Invasive Pulmonary Aspergillosis in Children: A Case Report and Literature Review

Haya Ibrahim Aljutaily

Abdullah Al-Shamrani

Patient: Female, 15-year-old

Final Diagnosis: Febrile neutropenia • invasive pulmonary aspergillosis

Symptoms: Cough • SOB

Medication: —

Clinical Procedure: —

Specialty: Oncology • Pediatrics and Neonatology • Radiology

Objective: Unusual clinical course

Background: Invasive pulmonary aspergillosis (IPA) is the major cause of mortality and morbidity in immunocompromised patients with prolonged neutropenia and is associated with poor prognosis. Multiple factors are associated with an increased risk of invasive aspergillosis, including persistent neutropenia, impaired lymphocyte engraftment following bone marrow transplantation, cytomegalovirus disease, respiratory virus infection, cytotoxic chemotherapy, and Aspergillus colonization. Unfortunately, attempts at fungal isolation are often unsuccessful.

Case Report: We describe a 15-year-old girl with a known case of acute myeloid leukemia (AML) with unusual cause of chest infection accompanied with a persistent radiological finding that worsened with time despite multiple levels of intervention. The optimal treatment was unclear, given that all cultures were negatives and the condition did not improve. Very interesting radiological findings will be elaborated in this case. Despite the typical radiological findings, we struggled to confirm the underlying cause of lung infection, which was demonstrated to be Aspergillus fumigatus by thoracoscopy and lavage. Eventually, when the patient started to improve, catastrophic bleeding occurred, confirming the angio-invasive nature of this organism.

Conclusions: IPA is still associated with very high morbidity and mortality. A high index of suspicion is needed for such cases. We recommend lavage on the third or fourth day of febrile neutropenia illness in patients who did not show clear improvement with the standard neutropenia protocol, and we suggest considering combined antifungal therapies at an earlier time point. IPA is angio-invasive and can lead to catastrophic bleeding. Earlier surgical intervention might be considered, especially in refractory localized aspergillus.

Keywords: Febrile Neutropenia • Hemoptysis • Invasive Pulmonary Aspergillosis • Pulmonary Aspergillosis

Abbreviations: PA – pulmonary aspergillosis; IPA – invasive pulmonary aspergillosis; CT – computed tomography; RLL – right lower lobe; ANC – absolute neutrophil count; WBC – white blood cell count; BAL – bronchoalveolar lavage; GM – galactomannan; IVIG – intravenous immunoglobulin; GCSF – granulocyte colony-stimulating factor

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Background

Aspergillus spp. are widespread in the environment and are commonly isolated from both the outdoor environment (e.g., soil, plant debris) and indoor environments, including hospitals. Pulmonary disease is caused by *Aspergillus fumigatus*, which is the most common pathogen [1]. PA is associated with a high mortality rate (generally 45%) and requires prompt diagnosis and treatment to prevent dissemination and death [2]. The disease is characterized by angioinvasion, arteriolar thrombosis, and hematogenous dissemination. Pathologically, pulmonary findings include necrotizing bronchopneumonia, hemorrhagic pulmonary infarction, micro-abcesses, solitary abscesses, lobar pneumonia, and tracheobronchitis [2]. Invasive pulmonary aspergillosis (IPA) is a severe disease and can be found in severely immunocompromised patients, critically ill patients, and those with chronic pulmonary diseases [1]. Chronic necrotizing aspergillosis (CNA) is locally invasive and is mainly observed in patients with mild immunodeficiency or chronic lung disease [1]. Symptoms of IPA are usually nonspecific and usually mimic bronchopneumonia: fever unresponsive to antibiotics, cough, sputum production, and dyspnea. Patients can also present with pleuritic chest pain (due to vascular invasion leading to thromboses that cause small pulmonary infarcts) and hemoptysis [1]. Immunocompromised patients, especially those with prolonged and profound neutropenia, are prone to systemic fungal infections, particularly invasive aspergillosis (IA) [3]. Early mycological detection of *Aspergillus* species is the cornerstone for prompt diagnosis, appropriate treatment strategy, and improved survival of patients with IA [4].

We present the case of an immunocompromised patient with febrile neutropenia, respiratory symptoms not responding to antibiotics, and a persistent radiological presentation suggesting invasive pulmonary aspergillosis.

