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Case Report

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A Case with Multiple Fungal Coinfections in a Patient who Presented with Pancoast Syndrome

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ABSTRACT

Invasive fungal infection (IFI) is a serious threat to pediatric patients with cancer given high morbidity and mortality. We present an 18-year-old male with precursor T-cell lymphoblastic leukemia who developed Pancoast syndrome, presented with paresthesia and numbness in the right shoulder and arm during a neutropenic fever period. He was diagnosed with pneumonia in the right upper lung field. He was later found to have an invasive pulmonary fungal infection caused by multiple fungi species, including *Rhizomucor*, confirmed by histology and polymerase chain reaction (PCR) (proven infection), *Penicillium decumbens* diagnosed by PCR, and *Aspergillus* suspected from galactomannan assay (probable infection). Unfortunately, the patient's condition further worsened owing to the aggravation of leukemia, chemotherapy-induced neutropenia, and bacterial coinfection, leading to multiorgan failure and death. Here, we report a case of IFI caused by multiple fungal species that presented as Pancoast syndrome.

Keywords: Pancoast syndrome; Lung diseases, fungal; Coinfection

INTRODUCTION

Fungal infections by *Rhizopus*, *Mucor*, and *Rhizomucor* species account for up to 75% of mucormycosis cases encountered in patients with hematologic malignancy.[1] In addition, *Aspergillus* species are an important cause of life threatening infection in immunocompromised patients. This at-risk population includes allogeneic hematopoietic stem cell transplant recipients, solid organ transplant recipients, and patients using corticosteroids; this group is predisposed to invasive fungal infections (IFIs).[2] High rates of mortality and morbidity have been reported among patients with IFI caused by multiple

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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fungal species, as each species has different sensitivity to antifungal agents.[2,3] Therefore, prompt clinical suspicion and appropriate therapy considering antifungal sensitivity is critical in such cases. Here, we present the case of an 18-year-old man with relapsed precursor T-cell lymphoblastic leukemia who initially presented with neutropenic fever and Pancoast syndrome (right shoulder and arm pain and paresthesia) and subsequently was diagnosed with pulmonary IFI caused by multiple fungal species that manifested the symptoms of Pancoast syndrome.

CASE

An 18-year-old man with relapsed precursor T-cell lymphoblastic leukemia was admitted with neutropenic fever and bacteremia caused by *Klebsiella pneumoniae*. Catheter-related blood stream infection was suspected and cefepime was administered. His fever subsided within 24 hours, and a follow-up blood culture was negative. The initial antimicrobial agent was continued along with the preexisting fluconazole prophylaxis. On the 5th hospital day, he developed right shoulder pain and paresthesia and numbness in the right arm. In addition, he showed right arm motor weakness and developed a fever of 38.3°C. Spine and brain magnetic resonance imaging (MRI) performed on the 9th hospital day revealed no significant abnormality in the bony structure of his spine and brain but showed edematous change and increased signal intensity at the right brachial plexus, suggesting brachial plexus impingement (**Figs. 1** and **2**). Furthermore, pulmonary consolidation in the right upper lobe with interstitial thickening was observed on MRI (**Fig. 2A**). On the 10th hospital day, chest computed tomography (CT) (**Fig. 2B and C**) revealed right upper lobe pneumonia. The patient was treated with liposomal amphotericin B (**Fig. 1**). On the same day, we performed a serum galactomannan (GM) assay using an ELISA kit (IBL International, Hamburg, Germany) targeting *Aspergillus fumigatus* IgG, which yielded negative results. However, his

