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Case report
Prikaz slučaja
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DISSEMINATED FUSARIOSIS IN A PEDIATRIC PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND PROLONGED FEVER – A CASE REPORT

DISEMINOVANA FUZARIOZA KOD PEDIJATRIJSKOG BOLESNIKA SA AKUTNOM LIMFOBLASTNOM LEUKEMIJOM I PRODUŽENOM FEBRILNOŠĆU – PRIKAZ SLUČAJA

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Summary

Introduction. Infections caused by fungi of Fusarium species occur in immunocompromised individuals as disseminated diseases. **Case Report.** This case report presents a 5-year-old boy with acute lymphoblastic leukemia who developed a disseminated fusarium infection during reinduction chemotherapy. Fever was the main symptom and it lasted for 15 weeks. Refractory fever despite broad-spectrum antibiotics, as well as nausea, myalgia, pulmonary symptoms with detection of pulmonary infiltrates, liver and spleen involvement indicated an invasive fungal infection. The patient received fluconazole, voriconazole, liposomal amphotericin B and caspofungin. Since high temperature was persistent, diagnostic laparoscopy of the abdomen was done. Scattered lesions, up to 2 mm in diameter, were observed macroscopically on the surface of the liver and spleen. The liver culture was positive for Acinetobacter and Fusarium species. After 38 days of therapy with liposomal amphotericin B and 3 days of ciprofloxacin, the patient became afebrile. Itraconazole (according to the antimycogram) was continued during maintenance therapy. Abdominal ultrasound was completely normal after 5 months of treatment with itraconazole. This boy was our first patient with a disseminated fusarium infection. At that time, Fusarium was detected in the hospital water system and in hospital air samples. **Conclusion.** A timely diagnosis of invasive fungal diseases in children is a big challenge. Over the past decade, there has been an increase in survival rate of patients with invasive fusariosis due to much more common use of voriconazole or combined antifungal therapy.

Key words: Fusariosis; Immunocompromised Host; Fever; Invasive Fungal Infections; Signs and Symptoms; Laparoscopy; Antifungal Agents

Sažetak

Uvod. Infekcije prouzrokovane plesnima iz roda *Fusarium* javljaju se kod imunokompromitovanih bolesnika kao diseminovana bolest. **Prikaz slučaja.** U ovom prikazu slučaja je predstavljen petogodišnji dečak sa akutnom limfoblastnom leukemijom kod koga se razvila diseminovana fuzarijum infekcija tokom reindukcije. Glavni simptom je bila povišena temperatura koja je trajala 15 nedelja. Temperatura koja nije reagovala na antibiotike širokog spektra, mučnina, bolovi u mišićima, plućni simptomi sa prisutnim plućnim infiltratima, zahvatanje jetre i slezine upućivali su na gljivičnu infekciju kod našeg bolesnika. On je dobijao flukonazol, vorikonazol, lipozomalni amfotericin B i kaspofungin. Pošto je visoka temperatura i dalje bila prisutna, urađena je dijagnostička abdominalna laparoskopija. Makroskopski su uočene rasute, tačkaste promene promera do 2 mm na površini jetre i slezine. Iz uzorka jetre našeg bolesnika iskultivisani su *Acinetobakter* i *Fuzarijum*. Nakon 38 dana primene lipozomalnog amfotericina B i tri dana terapije ciprofloksacinom, bolesnik je postao afebrilan. Itrakonazol (prema antimikogramu) primenjivan je tokom terapije održavanja. Ultrazvuk abdomena je bio uredan nakon pet meseci primene itrakonazola. Ovaj dečak je bio naš prvi bolesnik sa diseminovanom fuzarijum infekcijom. U to vreme, fuzarijum je nađen u bolničkom vodovodu i vazduhu. **Zaključak.** Pravovremena dijagnoza invazivne gljivične infekcije kod dece je veliki izazov. U protekloj deceniji, preživljavanje bolesnika sa invazivnom fuzariozom je poraslo zahvaljujući mnogo češćoj primeni vorikonazola ili kombinovane antigljivične terapije.

