

Fungal peritonitis in peritoneal dialysis: a 10 year retrospective analysis in a single center

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Abstract. – INTRODUCTION: Fungal peritonitis (FP) is a rare but serious complication in patients undergoing peritoneal dialysis (PD), and is associated with higher morbidity, mortality. We aimed to analyze the predisposing factors, etiological agents, outcome and treatment of FP in patients with PD.

METHODOLOGY: We evaluated retrospectively all PD patients PD center between 2001 and 2011. Sixteen patients with FP were included into the study.

RESULTS: The clinical records of 16 patients with FP among 355 patients were reviewed for the clinical and laboratory data. Among 506 episodes of PD-related peritonitis in 10 years, we identified 16 episodes of FP. Median PD duration was 36.7 ± 22.2 months. In 87.5% of patients had one or more previous episode of bacterial peritonitis that were treated with multiple broad-spectrum antibiotics. FP was primary infection in five patients, whereas eleven patients experienced FP during the course of treatment of bacterial peritonitis. Six patients died due to the fungal infection whereas others were transferred to haemodialysis.

CONCLUSIONS: Treatment of bacterial peritonitis with broad spectrum antibiotics was an important risk factor predisposing to the development of FP. The catheter removal and initiation of antifungal therapy as soon as possible are obligatory in episode of FP because it is responsible from high mortality rate.

Key Words:

Fungal peritonitis, Peritoneal dialysis, Bacterial peritonitis.

Introduction

Fungal peritonitis (FP) is an uncommon but serious complication of peritoneal dialysis (PD). The prevalence of FP in patients undergoing PD ranges from 3% to 7% in most reported series¹⁻⁴. FP in PD patients is associated with high rates of

mortality and technique failure. The mortality rate in PD-related fungal peritonitis ranges from 5% to 40%¹⁻⁴. We aimed to analyze the predisposing factors, clinical aspects, etiological agents, outcome and treatment of FP in patients with PD retrospectively.

Patients and Methods

The records of 378 patients for whom PD therapy were started due to end stage renal disease (ESRD) in our PD unit between June 2001 to December 2011 were evaluated retrospectively. Totally 23 patients were excluded. Exclusion criteria were recovering renal function and no longer requirement of dialysis, being below 18 years old, having missing data (coming from another city for the first PD control to us but inaccessible anyway after this time), being followed by another PD unit and history of PD less than 90 days. Remaining 355 patients' data were collected.

Demographic features and clinical manifestations were reviewed including age, gender, cause of end-stage renal disease, presence of potential risk factors for FP (diabetes, immunosuppressive therapy), follow-up duration of the PD. Details about peritonitis, e.g. incidence, presence of prior history of fungal or bacterial peritonitis, signs and symptoms, peritoneal fluid white blood cells (WBC) count, gram stain and culture results, causative fungus species, type of antifungal agents administered and outcome [survival, removal of catheter, time between diagnosis of FP and catheter removal, and definitive or temporary transfer to hemodialysis (HD)] were recorded.

In all patients, double-cuff Tenckhoff catheters were implanted by using Seldinger technique by the same nephrologist. They were educated thereafter. Initiation of PD means the time when the patient started to use standard 2 liters solution

four times for continuous ambulatory peritoneal dialysis (CAPD) regimen while it was the time that patient started PD at necessary exchange volume for APD (automated peritoneal dialysis). This time was approximately 2-3 weeks after PD catheter insertion.

The diagnosis of peritonitis was based on clinical manifestations (abdominal pain, nausea, and fever) and a cloudy peritoneal effluent count of 100 WBC/l or greater, consisting of at least 50% polymorphonuclear (PMN) cells. Secondary fungal peritonitis was defined as a case in which fungal peritonitis developed within 30 days exposure to antibiotics due to bacterial peritonitis or episode of fungal peritonitis concomitantly with bacterial peritonitis. Primary fungal peritonitis was defined as a case presenting without the above characteristics for secondary fungal peritonitis, confirmed with a KOH test, positive culture for fungi, and white blood cell counts in peritoneal fluid > 100 cells/l.

Almost all published series have found an association with both recent antibacterial use and episodes of bacterial peritonitis¹⁻⁸. When these series are combined, 65 percent of patients had been exposed to antibiotics within 30 days of the onset of fungal peritonitis and 48 percent had experienced an episode of bacterial peritonitis within the same time frame.

There are various kinds of treatment protocols for peritonitis. In our Center, ciprofloxacin, 500 mg/day per oral route and intraperitoneal 15-30 mg/kg/day vancomycin per 96-168 hours were given empirically to cover both Gram-positive and Gram-negative organisms. According to the culture and sensitivity results, antibiotic therapy was changed to narrow spectrum appropriately. If there was no improvement after 48 hours of treatment, cell counts and cultures were repeated. In addition to ceftazidime, cefepime, or meropenem was added.

