CONCISE COMMUNICATION

Two cases of subcutaneous Scedosporium apiospermum infection treated with voriconazole

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Scedosporium apiospermum is a mold that is increasingly being recognized as an opportunistic pathogen in immunocompromised patients, and treatment is complicated by intrinsic resistance to several antifungal agents. In our hospital, two cases of S. apiospermum infection occurring within 2 weeks were successfully treated with voriconazole. Since both patients were infected with an uncommon pathogen, a search for a common nosocomial source was performed. As environmental cultures yielded no S. apiospermum, and random amplified polymorphic DNA (RAPD) fingerprinting showed that the patients’ strains were genotypically unrelated, we considered a common nosocomial source of S. apiospermum to be unlikely.

Keywords Scedosporium apiospermum, fingerprinting, voriconazole

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INTRODUCTION

The genus Scedosporium contains two clinically important species: Scedosporium apiospermum (the asexual state of Pseudallescheria boydii), and Scedosporium prolificans. This saprophytic mold has a worldwide distribution, with reservoirs in water and soil. The most common presentations of scedosporium infections are cutaneous mycetoma and allergic bronchopneumonitis. Furthermore, malignant otitis externa, brain abscess, arthritis and invasive pulmonary infections have been described, including pneumonia after near-drowning and pulmonary colonization of cystic fibrosis patients [1–6]. Immunocompromised patients are at risk for often fatal disseminated scedosporiosis, especially when they are neutropenic [7,8]. Combinations of surgical excision and cryosurgery are used in the treatment of mycetoma of the skin and underlying tissues, but are often mutilating, and relapses occur [9]. Intrinsic resistance to fluconazole and amphotericin B complicates systemic antifungal therapy of scedosporium infections. Voriconazole is a promising broad-spectrum antifungalazole drug that has proved efficacious in treating invasive aspergillosis. In vitro data suggest that S. apiospermum isolates can be susceptible to voriconazole, itraconazole, and miconazole [10–13]. Previously, voriconazole was used successfully in the treatment of S. apiospermum infection [2,14,15].

Nosocomial outbreaks with S. prolificans have been described, and S. apiospermum has been cultured from potted plants in a hospital [16–18]. PCR fingerprinting proved a useful tool in evaluating an outbreak of S. prolificans infection in a hematology ward, where air samples yielding S. prolificans suggested airborne transmission [18]. We used this technique to investigate the possible relationship between two cases of S. apiospermum infection occurring in our hospital within 2 weeks.

PATIENTS AND METHODS

Case reports

Case 1

A 59-year-old-kidney transplant recipient with stable renal function (serum creatinine 111 μmol/L) received cyclosporin 75 mg twice daily (Neoral, Novartis, Arnhem, The Netherlands), prednisone
12.5 mg once daily, and azathioprine 150 mg once daily. After a stay in Morocco, he was treated parenterally for dehydration and diarrhea caused by *Campylobacter coli*. Twenty-nine days after discharge, he was readmitted with cellulitis at the previous insertion site of an intravenous catheter on the back of his left hand, without fever or chills. Several purple nodules and slight desquamation were observed, and MR imaging showed diffuse subcutaneous infiltration of the hand and lower arm, but no signs of osteomyelitis or arthritis. Skin biopsy showed active granulomatous inflammation of the dermis, with hyphal fragments in the deeper layers. Culture of the pus yielded *S. apiospermum*, and blood cultures remained sterile. Results of susceptibility testing according to the M38P protocol of the National Committee for Clinical Laboratory Standards (NCCLS) are shown in Table 1 [12]. After 3 days of itraconazole, intravenous treatment with voriconazole was started on the basis of compassionate use: 6 mg/kg every 12 h on the first day, and 4 mg/kg every 12 h thereafter. Meanwhile, the lesion on the hand was bandaged without the use of iodine or topical antifungal agents. Before admission, the use of cyclosporin was gradually being reduced in the process of a planned conversion to azathioprine. To avoid both the risk of disseminated scedosporiosis and the well known impairment of cyclosporin metabolism by azoles, cyclosporin was stopped when itraconazole was started. Chest radiography, ultrasound of the abdomen and total body IgG scanning revealed no signs of dissemination. Because of the patient’s good clinical condition and improving skin lesions, we switched to oral voriconazole 200 mg twice daily, after 10 days of parenteral therapy. Voriconazole serum levels were above the MIC for the infecting strain (>3.13 mg/L), as determined by bioassay [4,19]. After 6 weeks, voriconazole was stopped; the patient had fully recovered without deterioration of renal function.

