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Article

Fungal Peritonitis in Patients on Continuous Ambulatory Peritoneal Dialysis

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Abstract The purpose of this study was to analyze the microbiological and clinical features of fungal peritonitis in patients with endstage renal failure treated with continuous ambulatory peritoneal dialysis (CAPD). The diagnosis of peritonitis was based on abdominal discomfort or pain, cloudy peritoneal effluent with an elevated leukocyte count and isolation of fungi from the peritoneal effluent. Amphotericin B, flucytosine, ketoconazole, miconazole and more recently fluconazole were used for antifungal therapy. From 1983 to 1997 13 patients experienced 14 episodes of fungal peritonitis, comprising 3.1% of all episodes of peritonitis in the dialysis centre. Isolates from the peritoneal effluent comprised *Candida tropicalis* in two cases, *Candida parapsilosis* in two cases, *Candida albicans* in one case, *Candida lusitaniae* in one case,*Cephalosporium* spp. in three cases, *Aspergillus fumigatus* in two cases, and an *Aspergillus* sp., a *Trichoderma* sp. and a yeast in one case each. In eight cases bacterial infection shortly before the episode of fungal peritonitis was documented. In 12 (86%) cases the peritoneal catheter had to be removed. Four patients died during the treatment, and one patient died 2 months after the end of treatment due to intra-abdominal bleeding from peritoneal adhesions. Only two patients continued CAPD later; the other patients were switched to hemodialysis. It is concluded that fungal peritonitis is a rare but serious complication in CAPD patients with high rates of morbidity, mortality and drop-out from the CAPD programme (85%). The most frequent isolates were *Candida* spp. A predisposing factor for fungal peritonitis could be a recent bacterial infection treated with antibiotics. Early peritoneal catheter removal is recommended.

Introduction

Fungal peritonitis is a relatively uncommon complication of peritoneal dialysis; nevertheless, it accounts for up to 10% of all peritonitis episodes in patients on CAPD, and contributes significantly to morbidity, drop out from the CAPD programme, and mortality [1–3]. *Candida* spp. are the fungi most frequently isolated from peritoneal effluent [1, 4, 5].

Although there are no controlled studies demonstrating which treatment regimen has the best outcome, retrospective studies suggest that systemic or intraperitoneal antifungal agents should be administered for up to 4–6 weeks while continuing CAPD. If there is no clinical improvement after 4–7 days, removal of the peritoneal catheter and continuation of antifungal therapy orally for 10 days are recommended [6, 7]. The purpose of this study was to analyze the microbiological and clinical features of fungal peritonitis episodes in CAPD patients.

Patients and Methods

Fungal peritonitis was analyzed in 13 patients treated with CAPD due to endstage renal disease in the period from 1983 to 1997. Clinical data on the patients, including age, sex, underlying kidney disease, time spent on CAPD before onset of peritonitis, number of previous peritonitis episodes and recent episodes of bacterial infection treated with antibiotics, are shown in Table 1. One patient received methylprednisolone and azathioprine due to the presence of anti-neutrophil cytoplasmic antibody (ANCA)-related pulmonary disease.

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Table 1 Clinical data of 13 CAPD patients with fungal peritonitis

Episode no.	Age/sex	Underlying disease	Time on CAPD (months)	No. of previous peritonitis episodes	Recently treated bacterial infection
1	30/M	glomerulonephritis	7	2	catheter exit site
2	30/F	diabetic nephropathy	26	7	peritonitis
3	59/M	analgesic nephropathy	24	2	none
4	56/F	undefined nephropathy	5	0	none
5	32/F	diabetic nephropathy	8	0	none
6	60/F	diabetic nephropathy	15	1	catheter exit site
7[a]	60/M	diabetic nephropathy	1	0	none
8[a]	60/M	diabetic nephropathy	6	1	none
9	59/M	hypertensive nephrosclerosis	15	7	peritonitis
10	65/M	diabetic nephropathy	126	14	peritonitis
11	56/F	chronic pyelonephritis	9	1	catheter exit site
12	44/M	glomerulonephritis	19	1	peritonitis
13	71/F	hypertensive nephrosclerosis	22	1	peritonitis
14	64/M	undefined nephropathy	29	2	none

