, the patient was diagnosed with "Visceral leishmaniasis". Treatment with the liposomal form of amphotericin B was prescribed in a course of 40 mg / kg, a daily dose of 4 mg / kg, the first 5 days of daily administration, and then on the 10th, 17th, 24th, 31st, 38th day (under control of glomerular filtration rate indicators every 3 days), then switching to maintenance therapy 1 time in 2 weeks at a dose of 4 mg / kg, and after achieving remission - 1 time in 4 weeks throughout the year (under the control of ultrasound of the heart, ECG, potassium level in the biochemical analysis of blood and kidney function).

Remission was achieved for acute leukemia. Chemotherapy was interrupted for the first month of treatment for visceral leishmaniasis.

On the background of the treatment, the patient's condition improved. There were no febrile rises in temperature. She had sufficient diuresis. Increased activity, no pain. Appetite appears. Decrease in the size of the liver and spleen (+4 cm and +3 cm, respectively). In a biochemical blood test, a gradual decrease in total bilirubin to 57 μmol / L. Recovery of hematological parameters (Tr $129x10^9$ / L, L $5.1x10^9$ / L).

Revision of bone marrow smears from February 24, 2020 (after a week of leishmaniasis therapy) at the Minsk City Center for Hygiene and Epidemiology did not find the causative agent of leishmaniasis in the delivered stained bone marrow smears. Antiparasitic treatment was continued.

According to the results of bone marrow puncture from May 6, 2020, the patient was noted to have molecular and morphological remission of the underlying disease. No amastigotes were found in bone marrow smears from May 6, 2020. She continued antileishmania treatment.

On June 17, 2020, the patient was rehospitalized for a planned examination. No amastigotes were found in bone marrow smears dated June 17, 2020. According to the results of bone marrow analysis, minimal residual disease is positive, an increase of 1 Log. The patient was diagnosed with molecular recurrence of acute leukemia and was treated with monoclonal antibodies (blinatumomab 28 days). For the period of therapy, the patient was transferred to a more frequent regimen of administration of the liposomal form of amphotericin B (once every 2 weeks) without interrupting the general course of therapy for leishmaniasis.

On August 14, 2020 the patient was diagnosed with a combined relapse of III (bone marrow and central nervous system) acute leukemia. The patient received an individualized anti-relapse treatment for leukemia recurrence, as well as secondary prophylaxis of VL with the liposomal form of amphotericin B with the introduction of the drug at a dose of 4 mg / kg / day 1 time per month. Despite the immunosuppressive therapy of the underlying disease, no VL recurrence was detected during the 7-month follow-up period.

On August 14, 2020 the patient underwent allogeneic related HLA-incompatible (haploidentical) stem cell transplantation. The conditioning regimen was carried out according to the protocol: total body irradiation (TBI), etoposide 60 mg per kg (the dose is calculated for the required body weight of the 50th centile - 31.6 kg according to the protocol). Total doses: total body irradiation of 12 Gy + 6 Gy to the central nervous system, vepeside 1900 mg. In the post-transplant period, she received therapy for concomitant diseases and complications of transplantation: left-sided lower lobe pneumonia on December 13, 2020, left-sided pleurisy; toxic cardiopathy; toxic nephropathy; morbid obesity of mixed genesis, complicated; hyperinsulinism; transient hypocorticism; secondary hydrocephalus. In terms of preventing GVHD, she received cyclophosphamide (day +3, +4), mycophenolatemofetil, and cyclosporine. On the 17th day after transplantation, granulocytes are more than $0.5x10^9$ / L. On the 30th day after transplantation, in the bone marrow smears amastigotes were not identified. Bone marrow analysis for PCR chimerism by STR-metod revealed 100%. PCR analysis of peripheral blood chimerism: 100%. Determination of MRD in the bone marrow from January 6, 2021: TEL-AML negative. In the post-transplant period, she received a liposomal form of amphotericin B (Ambizom) 200 mg / day 1 time per week for leishmaniasis prophylaxis, the final administration of the drug was on January 11, 2021. In a compensated state, on January 15, 2021 the patient was discharged at home.

II. Conclusion

Without proper treatment VL has a high mortality rate [1]. VL is especially difficult in immunocompromised patients, including patients with primary and secondary immunodeficiencies. Immunosuppressive chemotherapy worsens the course of an infectious disease, and the absence of specific clinical signs and the need for morphological examination of the affected tissues complicate the diagnosis of VL. Treatment can be complicated by increased toxicity and interactions between antileishmania and immunosuppressive drugs [13]. Further study of the problem of leishmaniasis in immunocompromised patients will help to improve diagnostic measures and therapeutic approaches in the event of the development of the disease.

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