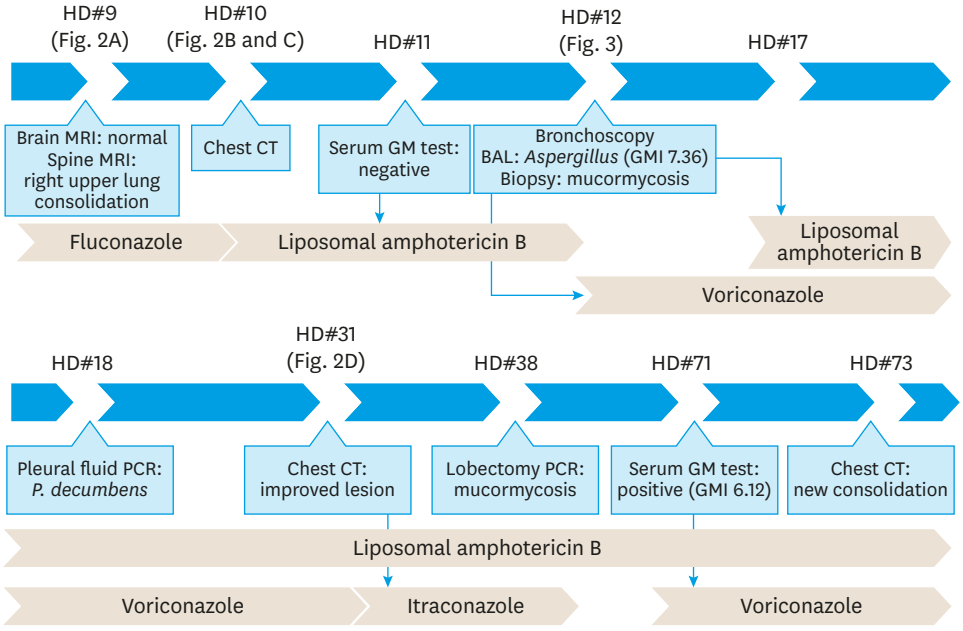

Fig. 1. Flow chart of the diagnostic methods and antibiotic use during the clinical course.
Abbreviations: HD, hospital day; MRI, magnetic resonance imaging; CT, computed tomography; GM, galactomannan; BAL, bronchoalveolar lavage; GMI, Galactomannan index, PCR, polymerase chain reaction.

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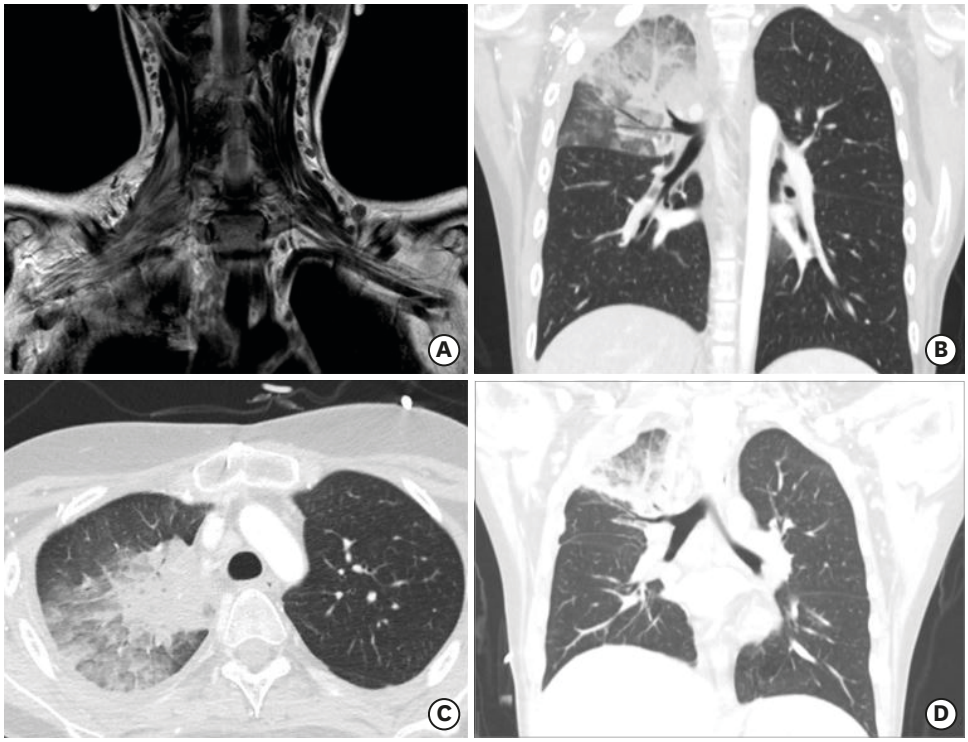

