Case report

Multiple debulking surgery and triple antifungal therapy in abdominal-cardiac--pulmonary invasive aspergillosis

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ABSTRACT

Children with acute leukemia are at a high risk of invasive fungal disease, which might manifest itself as clinically-resistant entity. The objective of this paper is to present an unusual clinical case of 17-year-old patient treated for acute lymphoblastic leukemia, with early development of disseminated invasive aspergillosis, involving the abdominal, pulmonary and cardiac structures. The patient was subjected to a combined targeted double, and later triple, antifungal therapy together with several debulking surgical interventions. The clinical course indicated a highly clinically-resistant invasive fungal disease, and the treatment was unsuccessful in this case. Limited current experience in triple antifungal therapy, abdominal aspergillosis, *Aspergillus* endocarditis, and possible causes of failure of antifungal therapy are discussed in the paper.

Key words: invasive fungal disease, invasive disseminated aspergillosis, abdominal aspergillosis, triple antifungal therapy

INTRODUCTION

Invasive fungal disease (IFD) is a systemic fungal infection which develops in patients with immune deficiencies. IFD is an opportunistic infection. Patients at a high risk of developing IFD include primarily those with hematologic malignancies, and acute leukemia in particular, and patients who had undergone allogeneic transplantation of hematopoietic stem cells and organs.

There are 3 levels of IFD diagnosis: proven, probable and possible [1]. Proven diagnosis is based on a positive result of culture harvested from a physiologically sterile location, and on an accurate identification of the pathogen, confirmed in a histopathology report. Probable diagnosis is based on the risk factors and clinical symptoms as well as on the typical imaging abnormalities and presence of fungal biomarkers. Possible diagnosis involves the presence of risk factors and characteristic clinical (imaging) signs and symptoms.

The most common type of malignancy diagnosed in pediatric patients under the age of 18 is acute lymphoblastic leukemia (ALL). The 2012–2013 national analysis in Poland confirmed that the incidence of IFD in a group of 430 children with ALL was 13%, including 0.7% of children with proven diagnosis, 4.1% of those with probable diagnosis, and 9.5% of patients with possible diagnosis [2].

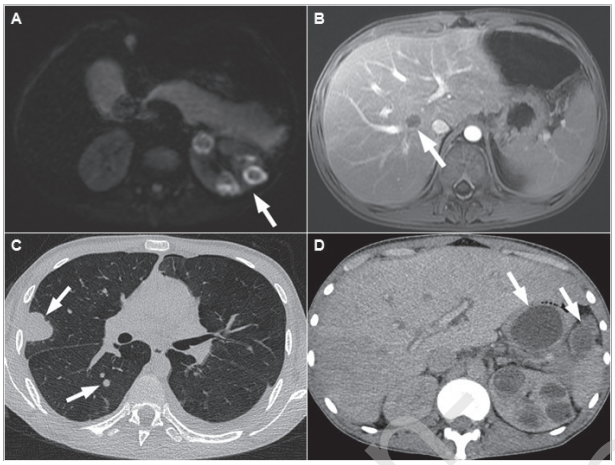
The aim of this paper is to describe an atypical IFD case in a 17-year-old boy with ALL and with disseminated invasive aspergillosis, with massive involvement of abdominal structures (in the form of multiple abscesses) as well as of the lungs and endocardium. Due to the clinical resistance in the patient, a double antifungal therapy was administered, followed by a triple regimen, with several concurrent surgical debulking procedures. As the course of treatment was unfavorable, the paper discusses potential causes behind the failure of antifungal therapy in immunosuppressed patients.