Ključne reči: fusarioza; imunokompromitovani bolesnik; febrilnost; invazivne fungalne infekcije; znaci i simptomi; laparoskopija; antimikotici

Introduction

Fusarium species (spp.) are environmental fungi widely distributed in the soil, organic substrates and water. They also cause a broad spectrum of human infections [1].

Infections caused by fungi of Fusarium spp. occur in immunocompromised individuals as a disseminated disease. A high resistance of Fusarium spp. to most antifungal agents leads to mortality rate over 50% among immunocompromised patients [1, 2].

We report a case of a pediatric patient with acute lymphoblastic leukemia (ALL) and prolonged fever due to a disseminated infection with fusarium with unusual properties.

Case Report

A 5-year-old boy was diagnosed with ALL. The previous treatment (induction, consolidation and most of the reinduction chemotherapy) lasted about 9 months and there were no complications or delays.

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Abbreviations

ALL – acute lymphoblastic leukemia
CRP – C-reactive protein
FLU – fluconazole
US – ultrasonography
VRC – voriconazole
CPFG – caspofungin
L-AMB – liposomal amphotericin B
CT – computed tomography
GMI – galactomannan index
WBC – white blood cells

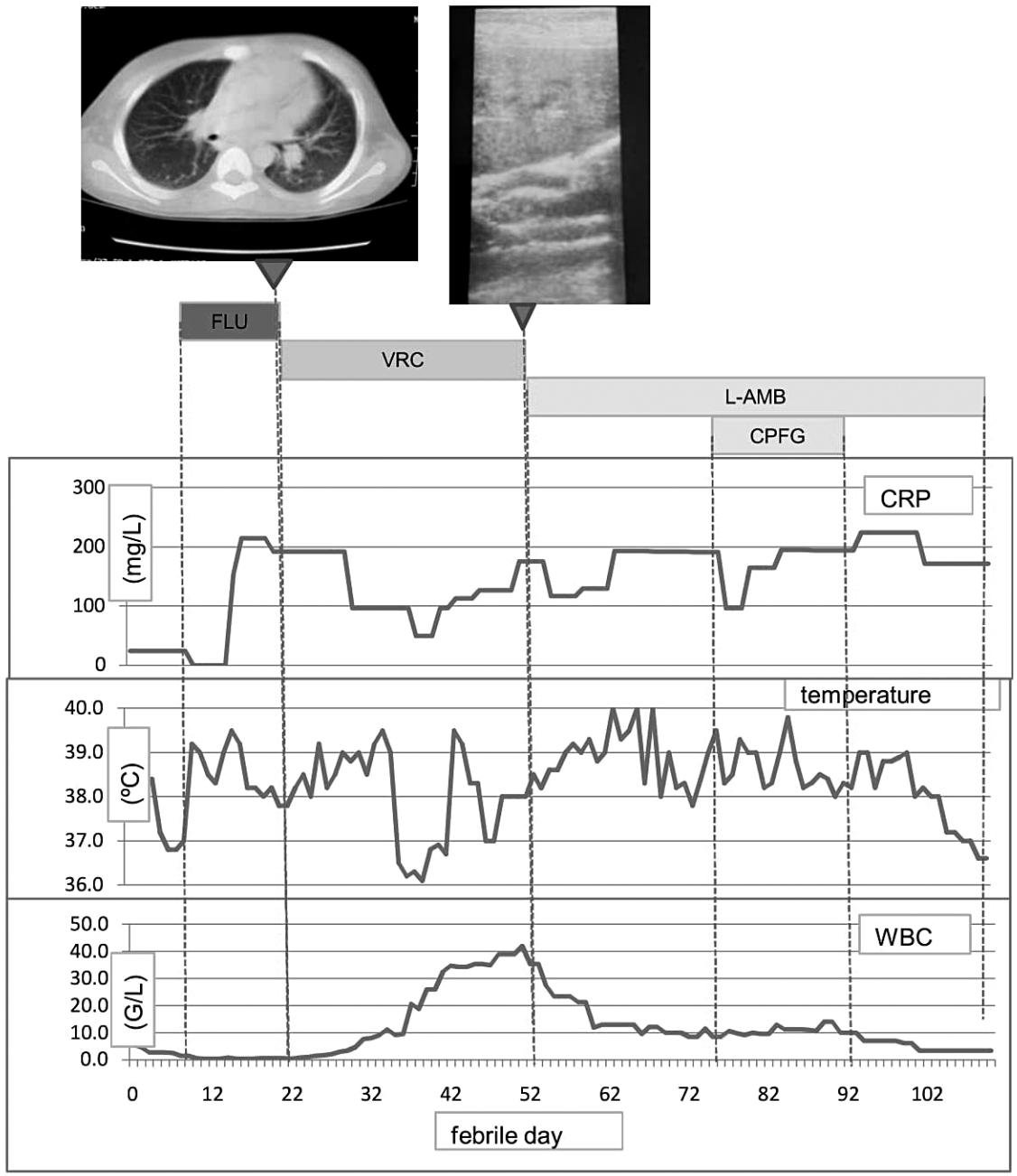
At the end of the reinduction phase, the boy developed fever and it lasted for the next 15 weeks.