Fig. 2. (A) Spine magnetic resonance imaging showing pulmonary consolidation in the right upper lobe, with edematous change and increased signal intensity at the right brachial plexus indicating brachial plexus impingement. (B, C) Chest CT images showing airspace consolidation, ground glass opacity, intralobular septal thickening in the right upper lobe of the lung and pleural effusion. (D) Chest CT image showing reduced consolidation and ground glass opacity in the right upper lobe after antifungal treatment.
Abbreviation: CT, computed tomography.

bronchoalveolar lavage (BAL) sample collected on the 12th hospital day later yielded a positive galactomannan index (GMI) of 7.36. Therefore, liposomal amphotericin B was switched to voriconazole for the treatment of the suspected pulmonary aspergillosis (**Fig. 1**). On the 17th hospital day, the histopathology of bronchial tissue collected at the time of bronchoscopy identified mucormycosis (**Fig. 3**). Based on this finding, liposomal amphotericin B was

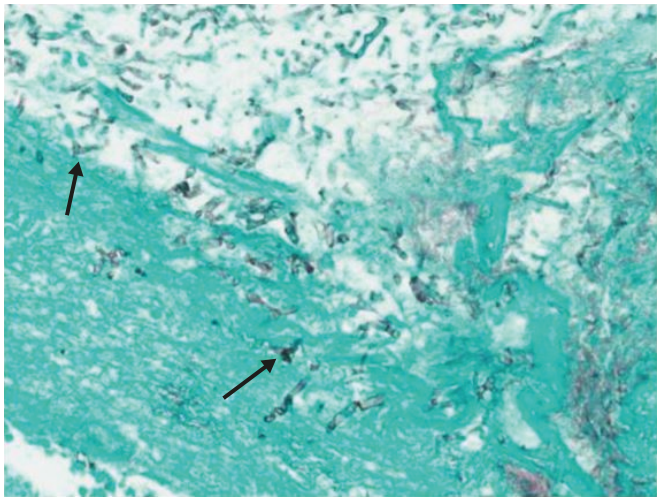

Fig. 3. Histopathologic examination of a bronchial tissue section in the right upper lobe and mediastinal lymph node showing non-septate broad filamentous fungi branching nearly 90° (arrow), suggesting mucormycosis.

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resumed to cover both aspergillosis and mucormycosis. On the 18th hospital day, a large volume of pleural effusion was noted and was drained. Fungal Sanger sequencing using the BigDye Terminator Cycle Sequencing Kit 3.1 on an ABI prism 3730 Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA) targeting fungus-specific internal transcribed spacer (ITS) regions covering ITS1, 5.8S, and ITS2 from the pleural fluid detected *Penicillium decumbens.* Multiple follow-up serum GM assay results were all negative for almost 3 months. Therefore, we considered the possibility of false-positive *Aspergillus* antigen assay result caused by *P. decumbens* infection. However, we could not completely rule out simultaneous multiple fungal infections and continued both liposomal amphotericin B and voriconazole (**Fig. 1**).

The patient's condition stabilized and the fever subsided. Lung lesions were resolved on chest CT on the 31st hospital day (**Fig. 2D**). On the 34th hospital day, voriconazole was switched to itraconazole (**Fig. 1**) because prolonged liposomal amphotericin B and voriconazole combination treatment is not reimbursed by the Korean national health insurance system. On the 38th hospital day, we performed a lobectomy of the right upper lobe to effectively decrease his fungal burden, with a plan to proceed to chemotherapy for his relapsed leukemia as soon as the fungal infection resolved. On the 48th hospital day, histologic examination of the lung tissue revealed fungal presence and DNA Sanger sequencing identified *Rhizomucor* species (*R. pusillus* and *R. tauricus*), and *Aspergillus* was not detected. Therefore, itraconazole was discontinued (**Fig. 1**). His shoulder and arm pain aggravated. The patient's bone marrow biopsy revealed lymphoblasts on the 51st hospital day, and chemotherapy was restarted to treat leukemia. Liposomal amphotericin B was continued to treat mucormycosis.

