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Fungal Peritonitis in a Patient Treated With Peritoneal Dialysis

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ABSTRACT
Peritonitis is one of the most common complications in peritoneal dialysis (PD) and fungal infections cause 1 to 15% of the cases. Mortality rate in these patients varies between 5 to 53%, while 40% require permanent termination of PD treatment. Candida species is the most common pathogen, that causes fungal peritonitis (FP) in PD patients – in 70 to 89,3%. Although there are reports of successful treatment of FP without removal of the peritoneal catheter, it is associated with 100% technical failure rate and 100% mortality rate when it is caused by Candida spp. and peritoneal catheter was left in situ.
We present a case of FP in a 41-year-old male patient, who has been treated with continuous ambulatory peritoneal dialysis (CAPD) for 38 months due to chronic glomerulonephritis and CKD V stage. After conducted treatment of pneumonia and suspicious bacterial peritonitis Candida albicans was isolated from pleural effusion and peritoneal dialysate. Antibiotics were stopped and has been pursued antifungal course with intraperitoneal Fluconazole and oral Itraconazole, which were later replaced with Nystatin. CAPD continued without interruption and lack of any problems. PD catheter was preserved and up to this day the patient continues CAPD without relapses of peritonitis.
FP is one of the severe complications of PD which is characterized with high mortality rates and require termination of PD treatment. This is why accurate diagnosis and aggressive treatment are essential for therapeutic success.
KEY WORDS:peritoneal dialysis, fungal peritonitis, Candida spp.

I. INTRODUCTION

Dialysis-associated peritonitis (DAP) is the most common infectious complication of peritoneal dialysis (PD). Peritonitis caused by fungi is relatively rare, and its frequency is between 3 and 6% of all reported episodes of DAP in adults [20]. Some authors report higher frequency of fungal peritonitis (FP) – up to 15% [2, 22]. K. Prasad et al. report in 2004 a frequency of 14,3% for the Indian population [18], and R. Ram et al. report an even higher frequency of FP – 23,9% in 2008 [19]. FP is associated with increased mortality, which varies from 15 to 53%. FP is associated with high risk of termination of PD, due to the formation of adhesions, peritoneal sclerosis and irreversible damage to the peritoneum, which requires transfer to hemodialysis treatment in about 40% of the patients [7, 20].

II. CASE PRESENTATION

We report a case of a 41-year-old male patient with chronic glomerulonephritis, end-stage kidney disease, undergoing treatment with continuous ambulatory peritoneal dialysis (CAPD) for 38 months since 2019. Heroin abuse has been registered from 2000 to 2005, following therapy with Methadone. Related to the substance abuse he has been diagnosed with chronic hepatitis C virus and underwent antiviral treatment up to 2015. In March 2022 he suffered from COVID-19 and was treated at home by a general practitioner. At the end of April 2022, he has been hospitalized with complains of shortness of breath, cough and severe fatigue. A chest X-ray and computer tomography showed right-sided pleural effusion and pneumonia. Antibiotic treatment with Cephtriaxon was initiated, thoracocentesis and drainage wereperformed, and biopsy was taken. Histological analysis of the sample showed inflammatory changes in the pleura. Thoracic drain was removed at the 18th postoperative day. The patient underwent assisted peritoneal dialysis in the early postoperative period. At the 13th postoperative day cloudy dialysis effluent was noticed – from the cell count there were 196x10^{9}/L white blood cells. Empirical antibiotic therapy with Gentamycin and Cephtazidim was initiated intraperitoneally. Microbiological testing of pleural fluid and peritoneal dialysis effluent showed growth of Candida albicans. Blood cultures showed no bacterial and fungal growth. During hospital stay patient presented with diarrhea and Clostridium difficile and Candida krusei were found in coproculture. Treatment with Cephtazidim and Gentamycin was terminated and therapy with Itrakonazol was iniated in dose 2x200 mg per os for 10 days, followed by Nystatin 3x1 000 000 U

for 14 days and Fluconazole x200 mg intraperitoneally for 14 days. Treatment of the enterocolitis caused by Clostridium difficile was performed with Vancomycin, Metronidazole and probiotic orally. On the first day after the therapy the dialysis effluent cleared out. On day 7 from the start of the antimycotic therapy microbiology from dialysis effluent showed no fungal growth. Until the end of treatment of FP peritoneal dialysis procedures were performed without problems, peritoneal catheter was not removed, and the patient continued treatment with CAPD following discharge.