The treatment of FP was done by administration of amphotericin B (20-25 mg iv q.d.) and 5-fluorocytosine (50 mg in every 2-L PD bag) until the culture results were available. If there was no clinical improvement on the fifth day of antifungal treatment, the PD catheter was removed, the patient was transferred to hemodialysis, and therapy was changed to fluconazole (100 mg p.o. q.d.) for 1 month.

Statistical Analysis

The statistical software package SPSS (SPSS Inc., Chicago, IL, USA), version 13.0, was used

for statistical analysis. The chi-square test was used to compare categorical parameters. The Mann-Whitney U-test was used to analyze normally distributed independent variables. Values of *p* less than 0.05 were accepted as statistically significant.

Results

Three hundred and seventy-eight patients were included to the study. Totally 23 patients were excluded from the study because of following reasons: 1 patient's renal functions recovered and required dialysis no longer; 2 patients were below 18 years old; 5 patients had missing data, 11 patients were followed by other PD units and; 4 patients' PD histories were less than 90 days. Remaining 355 patients with total follow-up period of 12842 patient-months were evaluated.

Between June 2001 and December 2001, 16 FP were identified. Demographic data of FP patients is given in Table I. Among 506 episodes of PD-related peritonitis, 3.16% was due to fungi. Total fungal peritonitis episode number (n=16) divided by total patient months yielded 802.6 patient-months that had 1 episode of bacterial peritonitis per 26.7±24.1 patient-months. At admission to the hospital, all patients had clinical signs and symptoms of peritonitis and cloudy dialysis effluent samples. Signs and symptoms of FP were not different from those of bacterial peritonitis. WBC counts were 150-7800 cells/mm³, with neutrophil predominance.

Among patients developing fungal peritonitis, fourteen (87.5%) patients had one or more previ-

Table I. Demographic data of fungal peritonitis patients'.

Gender, male/female	9/7
Age, years	43.4 ± 16
Peritoneal dialysis duration (months)	36.7 ± 22.2
Presence of diabetes status (n)	5
HD History (n)	3
Etiology n (%):	
Chronic glomerulonephritis	5 (31.25)
Diabetes mellitus	4 (25)
Unknown/other etiology	4 (25)
VUR, chronic pyelonephritis	3 (18.75)
Bacterial peritonitis frequency (patient-month)	26.7 ± 24.1
Fungal peritonitis frequency (patient-months)	
Primary fungal peritonitis (n)	5
Secondary fungal peritonitis (n)	11

ous episode of bacterial peritonitis that was treated with antibiotics. 12.5% (n=2) of patients had no peritonitis before. Six of them had more than two episodes of bacterial peritonitis. Three had two episodes and five had one episode of bacterial peritonitis.

Primary fungal peritonitis was seen in 5 (31.25%) patients. Two out of 5 patients had FP one month after antibiotic therapy (in three cases, the antibiotic was prescribed for bacterial peritonitis). Nine of our secondary fungal peritonitis patients had experienced FP during the course of treatment of bacterial peritonitis. Among patients with a preceding episode of bacterial peritonitis, 5 cases had been infected with Gram-negative organisms (3 with *Pseudomonas*, 2 with *Acinetobacter*) and 4 cases with Gram-positive organisms (3 with methicillin-resistant *Staphylococcus epidermidis*, 1 with methicillin-sensitive *Staphylococcus aureus*). Nine out of 11 patients occurred one month after antibiotic therapy (one case, the antibiotic was prescribed for sinusitis, one case was for pneumonia).

Candida species were the most common pathogens isolated from peritoneal effluent fluid. *Candida albicans* was diagnosed in 15 episodes. Only one episode was caused by *Candida glabrata*. Gram staining of the peritoneal fluid showed yeasts in 16 patients and the mean time for culture positivity was 5.6 days.

All peritoneal catheters with FP had been removed after the diagnosis. Mean lag time between signs of peritonitis and removal of catheter was 8.7 days (min 2-max 20 days). Mean catheter removal time was 2.2 days (range 1-3 days) in primary FP whereas 11.7 days (range 4-20 days) in secondary ones.

The treatment of FP included administration of amphotericin B (20-25 mg iv q.d.) and 5-fluorocytosine (50 mg in every 2-L PD bag). Mean total duration of antifungal treatment was 23.4 days. Ten patients' peritoneal catheter was removed because of absence of clinical improvement. They were transferred to hemodialysis. Peritoneal catheter have not been reimplanted until one month was completed after treatment. Six patients died (37.5%) in the hospital during the episode of peritonitis.

