PRIKAZ SLUČAJA – CASE REPORT

A 6-Year-Old Boy with Cough, Fever and Pancytopenia – A case report

Šestogodišnji dečak sa kašljem, temperaturom i pancitopenijom - prikaz slučaja

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Summary We present the case of a six-year-old boy suffering from a ten-day bout of intermittent fever, cough, and pancytopenia. After the initial diagnosis of sepsis and hemophagocytic lymphohistiocytosis was discounted, additional tests were performed and the boy was diagnosed with the visceral form of leishmaniasis. Clinical improvement and cessation of febrility were observed after a therapy consisting of a liposomal form of amphotericin B was introduced. Follow-up examinations, which were performed after one, three and six months, revealed that the boy was completely healthy, with normal vital functions and laboratory analyses.
Key words: fever, cough, visceral leishmaniasis, amphotericin B

Sažetak Prikazuje se šestogodišnji dečak sa desetodnevnom intermitentnom temperaturom, kašljem i pancitopenijom. Nakon isključivanja dijagnoze sepse i hemofagocitnog sindroma, dodatnim ispitivanjem, postavljena je dijagnoza viscelarne lajšmanioze. Klinički oporavak pacijenta kao i normalizacija laboratorijskih parametara nastaje nakon lečenja lipozomalnom formom amfotericina B. Na kontrolnim pregledima nakon 1,3,6 meseci dečak je bio potpuno zdrav i laboratorijske analize su bile u okviru referentnih vrednosti.
Ključne reči: povišena temperatura, kašalj, viscelarna lajšmaniaza, amfotericin B

Introduction

Intermittent fever is a symptom of many diseases. Common causes can be infection, sepsis, malignancy or autoinflammatory disease. However, there are also unusual causes of intermittent fever: hemophagocytic lymphohistiocytosis or protozoa infection (1,2,3). The visceral form of leishmaniasis can initially present itself as a severe sepsis or hemophagocytic lymphohistiocytosis (4). Therefore, the differential diagnosis of these conditions is very difficult and sometimes requires a longer period of observation. Pulmonary involvement can be present in 49% of the cases. Cough is the most common symptom (5). Cases of visceral leishmaniasis in children are rare, especially in the Balkan Region.

Case Report

A six-year-old boy, otherwise healthy, suffering from a 10-day long bout of intermittent fever, fatigue and non-productive cough occurring during the fever, arrived to our Clinic with pancytopenia. There was no history of hemoptysis, wheezing, allergic reactions or weight loss. There was no significant family history of similar or other illnesses. A year before the onset of symptoms, he stayed for 5 days in Montenegro.
Initially he was admitted to a different hospital where he was treated with antibiotics for 5 days. His condition worsened and laboratory analysis revealed pancytopenia, after which he was transferred to our hospital.

Clinical investigations

At admission the patient was obese with the following auxologic parameters: weight 46 kg (P >99) height 138,5cm (P>99), body mass index 24,2 (P>99). The patient´s initial vital signs were as follows: systolic/diastolic blood pressure of 118/67 mmHg, body temperature of 40 °C, respiratory rate of 24 breaths per minute, heart rate 117 beats per minute and oxygen saturation in a room environment was 98%. He suffered from general fatigue for 10 days before admission; his skin was pale and marmorized with dark circles around his eyes. Ear, nose, throat and neck examination revealed only small lymph node hypertrophy, but no enlarged or exudative tonsils. Heart sounds were normal, and chest auscultation showed decreased breath sound in both bases of the lung. Abdominal examination revealed an enlarged liver and spleen.

Laboratory data revealed a reduced white blood cell count (leucopenia) and platelets (thrombocytopenia), but in following days his condition worsened into a pancytopenia (Table 1).

	Ref.range	Day 1	Day 4	Day 10	Day 18
WBC count	5,014,5x109/L	2,9	2,0	3,6	11,7
Lymphocyte count	42-61%	53,7	53,9	40,2	44,1
Neutrophil count	32-38 %	37,9	38,9	28,9	48,43
Monocyte count	3-5 %	6,7	4,3	7,4	6,82
Basophile count	0,0-1%	1,5	2,4	3,4	0,05
RBC count	3,54,5x1012/L	3,95	3,64	3,19	3,85
Hemoglobin	110-125 g/L	94	88	77	81
Hematocrit	0,32-0,42L/L	0,28	0,25	0,22	0,27
Platelets count	140-350x109/l	62	54	50	159

