Peritonitis due to *Neosartorya pseudofischeri* in an elderly patient undergoing peritoneal dialysis successfully treated with voriconazole

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Aspergillus peritonitis is a rare life-threatening complication of peritoneal dialysis (PD). We report a case of symptomatic *Neosartorya pseudofischeri* peritonitis in a 60-year-old woman treated by continuous ambulatory peritoneal dialysis (CAPD) for 13 months, who performed peritoneal exchanges independently. This is believed to be the first published case of *N. pseudofischeri* in an elderly patient. Comprehensive treatment included early removal of the PD catheter and the use of voriconazole (200 mg Vfend twice daily) for a period of 5 weeks. This case supports the need for more effective prophylaxis and treatment of non-*Candida* fungal infections in CAPD patients. Our conclusions from this case and a review of the literature are that infection with this fungus can cause substantial morbidity and is best treated with prompt catheter removal, aggressive antifungal therapy with voriconazole or amphotericin B, and vigilant observation for complications. Our report describes for what is believed to be the first time the administration of voriconazole to treat a *Neosartorya* peritonitis case.

Introduction

Peritonitis due to both intermittent and continuous ambulatory peritoneal dialysis (CAPD) remains the most common and serious complication of peritoneal dialysis (PD) (Piraino, 1998; Bibashi et al., 2003). Gram-positive bacteria are isolated in 55–80% of cases (Gloor et al., 2003; Iqbal et al., 2008), and fungal isolates in up to 10% of cases (Pimentel et al., 2005; Ram et al., 2008). In fungal peritonitis (FP), *Aspergillus* is rare and associated with a high mortality rate (De Hoog et al., 2000; Donnelly, 2002; Ram et al., 2008). FP is a potentially life-threatening complication of both intermittent and CAPD. Significant numbers of PD-associated cases of FP due to yeasts have been reported by several investigators (Chan et al., 1994; Garcia-Martos et al., 1991; Melez et al., 1995). *Candida* species account for more than 85% of the cases, whereas filamentous FP is less frequent (Bibashi et al., 2003). Although filamentous fungi causing peritonitis are reported less frequently, they encompass a wide range of agents, from the classic, systemic fungi (Bibashi et al., 1993) to the teleomorphs (Varga et al., 2000). Neosartorya species are underdiagnosed in clinical practice because white aspergilli are often regarded as contaminants in the laboratory (Guarro et al., 2002). The morphology of such isolates should be carefully examined by using conventional cultures on malt extract or Czapek Dox agar (Difco), and sequence-based analysis should be used for species level identification.

Case report

A 60-year-old woman was on CAPD for end-stage renal insufficiency/failure due to renovascular disease and interstitial nephritis. Her past medical history included hypertension, hyperparathyroidism, and chronic obstructive pulmonary disease. She had commenced CAPD 13 months prior to this reported episode and performed peritoneal exchanges independently. During that period, there had been multiple episodes of suspected peritonitis, each treated empirically with 1 g cefazolin and 40 mg
Neosartorya pseudofischeri peritonitis in a CAPD patient

gentamicin, and with a single intraperitoneal dose of 500 mg ciprofloxacin. In September 2005, she had a 3 day history of abdominal pain, accompanied by fever and nausea, and cloudy PD bags. On examination, she was found to be febrile (37.8°C) with a tense abdomen, rebound tenderness and decreased bowel sounds.

