Original Article

Tuberculosis in dialysis patients: a nine-year retrospective analysis

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Abstract

Introduction: Diagnosis of tuberculosis (TB) among dialysis patients may be difficult because of increased frequency of extra-pulmonary presentations, atypical clinical manifestations, and non-specific symptoms. This study aimed to investigate the spectrum of clinical presentations and outcome in dialysis patients during a nine-year period.

Methodology: A total of 651 patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) for at least three months in our unit between 2001 and 2010 were studied. Dialysis and follow-up were performed in our tertiary care center located in the eastern region of Turkey. Diagnosis of TB was established by combining clinical, radiological, biochemical, microbiological, and histological findings. Choice of anti-TB drug used, the results of therapy, and patient outcome were noted.

Results: Out of 651 dialysis patients studied, 322 (49.4%) were on PD and the remainder on HD (50.6%). Twenty-six (4%) of the 651 dialysis patients were diagnosed with TB (15 PD, 11 HD), 5 of whom were diagnosed by microbiological assessment, 9 by pathological assessment, and 12 by clinical and radiological findings. Mean age at diagnosis was 41.5 ± 16.5 years and the female/male ratio was 1.18. Three patients had a history of pulmonary TB. Extra-pulmonary involvement was observed in 17 (65.4%) patients. All patients were treated with rifampicin isoniazid, ethambutol, pyrazinamide and pyridoxine. Four patients died during the study.

Conclusion: TB occurred in dialysis patients and extra-pulmonary TB was more commonly identified than pulmonary TB. Tuberculous lymphadenitis was the most frequent form of extra-pulmonary TB in our cohort.

Key words: tuberculosis; peritoneal dialysis; haemodialysis; ESRD

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Introduction

Incidence of active tuberculosis (TB) among patients on long-term dialysis is 6.9 to 52.5 times higher than it is in the general population [1,2], depending on regional factors. That is, while the incidence may range between 1.6% to 5.8% in developed countries [3], in developing countries such as Turkey it may be as high as 23.6% [4].

Chronic kidney disease (CKD) is associated with relative compromise in acquired cell-mediated immunity, which constitutes the major determinant of host resistance for further development of disease. In recent years, the increase in the number of patients with immune suppression, such as those with renal transplantation, has led to increased TB rates in the chronic kidney disease population [1].

Diagnosis of TB may be complicated and difficult in dialysis patients because of the increased frequency of extra-pulmonary involvement, atypical clinical presentations, and non-specific symptoms [1]. Data on the incidence and prevalence of TB in dialysis patients varies and depends on the study region [5,6]. Although noted mostly as case reports, PD patients have increased incidence of peritoneal involvement compared to the HD population, suggesting a direct relationship with dialysis [5].

In this study, we aimed to compare the prevalence and clinical characteristics of tuberculosis retrospectively in patients on HD and PD treatment.

Methodology

In this retrospective study, all patients undergoing HD or PD for at least three months in our unit between 2001 and 2010 were studied. Dialysis and follow-up appointments were all held in our tertiary care center which is located in the eastern region of Turkey. Data including demographical characteristics (age, gender, cause of renal failure, duration of dialysis, *etc*.) and clinical findings (fever, weight loss, anorexia, signs suggestive of a pulmonary or extra-abdominal involvement such as lymph nodes, genitourinary tract,

nervous system, musculoskeletal system and others) were collected from patients' chart.

Diagnosis of TB was based on interpreting the results of radiological findings, smear and culture specimens from sputum and possible other foci [peritoneal, pleural, pericardial or cerebrospinal (CSF) fluid]; related tissue biopsy sampling (lymph node, peritoneal, pleural or any other tissue involved); and purified protein derivative (PPD) skin or tuberculin test. Treatment with anti-TB drugs, the results of therapy, and the outcome of patients were also noted. Descriptive statistics were calculated using Statistical Package for Social Sciences version 13 (SPSS, IBM, Chicago, USA), while frequencies, percentages, and means and standard deviations were reported for non-numeric and numeric variables.