Table 1. Pancytopenia on the first day and during the treatment of visceral leishmaniasis
Tabela 1. Hematološki nalazi prvog dana hospitalizacije I tokom lečenja

The levels of serum inflammatory markers were: C – reactive protein 88,9 mg/l; procalcitonin 0,52 ng/mL and Interleukin-6 142 pg/mL. Abnormal laboratory findings on admission were increased ferritin 663,4 ug/l, triglycerides 5,47mmol/l, aspartate aminotransferase (AST 98 U/L), alanine aminotransferase (ALT 90 U/L). A quantitative immunoglobulin panel was significant for elevated immunoglobulin G Immunoglobulin G 16,40 g/L (ref. range 6,46-14,51 g/L). The levels of serum albumin were decreased 28 g/l. Coagulation screening showed a high level of D-dimer 14814ng/ml (table 2). The levels of serum electrolytes, glucose, blood urea nitrogen, creatinine, total proteins were normal.

Laboratory Findings	On admission	On discharge from the hospital
Inflammatory markers:		
CRP mg/L (<5 mg/L)	88,9	1,5
PCT ng/mL(0,000-0,050 ng/ml)	0,52	0,034
IL-6 pg/mL	142,6	<1,5
D dimer ng/ml (<230 ng/ml)	14814	571
Ferritin ug/L (6,0-320 ug/L)	663,4	66,4
Triglycerides mmol/L ((0,7-1,7 mmol/L)	5,47	1,12
Albumin g/L (35-52 g/L)	28	41
Transaminase		
AST U/L (10-37 U/L)	90	29
ALT U/L (10-42 U/L)	98	25
LDH U/L (220-450 U/L)	918	375

Table 2: Laboratory findings on the day of admission and discharge from the hospital
Tabela 2. Laboratorijski nalazi na dan prijema u bolnicu I na dan otpusta

Additional investigations

Radiography of the lungs revealed a discrete enlargement of hilar lymph nodes and bilateral interstitial reaction with a pronounced broncho-vascular pattern, but no lobar infiltrate (figure 1).

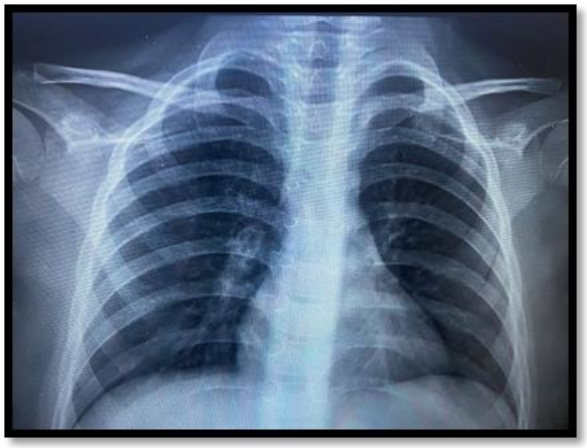


Figure 1: Lung radiography in PA position at admission
Slika 1. Radiografija pluća na prijemu u bolnicu

Abdominal sonography confirmed hepatosplenomegaly with a predominant enlargement of the spleen (interpolar diameter 180mm) (figure 2).