CASE DESCRIPTION

The paper presents the case of a 17-year-old boy with acute T-cell lymphoblastic leukemia, treated in accordance with the ALL-IC-2009 protocol, and stratified as an intermediate-risk patient, without the involvement of the central nervous system (CNS). Initially, response to treatment was changeable: response to steroid therapy was good on day 8, but on day 15, the M2 myelogram (i.e. percentage of bone marrow blasts > 5%). On day 21 of the treatment, the patient was diagnosed with acute pancreatitis, resulting in a discontinuation of L-asparaginase. During the implantation of a central venous catheter, left-sided pneumothorax developed. Following pleural cavity drainage, the left lung was expanded. Follow-up abdominal ultrasound revealed hypoechogenic lesions in the liver and kidneys. Abdominal MRI helped visualize the lesions as fungal abscesses, located in the liver as well as in the kidneys (fig. 1A, 1B). In terms of their clinical manifestation, the lesions took the form of hepatosplenic candidiasis with renal involvement. Therefore, in accordance with ECIL recommendations, the patient was started on caspofungin [3]. His chest HRCT revealed the presence of subpleural nodular lesions sized 27 × 25 × 28 mm (fig. 1C) and bilateral multiple nodules and ground glass opacities. Galactomannan was detected in the patient's blood in 3 consecutive tests. The patient was diagnosed with probable disseminated aspergillosis based on the EORTC criteria [1]. In line with ECIL recommendations, a recommended therapeutic management in such cases involves monotherapy with voriconazole [3, 4]. However, due to the disseminated and rapidly progressing course of invasive fungal infection, apart from the antibiotic therapy, the patient's antifungal treatment was also modified, replacing caspofungin with targeted combined anti-aspergillosis therapy, i.e. liposomal amphotericin B plus voriconazole. Despite the therapy, 2 weeks later, increased amounts of fluid building up in the left pleural cavity were observed, and at the same time, abdominal CT revealed the presence of a lesion suggestive of an abscess between the pancreatic tail, spleen and stomach (fig. 1D). The lesion compressed the patient's stomach, and in terms of its morphology, it resembled all the other abscesses found in the liver and kidneys. As fever set in, empirical antibiotic therapy was modified yet again, following blood cultures. Over the following two days, fluid was evacuated twice from the patient's pleural cavity. Chemotherapy was continued in order to complete the induction protocol. On day 33 of treatment, leukemia was in remission. Over the following days, though, the patient's respiratory function deteriorated due to the increasing amounts of fluid building up in both of the pleural cavities. His pain in the abdomen also intensified. Despite the combined anti-fungal therapy and pleural drainage, no improvement was observed: there was a hypoechogenic space within the abdominal cavity, with septa, and without vascular flows; there were abscesses within the patient's liver and kidneys; and there were increased amounts of fluid in his pleural cavities. Chest X-ray revealed shadows on both lung fields, reaching up to the level of anterior costal segments, fluid in the pleural cavity with accompanying atelectatic lesions, and persisting peripheral oval shadows in the middle right field.

Periodically, the patient suffered from symptoms of respiratory and heart failure. His echocardiogram revealed a pathological mass sized ca. 26 × 15 mm under the septal cusp, adjacent to

FIGURE 1.
Disseminated pulmonary and abdominal aspergillosis: **A.** – multiple abscesses in the left kidney in MRI (arrow), **B.** – liver abscess in contrast-enhanced T1-weighted MRI (arrow), **C.** – two *aspergillomas* in the right lung (arrow), **D.** – peritoneal abscess (arrow) and progression of the left kidney abscess.



the ventricular septum. Fluid in the pericardium was unevenly distributed, without compressing the cardiac muscle. Additionally, inferior vena cava was dilated and its respiratory mobility was reduced.

At that point of the treatment, caspofungin was added as the third drug in a triple antifungal therapy. In order to reduce the fungal mass, three surgical debulking interventions were carried out over the course of 2 weeks, targeting the kidneys and the peripancreatic abscess, achieving partial evacuation of very thick contents. During thoracoscopic procedures, 2 nodular pulmonary lesions were also removed. The histopathology report confirmed the presence of *Aspergillus fumigatus* both in the material harvested from the lungs as well as from the abdominal abscesses. Having accomplished partial improvement, chemotherapy was resumed with a month's delay. Leukemia was still in remission. The triple antifungal therapy was continued.

