Invasive pulmonary aspergillosis in a child with acute myeloid leukaemia: pharmacotherapy and surgical management

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ABSTRACT

This paper reports on diagnostic and therapeutic management of pulmonary invasive fungal disease (IFD) in a child with relapsed acute myeloid leukaemia, undergoing chemotherapy followed by haematopoietic stem cell transplantation. Surgical management with resection of the involved lung tissue was based on the location of fungal infiltrates close to large circulatory vessels. After examination of resected pulmonary tissue, a diagnosis of proven IFD was done. This case report is an example that aspergillosis is usually the cause for pulmonary IFD. Pharmacotherapy of pulmonary IFD should be based on compounds with good penetration to lung tissue: amphotericin B lipid form or voriconazole.

KEY WORDS: invasive fungal disease, invasive fungal infection, pulmonary aspergillosis, chemotherapy, haematopoietic stem cell transplantation, amphotericin B lipid form

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INTRODUCTION

According to current data on invasive fungal disease (IFD) in children treated for cancer in Poland, IFD occurs in 7.9% patients in whom 1.2% cases are confirmed (proven), 1.8% are probable and 5.3% are possible [1]. However, as much as 69.6% IFD episodes occur in children treated for acute leukaemia, including 13% with acute lymphoblastic leukaemia (ALL) and 43.2% with acute myeloid leukaemia (AML) [1]. IFD occurs in 27.3% children after a haematopoietic stem cell transplantation (HSCT) of whom as much as 51% are patients with acute leukaemia. IFD incidence is 31.3% in ALL children after allo-HSCT and 44.7% in AML children after allo-HSCT. IFD also occurs in 30.6% of children after allo-HSCT and in 17.1% of children after auto-HSCT [1]. In order to diagnose IFD, two types of methods are used [2]:

- invasive; tissue sampling from the involved area
- non-invasive.

Invasive methods are more precise in case of IFD because they provide material for direct microscopic studies and histological exams. The first method examines a stained preparation of clinical material, while the second focuses on a biopsied tissue specimen.

In practice, however, **non-invasive methods** are used more often. They rely on fungal marker testing and imaging, mostly high-resolution computed tomography (HRCT) scans. Detection of fungal markers comprises:

- testing for fungal antigens, including galactomannan (GM) and mannan, as well as anti-mannan antibodies
- testing for β-D-glucan (BDG)
- testing by the polymerase chain reaction (PCR) method.

Based on clinical, microbiological and radiologic criteria, the Working Groups at the EORTC (European Organisation for Research and Treatment of Cancer)/MSG (Mycoses Study Group) developed definitions and classified invasive fungal infections according to how precisely they can be diagnosed into: possible, probable and proven (tab. 1) [3, 4].

Depending on the certainty of IFD diagnosis, there are four diagnostic and therapeutic antifungal strategies which can be applied:

- prophylaxis
- fever-driven approach
- diagnostic-driven approach
- targeted therapy of a proven fungal infection.

Antifungal prophylaxis relies on antifungal agents administered to patients from the risk group. The empiric therapy (fever-driven approach) involves administration of antifungal medication to patients with neutropenia who have persistent or recurrent fever despite receiving broad-spectrum antibiotics. Preemptive therapy (diagnostic-driven approach) consists in administration of antifungal agents to patients with neutropenia, characteristic clinical symptoms (e.g. fungal pneumonia) and/or biologic markers of invasive fungal disease (e.g. galactomannan). Patients with a proven diagnosis of invasive fungal infection receive targeted therapy based on antifungal agents.

OBJECTIVE OF THIS PAPER

This paper includes a case report on pulmonary invasive fungal disease managed by surgery and pharmacotherapy in a patient with a relapsed acute myeloid leukaemia receiving chemotherapy followed by haematopoietic stem cell transplantation.

CASE REPORT

A female patient, aged 14, was treated since January 2014 due to acute myeloid leukaemia with neurological involvement in the form of meningeal leukaemic infiltration and presence of a mass in the vertebral canal resulting in a lateral interruption in the spinal cord at Th2–Th8 with paraparesis of the lower limbs and neurogenic bladder. In May 2015, leukaemic recurrence was detected. The patient received chemotherapy, complicated by extended grade 4 myelosuppression and severe infections

TABLE 1.
Levels of probability assigned to the diagnosis of invasive fungal infection according to EORTC/MSG [3, 4].