Results

A total of 651 dialysis patients were studied. Of these, 322 patients (49.4%) were on PD and the remainder on HD (50.6%). Mean age of the whole population was 48.3 ± 15.2 years. Three hundred fifty-one patients were female (53.9%) and 300 were male (46.1%). Twenty-six (4%) of the 651 dialysis patients were diagnosed with TB. The most common clinical features were abdominal pain, weight loss, anorexia, fever, and cloudy peritoneal fluid (PDF). Mean age of these patients was 41.5 ± 16.5 years and the female-to-male ratio was 14:12. Mean duration of dialysis before the diagnosis of TB, organ involvement, and primary renal disease of the patients are presented in Tables 1 and 2.

Fifteen (4.65%) TB patients with complicating PD were identified among 322 PD patients. The mean age of patients with TB was 38.8 ± 15.8 years. The female-to-male ratio was 8:7. Duration of dialysis before the diagnosis of TB was 26.6 ± 33.2 months. Two patients had a prior history of TB. Three patients had diabetes mellitus and factors known to predispose to TB, such as corticosteroid or immunosuppressive therapy, were present in two patients. The most common clinical features were abdominal pain, weight loss, anorexia, fever, and cloudy peritoneal fluid (PDF).

In PD patients, extra-pulmonary tuberculosis was observed in 60% of the cases (n = 9). Of these patients, four had TB lymhadenitis proven by pathologic examination, samples for which were taken from the mediastinum in two patients and the neck in two patients. Casefication necrosis was seen on sample examination. Four patients had TB peritonitis proven by peritoneal fluid Lowenstein-Jensen culture and adenosine deaminase (ADA) positivity, and one patient had miliary lesions on chest X-ray.

Four patients undergoing PD presented with productive sputum, prolonged cough of three or more weeks, appetite loss, weight loss, easy fatiguability, and hemoptysis. On chest X-ray examination, cavitary lesions on upper zones of the lungs were present in these patients. Additionally, pleural effusion and hilar lenfadenopathy were present in two patients. *M. tuberculosis* was produced in Lowenstein-Jensen culture of the two patients who presented with only cavitary lesions; it was proven in the other two patients by pleural fluid examination, by means of elevated ADA levels, and by lymphocyte predominance.

Two patients undergoing PD with presumed pulmonary tuberculosis presented with low-grade fever, weight loss, non-productive cough, and pulmonary infiltrates without cavity formation on chest radiography. Nonspecific and specific cultures of blood and sputum were negative. There was no clinical response to broad-spectrum antibiotics and the patients were accepted as having pulmonary tuberculosis. Appropriate treatment resulted in improved wellness and resolution of symptoms and radiologic findings.

TB was diagnosed in eight patients within the first 12 months of dialysis, in five patients between 13 and 36 months of dialysis and in two patients between 37 and 100 months.

Eleven (3.3 %) HD patients were found to have TB. The mean age of patients with TB was 46.5 ± 16.5 years. Five of the patients were male while six patients were female. Duration of dialysis before the diagnosis of TB was 27.2 ± 33.4 months. One patient had a prior history of TB. Corticosteroid or immunosuppressive therapy was present in one patient. HD patients with TB had no history of diabetes. The most common clinical features in patients with TB were intermittent fever, fatigue, cough, weight loss, night sweats, and anorexia. Pulmonary TB was noted in three patients (27.2%) who presented with classic symptoms. Chest X-ray revealed cavitary lesions in all patients and pleural effusions in only one patient. *M. tuberculosis* was produced in Lowenstein-Jensen culture of sputum. Examination of pleural effusion showed elevated ADA levels and lymphocyte predominance.

