Tuberculosis Peritonitis in Patients on Peritoneal Dialysis: Experience in a Medical Center

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Abstract

BACKGROUND. Owing to their compromised local immune system, patients with end-stage renal disease (ESRD), especially those undergoing peritoneal dialysis (PD), are prone to developing tuberculosis peritonitis (TBP). TBP is an uncommon complication, but the mortality rate is high in PD patients.

METHODS. We retrospectively reviewed all the cases of TBP occurring in patients receiving PD at our institution over the past 19 years. Seven cases were identified to have TBP during the study period. We presented the clinical and diagnostic features of these patients.

RESULTS. The calculated crude rate of TBP patients was 1.0%. The time between onset of symptoms and diagnosis of TBP was around two weeks. All patients presented with fever and abdominal pain. Three patients had co-existing extraperitoneal TB. Six patients had positive results of TB culture. The new TB polymerase chain reaction (PCR) method was applied to four patients who were diagnosed early by a positive peritoneal fluid TB PCR on an average of 6.5 days. All TBP patients received anti-tuberculosis therapy. Two patients suffered from side effects of rifampin, such as jaundice and gastrointestinal upset. Only one patient died from septic shock. Four patients were switched to hemodialysis. No recurrence of TBP was observed during a mean follow-up of 32.6 months.

CONCLUSION. Our experience suggests that an effective molecular diagnostic tool (TB PCR) offers better outcomes for patients with TBP, including early diagnoses, prompt therapy, and decreased mortality. (Acta Nephrologica 2011; 25: 17-21)

KEY WORDS: tuberculosis peritonitis, peritoneal dialysis, tuberculosis polymerase chain reaction

Introduction

Chronic kidney disease is associated with increased susceptibility to bacterial infection due to a decrease in cellular immunity, with other contributing factors being malnutrition, vitamin D deficiency, and hyperparathyroidism (1-4). Previous data have found increase in incidence of tuberculosis (TB) in patients with end-stage renal disease (ESRD) compared with that in those with normal renal function. TB is predominantly extrapulmonary in dialysis patients, occurring soon after the initiation of renal replacement therapy (1, 5). Patients with ESRD, especially those undergoing peritoneal dialysis (PD), are prone to developing TB peritonitis (TBP) (1, 6). Previous investigations on characteristics of TBP in PD patients were rare in western countries (1, 7-10), but there are a few equivalent studies in Taiwan (11-13). TBP is curable with proper diagnosis and treatment. The aim of this study is to describe the clinical and diagnostic
features of TBP among the patients undergoing PD in a single medical center.

Methods

We retrospectively reviewed all the cases of TBP from a database of 678 PD patients during the period of January 1, 1990 to December 31, 2009. The underlying renal disease, duration of dialysis, Kt/V, clinical presentations, biochemistry with microbiology records, peritoneal fluid WBC counts and differential counts, diagnostic methods, side effects of anti-tuberculosis drugs, treatment results, and patient outcomes were analyzed. All data were presented as mean ± SD.

A definitive diagnosis of TBP was established by a positive peritoneal fluid TB culture or a finding of caseating granulomata in a peritoneal biopsy. TBP was also highly suspected with a positive TB PCR or a TB smear with the atypical presentations of PD peritonitis. The old method of TB PCR used phenol-chloroform extraction, a liquid-liquid extraction technique (equal volumes of a phenol: chloroform mixture and an aqueous sample mixed, forming a biphasic mixture). This method was used in molecular biology for isolating DNA, RNA, and protein before 2004. After 2004, a new method using DNA extraction kit assays (The QIAmp® DNA Mini Kit and QIAamp® DNA Blood Mini Kit, Qiagen, Hilden, Germany) was designed for rapid purification of pathogen DNA from whole blood, body fluid, or solid tissue.

