Invasive *Scytalidium dimidiatum* Infection in an Immunocompetent Adult

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*Scytalidium dimidiatum*, a dematiaceous fungus, has been well established as an agent of dermatomycosis. There are few reports of invasive infection caused by *S. dimidiatum*; most infections occurred in immunocompromised hosts. We present an immunocompetent patient with pleural *S. dimidiatum* infection and review nine other published cases of invasive *S. dimidiatum* infections.

**CASE REPORT**

A 56-year-old male was admitted for evaluation after a few months of progressive dyspnea, fever, night sweats, and loss of weight. His past medical history was significant for rheumatic heart disease, which had necessitated mitral valve commissurotomy 20 years prior to his admission. As a consequence, he suffered from moderate mitral and tricuspid regurgitation and moderate right heart failure, manifesting as chronic pleural effusion. He was treated with 40 mg/day furosemide and warfarin due to chronic atrial fibrillation. The last thoracentesis, performed 3 years earlier, had yielded a bloody exudate, but no pathogen was isolated.

On admission the patient appeared cachectic, had mild dyspnea, and was afebrile. The jugular veins were maximally distended. Chest examination revealed dullness to percussion and reduced breath sounds over the right lung base, and a systolic ejection murmur was heard at the apex, compatible with mitral regurgitation. Hepatosplenomegaly and moderate peripheral edema were noted as well.

Significant laboratory findings were as follows: leukocyte count, 5,600 cells/μl with 61% neutrophils; hemoglobin level, 11.7 g/dl; platelet count, 164,000 platelets/μl; serum creatinine level, 111 μmol/liter; international normalized ratio, 2.41; lactate dehydrogenase, 751 IU/liter; γ-glutamyl transpeptidase, 133 IU/liter; alkaline phosphatase, 257 IU/liter. Chest computed tomography revealed a large loculated pleural effusion on the right with pleural thickening and total passive collapse of the right middle and lower lobes. Numerous enlarged mediastinal lymph nodes, up to 1.5 cm, were noted. Echocardiography showed enlargement of the right atrium and ventricle, in addition to mitral valve stenosis and regurgitation and moderate pulmonary hypertension.

A diagnostic thoracentesis revealed bloody exudative fluid with hemoglobin of 4.3 g/dl and white blood cell count of 2,000 cells/μl with 66% neutrophils. The lactate dehydrogenase level was 22,600 IU/liter. Septate hyphae were detected by calcofluor staining (Fig. 1A). Culture on blood agar plates yielded a white hairy mold (Fig. 1B), which progressed into a grayish black fungus (Fig. 1C). MICs were determined by Etest (AB Biodisk, Solna, Sweden). The mold was found to be susceptible to amphotericin B and voriconazole (MICs, 0.032 mg/liter) and to posaconazole (MIC, 0.75 mg/liter) but resistant to fluconazole (MIC, >256 mg/liter) and itraconazole and caspofungin (MICs, >32 mg/liter).

The patient was treated for 2 weeks with intravenous voriconazole at 4 mg/kg of body weight every 12 h with no clinical or radiological improvement, and an exploratory right thoracotomy was performed. Necrotic tissue covering both pleural surfaces and widespread fibrosis over the atelectatic right middle and lower lobes and over the entire mediastinum were seen. Extensive debridement and irrigation of the pleural space were performed, resulting in partial expansion of the right upper and lower lobes. Cultures taken during the procedure again yielded *S. dimidiatum*. The patient’s clinical condition gradually improved, and he was discharged 24 days after the surgery with a recommendation for continuance of the voriconazole treatment.

A month later, the patient was readmitted for dyspnea and recurrence of pleural effusion. Although septate hyphae were evident upon calcofluor staining of the pleural fluid, no mold growth was detected. The serum and pleural fluid voriconazole levels were within the therapeutic range, 1.45 mg/liter and 1.51 mg/liter, respectively (therapeutic range, 1 to 5 mg/liter [17]). Daily irrigation with amphotericin B (30 mg/day) injected through a pleural catheter was added to the treatment for 3 weeks and resulted in containment of the pleural effusion and clinical improvement. Six months later, with the patient still on voriconazole, the pleural effusion recurred.

