Diagnosis and treatment of peritoneal dialysis associated mycotic peritonitis caused by *Aspergillus fumigatus* infection

Dan Zhang [a], Guofeng Mao [a], Meichun Liang [a], Guiqin Sun [b], Debao Yu [a,*]

[a] Department of Clinical Laboratory Center, Shaoxing People's Hospital, Shaoxing, 312000, PR China
[b] School of Medical Technology and Information Engineering, Zhejiang Chinese Medical University, Hangzhou, 310053, PR China

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ABSTRACT

Aspergillus peritonitis is a rare but highly severe complication of peritoneal dialysis with a high mortality rate. We report a case of *Aspergillus fumigatus* peritonitis. Despite early removal of the catheter and oral voriconazole antifungal treatment for 3 weeks, the treatment effect was unsatisfactory, resulting in prolonged hospital stay and affecting the patient's quality of life. After switching to liposomalAmphotericin B, inflammation indicators rapidly decreased and infection was controlled. Liposomalamphotericin B provides an option for treatment of *Aspergillus* peritonitis.

1. Introduction

Fungal peritonitis is a rare but serious complication in peritoneal dialysis, accounting for approximately 3%–10% of continuous ambulatory peritoneal dialysis (CAPD) [1]. It can lead to failure of peritoneal dialysis treatment and even patient death. *Candida* is the most common pathogen of fungal peritonitis, while those caused by *Aspergillus* are relatively rare, accounting for about 2%–5%, but their severity and mortality rate are higher [2].

2. Case presentation

The patient, female, 59 years old, was admitted to the Nephrology Department of Shaoxing People's Hospital (day 0) due to peritoneal dialysis for 3 years and abdominal pain accompanied by turbidperitoneal dialysis fluid for 2 days. During peritoneal dialysis, the patient's dialysiscatheterwas unobstructed, no discomfort such as abdominal pain, diarrhea, and fever. Onday -2, the patient experienced abdominal pain presenting as paroxysmal colic, with an numerical rating scale (NRS)score of 3,accompanied by diarrhea, turbidperitoneal dialysis fluid, and a small amount of flocculent material. The routine examination of ascites (day 0) showed a milky white andturbid, protein test negative, nucleated cell count was 3700×10^6/L, and neutrophil ratio was 85%. Completeblood count showed WBC countwas 14.28×10^9/L, neutrophil ratio 87.6%, renal and electrolyte examination results

showed potassium2.95 mmol/L, calcium 2.06 mmol/L, urea 10.29 mmol/L, and creatinine 589.2 μmol/L. The patient was hospitalization for peritoneal dialysis related peritonitis. The patient had a history of hypertension, erosive gastritis, and gastroesophageal reflux disease.

The results of biochemical examination after admission showed albumin 30.7g/l and CRP 107.28mg/l. On day 0, after the peritoneal dialysis fluid was taken for culture, the initial treatment plan was given cefazolin 0.5g added to each bag of peritoneal dialysis fluid, ceftazidime 1.0g added to the nighttime peritoneal dialysis fluid, and ceftriaxone 2.0g intravenous drip QDfor infectiontreatment. The patient's abdominal pain symptoms did not improve significantly, and there were still recurrent low fevers. On day 5, the nucleated cell count of ascites was decreased to 1600×10^6/l, and the proportion of neutrophils was 80%. No bacteria were found in ascites smear. Ascites 1,3-β- D-glucan detection (G test) was 9777.38pg/ml (Beijing Gold Mountainriver negative: < 60 pg/ml; positive > 100 pg/ml), ascites galactomannan antigen detection (GM test) 12μg/l (Beijing Gold Mountainriver negative: < 0.25μg/l; positive > 0.45μg/l). The ascites culture showed no bacterial growth. All antibiotics were stopped, and fluconazole 200mg QD intravenous drip was started. The peritoneal dialysis tube was removed, and the celiac segment of the catheter was cultured. In addition, hemodialysis was started. The patient still had recurrent low fevers. On day 10, according to the results of catheter culture, *A. fumigatus* (Figs. 1 and 2) was cultured, followed by susceptibility test results (Table 1). Fluconazole was changed to voriconazole 150mg q12h orally.

