Hemodialysis International 2010; **14**:505–509

Tuberculosis in patients on hemodialysis in an endemic region

Rumeyza KAZANCIOGLU,[1] Savas OZTURK,[1] Meltem GURSU,[1] Umit AVSAR,[2] Zeki AYDIN1,[1] Sami UZUN,[1] Serhat KARADAG,[1] Emel TATLI,[1] Fuat SAR[2]

[1]Haseki Training and Research Hospital, Department of Nephrology, Haseki, Istanbul, Turkey; [2]Haseki Training and Research Hospital, Department of Internal Medicine, Haseki, Istanbul, Turkey

Abstract

Clinical presentation of tuberculosis is different in hemodialysis patients than in the general population. This study aimed to analyze hemodialysis patients with tuberculosis in Istanbul. Patients who were on a chronic hemodialysis program in Istanbul for more than 3 months and diagnosed to have tuberculosis at least 3 months after the start of hemodialysis were included. To discard the effect of immigration from other cities, we included only patients who had started their dialysis program in Istanbul. Their demographic and clinical data were analyzed using Statistical Package for Social Sciences for Windows ver. 13.0. Of the 925 patients screened from 7 different centers, 31 (3.35%) were found to have tuberculosis. The mean age was 52.3 ± 13.5 years. The male/female ratio was 18/13. The mean duration of dialysis therapy and the duration of dialysis till the diagnosis of tuberculosis were 62.6 ± 54.3 and 21.7 ± 25.7 months, respectively. Extrapulmonary tuberculosis constituted 48.39%. Treatment ended with a cure in 18 (58.05%); was still ongoing in 12 (38.70%) patients; and 1 (3.25%) died of pulmonary tuberculosis. The lower incidence of tuberculosis compared with previous reports may be related to the differences in the diagnostic criteria and the decrease in the rate of tuberculosis during recent years. The demographic and clinical parameters of the patients were quite similar to the average dialysis population in Turkey. Hence, we cannot address a subpopulation with additional risk. It is important to prevent tuberculosis in hemodialysis patients due to difficulties in the diagnosis and treatment. Thus we recommend routine screening of hemodialysis patients and effective isolation and treatment of infected patients.

Key words: Hemodialysis, tuberculosis, diagnosis, treatment

INTRODUCTION

Clinical presentation of tuberculosis is different in patients on hemodialysis than in those with a competent immune system. Pulmonary tuberculosis is still the most common form of presentation while extrapulmonary tuberculosis has increased substantially in frequency during recent years in this population. Rates of 38% and 50% have been reported for extrapulmonary involvement.[1,2] The diagnosis is usually late, sometimes postmortem, due to nonspecific clinical presentations (fever of unknown origin, fatigue, loss of weight), negative tuberculin skin test (anergy), and low probability of microbiologic evidence (acid-resistant bacilli, culture in tuberculosis media). In a study carried out with hemodialysis patients in our country, the incidence of tuberculosis has been reported to be 23.6%.[3] This fact necessitates the use of an effective program for prevention (isolation of patients proven to have tuberculosis), screening, early diagnosis, and treatment of tuberculosis in this population.[4,5] It has been recommended to treat empirically patients with strong clinical suspicion but negative microbiological examinations, although there is not enough proof for such a protocol.[3]

Correspondence to: M. Gursu, MD, Haseki Training and Research Hospital, Department of Nephrology, Aksaray, Istanbul, Turkey, 34090. E-mail: meltem1401@yahoo.com

DOI:10.1111/j.1542-4758.2010.00470.x

This study aimed to describe the characteristics of hemodialysis patients with tuberculosis and to determine its prevalence in Istanbul.

MATERIALS AND METHODS

Patients who were on a chronic hemodialysis program in our city for more than 3 months were involved in the study, and those who were diagnosed to have tuberculosis at least 3 months after the start of hemodialysis were examined for their clinical, demographic, and laboratory parameters. Seven hemodialysis centers that represent different socioeconomic and cultural characteristics of the population were chosen among the total 113 centers in Istanbul. The number of the patients who were on hemodialysis in these centers is more or less comparable to the number of inhabitants of the city and the local district.

Patients who were not residents of Istanbul but only guests; peritoneal dialysis patients who have switched to hemodialysis temporarily due to mechanical or metabolic reasons; those who had empirical antituberculosis treatment without microbiological verification; those with a duration of dialysis treatment <3 months; and patients who had a diagnosis of tuberculosis in another city were excluded from the study.