III. DISCUSSION

Most cases of FP are caused by Candida spp. (70-90% of all cases in adults and 80-100% of all cases in children), and the most isolated microorganism is C. albicans, followed by C. glabrata, C. parapsilosis, C. tropicalis and C. krusei. Some authors report elevated frequency of FP caused by C. parapsilosis [8, 23]. Around 10% of cases of FP are caused by the so-called filamentous fungi (Aspergillus spp., Penicillium spp., etc.), which usually require more aggressive therapeutic approach [7, 20].

The most important risk factor for development of FP is previous antibiotic treatment of bacterial infection, which most commonly develops following previous episodes of bacterial DAP [20, 24]. In 64-69% of cases FP develops about one month after antibiotic treatment [6, 7]. C. Chou et al. analyze 216 cases of DAP in 123 patients on PD, and in 19% of the cases FP develops in the following 6 months. They report significantly higher incidence of FP in patients with previous bacterial peritonitis, caused by Gram-negative microorganisms (42,1%) or polymicrobial peritonitis (22%), compared to patients with Gram-positive (4,7%) and culture-negative (5,8%) peritonitis. This could be explained with the fact that antibiotic treatment of Gram-negative peritonitis leads to overgrowth of fungi in the gastrointestinal tract and increased risk of peritoneal invasion [4]. Apart from that, patients with FP that developed following bacterial peritonitis, caused by Gram-negative bacteria, there is a greater frequency of peritoneal catheter removal [4, 10]. Other risk factors for FP development include immunosuppression, malnutrition, bowel perforation, diverticulitis, diabetes mellitus, neoplasms, vaginal candidiasis [8, 20].

In 1985 R. Johnson et al. report increased frequency of FP in patients treated with CAPD, compared to those on intermittent PD (IPD). In their study, they evaluate 200 patients on IPD and 50 patients on CAPD, and report that the frequency of FP is 4% (8/200) among patients on IPD and 18% (9/50) in patients on CAPD. They explain the differences with the larger number of CAPD procedures and more frequent opening of the catheter [9]. In 1989 I. Cheng et al. summarize data from literature for described 225 cases of FP, 74,2% of which are in patients with CAPD and 16,9% in patients on IPD [3].

Diagnosis FP is complicated because its symptoms are no different from those of bacterial peritonitis (cloudy dialysis effluent, increased white blood ell count in the effluent, fever, abdominal pain). In cases of peritonitis caused by filamentous fungi there is a possibility of developing bowel obstruction, hemoperitoneum and visible attachment of fungi to the peritoneal catheter, leading to its obstruction [20]. R. Johnson et al. report 17 cases of FP, with different etiological agents, in 8 of which there was retarded drainage, and in 4/17 – complete obstruction of the catheter [9].

Other factor that complicates the diagnosis and delays the treatment is the slow growth of fungal cultures, which requires from 7 to 14 days [20]. The average time from the beginning of the symptoms to the initiation of antifungal treatment is between 2,5 and 3,5 days (0-7 days) [17, 22], but in I. Cheng et al.'s study, which includes 27 cases of FP, this time is 10,3 days (5-21 days) [3]. Recent studies search for components of the cellular wall of fungi, which help for their faster identification (beta-D-glucan, galactomannan, genomic DNA) [20]. For quick diagnosis of FP ISPD recommends test of serum index of galactomannan, which has diagnostic sensitivity of only 65,2% and 85% specificity [15].

Regarding the treatment ISPD recommends immediate removal of peritoneal catheter after diagnosis of FP, which must be followed by at least two-week antibiotic therapy [12, 15]. Catheter removal is required because fungi form a biofilm around it, which makes their eradication extremely difficult [13]. Despite that, several studies recommend early, but not immediate removal of the catheter, since it can be used for intraperitoneal application of antimycotics and frequent lavage of the peritoneal cavity until dialysis effluent becomes transparent. Whether or not that can reduce the risk of peritoneal adhesion formation or not remains unclear [20].