**Morphological and molecular identification.** Culture on Sabouraud dextrose agar revealed effuse hairy colonies, dark gray to blackish brown, with a deep ochreous colony reverse. Microscopic examination demonstrated septate hyphae that were constricted at their prominent thick septations, giving the appearance of pseudohyphae (Fig. 1D). Chains of arthroconidia with brown walls were produced in abundance on the aerial mycelium; many had two cells separated by a thick septum. Smooth- and thick-walled pycnidia formed after 2 weeks, showing typical pycnidioconidia with two septate conidia and a darkened central cell upon dissection. The morphological features were compatible with the diagnosis of *S. dimidiatum*, also

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FIG. 1. (A) Calcofluor staining of the pleural effusion, demonstrating septate hyphae. (B) Culture on blood agar, demonstrating young white mold. (C) Culture on Sabouraud dextrose agar, demonstrating mature effuse hairy colonies, dark gray to blackish brown. (D) Microscopic examination demonstrating septate hyphae with constrictions at their prominent thick septations, giving the appearance of pseudohyphae.
known as *Fusicoccum dimidiatum* (8); the organism in its pycnidial state is referred to as *Nattrassia mangiferae*. For molecular identification, two analyses were carried out: analyses of 28S ribosomal DNA and the intergenic transcribed spacer. The sequence obtained by amplification and bidirectional sequencing of the 28S ribosomal DNA (region D1/D2) using primers NL1 and NL4 (4) was compared with those in the GenBank DNA database (BLAST). The results gave 100% query cover-
The dematiaceous (black) fungi are a large and heterogeneous group of molds that cause mostly cutaneous, subcutaneous, and corneal infections (2, 7, 9). These organisms are widespread in the environment, found in soil, wood, and debris, and corneal infections (2, 7, 9). These organisms are a melanin-deficient cultural mutant of S. dimidiatum (synonymous with S. hyalinum) strain ATCC 38906 as well as with S. hyalinum strain CBS 312.90. A search of the English language literature up until 2008 produced only nine additional cases of invasive S. dimidiatum infection (cases of cutaneous or subcutaneous onychomycosis and keratitis were excluded), mostly in immunosuppressed patients (1, 3, 6, 10, 11, 15, 20, 21, 24) (Table 1). The underlying conditions reported, similar to those of invasive mucormycosis, were diabetes mellitus, cirrhosis, trauma, immunosuppressive therapy and chemotherapy, and transplantation. No predisposing immune deficiency was reported in only two cases (1, 15), one of them occurring after traumatic implantation (1). Variable clinical forms, including central nervous system abscess, endophthalmitis, sinusitis, osteomyelitis, and fungemia, have been described. Five out of 10 patients died (50%), and one patient that suffered from endophthalmitis was cured only after enucleation.

Invasive mold infection is often difficult to eradicate by antifungal agents alone and usually necessitates surgical debridement. In the present case, the S. dimidiatum was isolated during the operation after 2 weeks of intravenous voriconazole treatment. Assessment of in vitro activities of various antifungal agents has demonstrated that amphotericin B and voriconazole exhibit the lowest MICs for S. dimidiatum spp. (14), though amphotericin B alone was found ineffective in treating cerebral infection in one case (10). It is thought that melanization in S. dimidiatum may play a role in drug resistance (16); however, it appears that the white and black isolates of S. dimidiatum spp. are equally resistant to antifungals (18).

Fungal thoracic empyema, which usually affects hospitalized patients, most often in intensive-care units, is associated with high morbidity and mortality rates, and its incidence has increased in recent years (12). In this retrospective analysis from Taiwan, overall mortality was estimated at 73%. Repeated thoracentesis was found to be among the major causes of fungal empyema, suggesting direct inoculation during the procedure. Those patients treated with systemic antifungal agents and surgery had a higher survival rate. In the present case of

