
Short communication

***Aspergillus* Peritonitis in Chronic Peritoneal Dialysis Patients: Review of the Literature and Report of Two Cases**

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Abstract

Although gram positive bacteriae are the most common causative microorganisms of chronic peritoneal dialysis (CPD) peritonitis, fungi are responsible for 1-15% of all cases. On the other hand, fungal peritonitis episodes may potentially cause serious consequences such as resistance to treatment, extended hospital stay and also a higher probability of death. Fungal peritonitis due to *Aspergillus spp* is relatively uncommon, but its mortality rate and severity is known to be even higher. It was our aim to conduct a review of the medical literature regarding the treatment and clinical outcome of *Aspergillus* related CPD peritonitis and to present two cases with *Aspergillus* related CPD events. Our current knowledge and the outcome of our two cases suggest that, despite the use of recommended therapeutic measures, *Aspergillus* induced fungal peritonitis in CPD patients may still be fatal. Therefore, there is a need for development of more efficient therapeutic approaches including the type, dose and route of antifungal therapy.

Key words: peritoneal dialysis, fungal peritonitis, *Aspergillus*, *Aspergillus flavus*, *Aspergillus niger*

Introduction

Peritonitis is one of the most important complications of chronic peritoneal dialysis treatment and is reported to be responsible for 40-47% of technical failure with mortality rates as high as 1-6% and frequent hospitalizations seen in that treatment modality [1,2]. Although gram-positive bacteriae are the most common cause of CPD peritonitis, fungi are responsible for 1-15% of all cases [3,4]. On the other hand, fungal peritonitis episodes may potentially cause serious consequences including resistance to treatment, extended hospital stay and also a higher probability of death [5]. Fungal peritonitis due to *Aspergillus spp* is relatively uncommon, but its mortality rate and severity is known to be even higher [6]. It was our aim to conduct a review of the medical

literature regarding the treatment and clinical outcome of *Aspergillus* related CPD peritonitis and to present two cases. One of the patients died due to *Aspergillus flavus* and the other was with fungal colonization in titanium adapter proven by positive fungal culture for the presence of *Aspergillus niger*.

Cases

Our first patient was a 49-year-old man with end-stage renal disease secondary to type I diabetes mellitus and has been included into our continuous peritoneal ambulatory dialysis (CAPD) program since 2008. He had undergone an inguinal hernia surgery at the 18th month after commencing CAPD treatment. He had also an episode of bacterial peritonitis in 2010 which had been treated successfully.

In 2012, he was admitted to the Emergency Department with abdominal pain, nausea and cloudy dialysate. His blood pressure was 130/80 mmHg, pulse 82 beat/minute and body temperature 37.2°C. The physical examination revealed disseminated abdominal tenderness and he was positive for signs and symptoms of peritoneal irritation. No signs of infection around the exit site and catheter tunnel was observed. Laboratory test results of our patient were as follows: peripheral blood white blood cell (WBC) count: 18,450/mm³ (N=4,800-10,800), hemoglobin 9.5 gr/dl (12-16 gr/dl), erythrocyte sedimentation rate 120 mm/hour, C-reactive protein 46.1 mg/dl (0-0.5 mg/dl) and creatinine 12.6 mg/dl (0.7-1.2 mg/dl). His peritoneal effluent WBC count was found to be 3020 /mm³ with a differential of neutrophils: 570/mm³, lymphocytes: 280/mm³, monocytes: 2080/mm³. Based on his clinical picture and laboratory criteria, he was diagnosed as having CPD-related peritonitis. Because of drainage problems in his peritoneal dialysis catheter, after initial samples for cultures and peritoneal effluent cell counts were taken, peritoneal dialysis catheter was removed and hemodialysis was initiated. Direct microscopic investigation of peritoneal fluid with gram staining showed no microorganisms. Peritonitis treatment was initiated with ceftazidime intravenous 1 gr 2x1 and ampicillin/ sul-

bactam 1 gr 4x1 empirically. But despite treatment, his abdominal pain and clinical condition have not improved. Cultures for aerobic and anaerobic bacteria and tuberculosis were negative. But eventually, *Aspergillus flavus* was isolated from his peritoneal fluid samples and also from his removed catheter tip cultures. Therefore, intravenous administration of liposomal amphotericin B 200 mg/day was initiated at the fourth day of his hospitalization. This treatment was continued for 26 days. At days 0, 7, 14, 21 and 26, his C-reactive protein (CRP) levels were 24.8 mg/dl, 18.4 mg/dl, 17.7 mg/dl, 21.7 mg/dl, 19.5 mg/dl and peripheral leukocyte counts were 9.180/mm³, 14.450/mm³, 11.820/mm³, 35.270/mm³ and 23.020/mm³, respectively. Unfortunately, no clinical and laboratory improvement was observed and our patient died the 30th day of his admission.

