

Pulmonary Aspergillosis Developing After the First Chemotherapy Session in a 15-Year-Old Boy: A Case Report

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Abstract: A 15-year-old boy diagnosed with acute myeloid leukemia (AML) was readmitted to the hospital with a fever and an atypical lung infection just one day after being discharged following his initial chemotherapy session. The symptoms continued and worsened with time even though multiple levels of antibiotic treatment were tried. It was the typical radiological findings aided in diagnosing the cause and demonstrated to be invasive pulmonary aspergillosis. Furthermore a dramatic response to the standard treatment and positive serum GM test confirmed the diagnosis.

Keywords: febrile neutropenia, invasive pulmonary aspergillosis, pulmonary aspergillosis, acute myeloid leukemia

Introduction

Aspergillosis, primarily caused by the fungus *Aspergillus fumigatus*, is the most common mold-related infection affecting the lungs. Its clinical manifestations vary widely, mainly influenced by the immune status of the host.¹ In patients with asthma or cystic fibrosis, *A. fumigatus* can trigger allergic bronchopulmonary aspergillosis (ABPA), characterized by hypersensitivity reactions in the lungs.² Chronic pulmonary aspergillosis, on the other hand, predominantly occurs in individuals who are either immunocompetent or only mildly immunocompromised and often have pre-existing lung diseases such as chronic obstructive pulmonary disease, post-tuberculosis scarring, nontuberculous mycobacterial infections, or lung cancer. Chronic pulmonary aspergillosis can present with a spectrum of overlapping conditions, ranging from isolated aspergillomas (fungal balls in pre-existing lung cavities) to more complex forms such as chronic cavitary, fibrosing, and microinvasive aspergillosis.^{1,3} A more severe variant of chronic pulmonary aspergillosis, termed subacute invasive aspergillosis (also referred to as semi-invasive or chronic necrotizing aspergillosis), develops as a progressive disease with tissue invasion and necrosis, typically affecting patients who are mildly immunocompromised.⁴ Acute invasive pulmonary aspergillosis, the most aggressive form, occurs in individuals with significant immune compromise, such as those with hematologic malignancies, chemotherapy-related neutropenia, or those receiving immunosuppressive therapies for autoimmune conditions or following organ transplantation.¹ Notably, IPA has recently been observed in intensive care unit (ICU) patients undergoing mechanical ventilation due to severe influenza or COVID-19, including those considered to have an intact immune system.¹ While *Aspergillus fumigatus* is the predominant cause of aspergillosis worldwide, other species such as *Aspergillus flavus* (more frequent in certain parts of Africa and Asia), *Aspergillus terreus*, and *Aspergillus niger* contribute to a smaller proportion of cases. Less commonly, species like *Aspergillus nidulans*, *Aspergillus calidoustus*, *Aspergillus glaucus*, *Aspergillus versicolor*, and cryptic species such as *Aspergillus lentulus* and *Aspergillus udagawae* account for fewer than 3% of cases.¹

Diagnosing and managing pulmonary aspergillosis remains challenging due to suboptimal sensitivity and specificity of diagnostic tools, which frequently cause delays in diagnosis and treatment initiation.¹ Therapeutic management is further complicated by limited treatment options, significant drug interactions—particularly involving triazole antifungals—adverse effects, and the increasing problem of antifungal resistance.

We present a case of an unusual lung infection in a 15-year-old boy with newly diagnosed acute myeloid leukemia, occurring immediately after his first chemotherapy cycle. This case serves to frame a broader discussion on current diagnostic methodologies, therapeutic strategies, and recent advancements in the management of invasive pulmonary aspergillosis, while also considering future directions for improving patient outcomes.

The patient's signs and symptoms were common in many other pulmonary infections and clinical symptoms were mild at the beginning and worsened by time. The patient's radiological findings remained persistent until the best possible treatment was performed. This case presents some highly intriguing radiological findings. Although the imaging is consistent with typical patterns seen in fungal infections, efforts to determine the exact cause of the lung infection were hindered as the patient's guardians declined the bronchoscopy procedure. However serum GM test was reported positive and confirmed the probable diagnosis of invasive pulmonary aspergillosis. Also a dramatic response to the choice treatment of pulmonary aspergillosis besides the typical radiological findings and positive serum GM made us confident about the exact diagnosis.

