Case Report

Paecilomyces lilacinus peritonitis complicating peritoneal dialysis cured by oral voriconazole and terbinafine combination therapy

Brian Pin-Hsuan Chang,¹ Pei-Lun Sun,² Fu-Yuan Huang,^{1,3}
Tsuen-Chiuan Tsai,⁴ Chun-Chen Lin,¹ Ming-Dar Lee,¹ Yee-Chun Chen,⁵
Jin-Cherng Sheu⁶ and Jeng-Daw Tsai^{1,3}

Correspondence

Jeng-Daw Tsai
tsajid@yahoo.com.tw

¹Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan

²Department of Dermatology, Mackay Memorial Hospital, Taipei, Taiwan

³Department of Pediatrics, Taipei Medical University, Taipei, Taiwan

⁴Department of Pediatrics, Taipei Medical University Wan-Fang Hospital, Taipei, Taiwan

⁵Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

⁶Department of Pediatric Surgery, Mackay Memorial Hospital, Taipei, Taiwan

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Fungal peritonitis (FP) is a serious complication in patients on continuous ambulatory peritoneal dialysis (CAPD). We report a case of CAPD-related FP caused by *Paecilomyces lilacinus* in a 15-year-old uraemic boy. The infection was successfully treated by combination therapy consisting of oral voriconazole and terbinafine, which has not been previously reported in the treatment of FP.

Introduction

Fungal peritonitis (FP) is a rare but serious complication in children on continuous ambulatory peritoneal dialysis (CAPD). In the past, most of the causative organisms have been *Candida* spp., especially *Candida albicans* (Prasad & Gupta, 2005). Recently, filamentous fungi have emerged as significant causes of invasive mycoses in immunocompromised patients. Only 14 cases of *Paecilomyces* peritonitis have been described in the literature (Wright *et al.*, 2003) and none of the infections were caused by *Paecilomyces lilacinus*, which has high antifungal drug resistance. We report the first case, to our knowledge, of *P. lilacinus* peritonitis in a patient on CAPD. The peritonitis did not respond to conventional antifungal agents, but was successfully treated by a combination of oral voriconazole and terbinafine in the outpatient department. This combination had only been studied *in vitro* previously, with no clinical use reported in the literature.

Case report

A 15-year-old boy was diagnosed with reflux nephropathy and chronic renal insufficiency at the age of 3 years. Renal

function gradually deteriorated and he underwent CAPD from 4 years of age. When the patient was 5 years old, he underwent cadaveric renal transplantation, and bilateral nephrectomy was simultaneously performed because of his heavy proteinuria. Triple immunosuppressive therapy (prednisolone, azathioprine and cyclosporin) was used and his creatinine level remained between 79 and 106 $\mu\text{mol l}^{-1}$ for approximately 2 years. However, his renal function worsened again due to chronic rejection and he was restarted on CAPD at the age of 7 years. At 10 years of age, he presented with diffuse cervical lymphadenopathy, dry and itching skin, and eosinophilia. Kimura's disease was diagnosed based on a lymph node biopsy.

In November 2005, when he was 15 years old, he had intermittent abdominal pain and a fever to 38.5 °C, but clear dialysate drainage. The white blood cell (WBC) count of the dialysate was 4×10^6 WBCs l^{-1} . The fever and abdominal pain persisted during the first week. The dialysate draining from the CAPD catheter was inoculated on Sabouraud's dextrose agar slants with and without antibiotics. The culture grew a mould 4 days later. He was admitted to the hospital on 24 November 2005. On admission, his body weight was 23 kg. A repeat peritoneal effluent analysis revealed $>10^9$ WBCs l^{-1} (5% lymphocytes and 95% neutrophils). The peripheral WBC count was $7.1 \times 10^9 \text{ l}^{-1}$ (67% neutrophils, 10% eosinophils, 8% monocytes and 15% lymphocytes). The C-reactive protein (CRP) level measured by nephelometry was 211 mg l^{-1} (normal range $<8 \text{ mg l}^{-1}$) and increased to 497 mg l^{-1} 1

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CRP, C-reactive protein; CT, computed tomography; FP, fungal peritonitis; WBC, white blood cell.

