Successful Treatment of Cryptococcus laurentii Peritonitis in a Patient on Peritoneal Dialysis

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Abstract

A 32-year-old man on peritoneal dialysis (PD) was hospitalized for seven days due to fever. A diagnosis of yeast-like fungal peritonitis was made by Gram staining. The patient was started on intravenous micafungin and oral fluconazole therapy following removal of the PD catheter. A fungal pathogen was isolated from the peritoneal fluid and identified as Cryptococcus species. Based on antifungal susceptibility testing, the treatment was changed to voriconazole and continued for 3 months. A genetic analysis identified the isolate as Cryptococcus laurentii (C. laurentii). This patient was diagnosed with C. laurentii PD-related peritonitis and was successfully treated with voriconazole and removal of the PD catheter.

Key words: Cryptococcus laurentii, peritoneal dialysis, voriconazole, catheter removal

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Introduction

Peritonitis is a major and potentially serious complication of peritoneal dialysis (PD) therapy and is one of the important reasons for withdrawal from PD (1). Although the most commonly identified pathogens are bacteria, fungal peritonitis is very serious and catheter removal is strongly recommended immediately following fungal identification by microscopy or culture (2). Candida species are reportedly the most frequently isolated fungi in PD-related peritonitis patients (3). Cryptococcal peritonitis is unusual and, to our knowledge, only 12 cases have been reported previously (4-7).

Cryptococcus neoformans infection in immunocompromised hosts is the most common of the cryptococcal infections. Other Cryptococcus species have traditionally been considered to be non-pathogenic (8). However, the incidence of infection due to these organisms, such as Cryptococcus laurentii (C. laurentii) and Cryptococcus albidus (C. al- bidus), has increased over the past four decades (8, 9). We know of two reported cases of peritonitis in PD patients caused by C. laurentii (10, 11). We herein report a case of peritonitis caused by C. laurentii in an adult patient on PD. To our knowledge, this is the first reported case of C. laurentii PD-related peritonitis that was successfully treated by voriconazole and the removal of the catheter.

Case Report

A 32-year-old man with IgA nephropathy had been on continuous ambulatory peritoneal dialysis (CAPD) since age 29. At age 30, CAPD was changed to combination PD and hemodialysis (HD) therapy. The PD bag exchange protocol was as follows: 2.5% glucose-based solution (Dianeal-N PD-2 2.5% \textsuperscript{TM}; Baxter, Tokyo, Japan) 2 L/daytime and icodextrin solution (Extraneal\textsuperscript{TM}; Baxter, Tokyo, Japan) 2 L/overnight. To change PD fluid (PDF) bags, the patient used a sterile connecting UV flash device (Clean Flash\textsuperscript{®}; Baxter). He was not treated with any immunosuppressive therapies.
The WBC count in the first cloudy PDF was 3,500 cells/mm³ at the hospital, the peritoneal fluid was noted to be cloudy. A yeast culture showed large Gram-positive budding structures were identified by microscopy (Fig. 1A). Blood and sputum cultures collected and a serological test for human immunodeficiency virus (HIV) was negative. The patient had never previously experienced peritonitis before this episode and had not taken any antibiotics for more than six months.

He presented to our hospital complaining of fever for the past seven days. His vital signs were as follows: blood pressure, 137/82 mmHg; pulse, 78/min; respiratory rate, 16/min; and temperature, 37.3°C. On physical examination, no abdominal tenderness was found. The clinical laboratory data at admission were as follows: peripheral white blood cell (WBC) count, 4,400 cells/mm³ (neutrophils, 60%; lymphocytes, 26%; eosinophils, 14%); blood hemoglobin level, 14.2 g/dL; and C-reactive protein level, 4.0 mg/dL. The serum cryptococcal antigen test (Eiken-Latex agglutination test; Sero direct®, Tokyo, Japan) was negative. A Tenckhoff catheter was in place in the left lower quadrant and did not appear to be infected. When PDF exchange was performed at the hospital, the peritoneal fluid was noted to be cloudy. The WBC count in the first cloudy PDF was 3,500 cells/mm³ (neutrophils, 60%; lymphocytes, 26%; eosinophils, 14%), indicating peritonitis. Gram staining of the centrifuged PDF sediment was performed, and yeast cells with large Gram-positive budding structures were identified by microscopy (Fig. 1A).