Case Report

A 15-year-old boy, recently diagnosed with acute myeloid leukemia (AML), was readmitted to the hospital just one day after being discharged. His diagnosis was confirmed about two weeks before this second hospitalization. During his initial stay, he had undergone his first round of chemotherapy, which included Daunorubicin, Cytarabine, Etoposide, and Intrathecal Cytarabine. One day after his discharge from hospital he developed fever and cough. His fever was unresponsive to acetaminophen and NSAIDs. He was noted to be neutropenic (WBC 400/ μ L). He was admitted with febrile neutropenia and the following vital signs. Temperature, 38.1°C; heart rate, 97 bpm; Blood Pressure, 110/70 mmHg; Respiratory rate, 23/m. Laboratory tests were taken and treatment began empirically with cefotaxime and GCSF. His admission Chest X-ray revealed consolidation in the left perihilar region (Figure 1).

After 4 days of treatment he was still febrile so antibiotic changed to meropenem and vancomycin. After 7 days of treatment there was no clinical improvement, so another Chest X-ray was performed to reassess the previous opacity and Liposomal amphotericin B was added to the regimen due to suspicion of fungal infections. In the second Chest X-ray haziness and ground glass opacities were increased in left lung (Figure 2).

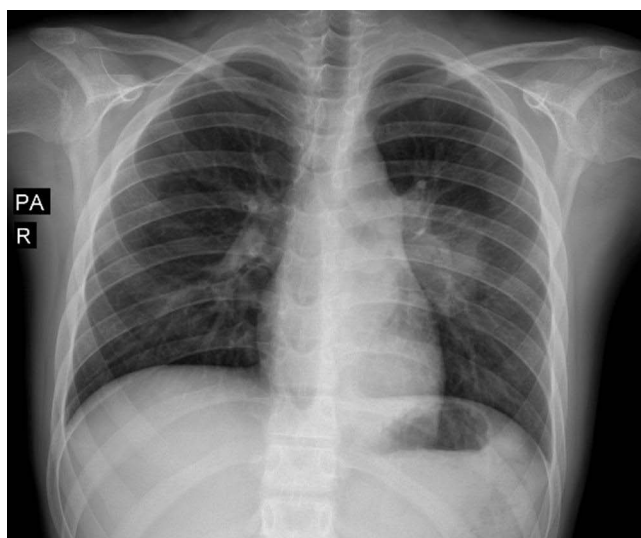


Figure 1 Chest X-ray shows a consolidation opacity in the left perihilar region. Additionally, there is mild haziness observed in the middle and lower lobes of the left hemithorax. No overt pleural effusion or pneumothorax is identified.

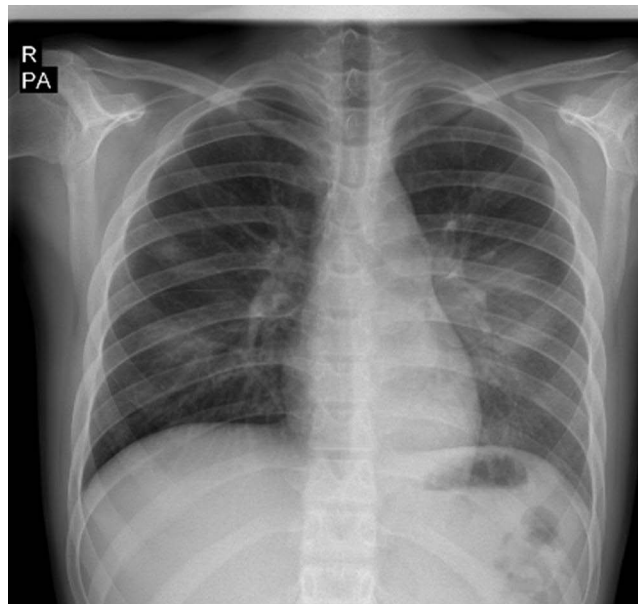


Figure 2 Second Chest X-ray demonstrates diffuse haziness and ground-glass opacity in the middle and lower zones of the left lung. Compared to the prior Chest X-ray, there is increased retrocardiac opacity. Additionally, two nodular consolidations are noted in the lower and middle zones of the right hemithorax, which were not previously noted.

