Pneumonia due to *Schizophyllum commune* in a Patient with Acute Myeloid Leukemia: Case Report and Literature Review

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**ABSTRACT**

*Schizophyllum commune* is a mold in phylum Basidiomycota and is an uncommon human pathogen. Sinusitis and allergic bronchopulmonary mycosis are the two major diseases caused by *S. commune*. Although there have been several reports of invasive fungal diseases, most of them were invasive sinusitis. We present a case of invasive fungal pneumonia due to *S. commune*, developed in a patient with acute myeloid leukemia presenting neutropenic fever. The diagnosis was made by characteristic macroscopic and microscopic findings of fungal isolate and was confirmed via sequencing of internal transcribed spacer region. The patient was improved after 8 weeks of antifungal therapy based on the susceptibility result. We propose that *S. commune* should be considered as an emerging pathogen of invasive fungal pneumonia when a patient is under immunocompromised state. We also reviewed global literatures focused on the invasive fungal diseases caused by *S. commune*.

**Keywords:** Fungal infection; Leukemia; Pneumonia; *Schizophyllum*

**INTRODUCTION**

*Schizophyllum commute*, a mold in phylum Basidiomycota, is a widely distributed fungi in organic matter such as rotten wood of trees [1, 2]. *S. commute* is rarely reported in humans, and its histopathological findings are indistinguishable to those of *Aspergillus* species in some instances, making it difficult to diagnose in many clinical settings [1]. Among the cases reported previously, sinusitis and allergic bronchopulmonary mycosis (ABPM) are two major diseases and are being reported with increasing frequency [3]. Although *S. commute* is one of the emerging fungi, data on clinical features and outcomes of invasive fungal disease (IFD) caused by *S. commute* are currently not sufficient. While there are several reports of IFD due to *S. commute*, most of them were invasive sinusitis [4-10]. Recently, we experienced a case of invasive fungal pneumonia due to *S. commute* in a patient with acute myeloid leukemia (AML). Herein, we describe the successful treatment of IFD due to *S. commute*, and also reviewed global literatures that can suggest clinical keys of invasive *S. commute* infections.
Invasive fungal pneumonia caused by *S. commune*

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**Ethics statement**
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**Conflict of Interest**
DGL is editor-in-chief of Infect Chemother; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

**Authors' contributions**
Conceptualization: SYC, DGL. Data curation: HK. Formal analysis: HK. Investigation: HK, HSC, CP. Supervision: SYC, DGL. Writing - original draft: HK. Writing - review & editing: YY, SYC, DGL, YJK, YJP.

**CASE REPORT**

A 73-year-old male patient with secondary AML, evolved from myelodysplastic syndrome, visited emergency department due to fever and oral pain. He was being treated with hydroxyurea for cytoreduction. He had been received 5-azacytidine for 6 cycles followed by cytarabine chemotherapy for 6 cycles in the remote past. No history of allergic or pulmonary diseases was identified, and he had subtotal gastrectomy for gastric carcinoma 10 years ago. No antifungal agents for prophylaxis were being given to the patient.

On physical examination, multiple whitish plaques were noted over oropharyngeal mucosa, and no other abnormal signs were identified. Absolute neutrophil count (ANC) was zero, and other laboratory tests and chest X-ray found to be normal. Intravenous fluconazole (200 mg/day) was given for oropharyngeal candidiasis, and intravenous cefepime (4 g/day) and isepamicin (400 mg/day) were empirically administered for neutropenic fever. On the fourth day of admission, however, chest X-ray started to show multifocal consolidations in both lung fields. Chest computed tomography (CT) scan was performed, and it revealed multifocal patchy consolidations (arrows) and ground-glass opacities (arrowheads) in both lungs (Fig. 1). There was no eosinophilia, and ANC was still zero. Based on the patient’s immune status of persistent neutropenia and the findings of chest CT, diagnosis of possible category of IFD was established according to the revision and update of the consensus definition of IFD from the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) education and research consortium [11]. Therefore, empirical therapy with liposomal amphotericin B (3 mg/kg/day) was initiated, and studies for detecting pathogen of pneumonia were undertaken. Bacterial culture of sputum revealed no growth of microorganism. Urinary antigen tests for *Streptococcus pneumoniae* and *Legionella* species, serologic tests for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were negative. While serum galactomannan assay showed negative results repeatedly, fungal culture of sputum (Grade 5) yielded hyaline fungi. Since radiographic findings were consistent with fungal pneumonia, fungal identification and antifungal susceptibility testing were performed.