Level of probability	Criteria
Proven	Confirmed by histologic study or positive result of a culture from the material obtained by biopsy or a biological fluid which is sterile under physiological conditions
Probable	Positive result of fungal marker test and radiologic criteria
Possible	Positive result of fungal marker test or radiologic criteria

including sepsis (*Staphylococcus hominis* and *Escherichia coli*), vaginomycosis (*Candida glabrata*) and infection of the sore in the posterior rugae (*Klebsiella pneumoniae*). The treatment was based on broad-spectrum antibiotics and prophylaxis, which was followed by antifungal therapy (tab. 2).

TABLE 2.
Antifungal therapy implemented.

Time	Stage of disease	Type of IFD therapy	Medication used
May	chemotherapy due to relapsed leukaemia	prophylaxis	posaconazole
June	myelosuppression	fever-driven approach	mycamine
July	infection (pneumonia)	treatment of possible fungal infection	amb
August	progression of pneumonia	treatment of possible fungal infection	combined therapy: amb + caspofungin
August–September	proven fungal infection	surgical treatment of pulmonary IFD	voriconazole
December	early period following allo-HSCT	no IFD; suspected idiopathic pneumonia	etanercept

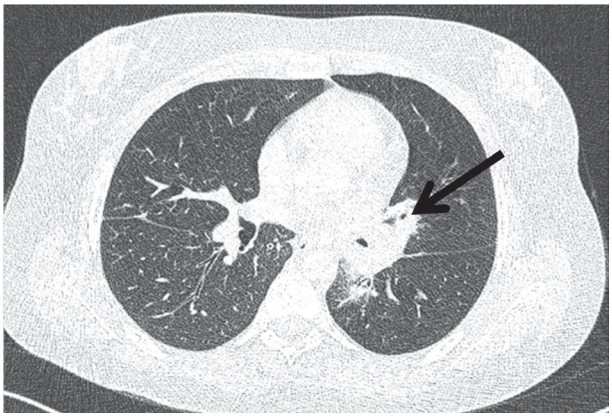
amb – amphotericin B lipid form; HSCT – haematopoietic stem cell transplantation; IFD – invasive fungal disease

In July 2015, the patient developed pneumonia which was treated with broad-spectrum antibiotics. Blood cultures from the central line and the peripheral vein grew *E. coli*. A thoracic HRCT scan showed a ground-glass opacity area and small nodular lesions of the lungs. The test result for galactomannan was negative. The patient was diagnosed with a possible pulmonary fungal infection and received amphotericin B lipid form in addition to the existing medication. Despite elimination of the pathological microorganism from the blood, the patient's overall health status deteriorated. Blood cultures grew a multi-resistant strain of *Klebsiella pneumoniae*. The patient was started on colistin, ciprofloxacin and imipenem which gradually improved her health and helped to eradicate the pathogen from the blood and the pressure sore.

In August 2015, a follow-up thoracic HRCT scan revealed that fungal lesions spread to both lungs, particularly the lower left segment, where a nodule 3 cm in diameter, an area of ground-glass opacity and single parenchymal densities were detected. A nodule with a small ground-glass halo was detected in the upper lobe. In the right lung, the HRCT scan showed areas of ground-glass opacity with overlapping small nodular peribronchial densities and tree-in-bud lesions. Antifungal treatment was modified to include caspofungin. However, a follow-up HRCT scan performed 4 days later revealed that the largest lesion in the perihilar region of the left lower lobe and the irregular nodular lesion 3 cm wide in segment 10 adhered to the inferior pulmonary vein, with the inferior lobar branch of the pulmonary artery seen in the upper part on the border (fig. 1).

As pneumonia did not improve and there were radiological signs of progression, the patient was referred for surgical treatment. Using thoracoscopy, pulmonary tissue of the left lower lobe inclusive of the lesion described in HRCT scan was removed by wedge excision technique. The sampled tissue was divided, with a piece subject to a microbiologic exam and another piece referred for a histopathological exam. An active drain was placed, and there were no signs of an air leak.

