Arab Journal of Nephrology and Transplantation. 2012 Sep;5(3):135-40

Original Article

Active Tuberculous Infection among Adult Sudanese Patients on Long Term Peritoneal Dialysis

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Abstract

Introduction: The prevalence of tuberculosis in Sudan is 209 cases per 100,000 populations. There are no reports available regarding the prevalence of tuberculosis among the end-stage kidney disease and dialysis populations.

Methods: We reviewed the medical records of all adults who were on peritoneal dialysis (PD) in the Sudan Peritoneal Dialysis Program, during the period from June 2005 to December 2011. Those diagnosed as having active tuberculous infections were retrospectively studied regarding their demography, clinical presentation and outcomes.

Results: Out of 350 patients in our program, 19 were diagnosed as having active tuberculosis (5.4%). All patients were diagnosed during their first year on peritoneal dialysis, 74% were males; the mean age was 37 ± 11 years, extrapulmonary tuberculosis was seen in 16/19 (84%) patients and it was abdominal in nine of the 16 (47%) patients. In addition to high clinical suspicion, the diagnosis of active tuberculosis was supported by tissue biopsy findings in 16%, positive polymerase chain reaction in 26%, exudative ascites with suggestive radiological features in 21%, strongly positive tuberculin test in 21% and a favourable response to empirical antituberculous therapy in 26% of patients. HIV test was negative in all 19 patients and only one patient tested positive for hepatitis B viral infection. Antituberculous drugs side effects were seen in 68% of patients. Forty seven percent of patients showed complete recovery and continued on peritoneal dialysis. Our case fatality was 32%.

Conclusion: Abdominal tuberculosis is common among PD patients and its diagnosis should always be considered in suspected patients.

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Keywords: Active Tuberculosis; Peritoneal Dialysis; Outcome; Sudan

The authors declared no conflict of interest

Introduction

A high burden of tuberculosis had been reported in Sudan, with a prevalence of 209 cases per 100,000 populations [1]. Several reports showed that dialysis patients are at increased risk of developing tuberculosis when compared to normal people, as uremic patients are immune-compromised, and are at an increased risk of reactivating silent tuberculous infections [2-5].

Among end-stage renal disease patients, extrapulmonary tuberculosis had been reported in as many as 60% to 80% of cases, either alone or in association with pulmonary disease. The diagnosis of active tuberculous infection among dialysis patients is often difficult to make because of the prevailing extrapulmonary involvement and the nonspecific presenting symptoms, often mimicking those of uremia [6-9]. Accordingly, empirical treatment is always considered whenever there is a strong clinical suspicion of active tuberculosis in these patients despite the increased risk of antituberculous drugs toxicities [10, 11]. The reported mortality rates of active infections among dialysis populations range from 0 - 75% [12-15].

Few reports are available regarding the prevalence of tuberculosis among end-stage kidney disease patients on peritoneal dialysis (PD). We hereby present our experience regarding the prevalence, management and outcome of active tuberculosis among PD patients enrolled in the Sudan National Peritoneal Dialysis Program, over a period of about six years.

Methods

We reviewed the medical records of all end-stage renal disease patients who were on PD at the Sudan National PD program during the period from June 2005 to December 2011. Those diagnosed as having active tuberculous infections were retrospectively studied regarding their demographic data, primary kidney disease, co-morbid diseases, past history of tuberculosis, duration on PD, clinical presentation, site of active tuberculosis, diagnostic methods used, antituberculous treatments given, antituberculous drugs adverse reactions and the overall response to therapy.

The diagnosis of tuberculosis was established by the presence of a strong clinical suspicion in addition to one or more of the following features [16-20]:

- Caseous necrosis or granulomata on tissue biopsy.
- Positive result of polymerase chain reaction (PCR) for Mycobacterium tuberculosis.
- Isolation of acid fast bacilli on Ziehl–Neelsen (ZN) stain or culture techniques.
- A strongly positive tuberculin test with more than 15 mm induration in a non-vaccinated patient.
- Suggestive ascitic or pleural fluid analysis in the presence of radiological features of tuberculosis.
- A definitive response to empirical antituberculous therapy.

In our center, the recommended initial antituberculous treatment regimen for those with chronic kidney disease or on dialysis therapy include two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of isoniazid and rifampicin; with appropriate dose adjustments for ethambutol and pyrazinamide [21, 22]. A six months treatment course is usually considered sufficient in uncomplicated cases of active tuberculosis [23]. An extended course of up to 12 months is always recommended in those with tuberculosis of the bones, joints as well as tuberculous meningitis [24]. In those with tuberculous meningitis, oral ethambutol is replaced by injectable streptomycin [25]. Among multidrug resistant patients, retreatment regimen is augmented by use of second line drugs such as fluoroquinolone or injectable streptomycin, till drug sensitivity data is available.