Case Report

A 15-year-old girl with a known case of acute myeloid leukemia (AML) for the last 6 months received a regular course of chemotherapy (daunorubicin, cystine arabinoside, L asparaginase). Seven days later, after chemotherapy, she developed fever and cough. She was noted to be neutropenic (WBC 0.1/mm$^3$, ANC 0.0/mm$^3$). She was admitted with febrile neutropenia treated empirically with vancomycin and ceftazidime. One week later, she continued to be febrile and did not respond to a change in the antibiotics to peptazocilline, gentamicin, and metronidazole and prophylactic doses of fluconazole to treat mycoses. This regimen was changed to a standard dose of amphotericin B. At the end of the second week, the patient was still febrile and neutropenic (ANC 0.0/mm$^3$) and started to experience respiratory distress. Her admission chest X-ray was entirely normal. Serial X-rays showed significant opacities in the lower lobes, and a trial of IVIG and GCSF was added to the amphotericin B regimen, with little improvement. Pulmonary consultation was performed. Necrotizing pneumonia was expected with viral infection, fungal infection, and TB. Bronchoscopy and lavage revealed an erythematous airway with increased secretions. Microscopy, Gram staining, and cultures were all negative (including pneumocystis stains and fungal cultures),
and GM was negative from BAL (GM was not taken as a blood sample). Azithromycin and acyclovir were added after lavage, and the patient was transferred to the Intensive Care Unit for cardiorespiratory monitoring because of hypokalemia and increasing respiratory distress requiring oxygen supplementation only. The chest X-ray showed lower-zone infiltrates (Figure 1).

The patient was unwell, with the following vital signs: temperature, 38.8°C; heart rate, 120/m; respiratory rate, 30/m; saturation, 88% on room air, and 98% with 0.5 l/m. Vesicular breath sounds and scattered bilateral lung crackles were observed, especially at the posterior aspect of the chest. Other systemic exam results were normal, with some pallor and mild hepatomegaly noted. The initial blood work indicated leukopenia (WBC 0.1/mm$^3$, neutrophils 0/mm$^3$). The Hb level was 10 g/dl and the platelet level was 150/mm$^3$. Electrolytes were within normal limits, and the viral screen was negative. Her initial atrial blood gas readings revealed mild respiratory acidosis (pH 7: 34, PCO$_2$ 42, HCO$_3$ 25 mmHg). The chest X-ray showed significant bilateral lung infiltration in the middle and lower zones. Blood cultures were negative, and the CT chest was alarming, with halo signs suggestive of invasive pulmonary aspergillosis (Figure 2). Later, during hospital weeks 3-4, the lesion progressed to a typical air-crescent sign (Figures 3, 4), and the infection progressed to a globular enhancing mass consistent with pseudoaneurysm formation (Figure 5).

The patient was initially admitted for febrile neutropenia and administered i.v. antibiotics. Her respiratory condition was monitored, as she started with mild cough and tachypnea. Despite starting the neutropenia protocol and further trials of multiple antibiotics over 4 weeks, her condition did not improve. In fact, radiological images worsened with time. Conference meetings were held to discuss the potential treatment options, and the team decided to prepare for transthoracic lung biopsy in the operating room. The patient was later developed a complication of mild pneumothorax that was treated conservatively.
Figure 6. Histopathology of the lung biopsy Grocott staining, with the black arrow pointing to the presence of branching septated hyphae.

Figure 7. Thoracic CT, axial view, showing marked improvement with no evidence of a focal lesion.

The histopathology confirmed the presence of hyphae consistent with *Aspergillus* and no evidence of malignancy (Figure 6). The antifungal drugs were changed to AmBisome (liposomal amphotericin) and caspofungin. The patient’s temperature decreased, and WBC counts started to increase. The patient started to show clear clinical improvement. During hospital week 8, the patient showed significant clinical improvement; she was afebrile and had a normal WBC count. Unfortunately, she suddenly experienced a massive hemoptysis of greater than 400 ml at night. Bleeding was anticipated due to pseudoaneurysm formation, in keeping with the angio-invasive nature of invasive pulmonary aspergillosis. The work-up for coagulation defects was negative, and platelets were normal. Other potential differential diagnoses, such as broncho-arterial fistula, pulmonary infarct or embolism, and organizing pneumonia, were considered. This patient was urgently taken to the operating room for a right lower lobectomy with a right upper lobe wedge resection as a mycotic aneurysm. She received 3 units of packed red blood cells and fresh frozen plasma. During the postoperative course, she was connected to a BIPAP device for 1 night and responded well. She remained hospitalized for i.v. treatment with AmBisome and caspofungin for 3 months. A repeat CT scan showed marked improvement. AmBisome was discontinued due to concern about renal adverse effects, and caspofungin continued to be administered. The duration of the treatment was several months until total recovery, including both clinical and radiological resolution, was obtained. Repeated CT was considered (Figure 7) and our patient was maintained on caspofungin.