In the beginning, the boy had a fever, but he was in a good condition with normal physical findings. The white blood cells (WBC) count was 2.4 G/l and C-reactive protein (CRP) level was 24 mg/l. Blood, urine and stool cultures were negative. He was initially treated with ceftriaxone and at the same time the reinduction phase was finished.

After that, in the next 4 weeks, the patient presented with high temperature every day **(Graph 1)**, (taken 2 to 3 times per day) associated with malaise, loss of appetite, and occasional vomiting without diarrhea. During the first two weeks he had a nonproductive cough. At the end of the fourth week, decreased breath sounds were noted in the right lung. In this period, the boy had severe granulocytopenia for 3 weeks. The CRP ranged from 96 – 192 mg/l. Urine analysis, chest X-ray, X-ray of the paranasal sinuses, echocardiography and abdominal ultrasonography (US) revealed no abnormal findings. Repeated blood, urine, and stool cultures were also negative. After 28 days of treatment with broad-spectrum antibiotics and a 10-day course of intravenous fluconazole (FLU), the patient still had daily fevers. Extensive infectious and autoimmune workup was negative and the source of fever was not revealed. Complete remission was confirmed on bone marrow examination. A chest computed tomography (CT) scan (22nd febrile day) revealed multiple lung nodules, 5 mm in diameter **(Graph 1)**. In addition to slightly enlarged liver and spleen, abdominal CT scan showed no abnormalities. Voriconazole (VRC) was initiated. The patient`s WBC stabilized at around 3 G/l, while the CRP was high despite antifungal therapy. A week later, while continuously febrile, the boy stopped coughing. However, he was extremely ill and complained of severe pain in the legs. Ferritin was high (2433 ug/l). In the sixth week, the patient was given a course of parenteral methylprednisolone (1 mg/kg daily) for 2 weeks with VRC concomitantly. On day 2 of steroids, there was a complete defervescence, and the CRP level decreased. During a reduction in the dose of steroids, the boy became febrile once again with an increase in CRP. Anti-Candida and anti-Aspergillus antibodies of the IgM and IgG classes, Aspergillus galactomannan and Candida mannan antigens values were monitored during the illness **(Table 1)**. VRC (used for 30 days) was switched to liposomal amphotericin B (L-AMB) in the 10th week of illness. The patient remained febrile and exhaustion worsened over the next weeks. Procalcitonin level was high and antibiotic therapy was reintroduced. Abdominal US (52nd febrile day) revealed multiple liver and splenic hypoechoic lesions, 7.5 mm in diameter, associated with hepatosplenomegaly **(Graph 1)**. Repeated abdominal US showed an increase in the size and number of these lesions. A peripheral venous catheter was applied at that point. At week 12 of high temperature, caspofungin (CPFG) was added to L-AMB. At the same time, maintenance therapy for ALL was initiated. As the high temperature was still present, in the 13th week a diagnostic abdominal laparoscopy was performed. Scattered spots up to 2 mm in diameter were observed macroscopically on the surface of the liver and spleen. The fungi were not detected by direct microscopy in the obtained samples. The sample culture remained positive for Acinetobacter spp. (susceptible to ciprofloxacin only) and Fusarium spp. Histopathology has shown chronic portal and light lobular hepatitis. Our patient received CPFG for 19 days and L-AMB for 45 days. After