FIGURE 1.
Perivascular fungal infiltration in the lungs.

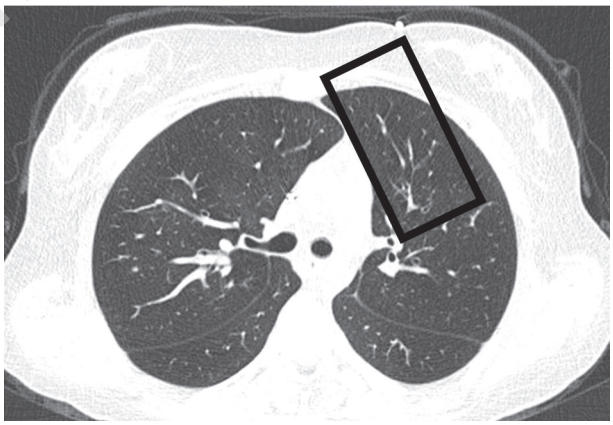


The microbiological exam of the pulmonary tissue extracted during the procedure confirmed *Aspergillus flavus* infection. The antifungal treatment was modified to ensure susceptibility of the pathogen to the agent used. The serum GM antigen detection test was positive. While receiving the treatment, the

patient gradually improved – cough resolved almost completely, auscultatory changes subsided and a follow-up HRCT scan showed reversal of pulmonary fungal lesions. However, inflammatory parameters remained high and grade 3 myelosuppression persisted. Thus, antibiotics, antifungal treatment, parenteral nutrition and nebulization were continued. The patient also underwent pulmonary and physical rehabilitation. As the patient was diagnosed with shingles of the ophthalmic nerve, intravenous acyclovir in maximum doses was implemented. Antiviral treatment was continued for 16 days as a result of which skin lesions subsided.

In August 2015, a molecular relapse was detected. The patient was referred for a transplant. Conditioning was based on intravenous busulphan, cyclophosphamide and melphalan. In September, the patient received haematopoietic stem cells from the peripheral blood of her sister who had a matching HLA, major blood types and Rh type. Cyclosporine A and methotrexate were used to prevent graft-versus-host disease. On the 6th day after the transplant, the patient received rituximab as prevention against EBV-positive post-transplant lymphoproliferative disorder. Early after the transplant, the patient developed complications in the form of neutropenic fever, oral and gastrointestinal mucositis and urinary tract bleeding. Antifungal treatment based on voriconazole was continued throughout the patient's hospitalisation. On the 27th day after the transplant, remission was confirmed and there were signs of haematopoietic recovery with improvement in the white and red blood systems, with evidence of single megakaryocytes. At that point, an acute intestinal form of graft-versus-host disease developed. The patient was initiated on methylprednisolone which improved her status. However, cytomegalovirus (CMV) reactivated, and the patient had to be treated with gancyclovir. In October 2015, a follow-up thoracic HRCT scan was performed. It showed a gradual regression of previously reported fungal lesions. A month later, a HRCT scan revealed a narrowing of the left main bronchus without an evident mass pressing on it from the outside, which presented with a distention of the left lower lobe and emergence of tree-in-bud lesions in the left lower lobe (fig. 2). A bronchoscopy showed a narrowing of the distal left main bronchus and inflammatory lesions of its mucosa. No pathological microorganisms (bacteria, fungi, *Mycobacterium tuberculosis* and *Pneumocystis jirovecii*) were identified in the bronchoalveolar lavage fluid. Epstein–Barr virus (EBV), CMV and adenovirus (ADV) infections were ruled out. Due to a suspicion of a non-infectious lung injury following allogeneic hematopoietic cell transplantation (IPS/BOS), classified as allo-immune pulmonary syndrome, the diagnostic tests were expanded to include pulmonary function tests. They showed a moderately reduced inspiratory and expiratory reserve volumes due to a possible obstruction and a reduced diffusing capacity of the lung for carbon monoxide (DLCO). Plethysmography could not be performed due to technical reasons (the patient remained in a horizontal position, unable to get into a sitting position by herself). Based on the comprehensive clinical picture, the patient was diagnosed with allo-immune pulmonary syndrome after allo-HSCT. Given that there was no evidence of the infectious background of the pulmonary lesions, antifungal medication was discontinued. The patient was referred for immunosuppressive therapy based on glycocorticosteroids and anti-TNFα. She received 8 doses of etanercept.