The GenBank/EMBL/DDBJ accession number for the rDNA sequence of *Paecilomyces lilacinus* is EU306174.

week after admission. There was no clinical sign of exit-site infection. Intravenous amphotericin B (1 mg kg^{-1} per day) and oral fluconazole (6 mg kg^{-1} per day) were used. A repeat dialysate fungal culture during the hospitalization grew the same mould, which was identified as *Paecilomyces* sp. by morphology. The peritoneal Tenckhoff catheter was removed due to persistent turbid effluent and he was transferred to haemodialysis.

The treatment response seemed poor because of persistent spiking fevers and a high CRP level. Clinically, the boy complained of abdominal pain, nausea, vomiting and decreased appetite. Abdominal ultrasound and abdominal computed tomography (CT; Fig. 1a) showed severe intestinal ileus, massive turbid ascites and a thickened bowel wall. A laparotomy was performed for bowel adhesions and ascites drainage. Thickened, leather-like plaques were noted on the bowel wall (Fig. 1b). Periodic

acid-Schiff and Gomori methenamine silver (Fig. 1c) stains showed fungal hyphae in the fibrous tissue of an adhesion band. Because of the persistent fever, sustained elevated CRP level (323 mg l^{-1} after laparotomy) and massive turbid ascites production on repeat tapping for relief of symptoms, fluconazole was changed to oral voriconazole (12 mg kg^{-1} per day) and amphotericin B was discontinued. The fever subsided after a 22 day course of voriconazole, but the aspirated ascites fungus culture still revealed *Paecilomyces* sp. The patient was discharged on 12 February 2006 on oral voriconazole therapy without fever, but the CRP level was still 74 mg l^{-1} .

His CRP level remained high during the follow-up in the outpatient department. Weekly peritoneocentesis yielded $\sim 800 \text{ ml}$ of turbid ascites, from which the same mould grew in fungal culture and was further identified as *P. lilacinus* by both morphology (Fig. 1d) and sequencing of

Fig. 1. (a) Abdomen CT scan showing severe intestinal ileus with massive turbid ascites and thickened bowel wall, indicating peritonitis. (b) Laparotomy showing thickened leather-like plaques on the bowel wall. (c) Gomori methenamine silver stain showing a few fungal hyphae in the fibrous tissue of adhesion band. (d) Culture showing pigmented and rough-walled conidiophores bearing whorls of phialides typical of *Paecilomyces lilacinus* by microscopy (potato dextrose agar, 7 days; lactophenol cotton blue stain, original magnification, $\times 400$).

an internal transcribed spacer of rDNA (GenBank accession no. EU306174). Therefore, in addition to voriconazole, terbinafine was added (62.5 mg, every other day) as combination therapy (Pastor & Guarro, 2006; Ortoneda *et al.*, 2004). The clinical signs of intestinal obstruction improved dramatically and the CRP level gradually decreased to 3.3 mg l⁻¹. The ascites fungal culture was also negative and the ascites decreased in amount and appeared clear. Combination therapy was used for 3 months and the patient is now undergoing regular haemodialysis in a stable condition. Hepatic enzyme tests were all within normal limits and no other side effects were noted during the treatment period. A follow-up ultrasound and CT scan after treatment revealed no ascites and the ileus had resolved.

Discussion

Peritonitis is one of the most frequent complications of peritoneal dialysis, and FP accounts for 1–15% of these episodes (Prasad & Gupta, 2005). The majority of FP episodes are caused by *Candida* spp., but filamentous fungi are increasingly recognized as pathogens of FP in immunocompromised peritoneal dialysis patients. The first case of *Paecilomyces* spp. CAPD-associated FP was reported in 1990 by Lye and there have been 14 such cases described in the literature (13 caused by *Paecilomyces variotii* and 1 caused by *Paecilomyces taitungiacus*), ranging from teenagers to adults (Wright *et al.*, 2003). However, there have been no previously reported cases of *P. lilacinus* peritonitis.