Our second patient was a 77-year-old man with end-stage renal disease secondary to hypertension, chronic obstructive pulmonary disease and cor pulmonale. He has been on automated peritoneal dialysis for 24 months with no history of peritonitis. The patient was seen in our Peritoneal Dialysis Outpatient Clinic because of his report of accidental cut in his Tenckhoff catheter at the distal tip over a point very close to titanium adapter approximately 15 hours ago. There were no signs and symptoms of peritonitis, including abdominal pain, fever or cloudy dialysate. His blood pressure was 90/50 mmHg, temperature 37°C, pulse 90 beats per minute. The physical examination did not reveal any acute health problem and he was also negative for abdominal tenderness and signs of peritoneal irritation. There was no evidence for any infection around the exit site and catheter tunnel. His basic laboratory tests were as follows: peripheral blood WBC: 8600/mm³ (4.800-10.800/mm³), hemoglobin: 12.7 gr/dl (N=12-16 gr/dl), hematocrit: 37 (N=35-52), sedimentation: 37 mm/hour, CRP: 0.2 mg/dl (N=0-0.5), BUN: 53 mg/dl (N=6-20 mg/dl), creatinine: 4.68 mg/dl (N=0.7-1.2 mg/dl); peritoneal dialysate was clear with a WBC count of 100/mm³ with 40% neutrophils. His titanium adapter was replaced with a new one and dialysate samples for aerobic, anaerobic, acid-fast bacteriae and fungal cultures were taken and the patient was initiated prophylactic oral amoxicilline/clavulonic acid 1000 mg BID. All cultures were reported to be negative except *Aspergillus niger* growth in his fungal culture. Considering no development of any peritonitis signs or symptoms at the fourth day from the accidental cut of his catheter, we have decided to observe the patient for development of any evidence of peritonitis and keep him on antibiotic prophylaxis without initiating any antifungal therapy. During the follow-up, the patient has remained peritonitis-free and control cultures for fungi were negative.

Although fungi may be found in the regular flora of human skin and mucosa, long-term antibiotic usage [7], use of immunosuppressive drugs and diseases suppressing immune system [8], possibly non-biocompatible high

glucose containing dialysis solutions [9] and mechanical and/or chemical irritations caused by peritoneal catheters may be among the causes of fungal peritonitis. Transvaginal entrance of fungi into the peritoneal cavity may also occur. Intestinal perforations caused by diverticulitis have also been reported to cause fungal peritonitis.

Discussion

Fungal peritonitis episodes in CPD patients present as severe clinical form of peritonitis with high mortality rate of 20-30% [10]. *Candida spp* are known to be the most common cause of fungal peritonitis. But much less frequently, PD peritonitis may be caused by *Aspergillus spp* such as *Aspergillus thermomutatus* [11], *Aspergillus niger* [12,13], *Aspergillus flavus* [14], *Aspergillus fumigatus* [8], *Aspergillus terreus* [15,16], *Aspergillus oryzae* [5], *Aspergillus sydowii* [17]. In 2002, Matsumoto, *et al.* reviewed 20 *Aspergillus spp* peritonitis cases that have been published between 1968-2002. In our literature review covering the period from 2002 to 2013, we were able to find the records of 13 published cases of *aspergillus* peritonitis, including our two cases presented here (Table 1) [18-21]. Combined outcome results of two series reveal that, out of 33 cases presented since 1968, 11(33%) died and 13(39%) had to be transferred to hemodialysis. Only 8 patients (24%), including two patients with no signs and symptoms of overt peritonitis with culture proven *Aspergillus* colonization in the catheters, (Reference 19 and our second case presented in this report), were able to continue chronic peritoneal dialysis treatment suggesting a high risk clinical profile. Presence of severe abdominal pain, fever, delay in withdrawal of catheter, intensive antibiotic usage longer than three months and technical difficulties are reported to be related with mortality in fungal peritonitis [3,4]. On the other hand, as we have reported in our patient, *Aspergillus spp*, also seen in peritonitis episodes caused by other fungi, have a tendency to form adhesive fibrin plugs causing drainage problems and total obstruction of peritoneal catheter [10]. Interestingly, in one case, *Aspergillus niger* peritonitis was reported to be associated with eosinophilia, which is a clinical sign of pulmonary *aspergillosis* [22]. In our patient, both initial peripheral blood cell and dialysate eosinophil counts were within normal limits (0.9% and 0.4%, respectively).