After five days of incubation on Sabouraud dextrose agar (SDA) at 35°C, dense, cotton-like-white colonies grew (Fig. 2A). Multiple branched, septated, hyaline hyphae with clamp connections (red arrows) were observed through microscopic examination, but

![Figure 1. Low-dose chest computed tomography reveals multifocal patchy consolidations (arrows) and ground-glass opacities (arrowheads) in both lungs.](https://icjournal.org)
no spicules were observed (Fig. 2B). Final fungal identification was done by sequencing of Internal Transcribed Spacer (ITS) gene as follows. Entire ITS regions were amplified using the primers ITS1-F_KYO2 (5’-TAGAGGAAGTAAAAGTCGTAA-3’) and ITS4 (5’-TCCTCCGCTTATATGATGC-3’), and with the enclosed 5.8S rDNA, we used the primers ITS2 (GCTGCGTTCTTTCATCGATGC) and ITS3 (GCATCGATGAAGAACGCAGC) in addition to primers ITS1-F_KYO2 and ITS4 [2, 12]. Amplicons of ITS were sequenced, and then were identified using BLASTN. As a result, the isolate was identified as S. commune. Antifungal susceptibility test was performed using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) [13]. Minimum inhibitory concentrations (MICs) of triazoles and amphotericin B, and minimum effective concentrations of echinocandins are presented in Table 1.

Confirming probable category of invasive fungal pneumonia due to S. commune, liposomal amphotericin B was administered for 14 days. As pneumonia was improving, liposomal amphotericin B was replaced with oral itraconazole (400 mg/day) at discharge, since the MIC of itraconazole was considered favorable. Finally, pneumonia resolved after 8 weeks of antifungal treatment, and the patient fully recovered without any complication.

Table 1. In vitro antifungal susceptibility data for Schizophyllum commune isolate

| Source of isolate | FLU (µg/ml) | ITR (µg/ml) | VOR (µg/ml) | POS (µg/ml) | AMB (µg/ml) | MICA (µg/ml) | ANID (µg/ml) | CAS (µg/ml) |
|-------------------|-------------|-------------|-------------|-------------|-------------|---------------|-------------|-------------|
| Sputum            | 64          | 0.06        | 0.06        | 0.06        | 0.125       | 0.06          | 0.06        | 0.25        |

MIC, minimum inhibitory concentration; MEC, minimum effective concentration; FLU, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; AMB, amphotericin B deoxycholate; MICA, micafungin; ANID, anidulafungin; CAS, caspofungin.
DISCUSSION

IFDs, one of the major infectious complications in patients with hematologic malignancies, have increased globally, and rare mold infections other than aspergillosis are also growing because of the expanding population of immunocompromised patients and azole prophylaxis [14]. Clinical significance of rare fungi is that the diagnosis could be delayed in many cases and appropriate treatment is not well established due to lack of susceptibility data.

\textit{Schizophyllum} is a genus of fungi classified under the family Schizophyllaceae, phylum Basidiomycota, class Agaricomycetes, and order Agaricales [1]. It is widespread genus often seen on sickly hardwood trees and contains six wood-rotting species. Of the \textit{Schizophyllum} species, \textit{S. commune} is known as a possible cause of fungal diseases in human according to the literatures to date. However, due to the rare isolation of \textit{Schizophyllum} spp. in human infections, it cannot be identified in routine diagnostic laboratory work using automated systems. Therefore, most of the reports performed additional sequencing of the ITS region to confirm fungal species. The clinical presentations varied from asthma, ABPM, otitis externa, sinusitis, or soft tissue granuloma, to invasive form involving lung, orbit, or brain [3, 15]. Similar to aspergillosis, \textit{S. commune} infection can be categorized into allergic, saprophytic, chronic, or invasive forms.