Table 1. Fungal biomarkers during and after the fever
Tabela 1. *Gljivični biomarkeri tokom i nakon febrilnosti*

Elisa immunodiffusion assay *Elisa imunodifuzijski test*	week 7 *7. nedelja*	week 10 *10. nedelja*	week 13 *13. nedelja*	week 25 *25. nedelja*	reference values *referentne vrednosti*
anti-Candida IgM antibody *anti-Candida IgM antitela*	> 500	440	> 500	420	≥ 80 U/ml positive *≥ 80 U/ml pozitivan*
anti-Candida IgG antibody *anti-Candida IgG antitetela*	300	330	225	230	≥ 100 U/ml positive *≥ 100 U/ml pozitivan*
Candida mannan antigen *Candida mannan antigen*	0,34	0,94	1,28	0,4	index ≥ 0,5 positive *indeks ≥ 0,5 pozitivan*
anti-Aspergillus IgM antibody *anti-Aspergillus IgM antitela*	112	130	200	66	≥ 70 U/ml positive *≥70 U/ml pozitivan*
anti-Aspergillus IgG antibody *anti-Aspergillus IgG antitela*	390	310	280	450	≥ 70 U/ml positive *≥ 70 U/ml pozitivan*
Aspergillus galactomannan antigen *Aspergillus galactomannan antigen*	0,25	3,33	0,3	0,28	index ≥ 0,5 positive *indeks ≥ 0,5 pozitivan*



Graph 1. Clinical, biological, radiographic evolution and drug therapy
Grafikon 1. *Klinički, biološki, radiografski tok i primenjeni lekovi*

Legend: CRP - C-reactive protein; WBC - white blood cells; FLU - fluconazole; VRC - voriconazole; l-AMB - liposomal amphotericin B; CPFG - caspofungin
Legenda: CRP - C-reaktivni protein; WBC - bela krvna zrnca; FLU - flukonazol; VRC - vorikonazol; l-AMB - lipozomalni amfotericin B; CPFG - kaspofungin

38 days of therapy with L-AMB and 3 days with ciprofloxacin (a total of 14 days) the patient became afebrile in the 15th week. Itraconazole (according to the antimycogram) was given during maintenance therapy. The CRP level was still high in the next 2 months (above 50 mg/l). The abdominal US was completely normal after 5 months of treatment with itraconazole. Six years after discontinuation of antifungal therapy, the patient remains in complete remission of his neoplastic disease without signs of clinical infection.

Discussion

Fusarium spp. are widespread in nature. This genus of fungal opportunists was first identified in 1958. Among immunocompromised patients, Fusarium spp. are second to Aspergillus spp. as the most common cause of invasive fungal infections [1, 3]. Only a few species cause disease in humans, most often F. solani complex, F. oxysporum complex and F. fujikuroi complex [1].

Disseminated fusariosis occurs only in conditions associated with immunosuppression and some risk factors. Our patient had most of them: acute leukemia, previous treatment with high doses of dexamethasone, prolonged and severe neutropenia and extended antibiotic treatment [4, 5].