At the 13th day of admission the patient still had no clinical improvement and started to experience respiratory distress. Bilateral lung crackles and skin lesions indicative of a fungal infection were observed and clotrimazole ointment was started. Pulmonary consultation was performed and suggested performing a CT scan and adding oseltamivir and azithromycin to the regimen. CT scan showed consolidation like air space opacity with air bronchogram and ground glass opacity in inferior lobe of left lung, air crescent was seen peripherally to a hypodense area with liquid density suggested necrosis, 6 nodular consolidations with ground glass halo sign around them were seen in both lungs which some of them were cavitory (Figures 3–5). The overall findings were in favor of opportunistic infections, primarily fungal infections, particularly aspergillosis. Among other differential diagnoses with lower probability, pulmonary mucormycosis, Staphylococcal pneumonia and other gram-negative bacteria were considered.

After viewing the CT scan, the team decided to start intravenous voriconazole and sent a serum sample for galactomannan testing. Blood cultures (the first test was performed on the day of admission, with a second test following a day 7 chest X-ray) were all negative but serum GM had been reported positive (GM 1.2) which confirmed the probable diagnosis. There was an impressive clinical improvement 3 days after receiving voriconazole. The second serum GM test was reported negative 11 days after the first test (GM 0.4). After 4 weeks of hospitalization the patient was discharged with voriconazole tablets 200 mg twice a day and CT-Scan was repeated 4 weeks after the first CT-Scan (Figures 3–5).

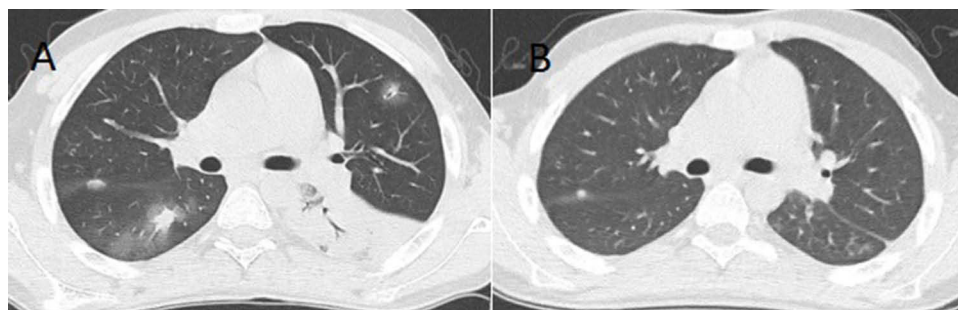


Figure 3 Thoracic CT scan parenchymal window. Axial view (A) shows multiple nodular consolidation with peripheral ground glass opacity (halo sign) and alveolar consolidation at left lower lobe. Some nodules show central cavitory change. In view (B), after 4 weeks of treatment almost all the consolidations have been cleared.

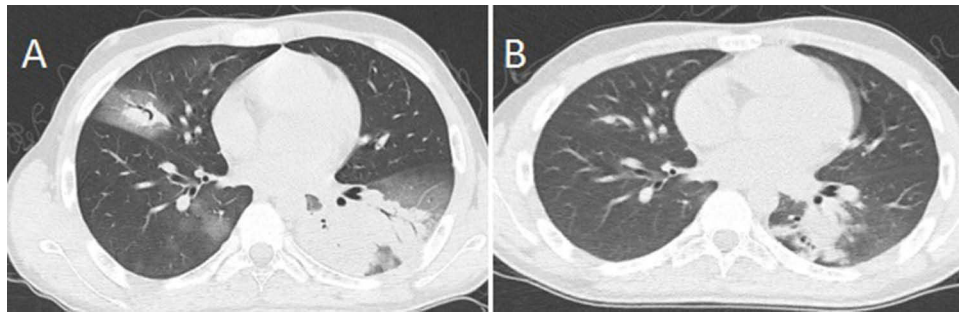


Figure 4 In axial view (A), Lung CT shows nodular consolidation with peripheral ground glass halo and central air-crescent in right middle lobe. Also patchy ground glass opacities at right lower lobe and alveolar consolidations with central cavity changes and peripheral ground glass opacity halo at left lower lobe were noted. In view (B), most of the opacifications are gone and only a part of consolidation opacities in the left lung remained.