We reviewed global literatures to identify clinical presentation, underlying disease of patients, and treatment for invasive human diseases caused by \textit{S. commune}, and categorized those cases according to the underlying conditions of host (Table 2) [4-10, 15-20]. We excluded non-invasive cases such as sinusitis without evidence of mucosal invasion in immunocompetent host. There were four cases of \textit{S. commune} invasive infection developed in immunocompetent host which were characterize to involve sino-orbital structure or brain [8, 16-18]. Although the four patients were classified as immunocompetent, one was an air conditioning installer which might be a risk of fungal infection by route of inhalation. Those cases are considered appropriate for invasive cases, despite the absence of well-known host factor corresponding to the immunodeficiency suggested in the EORTC/MSG criteria.

On the other hand, there were nine cases of \textit{S. commune} IFDs developed in immunocompromised host. Three had non-hematologic diseases including diabetes, heart transplantation, and human immunodeficiency virus (HIV), and six had hematologic malignancies. \textit{S. commune} fungemia was reported from antiretroviral therapy-naïve HIV patient in Brazil [20]. Among the seven patients with hematologic malignancies including our patient, invasive sinusitis (71.4%, n = 5) was more frequent than invasive fungal pneumonia (28.6%, n = 2). Interestingly, the early cases showed that fluconazole was used for treatment [10, 15]. In those reports, MIC for fluconazole was 4 µg/ml in Case 8, and the other (Case 5) showed no susceptibility results. In a 59-year-old male patient (Case 6) with diabetes, 3.5 cm sized brain abscess with invasive frontal sinusitis due to \textit{S. commune} was diagnosed, which was the first report treated empirically with liposomal amphotericin B for 5 weeks followed by azole antifungal agent [19].

In our case, \textit{S. commune} was the only pathogen recovered from sputum. Although the specimens were not collected invasively, it showed adequate quality (Grade 5, leukocytes >25/low power field, epithelial cells <10/low power field) for culture, and antifungal treatment resulted in clinical recovery. As the patient was in prolonged neutropenic state, this patient met the criteria for the probable category of IFD [11].
Invasive fungal pneumonia caused by *Schizophyllum commune*

Table 2. Literature review of invasive fungal infections due to *Schizophyllum commune*, categorized according to the host immune status

| Case No. | Sex/Age | Underlying condition | Diagnosis | FLU | ITR | VOR | POS | AMB | CAS | Antifungal treatment | Outcome | Country, reference |
|----------|---------|----------------------|-----------|-----|-----|-----|-----|-----|-----|---------------------|----------|---------------------|
| 1        | M/58    | Hypertension, CAD    | Multiple lung, brain mass | 8   | -   | -   | -   | 0.03 | -   | AMB-d and ITR        | Died     | US, 1996 [16]       |
| 2        | F/30    | None                 | Sino-orbital infection | -   | -   | -   | -   | -   | -   | AMB-d, LAmB, VOR (11 months) | Cure     | Korea, 2012 [17]    |
| 3        | M/53    | Air conditioning installer | Sinusitis, epidural abscess | -   | 1   | -   | -   | 0.75 | 32  | LAmB (25 days)       | Cure     | Japan, 2018 [18]    |
| 4        | F/50    | None                 | Sino-orbital infection | >64 | 0.25| 0.125| 0.5 | 0.25 | >8   | AMB-d (30d)         | Cure     | India, 2020 [6]     |

**Immunocompromised host, non-hematologic disease**

| Case No. | Sex/Age | Underlying condition | Diagnosis | FLU | ITR | VOR | POS | AMB | CAS | Antifungal treatment | Outcome | Country, reference |
|----------|---------|----------------------|-----------|-----|-----|-----|-----|-----|-----|---------------------|----------|---------------------|
| 5        | F/56    | Cardiac transplantation Diabetes | Multiple lung nodules | -   | -   | -   | -   | -   | -   | FLU (1 month, 400 mg a day) | Cure     | Taiwan, 2009 [10]   |
| 6        | M/59    | Cardiac transplantation Diabetes | Sinusitis, brain abscess | 12  | >32 | 0.12 | 0.25 | 0.25 | >32 | LAmB (5 weeks), POS | Cure     | Austria, 2013 [19]  |
| 7        | M/49    | HIV, ART naive       | Fungemia   | -   | -   | -   | -   | -   | -   | AMB-d (7 months), FLU | Cure     | Brazil, 2017 [20]   |