Extra-pulmonary TB was observed in eight patients (72.8%). The diagnosis of extra-pulmonary tuberculosis in HD patients was made through microbiological culture taken from bone marrow in one patient, and pathology taken from the neck and

Table 1. Clinical characteristics and laboratory findings of dialysis patients at the time of TB diagnosis

Parameters	Mean ± SD
Age (years)	41.5 ± 16.5
Female/male	14/12
Dialysis duration at the time of tuberculosis diagnosis (months)	25.5 ± 32.5
Laboratory findings	
Hb (g/dl)	9.4 ± 2.2
WBC (/mm3)	8600 ± 2400
Total protein (g/dl)	6.7 ± 4.5
Serum albumin (g/dl)	3.25 ± 0.75
ESR mm/hr	68.5 ± 33.3
CRP (mg/dL)	77.4 ± 35.4
Involvement	
Pulmonary (n, %)	9 (34.6%)
Extra-pulmonary (n, %)	17 (65.4%)
Primer Renal Disease	
Hypertensive nephrosclerosis (n, %)	4 (15.4%)
Chronic pyelonephritis (n, %)	4 (15.4%)
Chronic glomerulonephritis (n, %)	3 (11.5%)
Diabetes mellitus (n, %)	3 (11.5%)
Amyloidosis (n, %)	1 (3.8%)
Unknown (n, %)	11 (42.3%)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

Table 2. Clinical characteristics and laboratory findings of HD and PD patients

Parameters	PD groups	HD groups
Age (years) *	38.8 ± 15.8	46.5 ± 16.5
Female/male **	8/7	6/5
Dialysis duration at the time of tuberculosis diagnosis (months)**	26.6 ± 33.2	27.2 ± 33.4
Involvement **		
Pulmonary (n, %)	6 (40%)	3 (27.3%)
Extra-pulmonary (n, %)	9 (60%)	8 (72.7%)
Primer Renal Disease		
Hypertensive nephrosclerosis (n, %)	1 (6.7%)	3 (27.3%)
Chronic pyelonephritis (n, %)	2 (13.3%)	2 (18.2%)
Chronic glomerulonephritis (n, %)	2 (13.3)	1 (9.1%)
Diabetes mellitus (n, %)	3 (20%)	-
Amyloidosis (n, %)	-	1 (9.1%)
Unknown (n, %)	7 (46.7%)	4 (36.3%)

PD = peritoneal dialysis HD = hemodialysis

* Statistical significance was detected; $p < 0.05$

** Statistical significance was not detected; $p > 0.05$

mediastinum in 3 patients and 1 patient, respectively. Diagnosis of the remaining three patients was made by assessing clinical and radiologic data (lombar vertebral infiltration seen on magnetic resonance imaging in two patients and, mediastinal lymphoadenopathy seen on computerized tomography in one patient). TB was diagnosed in seven patients within the first 12 months of dialysis, in one patient between 13 and 36 months and in three patients between 37 and 96 months.

PPD tests performed on 22 patients with suspected TB detected 13 (59.1%) positive patients (10 PD / 3 HD), 5 (22.7%) negative patients (3 PD/2 HD), and 4 (18.2%) anergic patients (2 PD / 2HD). All patients were treated with rifampicin (600 mg/day), isoniazid (5 mg /kg/ day, max 300 mg/day), ethambutol (15-25 mg/kg every 48 hours), pyrazinamide (25-30 mg/kg/day) and pyridoxine (100 mg/day). Planned treatment for all patients involved the use of four antituberculosis drugs in the first two months; isoniazid and rifampicin treatment continued for four months thereafter. Mean duration to complete resolution of fever was 27.3 days (range 14 to 45 days). At the end of treatment in PD patients; treatment modality of one patient was shifted to hemodialysis after three months of treatment, and one patient died from multiorgan failure after one month. Both of the patients had extra-pulmonary infiltration of TB.

In addition, antituberculous treatment was stopped temporarily because of high AST and ALT levels in two patients. Thirteen patients continued to receive PD after completion of the antituberculous treatment. In HD patients with TB; three patients died, two from multiorgan failure in the first month, and the other from sudden cardiac death in third month. Extra-pulmonary infiltration was present in the patient who died from multiorgan failure and pulmonary TB was seen in other patient. Treatment was stopped because of ototoxicity in one patient. The antituberculous treatment was completed in the other patient who survived. None of the patients developed reactivation of tuberculosis. There was no multi drug resistant case.

Discussion

In our study of 651 patients with dialysis treatment, 26 patients were found to have tuberculosis. The prevalence of tuberculosis was higher in the PD group than in the HD group.