**Case 2**

An 84-year-old male with a history of congestive heart failure was using 10 mg prednisone once daily for chronic obstructive pulmonary disease (COPD), when he was admitted with a periprosthetic fracture of the proximal femur after he fell in the street. A Girdlestone procedure was performed, complicated postoperatively by abdominal sepsis. A laparotomy was performed, and the patient received piperacillin–tazobactam intravenously for 7 days. During admission, chronic inflammation with bullae had developed at the site of an abrasion of the right elbow, from which *S. apiospermum* was cultured. The results of susceptibility testing are shown in Table 1. Intravenous voriconazole was started, 6 mg/kg every 12 h on the first day, and 4 mg/kg every 12 h thereafter. The abrasion was treated conservatively. X-ray of the elbow showed no signs of osteomyelitis. Although there was a good initial response, the patient died 10 days after voriconazole treatment was started. Autopsy showed old and recent myocardial infarction and bilateral bronchopneumonia. There was no evidence of pulmonary or disseminated *S. apiospermum* infection: Grocott and periodic-acid-schiff staining of lung tissue showed no fungal hyphae, and post-mortem cultures of lungs, spleen and liver revealed no microorganisms, especially no fungi.

**Environmental sampling and RAPD fingerprinting**

Since both patients were infected with an uncommon pathogen within a 2-week period, we investigated the possibility of a common source of *S. apiospermum*. As cutaneous infection with *Scedosporium* spp. is considered to be the result of direct contact between skin and fungal spores, cultures were taken from plasters, bandages, pads, and skin disinfectants. However, *S. apiospermum* was not cultured. The patients had never been in the same ward, and there were no potted plants in their surroundings. To investigate whether the *S. apiospermum* strains of the patients were genotypically related, we performed random amplified polymorphic DNA (RAPD) fingerprinting with three primers (GC70, GC80, and M13), as described by Ruiz-Diez et al. [20]. Fungal DNA

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**Table 1** Results of susceptibility testing of *S. apiospermum*

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>MIC (mg/L)</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Terbinafine</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td></td>
</tr>
</tbody>
</table>
of both patients’ strains and three unrelated control strains was extracted using hexadecyltrimethylammonium bromide (CTAB/NaCl 2% w/v), RNase A (10 mg/mL), and chloroform–isoamyl alcohol, followed by ethanol precipitation. PCR products were visualized on agarose gel, and the results of fingerprinting with the 10-mer primers GC70 and GC80 are shown in Figure 1. The patients’ strains were genotypically unrelated, and the control strains confirmed adequate discriminative power.

**DISCUSSION**

*S. apiospermum* infection of the skin and underlying tissues is a deep fungal infection, and the risk of disseminated scedosporiosis in immunocompromised patients should not be underestimated. As mentioned in this journal before [21], the optimal treatment of *S. apiospermum* infections is not known; treatment should include surgical debridement when possible. In patients with *S. apiospermum* infection of the hand and lower arm, however, surgery may lead to amputation or loss of hand function. In our opinion, systemic antifungal drugs constitute the cornerstone of the management of invasive fungal disease; susceptibility testing can help in determining the drug of choice. We found a low MIC (0.5 mg/L) for voriconazole in both patients’ *S. apiospermum* strains, and both patients responded to systemic voriconazole therapy. Owing to this good clinical response, extensive surgical debridement could be avoided. Although we showed fairly good in vitro susceptibility of *S. apiospermum* to miconazole in a previous study (MIC₉₀ 1 mg/L) [12], we did not use it for topical antifungal therapy, on the assumption that the penetration of miconazole into the deeper layers of the skin and underlying tissues is unpredictable.

The use of an intravenous catheter at the site of infection provided a probable site of entry for *S. apiospermum* in the first patient. At the time of removal of the peripheral catheter, there were no signs of infection and the catheter was not cultured. The second patient might have been infected with *S. apiospermum* when he fell in the street and fractured his femur. Negative environmental sampling made bandage materials or disinfectants as sources of *S. apiospermum* infection less likely. Although the primers GC70, GC80 and M13 were originally described in RAPD fingerprinting of *S. prolificans*, GC70 was also suitable for *S. apiospermum* fingerprinting [6,23]. However, the fact that our patients’ *S. apiospermum* strains were not genotypically related does not completely rule out a common source in the hospital; genetic polymorphism among molds may be very high, as was shown for *Aspergillus fumigatus* [22]. However, only limited data are available on the genetic variability in *Scedosporium*, although different genotypes were found using RAPD and multilocus enzyme electrophoresis [6,23].

**CONCLUSION**

Voriconazole is a promising drug in the treatment of *S. apiospermum* infections. Molecular
epidemiology is important in our understanding of *S. apiospermum* as an emerging pathogen in immunocompromised patients.

REFERENCES