Results

Seven cases were identified to have TBP during the study period. The calculated crude rate of TBP patients was 1.0% (7 of 678). Two were men and five were women. Clinical characteristics, diagnostic methods and outcomes for these TBP patients are illustrated in Tables 1 and 2. The mean age for the patients at diagnosis was 62.5 ± 7.3 years. The duration of PD prior to the onset of TBP was 43.2 ± 30.1 months. The duration between onset of symptoms and diagnosis of TBP was 14.1 ± 5.3 days. The average of Kt/V was 2.01 ± 0.4. The underlying etiologies for ESRD were chronic primary glomerulonephritis (85.7%, 6/7) and diabetes mellitus (14.3%, 1/7). Laboratory studies revealed mean serum calcium (10.4 ± 0.8 mg/dL, range from 9.6 to 12.1), mean serum albumin (3.0 ± 1.0 g/dL, range from 1.4 to 4.4), and mean intact-parathyroid hormone (446.8 ± 333.5 pg/mL, range from 111 to 1092). The average of days of fever subsided after treatment was 5.1 ± 4.9 days and that of clearness of dialysate after therapy was 6.0 ± 1.9 days. All TBP patients presented with fever (100%, 7/7) and abdominal pain (100%, 7/7). There were also associated turbid dialysate (71.4%, 5/7), weight loss (28.5%, 2/7), and diarrhea (14.2%, 1/7). Peritoneal
fluid WBC counts ranged from 130 to 1,236/mm³ and the differential counts were neutrophil predominant (85.8%, 6/7). Chest X-rays of three patients (42.8%, 3/7) revealed bilateral upper and lower lobes infiltration or pleural effusion. The diagnoses of TBP were made from the positive results of TB cultures (100%, 6/6), TB-PCR (80%, 4/5), or positive TB smears (14.2%, 1/7) in the peritoneal fluid. Extraperitoneal TB was diagnosed as pulmonary TB (28.5%, 2/7) and TB arthritis (14.2%, 1/7). Only patient 1 had concomitant bacterial peritonitis and received intraperitoneal antibiotic therapy. Intravenous antibiotic was administered in patient 3 due to an associated pneumonitis.

All TBP patients received anti-tuberculosis therapy. The treatment protocol was administered using a combination of isoniazid (200-300 mg/day), rifampicin (450-600 mg/day), pyrazinamide (750-1000 mg/day) and ethambutol (400 mg/day), plus pyridoxine (50 mg/day) for a total 6-12 months. Pyrazinamide and ethambutol were stopped after 0.5-3 months. Six of the seven patients were successfully cured. Two of our patients (28.5%) suffered from the side effects of rifampin, such as jaundice and gastrointestinal upset. Only patient 3 died of septic shock related to TBP, complicated by pneumonia at day 21 of hospitalization. Four patients were switched to hemodialysis due to TBP. No recurrence of TBP was observed during a mean follow-up of 32.6 months (range from 6 to 120 months) after completion of therapy.

Discussion

TB is a devastating global health problem, and there is an increased risk (6.9- to 52.5-fold) of TB in patients with ESRD compared with the general population (14, 15). In our study, the calculated crude rate of TBP was lower (1%) than that reported earlier (10). None of these patients had previously received a renal transplantation or immunosuppressant therapy. We attribute this lower calculated crude rate of TBP to decrease in direct contamination via the use of twin-bag exchange systems. These twin-bag exchange systems offer the maximum protection against peritonitis during PD 16 and have been used in our unit since 1996. A significant difference (30.3 vs. 48.8 patient-months/episode of peritonitis, \( P = 0.021 \), by Wilcoxon rank sum test) in peritonitis rates was detected between the patients with twin-bag exchange and Y-set systems in our unit. We observed that the peritonitis rate decreased including TBP after the switch to twin-bag exchange system. However, the data were limited due to fewer patients before 1996 and lower diagnostic rate of TBP before 2004.

The average interval between onset of symptoms and diagnosis of TBP in recent studies by Talwani and Horvath was around six weeks, and 3 weeks by Hung et al. in Taiwan (7, 9, 13). In our study, the interval was around two weeks. This discrepancy might be related to the early application of the new diagnostic TB PCR kits. TB PCR detection is an important molecular diagnostic technique for species-specific and early diagnosis of TBP, but the sensitivity rate (43-77%) varies among different target organisms (17, 18). Nevertheless, conflicting results were noted on whether TB PCR should be a routine application or not (19, 20). In our study, four (80%, 4/5) patients were diagnosed early by positive peritoneal fluid TB PCR on an average of 6.5 days with prompt treatment given. TB PCR detection was not routinely used in our PD program prior to January 2002 because of the low sensitivity rate (13.4%). TBP was diagnosed by positive TB culture and/or acid-fast stains from peritoneal fluid or by caseating granulomata in a peritoneal fluid.
biopsy (12). In 2004, our molecular laboratory method switched to the new assay of TB PCR, which targets the 123 base pair of TB insertion sequence IS6110. The sensitivity rate of TB PCR from 2,319 cases in our hospital was 81.64% from 2002 to 2009 and the specificity rate of TB PCR was 96.85% in the same period. Positive predictive rate was 76.28% while negative predictive rate was 97.70%. False negative rate was 18.35% while false positive rate was 3.15%. Peritoneal fluid TB PCR would be examined when patients undergoing PD presented with prolonged symptoms despite of empiric antibiotic treatment, recurrent peritonitis, or negative bacterial cultures. Therefore, we emphasize that TB PCR plays a crucial role in the early rapid diagnosis of TBP and can notably improve the outcomes of the patients.