However, on the 73rd hospital day, follow-up chest radiography and CT showed a newly developed consolidation in the right lower and left upper lobes. Simultaneously, his serum GMI was positive at 6.12 for the first time during his fungal infection course. Voriconazole was reintroduced on the 71st hospital day because aspergillosis could not be ruled out and his GM assay results were positive ever since. He developed neutropenic fever and bacteremia caused by methicillin-resistant *Staphylococcus epidermidis* on the 87th hospital day. Thereafter, his condition rapidly deteriorated and he died of septic shock and multiorgan failure without responding to inotropes.

This study was conducted with approval of Samsung Medical Center Institutional Review Board (No. 2020-06-145).

DISCUSSION

We present the case of an 18-year-old man with T-cell lymphoblastic leukemia who experienced IFI presumably caused by multiple fungal species. Although we treated the patient with combinational antifungal therapy and surgical resection to control the persistent multiple fungal infections, the patient did not survive.

Early diagnosis of IFI remains a challenge. Currently, the gold standard for diagnosis of IFI is direct observation or culture tests from tissue samples for pathogens.[4] In patients with IFI, radiologic studies, including CT imaging, are useful diagnostic tools.[5]

Our patient developed Pancoast syndrome that led to the further radiologic imaging work-up, which in turn led to the diagnosis of pulmonary IFI. Pancoast syndrome is characterized by

shoulder and arm pain that radiates to the ulnar aspect of the arm and forearm. It is caused by the involvement of the spinal nerve roots from the 8th cervical spinal nerve to the 2nd thoracic spinal nerve of the brachial plexus. Apical lung cancer and other malignancies are predominant causes of Pancoast syndrome. Furthermore, infective conditions such as fungal infection (as in this case) caused by *Aspergillus*, *Cryptococcus*, and *Mucor* are reported to cause Pancoast syndrome.[6] Shoulder and arm pain in immunocompromised patients could be the first symptom of pulmonary infections such as IFIs. Pulmonary infections should additionally be considered when a patient presents with the symptoms of Pancoast syndrome.

Biomarkers are additional tools that can help diagnose IFI. At our center, sensitivity and specificity to serum GM assay among pediatric patients with cancer were 91.3% and 81.7%, respectively.[7] Several studies have assessed the utility of GM assays as a diagnostic tool in children with symptoms potentially indicative of IFI. A systematic review reported the pooled sensitivity and specificity at 89% and 85%, respectively.[8] Sensitivity and specificity to GM in BAL fluid seems higher than that in the serum among immunocompromised adult patients; however, such studies in pediatric patients are lacking.[4]

P. decumbens is found abundantly in natural sources and commonly in soil worldwide. *P. decumbens* was first identified in 1992 on an indirect fluorescent antibody test for a patient with pneumonia.[9] Recently, *Penicillium* species have emerged as opportunistic pathogens in immunocompromised hosts and have been reported to cause coinfections with the *Mucor* species.[10,11] *P. decumbens* alone can cause pulmonary IFI, similarly to other fungi. Studies have reported cross-reactions between *Aspergillus* and *Penicillium* or other fungal species on GM assays.[12] In our patient, the GM assay was positive on 2 different periods. We speculate that the first GM-positive identification with the BAL sample on the 12th hospital day was likely a false positive caused by *P. decumbens*. However, at that time, we could not ascertain whether it was an *Aspergillus* infection that was present from the beginning of the course or a *Penicillium* infection presenting as GM cross-reactivity. Therefore, we continued voriconazole although the pleural fluid returned positive for *P. decumbens.* The second positive result from the blood sample on the 72nd hospital day was considered to be a true infection by *Aspergillus* despite the patient being on liposomal amphotericin B.[13] We excluded the conditions that would cause false-positives for the following condition. In this patient, a newly identified lesion was observed on CT and consecutive GM values were significantly high. Antibiotics that can potentially cause false-positive results were not used, and we confirmed no issues with the sample collection process.