Initially the Tenckhoff catheter site was clean with no sign of inflammation. Full blood examination showed an elevated white cell count (WCC) of $13.8 \times 10^6$ cells $l^{-1}$ and a red cell count of $4.1 \times 10^6$ red blood cells $l^{-1}$. The C-reactive protein level was raised to 165 mg $l^{-1}$ and the albumin level was 33 g $l^{-1}$. The urea level was $12.2 \times 10^6$ mmol $l^{-1}$ and the creatinine level was $448 \times 10^6$ mmol $l^{-1}$. The fluid in the PD bag was pale yellow, cloudy with fibrous material and slow to drain. The PD fluid was sent for microscopy and culture, and was found to have a WCC of $3800 \times 10^6$ cells $l^{-1}$ with a red cell count of $676 \times 10^6$ cells $l^{-1}$, WCC decreased on the three following days to $400 \times 10^6$ cells $l^{-1}$, and rose again to $4400 \times 10^6$ cells $l^{-1}$ on the eighth day after first examination, whereas the red cell count remained between 40 $\times 10^6$ and 20 $\times 10^6$ cells $l^{-1}$. No organisms were observed with the use of the Gram stain. Neosartorya was isolated from repeated peritoneal fluid and Tenckhoff catheter culture. Even after removal of the catheter a week later, before voriconazole therapy was administered, we were able to detect Neosartorya pseudofischeri on culture plates from peritoneal fluid, which supports the causative factor of peritonitis. Therefore, the Neosartorya pseudofischeri was considered to be the causative factor of peritonitis.

Prior to removal of the catheter on the eighth day after first examination an abdominal computed tomography (CT) scan was performed (Fig. 1), which indicated an underlying oedematous inflammation due to the fungal infection. Subsequently, after the removal of the Tenckhoff catheter, the patient was transferred to haemodialysis treatment. The therapy with 200 mg voriconazole was administered on the fifteenth day after first examination, after the catheter had been removed, for 5 weeks twice daily after the Neosartorya pseudofischeri was identified.

Methods

Identification of Neosartorya pseudofischeri (teleomorph of Aspergillus thermomutatus). Colony characteristics of strains were initially observed by culture on blood agar, and then by subculture on Sabouraud dextrose agar (Oxoid), and malt extract and Czapek Dox agar (Difco Laboratories) plates at 25°C, 30°C and 45°C for 2 to 3 days; culture at 50°C revealed no growth. The culture on malt extract yielded abundant growth of ascomata at 25°C. Morphological features of strains were observed by lactophenol cotton blue staining. Conidiophores with mature conidia of Neosartorya pseudofischeri morphologically resemble Aspergillus fumigatus; however, their conidia are whitish to greyish yellow instead of a deep bluish green. Electron microscopy scanning was not available; therefore, there was no characterization of the ascospores. However, the species could not be identified by its conidia formation. To identify the species, species-specific internal transcribed spacer region (ITS1/ITS2)-based molecular identification was performed (Fujita et al., 2001; Hinrikson et al., 2005). A similarity of 100% to the Neosartorya pseudofischeri sequence with GenBank accession number EF669966.1 (ITS1/2) was determined.

Etest. An Etest (AB Biodisk) for voriconazole was used for MIC determination on RPMI agar plates (Viva Diagnostika). The Etest was performed according to the manufacturer’s instructions. Briefly, each RPMI plate was inoculated with 400 µl undiluted stock inoculum (ranging from $1 \times 10^5$ to $5 \times 10^6$ c.f.u. ml$^{-1}$) (Guinea et al., 2008). Plates were incubated at 35°C in a humid atmosphere, and MICs were determined following incubation times of 24 and 48 h. The MIC with the Etest was defined as the lowest voriconazole concentration at which the border of the elliptical inhibition zone intercepted the scale on the Etest strip. For Aspergillus spp. and the remaining moulds no breakpoints for the new triazoles have been established. For Candida spp., the classification of the strains for the MIC breakpoint for voriconazole was as follows: susceptible, breakpoint of <1 µg ml$^{-1}$; susceptible dose dependent, 2 µg ml$^{-1}$; resistant, >4 µg ml$^{-1}$ (Pfaller et al., 2006). For our isolate of Neosartorya pseudofischeri the MIC for

![Fig. 1. Patient’s abdominal CT scan on eighth day after first examination (after removal of the catheter); the white arrow indicates the oedematous inflammation of the peritoneum (peritonitis) due to Neosartorya pseudofischeri.](http://jmm.sgmjournals.org)
voriconazole was 1.0 (0.5–1.0) μg ml⁻¹. Where the elliptical inhibition zone intercepted the scale on the Etest strip between two MIC values, the MIC end point was taken as the higher value.

The determination of other antifungal MICs was carried out with the commercially available ATB fungus test (bioMérieux). The MICs obtained were >64 μg ml⁻¹ for flucytosine, >128 μg ml⁻¹ for fluconazole, 0.500 μg ml⁻¹ for amphotericin B and 1.0 μg ml⁻¹ for itraconazole.