Immunodeficiency is a feature of CKD, making these patients more susceptible to reactivation of TB or new infection. Identifying patients at risk of TB is not always straightforward, and diagnosing active disease can be delayed as the clinical presentation may be uncharacteristic [7]. Extra-pulmonary disease, particularly peritoneal disease, is relatively common and symptoms may be nonspecific [8].

The TB rates in dialysis patients are higher than they are in the general population, so screening remains important. There have been different reports about the incidence and prevalence of TB in patients on dialysis treatment [5,6], but literature comparing the modalities of dialysis regarding the prevalence and incidence of TB is scarce.

Kazancioglu *et al*. reported that out of 925 HD patients screened from seven different centers, 31 (3.35%) were found to have TB (9). Another large study involving 1,040 patients from eight different HD centers and 345 patients from five different PD units detected TB in34 (3.27%) patients from the HD group and 4 patients (1.16%) from the PD group [10]. In our study, the prevalence of TB in the PD group was higher than that in the HD group. The difference between the groups may be predicted considering the lower educational and socioeconomic status, higher co-morbidity rates, more frequent malnutrition, and inconsistency with treatment in the PD population in our country. Additionally, in our study group, five patients on chronic PD were observed, and peritoneal involvement contributes to higher incidence for TB. Taken together, these factors may be the cause of higher incidence of TB in our PD population.

Several studies mention a high frequency of cases of TB discovered in the first year of dialysis. This has been attributed to the poor general state of some patients at the start of the dialysis when host immunity might be most profoundly depressed [2]. Erkoc *et al*. reported TB diagnosed in 13.3% of patients within the first 12 months of dialysis, in 16 patients between 13 and 36 months of dialysis, and in 10 patients between 36 and 84 months (11). In our study, TB was discovered in 54.2% of the cases in the first year of dialysis. The reason for this condition might be severe malnutrition and depressed cellular immunity in the early stages of dialysis.

TB diagnosis is more complex and difficult in dialysis patients because of atypical clinical presentation, non-spesific symptoms, increased frequency of extra-pulmononary involvement, and frequent anergic skin tests. Cough and hemoptysis, classic symptoms of TB in the general population, are less frequently reported in dialysis patients (mean 22% of cases; range 5% to 71%) [11].

The localization is often extra-pulmonary, with percentages varying from 38% up to more than 80%,

whereas in the general population, extra-pulmonary TB is reported to account for only 4.5% of the total cases of TB (18-12). Extra-pulmonary involvement has been reported to be high in Turkey (38% to 77%) and in other countries (up to 50%) among the dialysis population (7,8,11,12,13). Erkoc *et al*. reported identifying 30 (10.5%) tuberculosis patients among 287 dialysis patients (223 HD, 64 PD), and 65.4% of these cases had extra-pulmonary disease [12].

The diagnosis of TB is hampered by the common occurrence of a negative purified protein derivative (PPD) skin test, which was found in 40% to 100% of the cases [1]. A positive test can be helpful but a negative result cannot be assumed to be a true negative. Anergy to the tuberculin skin test was noted in 55.6% of MTB patients compared with 15% of tuberculosis patients in the general population. In uremia there is a decreased T-cell response, as indicated by the high rate of anergy to intracutaneously administered antigens, reported to be as high as 32% and 40% (6,13,14,15).

Pulmonary and extra-pulmonary TB should be managed according to the same guidelines. Treatment of TB in CKD may be complicated by an increased risk of toxicity from antituberculous drugs, particularly isoniazid and ethambutol. Adverse effects of antituberculous treatment have been found to be more common in patients with renal disease than in those with normal renal function (16).

Some studies, especially from the early years of dialysis but also more recently, reported a high mortality of 17% to 75% in CKD patients with TB. The difference in outcome among the studies might have been an indirect result of delay in diagnosis and initiation of therapy. This delay might have led to deterioration in the nutritional status of the patients, a well-known negative prognostic factor in dialysis patients. Adverse effects were hepatotoxicity in two and optic neuritis in one patient. A clinical response to therapy was achieved in all of the surviving patients who completed treatment. Four patients died during the TB treatment, and mortality rate was higher in HD patients. We observed that HD patients with tuberculosis were older and had longer duration dialysis than PD patients with tuberculosis. These factors may be cause of higher mortality in the HD population.