Furthermore, the extraperitoneal TB rate was about 8-28% in Turkey and 15.4-20% in Taiwan (9, 12, 13, 21). Lungs were the most common site of the extraperitoneal lesions. Pleura, fallopian tube, lymph node, spleen, or joint lesions were also reported in previous studies (7, 9, 12, 21). In our study, three (3/7, 42.8%) patients had extraperitoneal TB. Two patients had pulmonary TB, and one patient had TBP with TB arthritis. Pulmonary TB was common in our TBP patients. We suggest that concomitant extraperitoneal TB in PD patients should be highly suspected upon diagnosis of TBP.

As for the treatment of TBP, no consensus has been established, and the ISPD 2005 guideline summarized concisely the principles of therapy for TBP patients. Four drugs were recommended, namely rifampin, isoniazid, pyrazinamide, and ofloxacin. However, this treatment protocol was established from the experience of treating extrapolumonary tuberculosis in end-stage renal disease (9, 22). Data from other studies on anti-tuberculosis treatment outlined regimens including at least three drugs, namely rifampin, isoniazid, and pyrazinamide (19, 23). According to previous data, adverse reactions to antituberculosis drugs were mainly pyrazinamide-induced hepatotoxicity, with risk factors such as age (> 60 years) or previous history of hepatitis (23-25). Lui SL reported rifampicin-induced liver function impairment and thrombocytopenia, and isoniazid-induced confusion in Chinese PD patients complicated with TB (8). In our study, a combined therapy using four drugs including rifampin, isoniazid, pyrazinamide and ethambutol was given, with ethambutol replacing ofloxacin. Ethambutol and pyrazinamide were administered for no more than 3 months with no obvious side effects observed. In addition, we also tapered the dosage of pyrazinamide and ethambutol in adjustment to renal function. The dosage of pyrazinamide was reduced by half to 0.75-1 g/day as compared with that of about 1.5-2 g/day 8, 9 in other studies, while the dosage of ethambutol was 400 mg/day. Two (28.5%) of our TBP patients suffered from side effects of rifampicin. Patient 6 developed gastrointestinal upset related to rifampicin after one-month treatment. The symptoms improved after rifampicin was withdrawn. Patient 7 suffered from rifampicin-induced jaundice after the treatment for 2 weeks. The jaundice disappeared after rifampicin was stopped. We believe that TBP treatments can be individualized with different dosages. The side effects of anti-tuberculosis agents should be kept in mind and carefully monitored, especially with rifampin or pyrazinamide.

According to the 2000 ISPD guideline, TBP was an indication for removing the catheter (26), but the 2005 ISPD guideline concerning TBP mentioned that “removal of the catheter is still a contentious issue” (22). Current data also support that primary removal of the Tenckhoff catheter is not indicated in TBP in either the western countries or in Asia (1, 8, 9). In our study, the four patients having TBP between 1990 and 2003 had their catheters removed and were switched to hemodialysis following the 2000 ISPD guidelines, while the other three patients who developed TBP after 2005 continued PD following the 2005 ISPD guidelines.

TBP is an uncommon complication with mortality rates ranging from 15-30% in PD patients (13, 27-30). The best known variable contributing to death due to TBP is delayed treatment (7, 9, 10). In general, patients whose treatment was delayed 4 weeks from the onset of symptoms ultimately died of TBP (13). In our study, the mortality rate for our TBP patients was around 14.3% and lower. The major reasons were early diagnosis and prompt treatment. Our average time lag between onset of symptoms and diagnosis was around two weeks, mostly attributable to the use of TB PCR. Only patient 3 died of TBP, complicated by pneumonia and septic shock, due to a delayed diagnosis. The duration between onset of symptoms and treatment was 30 days, and the diagnosis of TBP was derived via a positive culture for TB.

In conclusion, TBP is an infrequent disease with a high mortality rate in PD patients. Delayed diagnosis or treatment will influence the outcome and mortality of patients. Our experience suggests that an effective diagnostic tool such as the TB PCR test can provide an alternative choice for early TBP diagnosis, resulting in prompt therapy, better patient outcome, and decreased morbidity and mortality.

References