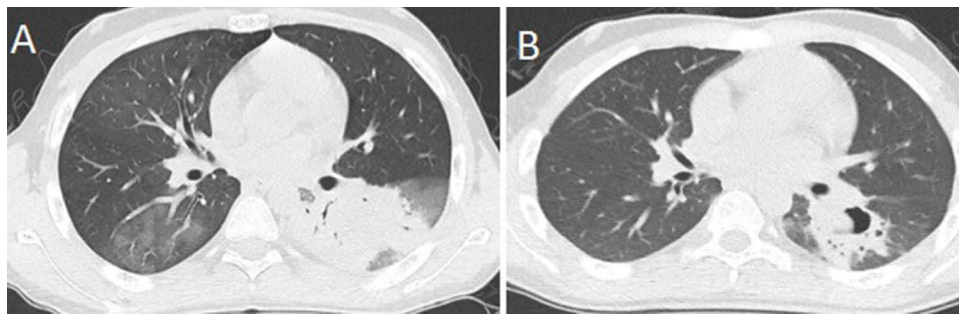


Figure 5 Thoracic CT shows ground glass opacifications at right lower lobe and alveolar consolidations with peripheral ground glass halo and central air-crescent at left lower lobe (A). 4 weeks after treatment, most of the opacities have been cleared and central area has been excavated (B).

Discussion

Invasive pulmonary aspergillosis is a serious and potentially fatal fungal infection that predominantly targets individuals with weakened immune systems.⁵ This case report discusses the difficulties encountered in the diagnosis and treatment of IPA, especially when compounded by underlying risk factors like neutropenia and intensive chemotherapy. The patient in this case presented with nonspecific symptoms, including fever and cough which are common in many respiratory conditions, underscoring the diagnostic complexity of IPA.^{1,6} While histopathological examination and culture of *Aspergillus* species from respiratory specimens remain the gold standard, these methods are often invasive and may not be feasible in all patients.^{5,7} Non-invasive diagnostic methods, such as serum galactomannan assay and beta-D-glucan testing, have improved the ability to detect IPA, but false positives and negatives can occur and do not rule out IPA.⁸⁻¹⁰ Serial Galactomannan testing is advised for early detection and ongoing monitoring of patients with invasive pulmonary aspergillosis. It serves as a valuable prognostic tool for assessing disease progression and evaluating the effectiveness of antifungal therapy.¹¹ The phenomenon of false positivity in the galactomannan assay may be attributed to a multitude of factors. Galactomannan is present in specific fungal and bacterial species, which can lead to erroneous positive results. Cross-reactivity may arise with certain beta-lactam antibiotics and with GM produced by some other fungal taxa, along with various epidemiological and biological factors that contribute to this issue. The ability to detect galactomannan in serum is diminished when mold-active antifungal therapy is administered concurrently. For example, in patients undergoing prophylactic treatment with posaconazole or voriconazole, these therapies may interfere with the circulation of galactomannan.^{1,12} In comparison between IPA and pulmonary mucormycosis, the halo sign is more indicative in patients with IPA, while the reverse halo sign is more frequently observed in patients with PM. Peribronchial consolidations, clusters of centrilobular nodules, ground-glass opacities, and smooth bronchial wall thickening are more frequently observed in patients with IPA compared to those with pulmonary mucormycosis.^{13,14} Due to the lack of distinct clinical symptoms and the restricted sensitivity or specificity of radiological and mycological tests, diagnosing IPA is categorized based on a probability scale, ranging from possible to probable and proven cases.