Two weeks later, a follow-up bone marrow examination revealed an ALL relapse with 55% blasts in the patient's bone marrow. He was qualified for treatment with IntReALL 2010 relapse protocol dedicated for high-risk patients, qualified for bone marrow transplantation. A week later, in the course of myelosuppression, septic shock symptoms occurred, and the patient, in a very severe condition, was transferred to the intensive care unit. He was diagnosed with severe leukopenia, agranulocytosis, disseminated invasive aspergillosis, escalating respiratory insufficiency, renal and heart failure. Upon his admission at the ICU, deep analgosedation was initiated, and mechanical ventilation was started. Continuous renal replacement therapy was implemented, as was catecholamine circulatory support. Several days later, the patient died, presenting symptoms of multi-organ failure.

In summary, our patient with acute T-cell lymphoblastic leukemia, undergoing chemotherapy, developed disseminated invasive aspergillosis, requiring combined antifungal therapy aided with surgical debulking procedures. The disseminated fungal infection resulted in multiple abscesses involving the liver, kidneys, and the space surrounding the pancreas, as well as numerous pulmonary lesions. The IFD caused a delay in the administration of chemotherapy, and thus resulted in a very early relapse, whose complications led to multiple organ failure and death of the patient.

The patient's primary disease was acute lymphoblastic leukemia, complicated by the invasive fungal disease, which put chemotherapy on hold, causing an early relapse of ALL, and eventually the patient's death. Disseminated invasive aspergillosis, which developed in the patient, took the form of a clinically resistant entity, despite the use of combined triple antifungal therapy for 2 months. In the above described case, the course of aspergillosis was not typical, originating in the abdomen, with abscessed formed in the kidneys, in the peripancreatic space, and within the endocardium. In spite of the several surgical debulking interventions, the treatment was unsuccessful.

DISCUSSION

The above presented case of an invasive fungal infection had an unfavorable course, and was not resolved successfully. There are few case studies available in literature that focus on hematologic patients treated with combined triple antifungal therapy. Triple therapy is rarely used, and there are no standard recommendations in that respect. The decision to implement triple antifungal treatment was preceded by ineffective administration of double antifungal therapy, which *a priori* constituted a negative prognostic factor. The analyzed case also points out the limits of efficacious therapy of infectious complications in pediatric hematooncology, and demonstrates the necessity of seeking new solutions. What has to be taken into consideration in the context of combined therapy is the risk of pharmacological interactions, and of different toxicities, related to the individual antifungals used, adding up. Aside from the above considerations, combined therapy also involves considerable costs.

Combined IFD treatment has a sound theoretical rationale, demonstrated in *in vitro* studies, animal models, and limited clinical data, including a randomized clinical trial involving a com-

bination of voriconazole and anidulafungin [5]. The theoretical rationale behind the use of combined antifungal therapy stems from the different mechanisms of action characteristic of different antifungal agents: polyenes damage the cellular membrane, binding with ergosterol; azoles inhibit the synthesis of cell membrane ergosterol; and echinocandins inhibit the synthesis of β-1,3-D-glucan in the cellular wall. *In vitro* studies indicate a synergistic or additive effect of combined administration of echinocandins with azoles and amphotericin [6]. Animal models also demonstrate a faster regression of infection, following the administration of echinocandins with amphotericin or azoles [7].

EBMT and ECIL1 studies reported that combined therapy was administered in 88% of the centers in the treatment of CNS mycoses, in 56% of the centers in the treatment of disseminated fungal infections, and in 44% of the centers in the treatment of pulmonary mycosis. ECIL6 includes the following recommendations with respect to combined treatment of invasive pulmonary aspergillosis: grade C I for first-line voriconazole plus anidulafungin (C I), and C III for other optional combinations; grade B II for second-line combined therapy. The proposed combinations include: caspofungin with voriconazole, and liposomal amphotericin B with caspofungin or voriconazole. On the other hand, ECIL6 recommendations for combined therapy in invasive mucormycosis grade it as C III in the first line of treatment, and as B III in the second line of treatment [4].