[a] Episodes no. 7 and 8 occurred in the same patient

Peritonitis was diagnosed on the basis of abdominal discomfort or pain, cloudy peritoneal effluent with an elevated leukocyte count and a positive effluent culture [8]. In severe cases of fungal peritonitis more intense abdominal pain, an elevated body temperature, nausea and vomiting were also present. In each case of suspected peritonitis, the abdominal fluid (peritoneal effluent) was examined for organisms. The following culture media were used for pathogen isolation, identification and resistance tests: thioglycolate bouillon, blood agar, glucose bouillon and glucose agar. In the last 5 years Gram staining of the sediment of the peritoneal effluent was also performed to detect microorganisms. Cell counts were routinely performed in the first peritoneal effluent and also thereafter to determine the efficacy of therapy. A leukocyte count in the peritoneal effluent of ≤ 100 cells/μl was considered normal. A higher count was considered consistent with peritonitis.

As soon as the diagnosis of fungal peritonitis was confirmed, antifungal drugs were administered in accordance with recommendations [7, 9–11]. Amphotericin B was given intravenously in increasing doses up to 50 mg daily, and intraperitoneally in a dosage of up to 10 mg daily. Flucytosine was given orally or intravenously in an initial dose of 2 g and a maintenance dosage of 1 g daily. Miconazole was given intravenously or intraperitoneally in an initial dose of up to 400 mg and a maintenance dosage of 200 mg daily. Ketoconazole was given orally in a dosage of 200 mg twice daily, and fluconazole intravenously or orally in a dosage of 100 mg daily. In the case of failure of antifungal therapy the peritoneal catheter was removed and patients were switched to hemodialysis.

Results

In the 14-year study 13 patients on CAPD experienced 14 episodes of fungal peritonitis, comprising 3.1% of all peritonitis events observed in our centre since the start of CAPD programme in 1983. The fungal isolates, treatment and outcome of the fungal peritonitis episodes are shown in Table 2. Episodes of fungal peritonitis occurred in all seasons with equal frequency. The change from a single-bag CAPD system to a twin-bag disconnect system in 1992 did not prevent the occurrence of fungal peritonitis. Males and females had approximately the same morbidity rate.

The initial clinical manifestations of fungal peritonitis were mild in seven cases and severe in seven cases. There was no apparent association with a specific underlying kidney disease or fungal agent. In eight (61%) cases bacterial infection shortly before episode of fungal peritonitis was documented. Antibiotic treatment of such bacterial infection did not seem to have an effect on the type of fungi isolated from peritoneal effluent later. Peritoneal catheter outflow disturbances were present in five cases. The catheter had to be withdrawn in 12 of the 14 (86%) cases, usually 1–2 weeks after the start of antifungal therapy, due to persistent signs and symptoms of infection. In patients with fever blood cultures were performed. The cultures were positive in one patient (episode no. 10, Table 2) in whom *Pseudomonas aeruginosa* was isolated, and in another patient (episode no. 13) in whom coagulase-negative staphylococci were isolated.

Antifungal agents were administered in all cases as soon as the diagnosis of fungal peritonitis was established. Four patients initially received amphotericin B intraperitoneally. This mode of application was later ceased because patients were experiencing abdominal pain. Intravenous administration of amphotericin B was associated with fever in three patients and with hypokalemia in one patient. Fever and shivering were also observed in a patient treated with a liposomal formulation of amphotericin B given intravenously.

