

FUNGAL PERITONITIS AMONG THE PERITONEAL DIALYSIS PATIENTS OF FOUR TURKISH CENTRES

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SUMMARY

This study evaluates the clinical findings and treatment of continuous ambulatory peritoneal dialysis (CAPD) patients with fungal peritonitis in Istanbul from 2000 to 2010. The clinical records of 15 patients with fungal peritonitis among the total 795 patients were reviewed for the clinical and laboratory data. The mean duration of dialysis from the initiation of treatment until the development of fungal peritonitis was 41.14 months. Fungal peritonitis was the primary episode of infection in eight patients. In five other patients previous intensive antibiotherapy was documented. The isolated microbes were *Candida albicans* in six, non-*C. albicans* in eight and *Aspergillus fumigatus* in one patient. Tenckoff catheters were removed in all cases and antifungal treatment was given for a minimum of three weeks. Two patients died in the hospital due to the fungal infection whereas others were transferred to haemodialysis.

This study highlights the importance of removing the catheter and initiating antifungal therapy as soon as possible in cases of fungal peritonitis because it is responsible for high morbidity and mortality.

KEY WORDS Fungal peritonitis • CAPD • mortality • morbidity • *Candida* species

INTRODUCTION

Peritonitis is a serious complication for patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and it is associated

with important morbidity and mortality. Fungi species are responsible for 1–15% of all episodes of peritonitis (Nagappan *et al.* 1992; Bren 1998; Prasad & Gupta 2005; Kocak *et al.* 2007). In cases of peritonitis 75–90% are produced by yeasts, mainly from the genus *Candida* (Bren 1998; Garcia-Martos *et al.* 2009). Regional variations are expected in pathogens as distance from a PD centre and weather characteristics represent geographic risk factors for peritonitis rates and patterns (Kim *et al.* 2000; Szeto *et al.* 2003). Arreola-Mucino *et al.* (1998) in his study reported a frequency of 20% yeasts as the cause of peritonitis in Mexican CAPD patients. In Argentina, the fungal peritonitis rate was reported to be 0.06 episodes/patient-year (Predari *et al.* 2007). Moreover, in Greece, 5.7% of all peritonitis episodes are fungal peritonitis and *Candida* species is the most common cause (Bibashi *et al.* 2003). In Spain, another Mediterranean country, 4% of CAPD peritonitis were caused by fungal peritonitis, mainly by *Candida* species (Molina *et al.* 2005). Prasad *et al.* (2004) in his study performed in India demonstrated that fungal peritonitis accounted for 14.3% of all peritonitis and *Candida* species was responsible for 89.3% of the episodes.

Although fungal peritonitis is uncommon, it can be life-threatening and usually requires immediate catheter removal and modifying treatment modality from PD to haemodialysis. Throughout the world the mortality rate due to fungal peritonitis

BIODATA

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is reported to be 5–25% and research shows that 40% of the patients were switched to haemodialysis after one episode of fungal peritonitis (Bren 1998; Prasad *et al.* 2005). This retrospective study evaluates the clinical findings and treatment of CAPD patients with fungal peritonitis in Istanbul, Turkey.

MATERIAL AND METHODS

The frequency, diagnosis and treatment of fungal peritonitis during a 10-year period (January 2000–January 2010) in four peritoneal dialysis units in Istanbul were retrospectively studied in 795 patients. Istanbul with its 10 million population is the most heavily populated and industrialised city of Northwest Turkey.

All the PD patients were trained by experienced PD nurses as primary trainers, in outpatient clinics of the participating centres, the ratio of patient to nurse was 1:1. A formalised training programme including aseptic technique, hand washing, masking, steps in exchange procedures, emergency measures for contamination, exit-site care and complications were followed at each clinic.

The clinical records of the patients were reviewed and data regarding the primary disease, duration of CAPD before the fungal peritonitis, potential risk factors, social environment of the patients, isolated pathogens, treatment strategies and outcomes of the patients were recorded.

DIAGNOSIS CRITERIA

Fungal peritonitis was diagnosed based on laboratory findings and clinical symptoms:

- fever,
- abdominal pain,
- cloudy dialysate,
- leukocyte count of more than 100/mm³ (with neutrophil predominance) in the dialysate and
- a positive fungus culture on one or more occasions.

The dialysate sample was evaluated for the leukocyte count and after centrifugation, the sediment was subjected to direct microscopic examination. The smears were stained with Gram, Ziehl-Neelsen and Giemsa. All samples were inoculated onto Sabouraud dextrose agar for fungal culture and onto blood agar for bacterial culture.

Immediately after the diagnosis, all patients were prescribed antifungal therapy for three weeks or until death which ever

was earlier according to the ISPD Guidelines/Recommendations (2005) for fungal peritonitis.