Discussion
In general, FP has a prevalence of 0.1 to 10%, with Candida albicans being the predominating aetiological agent (Bibashi et al., 2003; Ram et al., 2008). However, FP caused by filamentous fungi is much less common (Bibashi et al., 2003). Fungi can enter the peritoneal cavity through a catheter intraluminally or periluminally, but in a few cases a vaginal route of infection has also been observed (Stuck et al., 1986). FP is associated with a mortality rate of 5 to 25% (Bibashi et al., 1993). Risk factors for FP include recent exposure to antibiotics, immunosuppressive therapy, recent bacterial peritonitis and the presence of bowel perforation (Eisenberg et al., 1986; Ujhelyi et al., 1990).

The case report is believed to be the first case of Neosartorya peritonitis in an elderly patient (Matsumoto et al., 2002). The clinical presentations of other reported peritonitis cases are summarized in Table 1. A variety of Aspergillus-associated peritonitis cases have been documented (Ross et al., 1968; Afanania et al., 1981; Carpenter et al., 1982; Sridhar et al., 1990; Perez-Fontan et al., 1991; Bibashi et al., 1993; Tanis et al., 1995; Miles & Barth, 1995; Geiss, 1995; Park et al., 1996). Risk factors included recent antibiotic therapy, steroid therapy, recurrent peritonitis, an immunosuppressed state and hospitalization. A high mortality for FP has been reported, generally in cases where diagnosis was delayed and the catheter not removed (Tsai et al., 1991; Miles & Barth, 1995). Over the last four decades among our 19 selected FP cases (Table 1) in 3 cases with an outcome of death the catheter was not removed, 2 patients were treated with amphotericin and the third patient had no antifungal treatment. Only voriconazole treatment was administered in our peritonitis patient, although Balajee et al. (2005) reported that three isolates of N. pseudofischeri had higher MICs to voriconazole in vitro compared to A. fumigatus. In previous cases other antifungal agents were given, preferentially amphotericin B. Another N. pseudofischeri isolate from a different case in our clinic (data not shown) also presented a low MIC (<0.5 μg ml⁻¹) to voriconazole as in the case presented here.

Diagnosis can be quite difficult, since the symptoms are identical to bacterial peritonitis. A Gram stain can occasionally reveal the typical hyphae of Aspergillus. Otherwise, a positive culture result must be obtained, and preferably a positive result from repeated cultures, since Aspergillus can occur as a laboratory contaminant (Geiss, 1995). In most cases, positive cultures are obtained after 5 and 10 days. However, since delayed treatment has an increased mortality, one should not wait for the results of repeated cultures; intravenous treatment with vorico-