Paecilomyces spp. are common saprophytic fungi causing hyalohyphomycosis and are common contaminants of sterile solutions and clinical specimens because of their extreme resistance to the majority of commercial sterile techniques. *Paecilomyces* spp. have a distinct morphological feature which distinguishes them from *Penicillium* spp., i.e. an elongated slender neck protruding from the phialides (Tan *et al.*, 1992). *Paecilomyces* spp. are seldom associated with human infections, except some species such as *P. variotii*, *Paecilomyces marquandii* and *P. lilacinus* in the immunocompromised host or in patients associated with foreign bodies, such as prosthetic heart valves or ocular lenses.

P. lilacinus has been reported in respiratory, ocular and cutaneous infections, and fungaemia (Tan *et al.*, 1992). Filamentous fungi rarely cause CAPD-related peritonitis, and the causative organism is usually catheter-related or is present in contaminated commercial dialysis fluid (Nankivell *et al.*, 1991). The mechanism of infection in our patient was unknown. Because fungi easily colonize the surface of peritoneal catheters and form an antibiotic-resistant biofilm, catheter removal is often needed for successful treatment (Prasad & Gupta, 2005).

In fungal infections, it is important to identify the pathogen to species level, not only because of their different susceptibilities to antifungal agents, but because

of their distinct clinical outcomes. In the review of treatment of *Paecilomyces* peritonitis in CAPD patients, oral 5-fluorocytosine, ketoconazole and amphotericin B have been reported to be effective in *P. variotii* peritonitis (Kovac *et al.*, 1998; Prasad & Gupta, 2005). Data are limited regarding the *in vitro* antifungal susceptibility of *P. lilacinus* (Pastor & Guarro, 2006). *P. lilacinus* is highly resistant to polyene antibiotics (e.g. amphotericin B), fluconazole and flucytosine, with high MIC values (Aguilar *et al.*, 1998). Amphotericin B penetrates poorly from the blood into peritoneal fluid. This could be the reason that the treatment with intravenous amphotericin B in our patient with CAPD-related *P. lilacinus* peritonitis was ineffective. The intraperitoneal use of amphotericin B is not preferred because of chemical irritation (Prasad & Gupta, 2005).

Some antifungal drugs have been tested for *in vitro* activity against *P. lilacinus*, such as various triazoles, terbinafine and micafungin, but only the azole derivatives were active (Pastor & Guarro, 2006). Voriconazole is considered an alternative to amphotericin B when the pathogens are filamentous fungi (Prasad & Gupta, 2005). It is a fungistatic agent which acts on lanosterol 14 α -demethylase for the synthesis of ergosterol, and displays excellent oral bioavailability and tissue penetration (Martin *et al.*, 2002). Because of the high resistance of conventional antifungal drugs as monotherapy against *P. lilacinus*, various *in vitro* antifungal combinations have been tested and the benefits have been proposed based on synergic antifungal effects or pharmacological properties in invasive fungal infections (Cuenca-Estrella, 2004).

There are synergic interactions from combinations, such as amphotericin B with various triazoles or terbinafine, and terbinafine with voriconazole (Pastor & Guarro, 2006). Terbinafine combined with four azoles was reported to have the highest percentage of synergistic interactions (53%), and the combination terbinafine/voriconazole was the only combination that was synergistic against all tested strains of *P. lilacinus* (Ortoneda *et al.*, 2004). Oral terbinafine has been widely used in the treatment of superficial fungal infections, including onychomycosis and tinea pedis. Although some studies have demonstrated poor penetration of terbinafine into deep tissues, others suggest that it is effective in systemic mycoses (Cuenca-Estrella, 2004). From the mechanistic point of view, combination therapy with azoles and terbinafine will exhibit synergy since they act on different enzymes in the same pathway (Cuenca-Estrella, 2004). We combined terbinafine with voriconazole for 3 months to treat CAPD-related *P. lilacinus* peritonitis and this was a successful application of the *in vitro* result to clinical use.

In summary, we report what we believe to be the first case of severe CAPD-related FP caused by *P. lilacinus*. After failure of treatment with amphotericin B, followed by unsatisfactory voriconazole treatment, we successfully administered combination therapy consisting of oral

voriconazole and terbinafine. This could probably be further applied to other invasive infections caused by *P. lilacinus*, especially when the response to conventional therapy is poor.

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