STATISTICAL ANALYSIS

Statistical analysis was performed by SPSS 13.0 programme. Descriptive statistics of all numeric variables together with the proportions of all categorical variables were calculated. Numeric values were given as mean ± standard deviation.

RESULTS

During the 10-year period 15 patients had episodes of fungal peritonitis. Nine (60%) of the patients were male and six (40%) female and the mean age of the patients was 51.9 ± 17.4 years. During the same time-period, 670 episodes of peritonitis were encountered in 795 patients.

Thirteen of the (87%) patients were living in the urban districts of Istanbul. Two of the patients were living in nearby cities in the rural areas. One patient from the rural area had a big family living in the same house. All the other patients' had immediate families living under one roof. The academic and employment demographics of the patients are presented in Table 1.

The aetiologies of end stage renal disease (ESRD) are presented in Table 2. The mean duration of peritoneal dialysis from the beginning of treatment until the emergence of fungal peritonitis was 41.14 (3–156) months. Fungal peritonitis was the original peritonitis episode in eight (53.3%) patients. Five patients had one episode and two patients had two episodes of bacterial peritonitis before fungal peritonitis. In only five (33.3%) patients the use of previous intensive antibiotic therapy was documented. Two of those receiving intensive therapy had histories of Gram positive microorganism peritonitis.

The isolated pathogens were *Candida albicans* in six (40%) patients, non-*C. albicans* (NAC) in eight (53.3%) and *Aspergillus fumigatus* in one (6.7%) patient (Table 3).

Tenckoff catheters were removed as soon as the culture results were available. Seven (46.6%) patients received Fluconazole IV; five (33%) of them were given Ambisome and three (20%) received both therapies for three weeks.

Two (13%) of the patients died while in the hospital and the others (87%) were transferred to haemodialysis.

Level of education	Elementary school	High school	University graduates
Number of patients	5 = 33%	4 = 26.7%	6 = 40%
Employment status	Regular employment	Other = without active employment – retired, housewives	
Number of patients	6 = 40%	9 = 60%	

Table 1: Showing academic and employment demographics.

Cause	Number of cases
Diabetic nephropathy	2
Polycystic kidney disease	2
Hypertensive nephroclerosis	3
Glomerulonephritis	3
Unknown	5

Table 2: Causes of end stage renal disease.

Causative agent	No of episodes (%)
A. <i>Candida</i> species alone	14 (93.3%)
A1. <i>Candida albicans</i>	6 (40%)
A2. Non- <i>albicans Candida</i> species	8 (53.3%)
<i>Candida parapsilosis</i>	3 (20.0%)
<i>Candida guilliermondii</i>	1 (6.4%)
<i>Candida dupliniensis</i>	1 (6.4%)
B. <i>Aspergillus fumigatus</i>	1 (6.4%)

Table 3: Causative agents in 15 episodes of fungal peritonitis.

DISCUSSION

In the recent years, the frequency of bacterial peritonitis in CAPD patients has been reduced due to improvements in dialysis equipment, treatment and training strategies yet fungal peritonitis is still a serious complication of CAPD, which may lead to death or technical failure of the catheter (Prasad *et al.* 2005; Bender *et al.* 2006; Fried & Piraino 2009). According to the data of National Statistics Institute 2009, in the total population of Istanbul above the age of 15, 44.72% graduated from Elementary School, 28.18% from High School 11.15% from University and 9.35% had no education at all. Our patients were actually better educated than the general population of Istanbul (see Table 1); but they still encountered fungal peritonitis.

Observational studies suggest that fungal peritonitis accounts for approximately 3% of all peritonitis episodes (Nagappan *et al.* 1992; Goldie *et al.* 1996; Bren 1998; Prasad *et al.* 2005; Kocak *et al.* 2007). In a previous study conducted by Turkish

Multicenter Peritoneal Dialysis Study Group, it was demonstrated that 2.5% of 1,375 episodes of peritonitis were of fungal aetiology (Taşkapan *et al.* 2000).

The mortality rate varies from 5% to 53%, removal from CAPD occurs in up to 40% of the patients and usually requires replacement of CAPD with haemodialysis (Nagappan *et al.* 1992; Michel *et al.* 1994; Prasad *et al.* 2004; Prasad & Gupta 2005). In our study fungal peritonitis constituted 2.24% of all peritonitis episodes and mortality rate was 13%, which accords with the rates reported in previous literature, 87% of the patients were transferred to haemodialysis.