**Immunocompromised host, hematologic malignancies**

| Case No. | Sex/Age | Underlying condition | Diagnosis | FLU | ITR | VOR | POS | AMB | CAS | Antifungal treatment | Outcome | Country, reference |
|----------|---------|----------------------|-----------|-----|-----|-----|-----|-----|-----|---------------------|----------|---------------------|
| 8        | M/59    | Lymphoma, Gastric cancer | Pneumonia | 4   | -   | -   | -   | -   | -   | FLU (600 mg twice a day, 6 weeks) | Cure     | Italy, 2008 [15]    |
| 9        | F/23    | ALL, allogeneic HSCT | Sino-orbital infection | -   | -   | -   | -   | -   | -   | LAmB (2 months), VOR | Cure     | Japan, 2013 [4]    |
| 10       | F/25    | AML, allogeneic HSCT | Invasive sinusitis | -   | 1   | 0.03 | 1   | 16  | VOR | Diets | China, 2015 [5]    |
| 11       | M/66    | MDS, allogeneic HSCT | Invasive sinusitis | -   | -   | -   | -   | -   | -   | LAmB (38 days), VOR | Cure     | Japan, 2020 [6]    |
| 12       | M/65    | Non-Hodgkin lymphoma | Invasive sinusitis | -   | -   | -   | -   | -   | -   | LAmB (21 days), VOR (6 months) | Cure     | Portugal, 2020 [7] |
| 13       | F/59    | AML, chemotherapy | Invasive sinusitis | -   | -   | -   | -   | -   | -   | LAmB, VOR | Cure     | Japan, 2020 [9]    |
| 14       | M/73    | Secondary AML, s/p STG | Pneumonia | 64  | 0.06| 0.06 | 0.06 | 0.12 | 0.25 | LAmB (2 weeks), ITR (6 weeks) | Cure     | This report         |

The patient (Case No. 1) died of progressive bacterial pneumonia with respiratory failure with remained brain abscess.

The patient (Case No. 10) died of sepsis with irreversible shock and multiorgan failure, although symptoms related to sinusitis were remarkably improved.

Among 14 patients including 13 patients from literatures and our case, 12 showed clinical improvement, but two (14.3%) patients died. In our case, after administration of liposomal amphotericin B and itraconazole subsequently, the patient showed successful outcome. We analyzed susceptibilities for this clinical isolate, which showed that the MIC of fluconazole was high (≥64 µg/ml). Although there are currently no sufficient data regarding epidemiological cutoff values or clinical breakpoints in *Schizophyllum* spp., susceptibility data are considered as favorable for drugs known to have anti-mold activity. Eleven of 14 patients received polyene antifungal agents such as amphotericin B deoxycholate or liposomal amphotericin B. Although two patients were successfully treated with fluconazole, one of them treated with high-dose of fluconazole for 6 weeks. Since MIC against fluconazole is varied from 4 to 64 µg/ml in this literature review, we recommend prescribing anti-mold active antifungal agents as the initial choice in patients with respiratory tract IFD caused by *S. commune*. Further data accumulation is needed to determine the correlation between antifungal treatment and outcome of patients.

In conclusion, it should be considered that immunodeficiency is a potential risk factor for developing respiratory tract IFD caused by *S. commune* and the possibility of it underlines the significance of acknowledging a rare IFD to give precise diagnosis. Literature review suggests...
that IFDs caused by *S. commune* reveal relatively good prognosis under proper antifungal therapy. We also emphasize that accurate identification and obtaining in vitro antifungal susceptibility data are necessary for treatment to prevent high morbidities caused from IFDs.

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