Fig. 1. Colony morphology of *A. fumigatus* on blood agar cultured for 7 days.
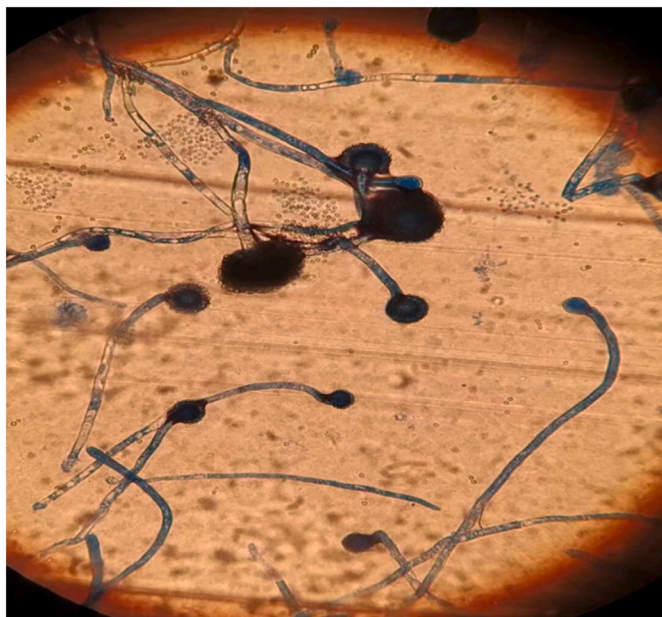

Fig. 2. Microscopic morphology of *A. fumigatus* under a 10 × 40 microscope.

Table 1
Drug sensitivity test results of *A.fumigatus*.

Antibiotic	MIC	Unit	Susceptibility	Breaking point
Itraconazole	0.12	μg/ml	S	≤1
Fluconazole	>256	μg/ml	R	Natural resistance
Amphotericin B	1	μg/ml	S	≤2
Voriconazole	0.12	μg/ml	S	≤1
Caspofungin	8	μg/ml	R	≤0.5

On day 31, 3 weeks after start voriconazole, and the blood concentration of voriconazole was monitored at 3.9 mg/L, and a decrease in serum G test (553.1 pg/ml), and serum GM test (7.13 μg/l) was seen. The

patient's CRP was still elevated, with low fevers, and abdominal ultrasound suggested the presence of peritoneal effusion, and a large number of segmentations were seen inside. Considering the poor clinical efficacy of the antifungal treatment, voriconazole was stopped after consultation with the infection department. On day 33, liposomal Amphotericin B (50mgd1, 100mgd2, 150mgd3 gradually increased) intravenously was startedn. The patient's temperature returned to normal on day 34 (Fig. 3), the serum G test became negative (<40 pg/ml), and the GM test decreased to 2.72 μg/l. On day 46, after 2 weeks of liposomal Amphotericin B treatment,the WBC counts, CRP, serum G test and GM test returned all to normal, and the infection was controlled. The patient was prescribed oral isaconazole 200mg q12h for 2 weeks for consolidation treatment after discharge.

3. Discussion

The causative fungi of fungal peritonitis mainly include *Candida*, *Trichosporon* and other yeasts, and *Aspergillus*, *Rhizopus* and other filamentous fungi. *Aspergillus*species related peritonitis mainly include *A. fumigatus*, *A. niger*,*A. terreus* and *A. flavus*. Among *Aspergillus* species, *A. fumigatus* has the highest isolation rate (17/55), followed by *A. niger* (15/55) and *A. terreus* (9/55) [3].

The diagnosis of *Aspergillus* peritonitis is relatively difficult. The clinical symptoms and signs of the disease are non-specific. The diagnosis mainly relies on ascites culture, but it usually takes several days to weeks, often leading to delayed diagnosis. Although the use of ascitic fluid Gram staining is helpful to establish an early diagnosis in 30% of cases [4], usually only *Candida* shows positive results, which is ineffective for *Aspergillus*. At present, G test and GM test are increasingly used for early diagnosis and treatment monitoring of fungal infection. SCOTTER [5] and ATES [6] reported *Aspergillus* peritonitis diagnosed by ascites, serum G test and GM test, respectively. The ascites G test and GM test of this patient were strongly positive, which increased the reliability of diagnosis. NAVAPORN [7] found that when G test cut-off value of peritoneal dialysate in peritoneal dialysis patients was 240pg/ml, GM test when the cut-off value is 0.5μg/l, its sensitivity for the diagnosis of fungal peritonitis is 83%–100%, and the specificity was 58%–77%. Therefore, G test and GM test may be used as alternatives for the diagnosis of *Aspergillus* peritonitis for the early diagnosis and treatment monitoring of the disease.