Mucormycosis can occur in various presentations such as rhinocerebral, pulmonary, cutaneous, and gastrointestinal diseases, and tends to disseminate. Surgery is the treatment of choice for mucormycosis, when complete removal of the fungus is feasible.[14] We considered surgical resection from the beginning of the patient's course. However, the patient's condition was not stable for surgery. When blast cells appeared again in peripheral blood, surgery was performed to achieve a more aggressive reduction of the fungal burden so chemotherapy could be initiated.

If more than one pathogen is found in the same anatomic region, mixed fungal infections should be considered. Such infections have high rates of mortality and morbidity.[2,3] In addition, comparatively rare and opportunistic species are found in higher proportions in mixed infections.[15] Therefore, early detection and appropriate antifungal therapy are crucial. Although uncommon, *Mucor* and *Aspergillus* coinfections are well-reported in the literature.

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Table 1. Case reports of invasive fungal infections caused by multiple fungal species

Age/sex	Underlying disease	Antifungal treatment	Pathogen(s)	Clinical course	Reference
53/F	Diabetes	Voriconazole, liposomal amphotericin B	Bacterial culture of bronchial aspirate: *Klebsiella pneumoniae* Fungal stain of bronchial aspirate: *Aspergillus*, *Mucor* Fungal culture of bronchial aspirate: *Aspergillus*	Dead	Gupta et al.[16]
17/F	Glioma (chemotherapy)	Liposomal amphotericin B	Oral swab: *Candida albicans*, *Candida parapsilosis* Nasal swab: *Aspergillus flavus* Maxillary sinus biopsy: *Rhizomucor*	Dead	Chermetz et al.[17]
52/M	Diabetes	Lobectomy and surgical debridement, posaconazole (refused liposomal amphotericin B treatment)	Galactomannan test of bronchoalveolar lavage: positive (5.09) Bronchial pathogen: *Aspergillus*, *Mucor*, *Actinomycetes*	Remission	Lin et al.[18]
68/M	Hypertension	Amphotericin B	Paranasal sinus biopsy: *A. flavus*, *Rhizopus arrhizus*	Discharged (no mention of recovery)	Vaidya et al.[19]
10/M	Aplastic anemia (hematopoietic stem cell transplantation)	Fluconazole, posaconazole, liposomal amphotericin B, removal of brain abscess, right partial nephrectomy splenectomy, left lower lobe resection of lung	Lung needle biopsy: *Rhizopus* Pus culture from brain, spleen, kidney: *A. fumigatus* Histopathologic exam from brain, kidney: *Rhizopus*	Recovered	Weng et al.[20]

Table 1 lists several reported cases of *Aspergillus* and *Mucor* coinfections. These patients had fungal infections in the orofacial region, lung, maxillary sinus, paranasal sinus, brain, spleen, and kidney. They all had an underlying disease and their clinical courses differed.[16-20]

We report a case of IFI caused by multiple fungi species including *Rhizomucor* (proven infection), *P. decumbens* (polymerase chain reaction [PCR] positive only), and *Aspergillus* (probable infection) as a symptom of Pancoast syndrome.

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요약

소아암 환자에서 발생하는 침습성 진균 감염은 사망과 후유증에 이르는 중대한 감염이다. 18세 남자 환자가 호중구감소 기간 동안 입원하여 치료받던 중 우측 견관절과 우측 팔에 감각이상과 신경쇠약을 호소하였고, 우측폐상엽의 폐렴이 진단되었다. 기관지의 조직학적 소견과 폐 수술검체에서 시행한 polymerase chain reaction (PCR)로 털곰팡이증을 확진하였으며, 흉수액의 PCR로 페니실리움 디쿰벤스 감염, 갈락토마난 항원법으로 아스페르길루스증을 추정하였다. 환자는 백혈병이 치료되지 못하고 *Staphylococcus epidermidis* 패혈증이 합병되어 사망하였다. 본 증례에서는 판코스트 증후군의 증상을 보인 환자에서 진단된 다발성 폐진균증을 보고 하는 바이다.