If we analyze the fatal outcome in one of our patients, regarding the risk factors given above, the patient was neither on any immunosuppressive drugs nor there were any laboratory or clinical signs of hematologic or oncologic problems which may potentially affect his immune system besides known type I diabetes. Clinically, only abdominal pain was observed as one of the stated mortality risk factors. His peritoneal dialysis catheter was removed appropriately on the first day of admission and he was not on any long-term broad spectrum antibiotic therapy. But despite practicing the recommended general

therapeutic measures, our patient died the 26th day of the admission. *Aspergillus*-related peritonitis episodes can be treated with amphotericin B alone or in combination with azol derivatives such as ketocanazol, fluconazole or itracanazol. Because of serious side effects such as fever, chills, rigor, nausea and hypotension intravenous use of conventional amphotericin B is often limited. Therefore, lipophilic form of amphotericin B is recommended and it

is reported to be equally effective [11]. On the other hand, intraperitoneal use of amphotericin B may induce a chemical peritonitis with severe abdominal pain and it is not recommended. Intravenous use of amphotericin B may not be sufficiently effective because of drug's high protein binding capacity and limited transfer to the peritoneal area [23]. *Aspergillus terreus* has been reported to be resistant to amphotericin B both in vivo and in vitro [24].

TABLE 1. Summary of reported CPD- related peritonitis cases caused by *Aspergillus spp* 2003-2013

Patient No	Gender	Species	Catheter removal	Antimicrobials	Outcome	Reference	Year
1	M	<i>Aspergillus terreus</i>	Yes	Amphotericin B	Death	17	2003
2	M	<i>Aspergillus fumigatus</i>	No	Amphotericin B, oral itracanazol	Death	15	2004
3	F	<i>Aspergillus terreus</i>	Yes	Amphotericin B, itracanazole	Death	16	2004
4	F	<i>Aspergillus fumigatus</i>	Yes	Amphotericine B	HD	6	2005
5	F	<i>Aspergillus sydowii</i>	Yes	No treatment	HD	17	2005
6	F	<i>Aspergillus fumigatus</i>	Yes	Amphotericin B	HD	18	2006
7	F	<i>Aspergillus terreus</i>	Yes	Itracanazole (Catheter colonization)	PD	19	2006
8	F	<i>Aspergillus terreus</i>	Yes	Voricanazole	Death	20	2007
9	M	<i>Aspergillus oryzae</i>	Yes	Amphotericin B+caspofungin, itracanazole	HD	5	2007
10	F	<i>Aspergillus nidulans</i>	Yes	Amphotericin B, voricanazole	HD	21	2011
11	M	<i>Aspergillus flavus</i>	Yes	Voricanazole	HD	14	2013
12	M	<i>Aspergillus flavus</i>	Yes	Amphotericin B	Death	Case I	2013
13	M	<i>Aspergillus niger</i>	No	No treatment (Catheter colonization)	PD	Case II	2013

Conclusions

In conclusion, despite the use of recommended therapeutic measures, *Aspergillus* induced fungal peritonitis in CPD patients may still be fatal. There is a need for development of more efficient therapeutic approaches including the type, dose and route of antifungal therapy.

Conflict of interest statement. None declared.