Discussion

Invasive aspergillosis (IA) is a serious medical condition in patients with hematological or oncological malignancies, and the mortality rate is increasing, reaching 40-50% in patients after chemotherapy and 80-90% in patients after hematopoietic stem cell transplantation [5]. It is well known that earlier treatment is associated with better survival, but the definitive diagnosis is difficult and often delayed [6]. It is also important to understand the disease progression of IPA and how to manage immunodeficient patients with pulmonary infiltrate.

We report our case with prolonged and refractory febrile neutropenia that did not respond to multiple adjustments of antibiotics.

Although pulmonologists were involved slightly late in this case, further lavage was negative for any organisms. Such a finding places a huge burden on treating physicians and on the family, given that no clear diagnosis could explain the persistent fever. A high index of suspicion of IPA needs to be considered in the case of immunodeficient patients with fever and shortness of breath, as noted in our case. Moreover, the initial images were nonspecific. Generally, CT findings of IPA are very informative, and the finding may include well-circumscribed lesion(s) with or without a surrounding “halo” of ground-glass gray attenuation, air-crescent sign, and cavity formation [7], all of which were positive at different stages and the diagnosis made late, during hospital week 4. A lung CT scan should be performed in a high-risk child with febrile neutropenia >96 h or with focal clinical findings. However, the appearance of any new infiltrate in chest CT in children with prolonged febrile neutropenia not responding to broad-spectrum antibiotics is a warning for potential fungal infection [8]. The air-crescent sign is frequently not seen in neutropenic patients, but can appear during the recovery phase [3]. The key in our case was that the lesion progressed from halo signs to air-crescent signs despite good antifungal therapy, raising the concern of choices of antifungal therapies. However, the incidence
of cavitation in the pediatric population appears to be significantly less than that in their adult counterparts. The air-crescent sign appears as a crescent-shaped area of radiolucency in a region of nodular opacity. Air crescents and cavitation are typically observed in older children [9]. However, the halo sign appears as ground-glass opacity surrounding a pulmonary nodule and is less specific than the air-crescent sign for invasive aspergillosis. Radiographic findings in patients with IPA include a nodule (the earliest radiographic sign), consolidation, wedge-shaped infarcts, and cavitation. The involvement of infective progression in the formation of a globular enhancing mass consistent with pseudoaneurysm formation indicates the angio-invasive nature of the organism. However, pulmonary hemorrhage is expected in the presence of large cavitating lesions or consolidations located close to larger pulmonary vessels. Although it can be associated with cavitation that occurs with neutrophilic recovery, as noted in our case, when the patient started to show some clinical improvement and resolution of neutropenia while on the i.v. antifungal regimen, she developed severe hemoptysis. Aspergillus species are not usually recovered from the blood, but are rarely (in less than 10% of patients) isolated from respiratory secretions such as sputum, and bronchoalveolar lavage can yield false-negative results [6]. In a study showing multiple bronchoscopies performed in immunocompromised children, the galactomannan (GM) assay in BAL fluid had a minimal impact on the clinical decision, and antifungal agents were continued despite a negative GM result in BAL fluid, as in our case [8]. The criterion standard in the diagnosis of IPA is tissue biopsy obtained by thorascopic or open-lung surgery (histopathological examination) [1]. This procedure is difficult to perform in critically ill patients with significant respiratory compromise and thrombocytopenia [6]. Galactomannan, a carbohydrate constituent of the Aspergillus cell wall, can also play a role in screening high-risk patients and assessing response to therapy [4,7]. Serum GM assays are not routinely performed in the oncology unit due to cross-reactivity and false-positive results for patients on beta lactam drugs, such as piperacillin and tazobactam [10]. Polymerase chain reaction (PCR) has become a promising diagnostic tool for the early detection of IA [4]. Galactomannan assays and PCR were not performed for our patient.