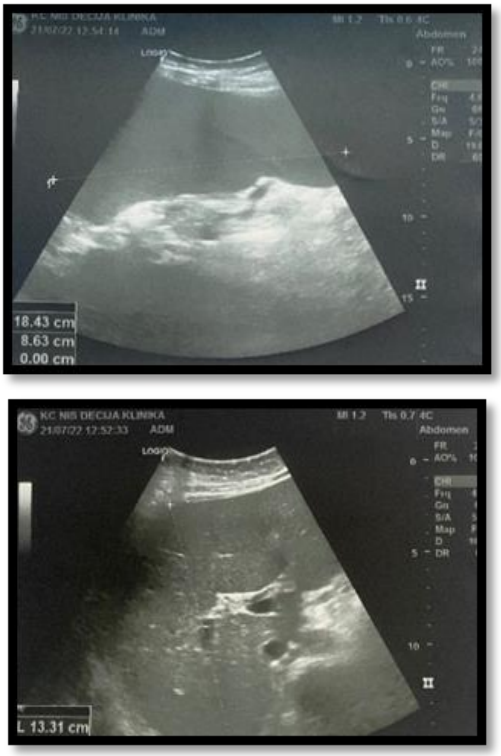


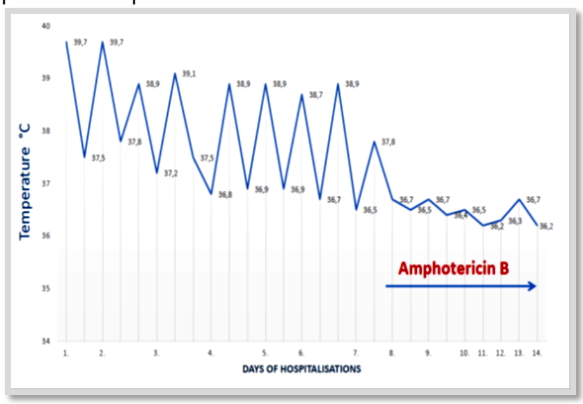
Figure 2: Abdominal ultrasound; enlarged spleen and liver
Slika 2. Ultrazvuk abdomena, prisutno uvećanje slezine I jetre

The results of bone marrow aspiration gave the following results: hypocellular bone marrow with no evidence of hematoproliferative diseases or hemophagocytosis.
Bacteriological culture (blood culture; urine culture; pharyngeal aspiration) for common pathogens was negative. Virology tests on Cytomegalovirus, Epstein Barr virus and Herpes simplex virus (CMV; EBV; HSV); Adenovirus; Parvovirus B1 9 (ELISA IgM/IgG) and HIV (Western blot, CENTAUR) were negative. A rapid antigen test for Leishmania and serological tests (ELISA IgM+IgG) for Leishmania infantum 20,5 (index positive >11) were positive. Re-examinations of BMA, which confirmed the existence of specific inclusive bodies of Leishmania amastigotes in macrophages, led us to a definitive diagnosis of visceral leishmaniosis.

Clinical course

Initially, dual antibiotic therapy was continued along with antifungal therapy, but as the condition worsened additional tests were required. After confirming the definitive diagnosis of visceral leishmaniasis, treatment with empiric antibiotics (cefotaxim, vancomycin) was discontinued and a specific therapy was introduced - a liposomal form of Amphotericin B. Administration of Amphotericin B was performed in 3 mg/kg doses on days 1 to 5, 14. and 21., for a total dose of 21 mg/kg. The patient also received metronidazole for two weeks and intravenous corticosteroids for 7 days while receiving amphotericin B loading doses. The general condition saw significant improvement after just a single dose of amphotericin B (on the eighth day of his hospitalization) and the boy was afebrile (Graph 1).

Graph 1. Effects of Amphotericin B therapy on fever and clinical course
Grafikon 1. Uticaj primene Amfotericin-a B na klinički tok I povišenu temperaturu



With the continuation of the treatment a complete reduction of symptoms and normalization of laboratory analyses was achieved: ferritin. 66,4 ug/l, D dimer 571 ng/ml, C–reactive protein 1,5 mg/l; procalcitonin 0,034 ng/mL and Interleukin-6 <1,5 pg/mL, albumin 41 g/l , triglycerides 1,12 mmol/l and ALT 29 U/L; AST 25 U/L and lactate dehydrogenase level 375 U/L. The patient was discharged home after 37 days of hospitalization in a good general condition and with normal vital signs. At the follow-up examinations conducted one, three and six months after his hospitalization, the boy was healthy, with normal vital functions and laboratory analyses.

Discusion

Intermittent fever in children can be a sign of infections, malignant, autoimmune and many other diseases (1,2). Clinical treatment of a febrile patient involves determining the pattern of elevated body temperature and a series of diagnostic procedures (6). Our patient was hospitalized for the first time due to an intermittent septic fever, with cough that was absent during afebrile periods. Considering the fact that his other symptoms were malaise, fever and pallor, it was unlikely that the disease was a recurring fever or some chronic autoimmune disease (1,7,8). However, due to the presence of hepatomegaly and splenomegaly with pancytopenia, initial tests were made to rule out autoimmune, malignant diseases and hemophagocytic lymphohistiocytosis (HLH), as one of the most serious, potentially life-threatening non-malignant disease (3,6). The diagnosis of HLH is complex and includes, in addition to a survey of clinical characteristics, immune and genetic markers, and typical laboratory indicators such as bi or pancytopenia, hypertriglyceridemia, hypofibrinogenemia, elevated levels of ferritin and transaminases, hypoalbuminemia. Examination of bone marrow aspiration, spleen biopsy or lymph nodes may produce the evidence of hemophagocytosis (4,7,9). Test results of our patient matched 5 out of 8 common clinical criteria (hyperpyrexia, splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia), which directed the diagnostic path towards HLH. However, HLH was ruled due to the discovery of amastigotes, found in the re-examination of the bone marrow aspiration, rapid antigen and serological tests, and, as a result, the diagnosis of visceral leishmaniasis (VL) was made. Differential diagnosis of visceral leishmaniasis and HLH is a challenge for physicians due to similar clinical and laboratory features. Scarpini et al. reported that a period of one year from the initial symptoms is needed to diagnose of visceral leishmaniasis. HLH is also mentioned as a rare but possible complication of this protozoal infection (4). Gagnair et al. report that a group of 12 children who were initially diagnosed with congenital or acquired HLH, were later diagnosed with visceral leishmaniasis (this was confirmed by subsequent tests) due to inadequate responses to therapy. The reasons for the late diagnosis in the case of these patients were a lack of awareness concerning the presence of infection in non-endemic areas, a lack of routine rapid serological tests for leishmaniasis and the early age of the children (10).