Reference

- Maiorca R, Cancarini GC, Brunori G, *et al.* Morbidity and mortality of CAPD and hemodialysis. *Kidney Int* 1993; 43 (Suppl.): 4-15.
- Burkart JM, Daeihagh P, Rocco MV. Peritoneal Dialysis. Brenner and Rector's The Kidney ed. by, 7 th Edition Philadelphia: W.B. Saunders, 2004.
- Prasad N, Gupta A. Fungal peritonitis in peritoneal dialysis patients. *Perit Dial Int* 2005; 25(3): 207-222.
- Taskapan H, Ozener H, Ates K, *et al.* The rate, risk factors, and outcome of fungal peritonitis in CAPD patients: experience in Turkey. *Perit Dial Int* 2000; 20(3): 338-341.
- Schwetz I, Horina J, Buzina W, *et al.* *Aspergillus oryzae* peritonitis in CAPD: case report and review of the literature. *Am J Kidney Dis* 2007; 49(5): 701-704.
- Bonfante L, Nalesso F, Cara M, *et al.* *Aspergillus fumigatus* peritonitis in ambulatory peritoneal dialysis: a case report and notes on the therapeutic approach. *Nephrology (Carlton)* 2005; 10 (3): 270-273.
- Kazancioglu R, Kiricki G, Albaz M, *et al.* Fungal peritonitis among the peritoneal dialysis patients of four Turkish centres. *J Ren Care* 2010; 36 (4): 186-190.
- Scotter JM, Stevens JM, Chambers ST, *et al.* Diagnosis of *Aspergillus* peritonitis in a renal dialysis patient by PCR and galactomannan detection. *J Clin Pathol* 2004; 57(6): 662-664.
- Kazancioglu R. Peritoneal defense mechanisms-the effects of new peritoneal dialysis solutions. *Perit Dial Int* 2009; 29 Suppl 2: 198-201.
- Matuszkiewicz-Rowinska J. Update on fungal peritonitis. *Perit Dial Int* 2009; 29(Suppl 2): 161-165.
- Matsumoto N, Shiraga H, Takahashi K, *et al.* Successful treatment of *Aspergillus* peritonitis in a peritoneal dialysis patient. *Pediatr Nephrol* 2002; 17: 243-245.
- Bibashi E, Papagianni A, Kelesidis A, *et al.* Peritonitis due to *Aspergillus niger* in a patient on continuous ambulatory peritoneal dialysis shortly after kidney graft rejection. *Nephrol Dial Transplant* 1993; 10: 1240-1243.
- Bulbul M, Demircin G, Oner A, Erdogan O. Peritonitis due to *Aspergillus niger* in a child on continuous ambulatory peritoneal dialysis. *Turk Neph Dial Transpl* 1997; 1-2: 88-90.

14. Roberts DM, Kauter G, Ray JE, Gillin AC. Intraperitoneal voriconazole in a patient with *Aspergillus* peritoneal dialysis peritonitis. *Perit Dial Int* 2013; 33(1): 92-93.
15. Kalishian Y, Miller EB, Kagan A, Landau Z. *Aspergillus terreus* peritonitis in a CAPD patient: Report of a case. *Perit Dial Int* 2004; 24(1): 93.
16. Nannini EC, Paphitou NI, Ostrosky-Zeichner L. Peritonitis due to *Aspergillus* and *zygomycetes* in patients undergoing peritoneal dialysis: report of 2 cases and review of the literature. *Diagn Microbiol Infect Dis* 2003; 46(1): 49-54.
17. Chiu YL, Liaw SJ, Wu VC, Hsueh PR. Peritonitis caused by *Aspergillus sydowii* in a patient undergoing continuous ambulatory peritoneal dialysis. *J Infect* 2005; 51(3): 159-161.
18. Schattner A, Kagan A, Zimhony O. *Aspergillus* peritonitis in a lupus patient on chronic peritoneal dialysis. *Rheumatol Int* 2006; 26(8): 762-764.
19. Guerra e Silva A, Takiya CM, Lima MG, *et al.* Early detection of *Aspergillus terreus* in a Tenckhoff Catheter. *Perit Dial Int* 2006; 26(6): 723-724.
20. Verghese S, Palani R, Thirunakarasu N, *et al.* Peritonitis due to *Aspergillus terreus* in a patient undergoing continuous ambulatory peritoneal dialysis. *Mycoses* 2008; 51(2): 174-176.
21. Ulusoy S, Ozkan G, Tosun I, *et al.* Peritonitis due to *Aspergillus nidulans* and its effective treatment with voriconazole: the first case report. *Perit Dial Int* 2011; 31(2): 212-213.
22. Sridha D, Thornley-Brown D, Rant RS. Peritonitis due to *Aspergillus niger*: Diagnostic importance of peritoneal eosinophilia. *Perit Dial Int* 1990; 10(1): 100-101.
23. Li PK, Szeto CC, Piraino B, *et al.* Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30(4): 393-423.
24. Walsh TJ, Anaissie EJ, Dennig DW, *et al.* Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008; 46: 327-360.