There are few reports available on the use of triple antifungal therapies [8–10]. Davoudi et al. described a successful triple therapy alongside a procedure of cerebral abscess evacuation in a patient with acute myeloblastic leukemia, following hematopoietic stem cell transplantation, with disseminated mixed invasive fungal infection (aspergillosis and mucormycosis) of the lungs, spleen, brain and bones. The treatment was continued in the form of secondary prevention with posaconazole for over 10 years [10]. A different scenario involves invasive mucormycosis, where apart from a double antifungal therapy, an additional chelating agent, deferasirox, may be used, as demonstrated in one of the studies [9].

In vitro studies which look into triple therapies targeting different species of *Aspergillus* demonstrated that adding AmB to the combination of caspofungin with azoles (voriconazole or ravuconazole) resulted in an increase in the fractional inhibitory concentration index (FIC) with respect to *A. fumigatus* and *A. flavus*. On the other hand, in the case of *A. terreus* infection, adding AmB would increase the synergism of combined triple therapy as compared with the double therapy involving caspofungin and an azole [11].

Another non-typical aspect of the case under analysis is the primary, massive involvement of the abdominal organs with aspergillosis. In hematologic patients, invasive candidiasis is most commonly found in that region. International literature contains very few reports on invasive abdominal aspergillosis in that particular group of patients. In an international analysis, Kazan et al. identified 21 patient with acute leukemia or after hematopoietic stem cell transplants, in whom digestive tract aspergillosis developed. In most of them (13 vs. 8), there was systemic aspergillosis. In 6 patients the diagnosis was made *post mortem*, and 7 out of the remaining 15 patients also died in the process. The analyzed patients received both antifungal agents as well as surgical treatment, but based on that analysis, the authors were unable to draw conclusions on an optimum management of abdominal aspergillosis [12]. Other known case reports fail to deliver unequivocal arguments in favor of particular therapeutic regimens in the treatment of invasive abdominal aspergillosis diagnosed in patients with acute leukemia or after hematopoietic stem cell transplants [13–15].

Similarly, there is limited experience with reference to the treatment of fungal endocarditis caused by *Aspergillus* species in hematologic patients [16–20]. Many factors might have impacted the failure of antifungal treatment of massive and disseminated aspergillosis in a pediatric patient with acute lymphoblastic leukemia. They have been presented in table 1.

TABLE 1.
Possible causes of the failure of antifungal therapy.

Cause	Literature
Severe and long-lasting neutropenia	[3]
Concurrent immunosuppressive therapy, causing neutropenia and lymphopenia	[3]
Mixed infection (e.g. *Aspergillus* and *Mucor* or 2 species of *Aspergillus*)	[4]
Inefficacy of azoles: • reduced bioavailability in oncohematologic patients (65%) • drug resistance (mold fungi CYP51) • breakthrough infection (*Mucor*) • hepatic metabolism (CYP2C19) • interactions with other drugs	[21]
Inefficacy of echinocandins: • resistance of *C. parapsilosis* (mutations in *Fks1*) • breakthrough infections (*C. parapsilosis*, *Fusarium* sp., *Aspergillus* sp.) • interactions with other drugs	[22]

SUMMARY

Triple antifungal therapy and surgical debulking procedures, aimed at reducing the fungal mass volume in the abdominal cavity and lungs was unsuccessful in the case presented above. The fundamental cause behind the failure of antifungal therapy in

the above described patient with acute lymphoblastic leukemia was the massive fungal infiltration of his kidneys, lungs, peripancreatic space and endocardium. Despite the multiple surgical interventions, the volume of fungal infiltrates and abscesses could not be reduced to an extent that would render pharmacotherapy effective.

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Przemysław Gałązka: design of the study, manuscript writing; Ewa Demidowicz: data collection, manuscript writing; Natalia Bartoszewicz: data collection; Krzysztof Czyżewski: design of the study, data collection; Zbigniew Serafin: radiological analysis and data; Patrycja Zalas-Więcek: microbiological analysis; Jan Styczyński: design of the study, critical review of manuscript.
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