Leishmaniasis is an infectious disease caused by an intracellular parasite of the genus Leishmania. Cutaneous, mucocutaneous and systemic forms have been described (11). Leishmania donovany and Leishmania infantum are the most common causes of a severe, potentially fatal form of the disease, visceral leishmaniasis (kala-azar also popularly known as ″the black death″). It is a vector-borne disease and is transmitted by sandflies of the genus Phlebotomus (11,3). Five cases of visceral leishmaniasis were reported in Serbia in the period from 2001 to 2021, while 90 cases were reported to the World Health Organization in Montenegro during the same period (12). The incubation period for the disease lasts from 2 weeks to 18 months (11,13). The basic clinical characteristics of VL are: elevated temperature, bi or pancytopenia and splenomegaly, which was the clinical finding observed in the case of our patient (4,3). Other symptoms that our patient complained about were fatigue, loss of appetite and cough; laboratory analyses indicated pancytopenia, an increase in liver enzymes, triglycerides, inflammation parameters, hypoalbuminemia and hypergammaglobulinemia. The cause of pancytopenia is multifactorial: suppression of hematopoiesis, hemolysis and damage to an enlarged spleen (4). Splenomegaly is the predominant finding during abdominal examination. Recent studies have shown that the presence of nodal changes in the spleen is a top symptom of visceral leishmaniasis in children (14). Liver failure and a tendency for bleeding occur in the later stages of the disease (4). Pulmonary pathology in immunocompetent patients is very rare. The dominant symptom is cough (47%), tachypnea (14.1%) and chest pain (5%). In the case of our patient, an irritating cough accompanied the fever. An interstitial reaction is most often recorded on lung radiography, which was also the case with our patient. More severe lung problems in the form of pneumonitis, obliterating bronchiolitis, ARDS, solitary pulmonary nodules or hilar lymphadenopathy are found in immunocompromised patients, AIDS patients and VL patients (5,15). The immune response in patients with VL is accompanied by a mixed cytokine profile, Th1 and Th2 with the production of cytokines IL 10, IL-4, TNF-α, IFN-γ (16). We detected high levels of IL 6 in the case of our patient, which are associated with a more severe clinical picture and higher mortality (17,18).

The diagnosis was based on a direct identification of parasitic amastigote forms in the bone marrow, spleen or lymph node biopsy, serological tests (ELISA; IFAT; IHA), direct agglutination test (DAT), immunochromatographic strip test (ICT), PCR testing. Direct identification of the amastigote forms in the sample tissue is still of greatest importance, but additional serological or rapid antigen tests, disregarding their high specificity and sensitivity can greatly help in guiding the examination and providing additional proof for the diagnosis (19). In our case study, the diagnosis of VL was based on the overall clinical picture, amastigote forms found in the bone marrow biopsy and serological tests. American Association for Infectious Diseases and the FDA recommend a therapy consisting of a 21 mg/kg dose of Amphotericin B, distributed in intervals (3 mg/kg for 5 days, then 3 mg/kg on the 14th and 21st days). Our patient also received this type of therapy (20, 21, 22). Treatment success is determined by resolution of clinical and laboratory findings.

Conclusion

Visceral leishmaniasis in children is a rare disease which, if not diagnosed in time, leads to a possibly fatal outcome. Mimicry with many malignant, autoimmune and infectious diseases makes diagnosis difficult, with hemophagocytic lymphohistiocytosis constituting the most common differential diagnostic problem. Routine examinations with rapid antigen tests for this parasitosis in children with pancytopenia, splenomegaly and elevated temperature is helpful in determining the direction of further examination, faster diagnosis and timely initiation of specific therapy.

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