In conclusion; TB occured in dialysis patients and extra-pulmonary TB was more commonly identified than pulmonary TB. Tuberculous lymphadenitis was the most frequent form of extra-pulmonary TB detected in our study.

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References

1. Siriram SN and Arvind M (1992) Optimal tuberculosis screening of hemodialysis patients. Nephron 82: 356. DOI: 10.1159/000045452.
2. Hussein MM, Mooij MJ, Roujouleh H (2003) Tuberculosis and chronic renal disease Semin Dial 1: 38-44. DOI: 10.1046/j.1525-139X.2003.03010.x.
3. Andrew OT, Schoenfeld PY, Humphyres MHT (1980) Tuberculosis in patients with end-stage renal disease. Am J Med 68: 59-65. PII: 0002-9343(80)90166-7.
4. Cengiz K (1996) Increased incidence of tuberculosis in patients undergoing hemodialysis. Nephron 73: 421-424. DOI: 10.1159/000189104.
5. Kayabasi H, Sit D, Kadiroglu AK, Kara IH, Yilmaz ME (2008) The prevalence and the characteristics of tuberculosis patients undergoing chronic dialysis treatment: experience of a dialysis center in southeast Turkey. Ren Fail 30: 513-519. DOI: 10.1080/08860220802064721.
6. Zahiri K, Ramdani B, Hachim K, Benghanem MG, Fatihi E, Zaid D (1997) Tuberculosis in hemodialysis. Nephrologie 18: 303-306. PMID: 9496572.
7. Milburn HJ (2010) How should we treat tuberculosis in adult patients with chronic kidney disease? Pol Arch Med Wewn 120: 417-422. PMID: 20980948.
8. Alvarez S and McCabeWR (1984) Extrapulmonary tuberculosis revisited: a review of experience at Boston City and other hospitals. Medicine 63: 25-55. PMID: 6419006.
9. Kazancioglu R, Ozturk S, Gursu M, Avsar U, Aydin Z, Uzun S Karadag S, Tatli E, Sar F (2010) Tuberculosis in patients on hemodialysis in an endemic region. Hemodial Int 14: 505-509. DOI: 10.1111/j.1542-4758.2010.00470.x.
10. Karadag P, Gursu M, Ozturk S, Karadag S, Aydin Z, Uzun S (2011) Prevalance of tuberculosis in patients on hemodialysıs and peritoneal dialysis. J Infec Dis Immun 3: 189-192. ISSN 2141-2375.
11. Chou KJ, Fang HC, Bai KJ, Hwang SJ, Yang WC, Chung HM (2001) Tuberculosis in maintenance dialysis patients. Nephron 88: 138-143. DOI: 10.1159/000045974.
12. Erkoc R, Dogan E, Sayarlioglu H, Etlik O, Topal C, Calka F, Uzun K (2004) Tuberculosis in dialysis patients, single center experience from an endemic area. Int J Clin Pract 58: 1115-1117. DOI: 10.1111/j.1742-1241.2004.00212.x.
13. Pien FD, Younoszai BG, Pien BC (2001) Mycobacterial infections in patients with chronic renal disease. Infect Dis Clin N Am 15: 851-876. PII: S0891-5520(05)70176-8.
14. Woeltje KF, Mathew A, Rothstein M, Seiler S, Fraser VJ (1998) Tuberculosis infection and anergy in hemodialysis patients. Am J Kidney Dis 31: 848-852. PII: S0272-6386(98)70055-1.
15. Smirnoff M, Patt C, Seckler B, Adler JJ (1998) Tuberculin and anergy skin testing of patients receiving long-term hemodialysis. Chest 113: 25-27. DOI: 10.1378/chest.113.1.25.

16. Quantrill SJ, Woodhead MA, Bell CE, Hardy CC, Hutchison AJ, Gokal R (2002) Side-effects of antituberculosis drug treatment in patients with chronic renal failure. Eur Respir J 20: 440-443. DOI:10.1183/09031936.02.00298002.

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