<p>| Table 1. A selection of reported cases of Aspergillus and Neosartorya peritonitis |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Age of patient (years)</th>
<th>Sex</th>
<th>Fungal species</th>
<th>Catheter removal</th>
<th>Antimycotic</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>F</td>
<td>A. fumigatus</td>
<td>No</td>
<td>None</td>
<td>Death</td>
<td>Ross et al. (1968)</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>A. fumigatus</td>
<td>No</td>
<td>Amphotericin B (i.v., i.p.)</td>
<td>Death</td>
<td>Afanania et al. (1981)</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>A. flavus</td>
<td>No</td>
<td>Amphotericin B (i.v.)</td>
<td>Death</td>
<td>Carpenter et al. (1982)</td>
</tr>
<tr>
<td>40</td>
<td>M</td>
<td>A. niger</td>
<td>Yes</td>
<td>Amphotericin B (i.v.)</td>
<td>Death</td>
<td>Rodriguez-Tudela et al. (1988)</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>A. niger</td>
<td>Yes</td>
<td>Amphotericin B (i.v.)</td>
<td>CAPD</td>
<td>Prewitt et al. (1989)</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>A. niger</td>
<td>Yes</td>
<td>Amphotericin B (i.v.)</td>
<td>HD</td>
<td>Sridhar et al. (1990)</td>
</tr>
<tr>
<td>68</td>
<td>F</td>
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<td>HD</td>
<td>Stein et al. (1991)</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
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<td>Yes</td>
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<td>CAPD</td>
<td>Perez-Fontan et al. (1991)</td>
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<tr>
<td>35</td>
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<td>CAPD</td>
<td>Bibashi et al. (1993)</td>
</tr>
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<td>68</td>
<td>M</td>
<td>A. fumigatus</td>
<td>Yes</td>
<td>Amphotericin B (i.v.) + itraconazole</td>
<td>CAPD</td>
<td>Tanis et al. (1995)</td>
</tr>
<tr>
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<td>Yes</td>
<td>Amphotericin B (i.v.) + fluconazole</td>
<td>Death</td>
<td>Tsoufakis et al. (1995)</td>
</tr>
<tr>
<td>37</td>
<td>M</td>
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<td>Kitiyakara et al. (1996)</td>
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<tr>
<td>60</td>
<td>F</td>
<td>A. fumigatus</td>
<td>Yes</td>
<td>Ketoconazole</td>
<td>HD</td>
<td>Bren (1998)</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>A. fumigatus</td>
<td>Yes</td>
<td>Amphotericin B (i.v.)</td>
<td>Death</td>
<td>Bren (1998)</td>
</tr>
<tr>
<td>30</td>
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<td>Aspergillus sp.</td>
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<td>Amphotericin B (i.v.) + flucytosine</td>
<td>Death</td>
<td>Bren (1998)</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>A. niger</td>
<td>Yes</td>
<td>Amphotericin B (i.v.) + fluconazole</td>
<td>HD</td>
<td>Basok et al. (2000)</td>
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<td>8</td>
<td>F</td>
<td>N. pseudofischeri</td>
<td>Yes</td>
<td>Liposomal amphotericin B (i.v.) + itraconazole</td>
<td>HD</td>
<td>Matsumoto et al. (2002)</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>A. fumigatus</td>
<td>Yes</td>
<td>Amphotericin B (i.v.)</td>
<td>CAPD</td>
<td>Schattner et al. (2006)</td>
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<tr>
<td>60</td>
<td>F</td>
<td>N. pseudofischeri</td>
<td>Yes</td>
<td>Voriconazole (i.v.)</td>
<td>HD</td>
<td>This study</td>
</tr>
</tbody>
</table>

A., Aspergillus; F, female; HD, haemodialysis; i.v., intravenous; i.p., intraperitoneal; M, male.
nazole or amphotericin B should be administered immediately. Susceptibility testing revealed that amphotericin B is also an antifungal agent to which the organism had a low MIC of 0.5 μg ml⁻¹. On the other hand, N. pseudofischeri had a high MIC for fluconazole and fluconytosine. With respect to the removal of the catheter, there is general agreement in the literature that this is mandatory and should be performed as soon as possible (Stein et al., 1991; Perez-Fontan et al., 1991; Tanis et al., 1995; Miles & Barth, 1995; Park et al., 1996).

In summary, we conclude that Neosartorya peritonitis is a severe form of peritonitis in CAPD patients. The need for more effective treatment and prophylaxis for fungal infections in CAPD is obvious; which means in cases where bacterial culture of peritoneal fluid is negative, this may indicate the possibility of fungal infection. If a positive fungal culture is obtained, antymycotic therapy should be started immediately, and the Tenckhoff catheter removed as quickly as possible, preferably within 24 h of the diagnosis, as it is mostly impossible to eradicate the infection without removing the catheter. In addition to blood agar, Sabouraud dextrose agar for Aspergillus species and Candida chromogenic agar should be used for the initial culture. A recent bacterial infection treated with antibiotics could be a predisposing factor for FP. An earlier CT scan might help raise suspicion of a fungal inflammation being present and indicate the need for administration of antymycotics as well as antibiotics. The prompt diagnosis of FP and the early institution of therapy (e.g. amphotericin B) decrease the rates of morbidity and mortality. As in our case, the removal of the catheter alone did not resolve the peritoneal inflammation within a few days (up to 1 week), which would support the administration of antymycotic therapy simultaneously to catheter removal.

References