The typical clinical presentation is neutropenic fever in patients with myalgia and sudden appearance of erythematous papular or nodal painful skin lesions with central necrosis. Cutaneous lesions were not observed in our patient, although they are seen in approximately 85% of patients with early stage disseminated fusarium infections [6]. Pneumonia may be the only manifestation of the disease or part of a disseminated disease. It is very similar to invasive pulmonary aspergillosis with angioinvasion, lung infarction and characteristic nodules with or without the halo sign [6, 7]. The clinical signs of hepatosplenic disease typically develop after neutrophil recovery [7].

Despite broad-spectrum antibiotic therapy, refractory fever, nausea, myalgia, pulmonary symptoms with pulmonary infiltrates, liver and spleen involvement indicated an invasive fungal infection.

Standard diagnostic procedures for fungal infections include microscopic examination of liquid and solid diagnostic specimens, blood cultures and all clinical cultures, non-culture assays for fungal antigens and imaging studies [8].

Direct microscopic examination of biological samples is the fastest way for obtaining the diagnosis [6]. The sensitivity of blood culture to detect fungemia ranges between 21 and 71% for Candida, but it is very low for the infection caused by Aspergillus spp. [9]. Our patient did not have positive blood cultures, although they are often positive with the infections caused by Fusarium spp.

Fusarium spp. may contaminate laboratory specimens. The growth of fusarium from non-sterile samples in high risk patients should be interpreted as a probable infection until proven otherwise [6]. Liver culture from our patient was positive for Acinetobacter and Fussarium spp. The genus Acinetobacter is a major cause of nosocomial infections. Its ability to develop multidrug resistance and to persist in any environmental conditions makes infections by Acinetobacter very dangerous [10]. Our patient received antibiotics from all groups except fluoroquinolones. In this case, Acinetobacter was susceptible to ciprofloxacin only.

Identification of the genus Fusarium is not difficult. However, species identification requires molecular methods (matrix-assisted laser desorption ionization-time of flight mass spectrometry, multiplex PCR assay) [2, 6].

Remarkable advances in the early detection of invasive fungal infections have been made by the development of non-culture assays for fungal antigens [8]. Routine antigen detection with the Aspergillus galactomannan index (GMI) enzyme-linked immunosorbent assay (ELISA) test should be considered in high-risk patients. Positive GMI tests should be interpreted as indicative of invasive aspergillosis or invasive fusariosis [6]. Cross-reactivity has been observed for a number of other fungi including Fusarium species and some beta-lactam antibiotics. Serial GM assessments can also be used to monitor the effectiveness of antifungal therapy [9]. Routine Candida antibody and antigen testing and routine testing for Aspergillus antibodies are not recommended for patients with hemato-oncological malignancies [7]. In our patient, positive test for mannan and GMI, as well as antibodies to Candida and Aspergillus were probably due to cross-reactivity.

Our patient developed a disseminated fusarium infection. He received a broad spectrum of antibiotics and FLU first. After detection of pulmonary nodes he received an empiric treatment with VRC and later L-AMB for suspected aspergillosis. In the meantime, the cough has stopped. Chest X-ray findings were still normal. Due to suspicion of hemophagocytic lymphohistiocytosis, he received a short course of corticosteroids. Later, CPFG was added due to positive anticandida antibody and mannan antigen. Considering that the infection spread to the liver and spleen, both fusarium and acinetobacter were isolated from the liver sample. The fungigram revealed that the pathogenic agent was resistant to antifungal polyene, FLU, VRC and was sensitive to itraconazole, which is inconsistent with literature data.

This boy was our first patient with a disseminated fusarium infection. At that time, the Fusarium spp. was detected in the hospital water system and in hospital air samples.

Conclusion

A timely diagnosis of invasive fungal disease in children is a big challenge. Over the past decade, survival from invasive fusariosis has increased. This is most likely the result of much more frequent use of voriconazole or combined antifungal therapy, although European Guidelines recommend only one week of combination therapy.

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