Table. Antifungal Susceptibility Testing Results of C. laurentii Isolated from Peritoneal Fluid

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0.25</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>8</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.25</td>
</tr>
<tr>
<td>Miconazole</td>
<td>1</td>
</tr>
<tr>
<td>Micafungin</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The Testing was Performed According to the CLSI-M27-A3 Guidelines

Figure 1. Gram stain (A) and India ink stain (B) of centrifuged sediment of the peritoneal effluent. (A) Yeast cells with large Gram-positive budding structures were identified in the peritoneal dialysis fluid by microscopy. (B) India ink staining of the isolate showed capsule formation around the cells.

Fungal peritonitis in PD patients is a serious complication, leading to death in approximately 25% of episodes (14, 15). Although the majority of cryptococcal infections are due to C. neoformans (16), the incidence of infection due to other Cryptococcus species, such as C. laurentii...
and *C. albidos*, has increased over the past four decades (8, 9). There have been reports of lung, eye and cutaneous infections, meningitis, and fungemia caused by *C. laurentii* and *C. albidos* (8, 9).

A review of the cryptococcal PD-related peritonitis literature was performed by Yinnon et al. (4, 5). This report included 10 cases of cryptococcal peritonitis during CAPD, and 2 of these 10 patients died. Cultures of samples yielded *C. laurentii* in 2 cases, and *C. neoformans* in 6 cases, but the *Cryptococcus* species of the remaining 2 cases were not stated. Therefore, to the best of our knowledge, only 2 cases of peritonitis in PD patients caused by *C. laurentii* have been reported (10, 11). Both were adolescent females, and neither was on immunosuppressive therapy. The natural habitats of *C. laurentii* are unknown (8, 9), and therefore we could not precisely identify the infection route for the current patient. However, these previous reports and our present case suggest that an indwelling PD catheter may be a risk factor even without significant immunosuppressive therapy.

Primary resistance to fluconazole and flucytosine has been reported in *Cryptococcus* species other than *C. neoformans* (17), although the interpretative clinical minimum inhibitory concentration (MIC) breakpoints in *C. laurentii* have not been determined. In the current case, the isolated *C. laurentii* had low MICs for itraconazole, amphotericin B and voriconazole, while the MIC for fluconazole was relatively high and the MIC for flucytosine was over the upper limit (Table). As far as we could determine, there is no previous report of the use of voriconazole to treat cryptococcal peritonitis in general, or specifically *C. laurentii* infection. In the previous reports, *C. laurentii* infections were successfully treated by combinations of amphotericin B, fluconazole and flucytosine, or intravenous amphotericin B alone (8). However, the use of intravenous amphotericin B results in poor peritoneal bioavailability (18). Conversely, dose adjustment was not necessary when voriconazole was administered to patients on PD therapy (19). In addition, *in vitro* activities of voriconazole, posaconazole and fluconazole against 237 *C. neoformans* isolates were assessed by Pfaller et al. (20) who reported that voriconazole was more active than fluconazole. Furthermore, the ISPD guideline states that voriconazole is effective against fungal peritonitis, but there is no statement indicating that itraconazole is effective (2). Considered together, this information suggests that voriconazole is an effective agent for the treatment of cryptococcal peritonitis. Based on these data and information, we selected voriconazole to treat the current patient.

Experience regarding the optimal duration of treatment for *C. laurentii* infections is limited due to the limited number of reported cases and lack of controlled trial data. However, it was reported that a PD patient with *C. neoformans* peritonitis died after nine weeks of treatment with antifungal drugs, including amphotericin B; at the postmortem examination, cryptococcosis in the lung, spleen and brain was revealed (5). Our patient was successfully treated by 3 months of voriconazole. Further accumulation of data from successfully-treated cases will inform future decisions regarding selection of the most suitable antifungal agents and the optimal duration of treatment for *C. laurentii* PD-related peritonitis.

**Figure 2.** The patient’s clinical course. The left Y axis indicates the WBC count in the CAPD fluid (/μL) and the right Y axis indicates the CRP level (mg/dL). MCFG: micafungin, FLCZ: fluconazole, VRCZ: voriconazole.
The authors state that they have no Conflict of Interest (COI).

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