The European Organization for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium (EORTC-MSGERC) has developed standardized definitions to determine these diagnostic categories specifically for immunocompromised patients.¹ According to the EORTC-MSGERC criteria, the diagnosis of IPA is based on four key components. Host factors, identifying immunocompromised patients at risk. Clinical criteria, including specific radiological findings on a CT scan. Mycological evidence, positive laboratory tests, such as GM in serum or bronchoalveolar lavage fluid. Proven infection, definitive proof from positive histopathology or culture, supported by clinical and radiological evidence.¹ In this case, the combination of host immunosuppressive condition, radiological findings, such as the halo sign, ground glass opacities and cavitary lesions on CT imaging, along with clinical improvement after starting proper antifungal therapy for IPA and a positive serum GM test provided strong supportive evidence for IPA. However, the absence of histopathological confirmation emphasizes the necessity of maintaining a high level of suspicion in patients with compromised immune systems.^{1,9} The management of IPA requires a multidisciplinary cooperation, involving antifungal therapy, optimization of immune status, and, in some cases, surgical intervention. Voriconazole serves as the primary treatment option for IPA, supported by Cheng's meta-analysis demonstrating its superiority over amphotericin B.¹⁵ Patients treated with voriconazole showed a higher favorable response rate by week 12, achieving 53% compared to 32% in those treated with amphotericin B. Additionally, the 12-week survival rate was higher for voriconazole patients at 71%, versus 58% for amphotericin B recipients.^{1,6,9,15,16} However, the azole-resistant *Aspergillus* strains pose a growing concern, necessitating antifungal susceptibility testing when feasible.⁵ The standard treatment for PM is liposomal amphotericin B, which did not respond adequately in this case.¹⁷ In our case voriconazole response was much better than amphotericin B which strongly supported our diagnosis of IPA. Adjunctive therapies, such as granulocyte transfusions or interferon-gamma, may be considered in refractory cases, although their efficacy remains controversial.^{5,18}

The prognosis of IPA is closely tied to the timeliness of diagnosis and the underlying immune status of the patient.^{1,19} Delaying the start of antifungal therapy has been linked to a notable increase in mortality rates, highlighting the critical need for prompt diagnosis and timely treatment.^{1,20} In this case, the patient's favorable outcome was attributable to the prompt initiation of voriconazole and the gradual recovery of neutrophil counts. However, long-term follow-up is crucial, as relapses can occur, particularly in patients with persistent immunosuppression.^{1,19} One important point of this case was that the patient was infected just after the first session of chemotherapy showing that every chemotherapy-induced immunosuppression is an opportunity for IPA. This case also shows the importance of preventive strategies in high-risk populations. Antifungal prophylaxis with posaconazole or voriconazole is recommended in patients with prolonged neutropenia or those undergoing hematopoietic stem cell transplantation. Environmental actions, including the application of HEPA (high-efficiency particulate air) filters, can further reduce the risk of *Aspergillus* exposure in healthcare settings.⁵

Conclusion

Invasive pulmonary aspergillosis continues to be a significant contributor to morbidity and mortality among immunocompromised individuals. Challenges associated with IPA emphasize the importance of maintaining a high level of suspicion, early initiation of appropriate antifungal therapy and a multidisciplinary approach to management. Febrile neutropenia is a significant risk factor for opportunistic infections, including fungal infections. We recommend CT-Scan in patients who have abnormal CXR or in patients who do not show clinical improvement after three or four days of hospitalization with febrile neutropenia. Also early initiation of combined antifungal therapies should be considered. Radiologists can play a significant role in these cases. They can help in diagnosing and anticipate complications such as air-crescent signs. IPA is angio-invasive and carries a risk of catastrophic bleeding. In cases of suspected angioinvasion or refractory localized aspergillus infection, early surgical interventions should be taken into consideration. Further research should focus on improving diagnostic accuracy and optimizing preventive strategies to reduce the burden of this infection. For such patients multidisciplinary hospital case conferences can be recommended to determine the best treatment strategy and despite the high mortality rate, full recovery is achievable.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors did not use artificial intelligence (AI)-assisted writing tools when preparing this work.

Abbreviations

IPA, invasive pulmonary aspergillosis; WBC, white blood cell count; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; GM, galactomannan; GCSF, granulocyte colony stimulating factor; CXR, chest x-ray; PM, pulmonary mucormycosis; CT, computed tomography.

Consent and Ethical Approval

Written informed consent was obtained from the patient's guardian for publication of this case report and any accompanying images. The patient has been informed about the details of the case and has provided approval for the information to be published in this case report. This study was also approved by the ethical committee of Babol University of Medical Sciences and the following number of IR.MUBABOL.HRI.REC.1404.045. The authors confirm that the approval of an institutional review board was not required for this work but it was done in good faith.

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Disclosure

All authors report no conflicts of interest in this work.

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