In one patient, who experienced two episodes of fungal peritonitis within a period of 6 months, a lower degree of ultrafiltration by the peritoneal membrane was observed after the first episode of peritonitis, requiring an additional hyperosmolar glucose dialysis solution

Table 2 Severity of peritonitis, leukocyte count in peritoneal effluent, fungal isolates, treatment and outcome of 14 episodes of fungal peritonitis

Episode no.	Severity of peritonitis	Leukocyte count (cells/μl)	Isolate	Treatment	Duration of treatment (days)	Success of treatment	Catheter removal	Outcome
1	severe	1140	yeast	amphotericin, flucytosine	23	yes	no	CAPD
2	mild	860	*Aspergillus* spp.	amphotericin, flucytosine	9	yes	yes	HD, died 2 months later
3	mild	525	*Cephalosporium*	miconazole	39	yes	yes	HD
4	mild	478	*Cephalosporium*	amphotericin	30	yes	yes	HD
5	mild	220	*C. tropicalis*	amphotericin, miconazole	28	yes	no	CAPD
6	mild	3350	*A. fumigatus*	ketoconazole	10	yes	yes	HD
7[a]	severe	1386	*C. lusitaniae*	ketoconazole	12	yes	yes	CAPD
8[a]	mild	460	*Trichoderma*	ketoconazole	22	yes	yes	HD
9	severe	600	*Cephalosporium*	fluconazole	12	no[b]	yes	CVA, died
10	severe	300	*C. parapsilosis*	amphotericin, fluconazole	8	no[b]	yes	AMI, died
11	mild	500	*C. parapsilosis*	amphotericin (liposomal)	1	yes	yes	HD
12	severe	500	*C. albicans*	fluconazole, flucytosine	27	yes	yes	HD
13	severe	3700	*C. tropicalis*	fluconazole, amphotericin	47	no	yes	septic shock, died
14	severe	303	*A. fumigatus*	amphotericin	7	no	yes	septic shock, died

[a] Episodes no. 7 and 8 occurred in the same patient
[b] Both patients died on antifungal treatment from causes other than infection
HD, hemodialysis; CVA, cerebrovascular accident; AMI, acute myocardial infarction

exchange daily. Eleven (85%) patients dropped out of the CAPD programme. Four patients died during treatment of fungal peritonitis. In two patients with signs of septic shock death was directly connected with peritonitis. In one patient death was associated with acute myocardial infarction, and in another with a cerebrovascular accident.

One patient (episode no. 2) successfully treated with amphotericin B died 2 months later during hemodialysis due to bleeding from intestinal adhesions (ascertained on autopsy).

The fungal species isolated in the 14 episodes of peritonitis are listed in Table 2. In six cases *Candida* spp. were isolated and in three cases *Aspergillus* spp. Gram staining revealed hyphae in only one case and the presence of fungi was confirmed on culture.

One patient (episode no. 2) with *Aspergillus* peritonitis presented initially with mild signs and symptoms, but the peritoneal catheter was obstructed and had to be removed. The patient was successfully treated with amphotericin B and switched to hemodialysis. She died 2 months later during hemodialysis (see above), 10 days after reinsertion of a new peritoneal catheter.

A second patient (episode no. 6) with *Aspergillus fumigatus* also had clinically mild peritonitis and catheter obstruction problems. After catheter removal and a short course of ketoconazole treatment the patient was cured. Peritoneal dialysis was discontinued and she was treated further with hemodialysis.

A third patient (episode no. 14) with *Aspergillus fumigatus* peritonitis experienced severe peritonitis. Catheter obstruction problems were also present. A factor probably predisposing to peritonitis was treatment with azathioprine (75 mg daily) and methylprednisolone (28 mg daily) due to pulmonary vasculitis. Fungi were isolated from the peritoneal effluent and also from the intra-abdominal tip of the catheter. In spite of catheter removal and antifungal drug treatment, signs and symptoms of infection persisted, and laparoscopy with drainage plus lavage with amphotericin B was performed. All of these measures were ineffective, septic shock developed and the patient died 2 weeks after onset of the infection. At autopsy diffuse signs of both chronic fibrous and acute exudative peritonitis were found.