The predisposing factors of *Aspergillus* peritonitis have not yet been fully defined. Currently, the reported predisposing factors mainly include long-term use of antibiotics, recent occurrence of bacterial peritonitis, immunosuppressive state and diabetes mellitus [1,8], among which having bacterial peritonitis and receiving antibiotic treatment is the most common predisposing factor. Studies have shown that compared with patients with bacterial peritonitis, patients with fungal peritonitis have the characteristics of hypoproteinemia, anemia and hypokalemia, and about 63.6% of patients have gastrointestinal symptoms [9]. Although this patient had no previous history of bacterial peritonitis, antibiotic use, immune disease and diabetes, there were factors such as hypoproteinemia, anemia, hypokalemia and
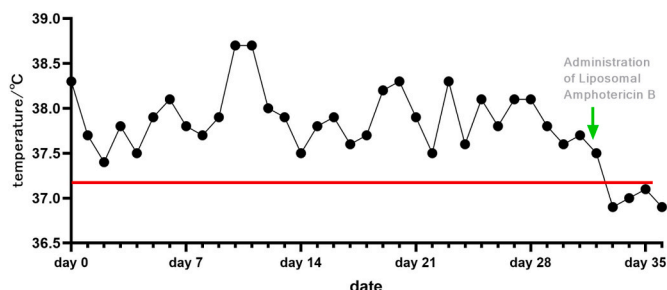

Fig. 3. Daily temperature changes at 2:00PM during hospitalization.

gastrointestinal symptoms, which increased the probability of fungal peritonitis.

The latestISPD guidelines recommend that peritoneal dialysis catheters should be removed immediately once fungal peritonitis is diagnosed. Because fungi can form biofilms on the surface of peritoneal dialysis tubes, which leads to difficulties in drug treatment and easy recurrence. Although the guidelines recommend immediate removal, some recent studies suggest that early removal rather than immediate removal is preferred for pediatric fungal peritonitis, mainly in the hope of reducing abdominal adhesion and maintaining the structure and function of the peritoneum through peritoneal lavage with antifungal drugs [10]. At present, there is no unified treatment plan for *Aspergillus* peritonitis. Intravenous liposomal Amphotericin B or oral triazole drugs, such as voriconazole or isaconazole [11], are recommended. Triazole drugs usually represent first-line drugs. Oral voriconazole has been shown to rapidly achieve good peritoneal concentration with minimal peritoneal clearance [12,13]. The patient we reported had poor effect after oral voriconazole for 3 weeks, despite a low MIC for voriconazole and good serum levels. After intravenous injection of liposomal Amphotericin B, the patient's temperature recovered, the inflammatory indicators decreased significantly, and the infection was controlled. Liposomal Amphotericin B is a biological agent of Amphotericin B used to treat fungal infections, such as *Aspergillus* and *Candida* infections [14], as well as other less common infections, such as visceral leishmaniasis [15]. With the development of Liposomal Amphotericin B, compared with Amphotericin B, higher drug concentration can be obtained in plasma and tissues while reducing toxicity [16]. However, due to its high price, it is limited in clinical use in several parts of the world [17].

In conclusion, *Aspergillus* peritonitis is a rare disease with poor prognosis. Because of its nonspecific clinical characteristics, for patients with high-risk factors, ascites culture and susceptibility testing is of key importance. At present, there is no unified standard for the treatment of this disease. The latest ISPD guidelines recommend voriconazole therapy as its preferred drug. When voriconazole treatment is not effective, liposomal Amphotericin B is a good alternative drug.

Ethics statement

This studyand included experimental procedures were approved by the institutional. This study was approved by the ethics committee of Zhejiang University Shaoxing People's Hospital. We certify that the study was performed in accorgenc e1964 declaration of HELSINKI and later amendments. Written informed consent was obtained from all the participants prior to ths ers of this case report.

CRediT authorship contribution statement

Dan Zhang: Data curation, Conceptualization. **Guofeng Mao:** Validation, Methodology. **Meichun Liang:** Software, Resources. **Guiqin Sun:** Writing – review & editing, Funding acquisition. **Debao Yu:** Data curation.

Declaration of competing interest

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