FIGURE 2.
Tree-in-bud lesions with visible "buds" in "tree branches".



However, in January 2016, a HRCT scan revealed progression of the pulmonary nodules, as a result of which recurrence of fungal disease was suspected despite negative results of fungal marker tests. Oral voriconazole was implemented. In February 2016, another HRCT scan showed that some of the nodules present in the pulmonary tissue progressed. As the patient showed no clinical respiratory symptoms, antifungal therapy was discontinued and a wait-and-see attitude was adopted.

In follow-up HRCT scans, the lung parenchyma presented a stable pattern, nodular lesions persisted, a tendency towards subpleural consolidation was identified and tree-in-bud lesions were found.

DISCUSSION

IFD diagnosis should lead to proving invasive fungal disease in patients from the risk group who present with clinical symp-

toms [4, 5]. The high-risk group includes patients with cancer, bone marrow failure and severe immune system disorders who have received cell or organ transplants. Clinical symptoms of IFD are signs of severe infection, usually of the lungs, paranasal sinuses, liver and spleen, as well as sepsis, less frequently infections of the central nervous system and soft tissue. IFD symptoms usually co-occur with microbiological symptoms, such as presence of fungal genetic material or fungal antigens as well as inflammatory markers [5].

IFD is considered to be proven when fungal infection is confirmed by a histologic study, a positive result of a culture based on material from a normally sterile site or a positive blood culture test. IFD is probable when both clinical and microbiologic criteria for diagnosing an invasive fungal infection (IFI) are met in a patient from the risk group. Patients are diagnosed with a possible IFD, when only clinical or only microbiological criteria are met in a patient from the risk group. According to most scientific analyses, a possible IFD is not regarded to be actual IFD. It is believed that invasive fungal disease is actually found only in 5–15% episodes of possible IFD.

In children suffering from cancer and showing IFD symptoms, the disease is rarely managed surgically although this approach should be preferred due to diagnostic reasons [5]. The surgical modality is particularly important when the location of IFD is life-threatening, e.g. close to vital blood vessels in the lungs [6]. That was the case with the patient from this case report. The decision was obvious and fungal lesion was excised from the lung urgently. Initially, clinical and microbiological symptoms weighed in favour of invasive aspergillosis: pulmonary location, typical radiologic lesions (nodules, halo and tree-in-bud) and the presence of galactomannan antigen. An examination of the excised pulmonary tissue confirmed infection with *Aspergillus flavus*. In that case, the drug of choice was voriconazole or amphotericin B lipid form which show a very good penetration to lung tissue [5]. It is important to note that patients after chemotherapy or transplants rarely develop primary pulmonary IFD caused by *Candida spp.* [7].

In grade invasive aspergillosis, surgical management is not the standard procedure. However, the European Conference on Infection in Leukaemia (ECIL) recommends it in case of [6]:

- close proximity of fungal lesion to large blood vessels
- haemoptysis
- non-pulmonary location of the lesion, including in the central nervous system.

The guidelines are optional (C III) as these conditions are usually preceded by earlier stages of the disease when antifungal agents are implemented. It should be stressed that indications for surgical management in invasive aspergillosis pertain to life-threatening conditions [8–10].

Initially, at the time of diagnosing a possible fungal infection (with negative galactomannan test result), antifungal therapy was based on amphotericin B lipid form. Aspergillosis infection could not be diagnosed at that point. Amphotericin B lipid form was chosen due to its most extensive antifungal action and very good penetration to lung parenchyma. As soon as aspergillosis was confirmed, antifungal treatment was modified to include voriconazole, an agent recommended in invasive aspergillosis.

SUMMARY

The report shows development of pulmonary IFD in a child with AML. In the course of the disease, the right diagnostic and therapeutic decisions were made. A complex course of the primary disease necessitated multiple therapeutic interventions, while the radiologic lesions evolved very slowly towards residual lesions.

Acknowledgments

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