Side effects of antimycotic therapy (elevated liver enzymes) were recorded in three patients. They were related to the use of 5-fluorocytosine. The enzymes gradually felt to the normal levels after the discontinuation of the drug.

Discussion

Our fungal peritonitis series constituted 3.16% of all peritonitis episodes in our PD unit. It was similar to the reported other prevalence schanging from 2% to 10.2%^{1,2,5-8}. Both prevalence of prior antibiotic exposure and development of FP following a course of bacterial peritonitis antibiotic treatment was found higher to that reported in literature^{3,9,10}. Mortality rate was 37.5%.

Fungi enter the peritoneal cavity through touch contamination at the time of PD exchange or invasion of skin by the offending organisms from the exit site through the tunnel to the peritoneum¹¹. Many factors are believed to predispose to FP in CAPD patients, including underlying diseases such as HIV and diabetes, previous bacterial peritonitis or previous antibiotic treatment, an interruption of the peritoneal barrier due to the catheter, and reduced cellular immunity due to uremia. Almost all published series have found an association with both recent antibacterial use and episodes of bacterial peritonitis. When these series were combined, it was seen that 65 percent of patients had been exposed to antibiotics within 30 days of the onset of fungal peritonitis and 48 percent had experienced an episode of bacterial peritonitis within the same time frame. The reported prevalence of prior antibiotic exposure in CAPD patients with fungal peritonitis ranges from 34% to 80%^{1,5,6,7,12}.

Our fungal peritonitis series constituted 3.16% of all peritonitis episodes in our unit over a survey period of 10 years. That percentage was slightly lower than the reported other local series which were 6.0%-6.3%^{1,2}.

In our study, 87.5% of patients had one or more previous episodes of bacterial peritonitis that was treated with multipl broad-spectrum antibiotics. In 68.75% of patients, fungal peritonitis was experienced during the course of treatment of bacterial peritonitis³. The previous use of antibiotics for bacterial peritonitis may kill the normal bowel flora and allow fungal proliferation and overgrowth, which migrate across the intestinal wall and invade the inflamed peritoneum¹.

Candida species were the most common causative agents for the fungal peritonitis, accounting for 60-100% of episodes. *Candida albicans* was reported to be more common than non-albicans¹³⁻¹⁵. In our study, all cases (100%) of FP were caused by *Candida* species. *Candida albicans* were the most pathogen (93.75%).

The current guidelines for the treatment of FP in our center include immediate catheter removal, culture and, intraperitoneal (150 mg once daily) or oral fluconazole (100 mg once daily) while awaiting results of sensitivity. The treatment continues for three-four weeks if the fungal isolates are sensitive to these drugs. Unresponsive cases are treated with intravenous amphotericin B (20 mg daily) for 21 days.

Fungal peritonitis in PD patients is associated with high rates of mortality and technique failure. Eisenberg et al⁵ also reported mortality in 16 of 60 patients (27%); Cheng et al⁶ reported mortality in 33 of 190 patients (17%) and Michel et al⁷ reported it in 5 of 20 patients (25%). In our study, 6 of 16 patients died (37.5%) in the hospital due to the FP. In our patients, all PD catheters were removed (100%) during episodes of FP. This rate was higher than the rate described in other reports¹⁶⁻¹⁸. However, according to other studies^{19,20} catheter removal time was longer in our clinic which may be an effective factor in high mortality rates.

The International Society of Peritoneal Dialysis (ISPD) guidelines²¹ recommend that fungal prophylaxis during antibiotic therapy may prevent some cases of *Candida* peritonitis in programs that have high rates of fungal peritonitis. Zaruba et al²² used nystatin as oral antifungal prophylaxis (500,000 IU three times per day) during every course of antibiotic treatment in CAPD patients. They reduced the risk of secondary/antibiotic-related FP from 10.5% of all peritonitis episodes (before nystatin) to 3.1% after its introduction. None of them had received prophylactic antifungal treatment during antibiotic therapy. This fact might lighten partially the reason for the high mortality rates in our study. Prophylactic antifungal therapy may be considered in patients with one or more previous episode of bacterial peritonitis.

Conclusions

Catheter removal and initiation of antifungal therapy as soon as possible is mandatory in FP because it is responsible from high mortality rates. Both prior antibiotic exposure due to peritonitis attacks and treatment of bacterial peritonitis with broad spectrum antibiotics were an important risk factors predisposing to the development of FP and high mortality rates, so antifungal prophylaxis might be considered.

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