An alternative approach is presented in a study by W. Boer et al. They treat successfully eight episodes of Candida peritonitis by preserving the peritoneal catheter in all patients. In addition to

therapy with 5-Flucytosine 2x500 mg/daily orally and Fluconazole x 150 mg/every other day, administered intraperitoneally, after each exchange they lock the catheter with 10 ml solution of Amphotericin B, 0,1 mg/ml, which "clears" with the next exchange. That way, a constant high concentration of antimycotic remains in the catheter lumen. After the treatment they do a follow-up on their patients from 1 to 7 years and do not register a single episode of FP [1].

There are no strict recommendations regarding the medication therapy of patients with FP based on drug choice, dose and drug combination [20]. In the past, ISPD recommended initial combined therapy with Amphotericin B and 5-Flucytosine, which could be administered orally, intravenously or intraperitoneally. The disadvantages of treatment with Amphotericin B are related to the fact that 90% of it binds with plasma proteins, which determines its low bioavailability in the peritoneal cavity during oral administration [20], whereas its intraperitoneal administration is associated with abdominal pain and increased risk of peritoneal adhesions and fibrosis [2, 6, 17].

R. Johnson et al. report a case of one patient who has been treated with Amphotericin B, and developed bowel obstruction during the course of treatment. Multiple peritoneal adhesions were found intraoperatively. In their study, they report 14 patients treated with intraperitoneal Amphotericin B, half of which developed severe abdominal pain at the time of infusion, which required opioid analgesics to be administered [9]. This is why Amphotericin B is recommended for treatment of FP only in cases where other antimycotics, which are better tolerated, do not improve the symptoms, which is the case with FP caused by filamentous fungi [11]. The recommended dose for intravenous application is between 0,5 and 1 mg/kg/daily [20].

5-Flucytosine may also be used for treatment of FP, because it gives high concentrations in the intraperitoneal cavity even when taken orally. A disadvantage is its narrow spectrum of action, which requires it to be combined with other antimycotic drugs [17]. In 1989 I. Cheng et al. compare results from different therapeutic protocols and prove, that the combination of 5-Flucytosine administered intraperitoneally and Ketoconazole taken orally give better results in management of the infection and a possibility of preserving PD treatment [3].

In patients with peritonitis caused by Candida spp. it is recommended that treatment should begin with Fluconazole, administered intraperitoneally in dose 200 mg/24-48 hours, intravenously or orally in dose 100-200 mg/daily, because of its good reabsorption in the gastrointestinal tract and good bioavailability in the peritoneal cavity, as well as its lower toxicity compared to Ketoconazole [5, 15, 20]. Two independent studies state that Fluconazole decreases the risk of peritoneal adhesions formation during peritonitis caused by Candida spp. [14, 21]. More severe cases of Candida peritonitis, as well as Aspergillus peritonitis require treatment with Voriconazole, which in oral administration provides a good concentration in the intraperitoneal cavity and has low peritoneal clearance. Treatment is recommended to last at least 14 days after removal of peritoneal catheter, but many cases require a course of treatment between 4 and 6 weeks [15].

Studies regarding prophylaxis of FP in patients with bacterial DAP give promising, although controversial results. In a study from 1991, divided in two periods, K. Zaruba et al. follow up patients on PD. The first period is from 4 years and they report 94 cases of bacterial DAP, 10,5% of which develop FP after that. In the second period, which is from 7 years, they report 127 episodes of DAP, and during treatment of bacterial peritonitis they begin antifungal prophylaxis with Nystatin 3x500 000 U/daily. As a result, FP develop only four patients, three of whom refused to take the medication [24].

Another study of W. Lo et al. follows up 397 patients on PD for two years, who have also been divided into two groups – patients who do not receive antifungal prophylaxis and those who receive it with Nystatin in dose 4x500 000 U/daily. Surprisingly, they report no difference in the frequency of FP development in both groups [16].

Newer research from 2014 by K Kumar et al. analyses two groups of patients –those who during antibiotic treatment for bacterial peritonitis underwent prophylactic treatment with Fluconazole x200 mg/daily for 7 days, and those who have not. Results showed significantly lower frequency of FP in the group that did prophylactics (5%), compared to the other group, who did not do prophylactics (17,6%) [13].

ISPD recommends antimycotic prophylaxis only in centers with high frequency of FP [15].

IV. CONCLUSION

Despite therapeutic progress FP remains a severe complication of PD, which can lead to termination of PD treatment or patient death. PD patients require prolonged hospital stay, which is

connected with the longer time, necessary for diagnostics and continuous treatment, which increases the expenses of the dialysis unit.

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