Candida species were the most common causative agents for the fungal peritonitis, accounting for 70–89.3% of episodes as the sole pathogen (Manzano-Gayosso *et al.* 2003; Rosa *et al.* 2006). Moreover, the incidence of invasive infections caused by *Candida* species has notably increased within the past two decades (Pasqualotto *et al.* 2006). Among *Candida* species, NAC is 53.6% more common than *C. albicans*, which is 35.7%. Some of these NAC species may be highly resistant to antifungal treatment (Manzano-Gayosso *et al.* 2003; Pasqualotto *et al.* 2006). Similarly, our study demonstrated that NAC was responsible for 53.3% of the episodes whereas *C. albicans* was the primary cause in 40% of the episodes (Wang *et al.* 2000; Prasad & Gupta 2005) (see Table 3).

Fungi are widely found in human environments, being part of the normal flora of the skin and mucosa, but in certain conditions, they can become pathogenic (Matuszkiewicz-Rowinska 2009). The rupture of the cutaneous barrier as a result of the presence of the peritoneal catheter and decreased cellular immunity due to uraemia also predispose to fungal peritonitis (Miles *et al.* 2009). Moreover, continuous exposure of peritoneal cells to nonphysiological peritoneal dialysis solutions may result in an impairment of the local peritoneal host defence mechanisms increasing susceptibility to fungal infections (Kazancioglu 2009).

Fungi enter the peritoneal cavity through touch contamination of the dialysis tubing or by direct extension of the infection from the catheter exit site and very rarely via the vaginal route as an ascending infection (Fried & Piraino 2009; Indhumathi *et al.* 2009). The route of fungal peritonitis in our cases could not be clearly isolated.

The aetiology of ESRD, especially diabetes mellitus and certain comorbidities such as neoplastic diseases have been suggested as predictors, but in this study we could not demonstrate any association between fungal peritonitis and primary cause of ESRD or any comorbidity (Prasad *et al.* 2004; Matuszkiewicz-Rowinska 2009).

The strongest risk factors for fungal peritonitis in CAPD patients are prolonged use of antibiotics and previous bacterial peritonitis (Prasad *et al.* 2004; Rosa *et al.* 2006; Matuszkiewicz-Rowinska 2009). Prasad & Gupta (2005) reported in their study that fungal peritonitis was more frequent in patients who had previous bacterial peritonitis than others and mortality rate was higher in patients with abdominal pain, fever and the catheter remaining in situ. Kaitwatcharachai (2002) reported in his study that fungal peritonitis is seen especially after Gram negative peritonitis episodes. In our study, seven (47%) of our patients had a prior history of bacterial peritonitis. Furthermore intensive antibiotic therapy was documented in five (33%) of them.

Fungi can colonize the PD catheters by biofilm spread along its surface (Bibashi *et al.* 2003; Matuszkiewicz-Rowinska 2009). Wang *et al.* (2000) divided the factors which lead to failure in the therapy of fungal peritonitis patients into factors predicting technique failure and mortality factors. They defined the mortality factors as:

- presence of abdominal pain,
- bowel obstruction and
- history of antibiotic use within preceding three months.

In addition to these, those with catheters remaining in situ are also associated with technical failure (Wang *et al.* 2000).

Most recent ISPD recommendations suggest that early catheter removal is essential for successful eradication of fungal peritonitis and some have argued that it may be the only therapy needed (ISPD guidelines 2005). Because of these recommendations, catheter removal as well as antifungal therapy is essential if cure is to be achieved in most cases. The PD catheters

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were removed in our patients as soon as possible after obtaining the effluent culture results. However recent paediatric studies have suggested that the catheters should be removed early but not immediately. As repetitive peritoneal lavage with antimycotics can be helpful in preventing adhesions (Matuszkiewicz-Rowinska 2009).

Amphotericin B (IP or IV), Fluconazole (peroral or IP), Itraconazole, Voriconazole, Ketoconazole, 5-Flucytosine can be used alone or in combination therapy as antifungal drugs (Bren 1998; Kaitwatcharachai 2002; Prasad & Gupta 2005). Seven patients received Fluconazole IV; five of them were given Amphotericin B and three received both therapies for three weeks. Both of the patients who died were female and older than 65 years and had been on PD treatment for the last 11 months. History of recurrent peritonitis episodes and diabetes mellitus were the further comorbid findings in one of them.

The role of new antifungal agents such as the extended-spectrum azoles or caspofungin in fungal peritonitis has not yet been clarified. However better safety profiles and broad spectrum activity of the drugs may change treatment strategies in the near future (Matuszkiewicz-Rowinska 2009).

CONCLUSION

In conclusion, incidence of fungal peritonitis in our region is similar to other countries as demonstrated in this study and it is associated with high rate of technical failure. If there is recurrent peritonitis episodes and a poor response to antibacterial therapy, fungal peritonitis should be suspected. For the successful management of any fungal peritonitis episode besides the initiation of antifungal therapy, early catheter removal is crucial to decrease the mortality.

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