Combined antifungal therapy and early surgical excision is a feasible and effective strategy in pediatric patients with IA. Given that early definitive diagnosis is difficult, empiric administration of antifungal agents has become a standard of practice in neutropenic patients who remain persistently febrile despite broad-spectrum antibacterial therapy [11]. Surgical resection of the cavity and removal of the fungal mass are indicated in patients with recurrent hemoptysis [1]. However, surgery is often conducted either as an emergency procedure to prevent massive hemoptysis before marrow recovery or as an elective procedure after neutropenia resolution. Patients with localized pulmonary aspergillosis treated with both antifungal drugs and early lung resection showed a reduced progression of fungal disease at 6 months and a better overall survival compared to patients treated only with antifungal drugs. Resection of the fungal lesion (before bone marrow recovery) might reduce the risk of death related to arterial perforation [12]. Caspofungin and L-amphotericin B were comparable in tolerability, safety, and efficacy as empiric antifungal therapies for persistently febrile neutropenic pediatric patients, and both are known as primary antifungal regimens for IPA in neutropenic patients. In the present patient, these regimens were administered during the 4th week of illness [11]. A new broad-spectrum antifungal triazole, voriconazole, has been approved as the initial treatment of invasive aspergillosis and is considered the drug of choice in many patients with IPA. Patients receiving voriconazole had a higher favorable response rate at week 12 (53% versus 32% in patients receiving amphotericin B) and higher 12-week survival (71% versus 58%) [1]. Voriconazole is available in both intravenous and oral formulations. In our case, double-agent antifungal therapy with AmBisone and caspofungin response resulted in improvements in fever and increased WBC counts. In our case, the response to therapy was complete, as all the symptoms and signs of fungal infection disappeared. The optimal duration of antifungal treatment for invasive aspergillosis has not been established in pediatric patients. Aspergillus is slow growing and more difficult to eradicate because the duration of therapy can be several months. Lung resection can clear fungal infection in approximately 80% of patients. Mid- to long-term survival can be achieved if the underlying hematologic disease is under control [13,14]. Our patient was urgently taken to the emergency room for a right lower lobe aneurysm preceded by massive hemoptysis, which can be explained by the angio-invasive nature of the disease. The condition was controlled in the operating room by blood transfusion, and surgical excision exhibited a smooth postoperative course. The patient remained on combined i.v. treatment with AmBisome and caspofungin for 3 months, then stepped down to caspofungin for 3 more months when she showed complete resolution of the respiratory symptoms, accompanied by marked resolution of the radiological findings.

Conclusions

IPA still has very high morbidity and mortality rates. A high index of suspicion is needed for such cases. Febrile neutropenia is a major risk factor for opportunistic infections, including fungal infections. We recommend lavage in the third or fourth day of illness in patients who do not show clear improvement in febrile neutropenia and suggest consideration of combined antifungal therapies as soon as possible. Radiologists can help
anticipate certain complications, such as air-crescent signs. IPA is angio-invasive and can lead to catastrophic bleeding. Earlier surgical intervention might be considered, especially in refractory localized Aspergillus or if there is a question of angioinvasion. Serial case conferences are recommended for such patients to discuss the best therapeutic option; full recovery is possible despite the high mortality rate.

References:

1. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: A clinical review. Eur Respir Rev. 2011;20(121):156-74
2. Steinbach W. Invasive aspergillosis in pediatric patients. Curr Med Res Opin. 2010;26(7):1779-87
3. Rubio P, Sevilla J, González-Vicent M, et al. Increasing incidence of invasive aspergillosis in pediatric hematologic oncology patients over the last decade. J Pediatr Hematol Oncol. 2009;31(9):642-46
4. Rolides E, Pana Z. Application of diagnostic markers to invasive aspergillosis in children. Ann NY Acad Sci. 2012;1272:1-8
5. Cesaro S, Cecchetto G, De Corti F, et al. Results of a multicenter retrospective study of a combined medical and surgical approach to pulmonary aspergillosis in pediatric neutropenic patients. Pediatric Blood Cancer. 2006;49(7):909-13
6. Owens C, Novelli V, Costoli V, et al. The radiological spectrum of invasive aspergillosis in children: A 10-year review. Pediatr Radiol. 2003;33(7):453-60
7. Koltsida G, Zaoutis T. Fungal lung disease. Paediatr Respir Rev. 2021;37:99-104
8. Lehmbecher T, Hassler A, Groll A, Bochenerk K. Diagnostic approaches for invasive aspergillosis – specific considerations in the pediatric population. Front Microbiol. 2018;9:518
9. Burgos A, Zaoutis T, Dvorak C, et al. Pediatric invasive aspergillosis: A multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008;121(5):e1286-94
10. Maertens J, Theunissen K, Verhoef G, Van Eldere J. False-positive aspergillus galactomannan antigen test results. Clin Infect Dis. 2004;39(2):289-90
11. Maertens J, Madeno L, Reilly A, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J. 2010;29(5):415-20
12. Caillot D, Mannone L, Cuisenier B, Couaillier J. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. Clin Microbiol Infect. 2001;7:54-61
13. Matt P, Bernet F, Habicht J, et al. Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. Chest. 2004;126(6):1783-88
14. Cesaro S, Cecchetto G, De Corti F, et al. Results of a multicenter retrospective study of a combined medical and surgical approach to pulmonary aspergillosis in pediatric neutropenic patients. Pediatr Blood Cancer. 2007;49(7):909-13

Institution Where Work Was Done
Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia.

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