Data were extracted from the various PD Units' medical records and entered into a specially designed questionnaire. We analyzed the concomitant risk factors for developing tuberculosis, clinical presentations and laboratory findings, treatment regimens given, response of therapy, drugs adverse effects, compliance and outcomes. Therapeutics methods and outcomes were reviewed and analyzed. Results were expressed as

Table 1: Characteristics of PD patients with active tuberculosis

Characteristics	Number of Patients (%)
Total	19 / 350 (5.4%)
Mean age in years	37 ± 11
Sex (male / female)	14 (74%) / 5 (26%)
Past history of tuberculosis	3 (16%)
Primary kidney disease	
Glomerulonephritis	8 (42%)
Obstructive uropathy	4 (21%)
Diabetic nephropathy	2 (11%)
Hypertensive nephrosclerosis	1 (5%)
Lupus nephritis	1 (5%)
Unknown	3 (16%)
Site of tuberculosis	
Abdomen	9 (47%)
Pulmonary	3 (16%)
Lymph nodes	3 (16%)
Disseminated*	3 (16%)
Joint	1 (5%)
Outcome	
Improved and on peritoneal dialysis	9 (47%)
Shifted to hemodialysis	4 (21%)
Died	6 (32%)

* Multiple sites with tuberculous involvement

Table 2: Clinical manifestations among PD patients with active tuberculosis

Clinical manifestation	Frequency (%)
Fatigability	16 (84%)
Fever	12 (63%)
Marked weight loss	9 (47%)
Abdominal Pain	6 (32%)
Turbid PD effluent	6 (32%)
Cough	4 (21%)
Multiple lymph node enlargements	3 (16%)
Painful swollen joint	1 (5%)

Overlap of symptoms was seen in more than one patient

Table 3: Occurrence of antituberculous drugs adverse reactions

Adverse Reactions	Frequency (%)
Gastrointestinal symptoms	4 (31%)
Psychiatric manifestations	3 (23%)
Optic neuritis	3 (23%)
Peripheral neuropathy	2 (15%)
Hepatotoxicity	1 (8%)

Table 4: Characteristic features of mortality patients

Sex	Age	Kidney isease	Co-morbid Conditions	Site of Tuerculosis	Diagnostic Test	Cause of Death
M	60	Obstructive uropathy	Hepatitis B infection, chronic liver disease, history of treated TB	Disseminated TB	PCR	Hepatic failure
M	18	GN	Long course of steroids	Disseminated TB	PCR	Brain tuberculoma
M	45	Unknown	Cardiomyopathy	Disseminated TB	PCR	Sepsis, coma
M	50	HTN	Malnutrition	TB Lymphadenitis	Tissue biopsy	Peritonitis, sepsis
M	24	GN	-	TB Lymphadenitis	Tissue biopsy	Unknown
M	42	Obstructive uropathy	-	Abdominal TB	Exudative ascitis, suggestive CT, tuberculin test	Adrenal failure

TB: tuberculosis; PCR: polymerase chain reaction for tuberculosis; GN: glomerulonephritis; HTN: hypertension; CT: computed tomographic scan; tuberculin test: strongly positive tuberculin test

means and standard deviations for continuous data, and frequencies and percentages for categorical data.

Results

During the period from June 2005 to December 2011, 350 adult patients were on PD (231 male, 119 female), of these 19 patients were diagnosed and treated as having active tuberculous infection, making a prevalence rate of tuberculosis of 5.4% in our program. Those 19 patients with active tuberculosis were included in the study. They were all on continuous ambulatory peritoneal dialysis; their mean age was 37 ± 11 years (range 18 - 60 years). Males were predominantly affected, 14 out of 19 patients (74%). All patients were diagnosed as having tuberculosis during their first year on PD. Primary glomerulonephritis was the native kidney disease in eight patients (42%), followed by obstructive uropathy in four patients (21%). Three patients (16%) gave a past medical history of tuberculosis for which they received previous full courses of antituberculous therapy; two patients (10%) were diabetics, whereas three patients (16%) were on long term steroids for their primary kidney diseases before reaching end-stage renal disease. Patients' characteristics are shown in Table-1.

Extra-pulmonary tuberculosis was seen in 16 patients (84%), of these nine (47%) presented with abdominal tuberculosis. Isolated pulmonary tuberculosis was seen in three out of 19 patients (16%). The most common presenting symptoms were fatigue, fever and marked weight loss was seen in 84%, 63% and 47% of patients, respectively (Table-2). In addition to high clinical suspicion, the diagnosis of tuberculosis was supported by histological evidence of tuberculosis on tissue biopsy in three patients (16%), positive PCR in five patients (26%) and strongly positive tuberculin tests of more than 15 mm induration in four patients (21%). In four patients (21%) the diagnosis of abdominal tuberculosis was supported by the presence of exudative ascites together with suggestive radiological features on computed tomographic scanning. An overlap of these diagnostic findings was seen in few patients; whereas empirical antituberculous therapy was given in five patients (26%). Acid fast bacilli were not isolated in any of our patients including those with pulmonary tuberculosis. Assessment for HIV was done for all patients and was negative. Hepatitis B viral infection was found in one patient. The mean serum albumin level was 3.3 ± 0.5 g/dl.

