**Scedosporium prolificans** Endocarditis: Case Report and Literature Review

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**Abstract**

*Scedosporium prolificans*, a hyaline filamentous fungus, is widely distributed in the environment and is currently an emerging human pathogen, especially among immunocompromised patients. However, *S. prolificans* endocarditis is rare. We herein report a case of *S. prolificans* endocarditis in a 64-year-old patient with breast cancer in complete remission for 30 years after chemotherapy and radiation treatment who was not cured. Susceptibility testing showed resistance to all antifungal drugs, except echinocandin. A review of the literature revealed 10 cases of *S. prolificans* endocarditis; of these, only one involved an immunocompetent host with no risk factors and only two patients survived. In order to improve the mortality rate, it is necessary to establish rapid diagnostic methods and efficient therapeutic approaches.

**Key words:** *Scedosporium prolificans*, Endocarditis, β-D glucan, fungal infection

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**Introduction**

*Scedosporium prolificans* is a hyaline filamentous fungus found in soil, sewage and air (1). The genus *Scedosporium* consists of *S. apiospermum* and *S. prolificans*, which are clinically important pathogens. The first reported *S. prolificans* human infection was in 1984, involving a case of osteomyelitis diagnosed based on a bone biopsy (2). The incidence of *S. prolificans* infection, however, is currently increasing; these infections are often fatal in immunocompromised patients (3). Despite the high rate of detection of *S. prolificans* from blood cultures, the natural resistance of this pathogen to various antifungal drugs makes treatment difficult (4). *S. prolificans* often disseminates to various organs, yet there are few reports of *S. prolificans* infective endocarditis (4). Unlike that observed in HACEK endocarditis, the sensitivity of blood cultures for *S. prolificans* is very high (4); thus, endocarditis is considered to be highly detectable if present.

In this study, we report a fatal case of disseminated *S. prolificans* infection and endocarditis and review the literature on endocarditis caused by this fungus.

**Case Report**

A 64-year-old woman with a complex past medical history and 3-week history of hoarseness and fever was admitted to our hospital for the treatment of symptoms of septic shock and the sudden loss of vision in the right eye. Laboratory tests performed during the preceding three weeks revealed increased levels of inflammatory markers, such as the C-reactive protein level and white blood cell (WBC) count, and a chest computed tomography (CT) scan showed an aneurysm in the aorta. The patient had undergone left classical radical mastectomy 30 years previously. Subsequently, left supraclavicular and sternal border lymph node swelling noted five years later led to a referral to our hospital for chemotherapy and radiation treatment (total: 72 Gy) to the lymph nodes. How-
ever, as side effects of the radiation therapy, chronic heart failure due to constrictive pericarditis, radiation dermatitis with ulceration in addition to left sternal osteoradionecrosis and chronic osteomyelitis developed. More than 10 years prior to admission (PTA), part of the sternum had become exposed as an open wound; pericardectomy, sequestrectomy and latissimus dorsi myocutaneous flap reconstruction were performed eight years PTA, and no cancer recurrence or metastasis was found at that time. A cutaneous fistula drain was formed after the surgery, and the patient drained the pus secondary to post-radiation dermatitis, leading to disorganization with S. prolificans in the drain was considered, as no signs of exacerbation of the wound or osteomyelitis were observed.

On admission, the patient’s blood pressure was 88/52 mmHg, her body temperature was 37.2°C, her heart rate was 100/min and her oxygen saturation was 97% on ambient air. Admission laboratory data included the following findings: WBC 15,100/μL, platelets 52,000/μL, C-reactive protein 6.95 mg/dL, PT-INR 1.23, fibrinogen 414 mg/dL and plasma (1, 3)-β-D-glucan 454.7 pg/mL. Acute exacerbation of chronic osteomyelitis was diagnosed, along with an aneurysm of the proximal aortic arch, based on the previous CT and magnetic resonance imaging (MRI) findings. On admission day 1, a transthoracic echocardiogram revealed a large site of vegetation involving the aortic and tricuspid valves as well as myocardial necrosis extending from the aortic annulus to the tricuspid valve (Figure). According to Duke’s modified criteria, definitive infective endocarditis with a disseminated infection was diagnosed according to one major criterion and three minor criteria. Antibiotic therapy with meropenem and vancomycin was started immediately. Surgical treatment was considered but ultimately rejected because of the patient’s poor clinical condition. On admission day 2, filamentous fungi were detected in blood cultures. On day 4, the patient died from multiple organ failure. After her death, the filamentous fungus was identified to be S. prolificans using sequencing of the nuclear ribosomal internal transcribed spacer (ITS) 1-5.8s-ITS2 ribosomal RNA region. The sequences were compared with the findings in the BLAST database (www.ncbi.nlm.nih.gov/BLAST), and the isolate showed 100% homology with GenBank accession no. KP132388, KP132685, KP132396 and KP132392.