### Table 1. Case reports of patients with invasive Scytalidium dimidiatum infection

<table>
<thead>
<tr>
<th>Source (reference)</th>
<th>Age (yr)/sex</th>
<th>Yr</th>
<th>Country</th>
<th>Clinical form</th>
<th>Immune status</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al. (21)</td>
<td>31/M</td>
<td>2008</td>
<td>Canada</td>
<td>CNS(^a) abscess</td>
<td>Renal transplant</td>
<td>Voriconazole</td>
<td>Died</td>
</tr>
<tr>
<td>Mani et al. (15)</td>
<td>18/M</td>
<td>2008</td>
<td>India</td>
<td>CNS abscess</td>
<td>Immune competent</td>
<td>Amphotericin B</td>
<td>Died</td>
</tr>
<tr>
<td>Sadeghi Tari et al. (20)</td>
<td>60/M</td>
<td>2005</td>
<td>Iran</td>
<td>Endophthalmitis</td>
<td>Posttrauma + diabetes + cirrhosis</td>
<td>Amphotericin B/posaconazole</td>
<td>Died</td>
</tr>
<tr>
<td>Willinger et al. (24)</td>
<td>62/M</td>
<td>2004</td>
<td>Austria</td>
<td>Skin + vertebra + lungs</td>
<td>Renal transplantation</td>
<td>Amphotericin B/voriconazole</td>
<td>Died</td>
</tr>
<tr>
<td>Geramishoar et al. (10)</td>
<td>17/M</td>
<td>2004</td>
<td>Iran</td>
<td>CNS abscess</td>
<td>Immunosuppressive therapy</td>
<td>Amphotericin B</td>
<td>Died</td>
</tr>
<tr>
<td>Dunn et al. (6)</td>
<td>51/F</td>
<td>2003</td>
<td>United States</td>
<td>Sinusitis</td>
<td>Lung transplantation</td>
<td>Amphotericin B/voriconazole</td>
<td>Cured</td>
</tr>
<tr>
<td>Gumbo et al. (11)</td>
<td>60/M</td>
<td>2002</td>
<td>Zimbabwe</td>
<td>Endophthalmitis</td>
<td>Posttrauma + diabetes + cirrhosis</td>
<td>Ketocanazole</td>
<td>Cured</td>
</tr>
<tr>
<td>al-Rajhi et al. (1)</td>
<td>46/M</td>
<td>1993</td>
<td>Saudi Arabia</td>
<td>Endophthalmitis</td>
<td>Posttrauma</td>
<td>IO miconazole + Amphotericin B; Top. natamycin + Amphotericin B</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Benne et al. (3)</td>
<td>13/M</td>
<td>1993</td>
<td>The Netherlands</td>
<td>Bacteremia</td>
<td>Chemotherapy</td>
<td>Amphotericin B</td>
<td>Cured</td>
</tr>
<tr>
<td>Present case</td>
<td>56/M</td>
<td>2007</td>
<td>Israel</td>
<td>Empyema</td>
<td>Immune competent</td>
<td>Voriconazole</td>
<td>Alive</td>
</tr>
</tbody>
</table>

\(^{a}\) CNS, central nervous system.
\(^{b}\) Amphotericin B, amphotericin B; IO, intraocular; Top., topical.
\(^{c}\) Amphotericin B was changed to posaconazole.
\(^{d}\) Amphotericin B was changed to voriconazole.
invasive pleural *S. dimidiatum* infection, the port of entry of the mold into the pleural space is unknown. The previous thoracentesis was performed 3 years prior to admission, the patient had no onychomycosis, and no history of trauma was reported. Although the route of invasion to the pleural space is unknown, the chronicity of the disease, as evidenced by hepatosplenomegaly and polyclonal gammonphathy, suggests that it was introduced to the pleural space during the thoracentesis of 3 years previously. It is possible that the chronic pleural effusion and the presence of blood in the pleural space encouraged fungal growth and invasiveness.

Despite extensive debridement and irrigation of the pleural space and prolonged systemic antifungal therapy, local symptomatic disease recurred a month later. Reoperating was not an option due to the patient’s poor general condition, and an alternative treatment was required. Intrapleural amphotericin B injection via pleural catheter was added to the treatment based upon a recent publication regarding the use of indwelling pleural catheters for chronic pleural infection (5). Clinical laboratory and radiographic studies performed 6 months later suggested stabilization of the patient’s pleural disease, with marked diminution of the fluid and absence of *S. dimidiatum*.

This case of invasive *S. dimidiatum* infection is unique in the organ involved, the chronicity of the infection, and the absence of immunodeficiency. Along with the reviewed cases, it emphasizes the rarity of this entity and its relatively poor prognosis. In addition to appropriate antifungal therapy, it would be prudent to consider surgical intervention early in the course of the disease in order to improve outcome.

**Nucleotide sequence accession number.** The nucleotide sequence of the case isolate has been submitted to the GenBank under accession no. FJ648577.

There are no potential conflicts of interest.

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**ADDITIONAL**

Since this paper was accepted for publication, we have been notified by GenBank that the organism we deposited as *Scytalidium dimidiatum* (accession no. FJ648577) will appear in the database as *Necysytalidium dimidiatum* according to its recently revised taxonomic status (see Index Fungorum, available at http://www.indexfungorum.org/Names/NamesRecord.asp?RecordID=500869, and Mycobank, at http://www.mycobank.org/MycToxasp.aspx?Link= &Rec= 500869, accessed on 22 February 2009).

**REFERENCES**