Sixteen patients were treated with isoniazid, rifampicin, pyrazinamide and ethambutol for 6-12 months. Three patients were treated with second line protocol regimen due to history of tuberculosis previously treated with full antituberculous therapy. All patients received oral pyridoxine as part of the antituberculous protocol. Drug compliance was ensured in all patients by the close follow-up of enthusiastic PD nursing staff. Antituberculous drugs adverse effects were seen in 68% of patients (Table-3). Adverse effects were severe enough to alter therapy in four out of 19 patients (21%); those side effects were optic neuritis (three patients) and hepatic encephalopathy (one patient).

Out of a total of 19 patients, nine patients (47%) showed complete recovery and continued on PD, four patients (21%) were shifted to hemodialysis and six patients (32%) died. Among those shifted to HD, three had abdominal

tuberculosis, while the fourth patient had tuberculous lymphadenitis. Reasons for switching to hemodialysis were abdominal adhesions in one patient, PD catheter tip migration in one patient and recurrent bacterial peritonitis in two patients. The characteristic features of those who died are shown in Table-4.

Discussion

Sudan was reported as a country with high prevalence of tuberculosis. In this study we reviewed the records of all adult patients with active tuberculosis who were on PD. Similar to previously published reports, active tuberculosis among our patients was mostly diagnosed during the first year on PD, with a relatively high prevalence of extra-pulmonary disease, 84% [12, 13], a fact that had been attributed to the poor general health at the start of dialysis, a time at which patients' cellular immunity is mostly depressed [5]. The commonest extrapulmonary site affected was the abdomen. This is in agreement with work of Sanai and Bzeizi who noted that abdominal tuberculosis included involvement of the gastrointestinal tract, peritoneum or the mesenteric lymph nodes, with occasional overlaps of these forms [23].

Isolation of the mycobacteria by culture techniques remains the gold standard for the diagnosis of tuberculosis [26]. Culture techniques for the isolation of acid- fast bacilli and laproscopic peritoneal biopsy are not readily available at our centers. Ziehl–Neelsen staining of sputum and/or ascitic fluid for mycobacteria, though performed in all suspected patients, was confronted by a poor detection yield at our centers. It had been reported that for the detection of mycobacteria in stained smears, a presence of at least 5000 bacilli/ml of specimen is required [27, 28]; usually, only about 3% of proven tuberculous peritonitis patients are expected to show positive tests on ascitic fluid ZN staining [23]. Failure of isolation of mycobacteria via ZN staining of sputum and/or ascitic fluid among our patients denotes the poor sensitivity of this technique [17].

Detection of mycobacteria by gene amplification and PCR is known to have a high sensitivity of up to 95% in smear positive patients. The PCR detection yield in smear negative patients is also known to be disappointingly low, reaching 48% [29]. Detection of mycobacteria via PCR was available only of late at our program and the test was applied for 12 out of 19 PD patients, it showed a positive detection yield of 42%.

The tuberculin test is greatly relied on in our country for screening and diagnostic support. Among dialysis patients, the presence of a negative tuberculin test is the usual rule due to the altered immunity, thus greatly reducing the sensitivity of the test. However the high specifity of this test (ranging between 95 – 99%) is not altered among dialysis patients, making the presence of a strongly positive tuberculin test in suspected unvaccinated patients of great diagnostic value [30, 31].

In endemic areas the diagnosis of tuberculosis should always be considered in suspected patients. It is believed that favorable outcomes are greatly attributed to the early diagnosis and initiation of therapy [32, 33]. Removal of PD catheters was not essential to attain cure among patients with abdominal tuberculosis. Despite antituberculous therapy our mortality was high reaching 32%, raising the issue of screening for latent tuberculosis among dialysis patients in endemic areas like Sudan [34].

Conclusion

In conclusion, the diagnosis of active tuberculosis among PD patients requires a high index of clinical suspicion [35]. Abdominal tuberculosis remains to be common among PD patients and its diagnosis should always be considered in those with culture negative peritonitis. The high incidence of antituberculous drugs adverse effects warrants additional close monitoring in this group. Early initiation of dialysis and improvement of nutritional support among end-stage kidney disease patients might reduce the high risk of tuberculosis among dialysis patients [36].

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