Antifungal susceptibility testing was performed according to Clinical and Laboratory Standards Institute M38-A2 methods and revealed resistance to many antifungal drugs, including micafungin (0.5 μg/mL), amphotericin B (>8 mg/L), 5-flucytosine (>32 mg/L), fluconazole (>32 mg/L), itraconazole (>4 mg/L) and voriconazole (>4 mg/L).

Discussion

The most common presentations of Scedosporium infection are pulmonary mycosis and bone and soft tissue infections in immunocompetent hosts (4). As with other fungal pathogens, Scedosporium can cause invasive infection in immunocompromised patients. Disseminated infections are more common and often more complicated in immunocompromised patients with hematological malignancies or those on immunosuppressive treatment regimens. Rodriguez-Tudela et al. reported a total of 72 cases of disseminated S. prolificans infection, only one of which involved no underlying conditions (4). Our patient did not have any hematological malignancies and was not on an immunosuppressive treatment regimen at the time of infection onset, having been in complete remission for breast cancer for 30 years after undergoing chemotherapy and radiation.

The most common entry sites of S. prolificans are the respiratory tract and central intravenous catheters (5). In immunocompetent hosts, S. prolificans often invades through sites of trauma or ulcers (2). In the current case, S. prolificans was suspected to have invaded from the open sternum wound secondary to post-radiation dermatitis, leading to disseminated infection. Contamination with S. prolificans in the drain occurred one year PTA. Eliminating S. prolificans from the site may thus be difficult, as the S. prolificans isolates were resistant to most antifungal drugs. It was also difficult to determine whether the cause of the chronic osteomyelitis was radiation or infection.

S. prolificans endocarditis is rare; from 1993 to March 2015, 10 cases were reported, as summarized in Table (6-15). Of these, six patients were immunocompromised and three were immunocompetent but had risk factors for endocarditis - one patient was an intravenous drug user, one patient had a pacemaker and one patient had porcine bioprosthetic valves. Only one of the 10 patients was immunocompetent with no risk factors. Therefore, the onset of S. prolificans endocarditis is extremely rare in immunocompetent hosts.