Discussion

The incidence of fungal peritonitis in our centre was comparable to that reported elsewhere [1, 4, 6]. In accordance with findings in other studies, we found that recent episodes of bacterial infection treated with antibiotics were associated with fungal peritonitis and

could thus be a risk factor, and that fungal peritonitis was not associated with underlying kidney disease [12, 13]. In one patient a predisposing factor could have been the administration of methylprednisolone and azathioprine due to ANCA-related pulmonary disease.

In contrast to some investigators, we did not observe a higher frequency of fungal peritonitis in the summer months [14]. The use of a twin-bag disconnect system instead of a single-bag system resulted in a significant overall decrease in the rate of peritonitis in our patients; however, fungal peritonitis was still not eliminated by its use [15]. In some studies up to 90% of cases of fungal peritonitis have been caused by *Candida* spp. [1, 5, 12]. The rate of *Candida* infection was somewhat lower in our group, a relatively high percentage of cases being caused by other fungal species. There were no important differences in the severity of clinical manifestations, leukocyte count in peritoneal effluent or outcome between peritonitis caused by *Candida* spp. and peritonitis caused by other fungal species; however, the overall number of cases of fungal peritonitis was low. Although *Aspergillus* is a rare cause of peritonitis, we observed three such cases. We believe that in all our cases the fungi were the cause of the infection and not just contaminants as all patients had signs or symptoms of infection. We could not establish any connection between the fungal pathogen and the severity of the initial clinical manifestations of peritonitis.

There is no consensus as to whether or when peritoneal catheters should be removed. Some authors advise retaining the catheter in the case of infection with *Candida* or other yeasts, while in the case of infection with filamentous fungi the catheter should be removed immediately [16]. Many authors recommend therapy with antifungal drugs in the course of fungal peritonitis, although in some cases removal of the catheter alone seems to suffice [1, 4, 6, 7, 9–11, 17]. Recently, removal of the peritoneal catheter was recommended if no clinical improvement was seen after 4 to 7 days of antifungal drug treatment [7]. Although amphotericin B remains the drug of choice for treatment of many fungal infections, especially those that are life threatening, a retrospective analysis suggests that a combination of imidazole or other triazoles with flucytosine is as efficacious as amphotericin B, particularly for treatment of infection with nonfilamentous fungi [7, 18]. The outcome was usually poor when we attempted to treat the peritonitis with antifungal drugs but to retain the catheter. On the basis of this albeit limited experience, we suggest early removal of peritoneal catheters and short-term administration of antifungal drugs. In one of our patients fungal peritonitis was cured after catheter removal and a single intravenous dose of a liposomal formulation of amphotericin, which was ceased due to side effects.

The relatively low number of cases of fungal peritonitis does not permit a prospective randomized study to be conducted to establish with certainty the optimal antifungal drug regimen. All our patients received antifungal drugs, but the route of administration and total dose varied, depending on the clinical status and timing of catheter removal. Some authors suggest oral prophylaxis with nystatin during every course of antibiotics in CAPD patients to prevent fungal peritonitis [19]. This was not practiced in our patients. The mortality among our patients was 38%, which is comparable to rates in other studies [5, 20]. Fungal peritonitis alone was not the main cause of death in all of our patients, but was probably an important contributing factor.

In conclusion, fungal peritonitis is rare (3.1% of all peritonitis episodes) in our dialysis centre, and a serious complication with high rates of morbidity, mortality (38%) and drop-out from the CAPD programme (85%). A predisposing factor for fungal peritonitis could be a recent bacterial infection treated with antibiotics, as was the case in eight (65%) patients in our study. The fungi most frequently isolated from peritoneal effluent were *Candida* spp. In the case of fungal peritonitis early catheter removal and short-term administration of antifungal drug is recommended.

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