S. prolificans vegetation was detected in the aortic valves of four patients and the mitral valves of five patients. Myocarditis was present in four patients. In general, left-sided endocarditis is more common than right-sided endocarditis. Infection often spans the distance between the mitral and aortic valves.
SUMMARY OF REPORTED CASES OF SCEDOSPORIUM PROLIFICANS ENDOCARDITIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Infected valve</th>
<th>Underlying disease</th>
<th>Other site of infection</th>
<th>Positive culture source</th>
<th>Other therapy</th>
<th>Surgical interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>M</td>
<td>30</td>
<td>Mitral valve</td>
<td>None</td>
<td>Blood</td>
<td>Blood</td>
<td>AMPH</td>
<td>Valvectomy</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>50</td>
<td>Mitral valve</td>
<td>Intravenous drug use</td>
<td>Arthritis</td>
<td>Blood</td>
<td>AMPH + FLUCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>50</td>
<td>Mitral valve</td>
<td>Myocardium</td>
<td>Lung transplant</td>
<td>Blood</td>
<td>AMPH + FLUCZ</td>
<td>Valve replacement</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>60</td>
<td>Myocardium</td>
<td>AIDS, Burkitt lymphoma</td>
<td>Bone, kidney, spleen, GBS</td>
<td>Blood</td>
<td>L-AMPH+VCZ</td>
<td>Pacemaker replacement</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>52</td>
<td>Aortic valve</td>
<td>AIDS</td>
<td>Endophthalmitis, brain emboli, lung emboli, liver emboli, brain aneurysm</td>
<td>Blood, pacemaker</td>
<td>L-AMPH+VCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
<td>15</td>
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<td>75</td>
<td>Aortic valve</td>
<td>None</td>
<td>Endophthalmitis, venteral osteomyelitis, cerebral emboli</td>
<td>Blood, cerebral fluid, cerebrospinal fluid</td>
<td>L-AMPH+FLUCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
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<td>F</td>
<td>59</td>
<td>Mitral valve</td>
<td>None</td>
<td>BRAZMA</td>
<td>Blood</td>
<td>L-AMPH+FLUCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>38</td>
<td>Mitral valve</td>
<td>Acute leukemia</td>
<td>Endothelial emboli, cerebral emboli</td>
<td>Blood, sputum, blood, cerebrospinal fluid</td>
<td>L-AMPH+VCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>66</td>
<td>Mitral valve</td>
<td>Acute leukemia</td>
<td>Endothelial emboli, cerebral emboli</td>
<td>Blood, sputum, blood, cerebrospinal fluid</td>
<td>L-AMPH+VCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
<tr>
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<td>Aortic valve</td>
<td>Chronic osteomyelitis</td>
<td>Endothelial emboli, cerebral emboli</td>
<td>Blood, sputum, blood, cerebrospinal fluid</td>
<td>L-AMPH+VCZ</td>
<td>Valve replacement</td>
<td>Died</td>
</tr>
</tbody>
</table>

**S. prolificans** of (1, 3)-β-D glucan, consist of this molecule. High serum concentrations of this parameter are helpful for obtaining a rapid diagnosis of fungal infection, as the cell walls of most fungi, including Scedosporium spp., consist of this molecule. High serum concentrations of (1, 3)-β-D glucan were found in previously reported cases of S. prolificans infection, and our patient also had an elevated plasma concentration of this parameter. Evaluating the (1, 3)-β-D glucan level can be useful for therapeutic monitoring in cases of Aspergillus infection, although there are not enough data for Scedosporium infection regarding this issue and further research is thus needed.

All of the 10 previously reported S. prolificans endocarditis patients were hospitalized and treated with antifungal therapies - six patients received more than two drugs. Selecting appropriate antifungal drugs is difficult due to the organism's intrinsic resistance to most antifungal agents (4). Troke et al. reported a 40% clinical response to voriconazole, despite an MIC<sub>50</sub> of 4 mg/L (17), indicating that this drug may be clinically useful for treatment in these patients. Combination antifungal drug therapy was successful in several cases. In vitro, the combinations of itraconazole + terbinafine, voriconazole + terbinafine, ravuconazole + caspofungin and voriconazole + miltefosine have synergic effects (18, 19). However, no standard therapy for S. prolificans based on clinical evidence has been established.

The overall mortality of S. prolificans infection is 46.9%; the mortality rate is 87.5% in patients with disseminated disease (4) and 81% in patients with endocarditis. S. prolificans endocarditis has a poor prognosis. There is a previous report of 17 patients with S. prolificans osteomyelitis who underwent surgery, all of whom survived. Our literature review revealed that all six patients with endocarditis who did not receive surgery died, whereas only two patients who underwent drainage or removal of the infectious site survived. However, all patients treated with valve replacement died. This result indicates that mortality is very high even if valve replacement is performed. Surgical treatment may raise the survival rate of Scedosporium endocarditis, although this therapy was not possible in the current case because of the patient's medical condition. For a cure, both treatment with
antifungal drugs and surgical intervention should be considered.

In conclusion, *S. prolificans* endocarditis is rare, and the mortality rate is extremely high. In order to improve the clinical outcome, novel rapid diagnostic methods and efficient therapeutic approaches should be established. Moreover, blood cultures must be performed, and the (1, 3)-β-D glucan test is helpful for confirming the diagnosis of *S. prolificans* endocarditis. Empiric therapy, including that with antifungal agents, may be needed in immunocompromised patients or those at risk of endocarditis.

The authors state that they have no Conflict of Interest (COI).

References