The demographic parameters (age, gender, birth place, educational status, and occupation) as well as primary renal disease, co-morbid diseases, and duration of hemodialysis have been recorded.

All hemodialysis patients are routinely checked with chest X-ray annually in our country. If there is a clinical or a radiological suspicion of either pulmonary or extrapulmonary tuberculosis, then further radiological and microbiological examinations are performed. We examined the files of the patients and identified those who were diagnosed to have tuberculosis.

Regarding tuberculosis, the timing of diagnosis, previous history of antituberculosis treatment, family history, site of presentation, names, doses and durations of drugs, side effects of the treatment, and outcome of the disease were recorded on a preformed chart. If patients had changed their hemodialysis center, they were recorded in the centers where they were diagnosed to have tuberculosis.

Statistical analysis was carried out using statistical package for social sciences (SPSS, Chicago, USA) for Windows ver. 13.0. Numerical parameters were expressed as mean $\pm$ standard deviation.

RESULTS

Of the 925 patients screened from 7 different centers, 31 (3.35%) were found to have tuberculosis. The mean age was 52.3 ± 13.5 years (minimum: 20, maximum: 75). Eighteen (58%) of the patients were males while 13 (42%) were females. Of the 31 patients, 70.97% had graduated from elementary school, 6.45% from high school, and 3.2% from university while 19.35% were not educated at all.

The mean duration of dialysis therapy and the duration of hemodialysis up to the time of diagnosis of the tuberculosis are presented in Table 1.

Primary renal diseases of the patients were diabetic nephropathy in 22.58%, hypertensive nephrosclerosis in 16.13%, chronic pyelonephritis in 9.68%, polycystic kidney disease in 6.45%, amyloidosis in 6.45%, and unknown in the remaining 35.49%. Besides these diseases, 16.13% of the patients had ischemic heart disease and 9.68% had chronic obstructive pulmonary disease as co-morbidities.

It was seen that pulmonary involvement (51.61%) was the most common form, while extrapulmonary tuberculosis formed the remaining 48.39% (Figure 1). There was no relationship between the duration of dialysis and extrapulmonary involvement ($P=0.34$).

Eleven patients had a prior history of tuberculosis. These cases were before the dialytic period and the details of the tuberculosis treatment could not be obtained. Twenty-seven patients received isoniazide+rifampicin+ethambutol+pyrazinamide, one had an isoniazide+rifampicin+ethambutol+a quinolone antibiotic; while in 3 patients, drugs other than isoniazide and rifampicin were unknown. The doses of ethambutol and pyrazinamide were reduced and given every other day. All patients had oral or parenteral vitamin B treatment.

Table 1 Dialysis duration

	Mean $\pm$ SD	Minimum	Maximum
Age (years)	52.3 ± 13.5	20	75
Hemodialysis duration (months)	62.61 ± 54.3	4	235
Hemodialysis duration at the time of tuberculosis diagnosis (months)	21.71 ± 25.7	3	106

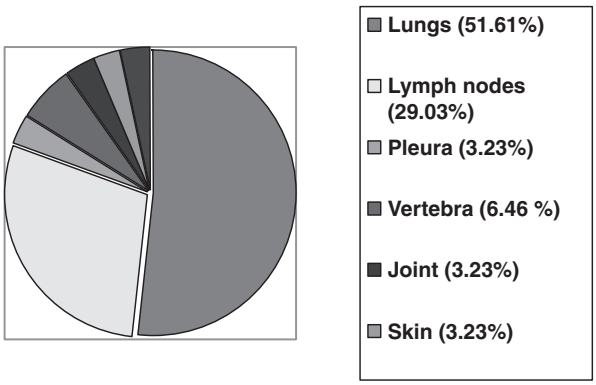

Figure 1 Sites of involvement in patients with tuberculosis.

The treatment ended with a cure in 18 (58.05%) patients, was still ongoing in 12 (38.70%) patients, and 1 patient (3.25%) died of pulmonary tuberculosis.

Of the side effects seen in 51.9% of the patients, the most common one was related to skin-like pruritus, red, and dry skin. Decreased visual acuity in 1 and color blindness in 1 patient have been reported (Table 2).

DISCUSSION

The rates of tuberculosis in dialysis patients have declined along with the national rates. But the rates in dialysis patients remain far higher than the general population and screening remains important. The number of incident and prevalent hemodialysis patients has been reported to be 15,313 and 39,208, respectively, according to the 2008 registry.[6] There have been studies on the incidence and prevalence of tuberculosis in the dialysis population, with varying results. With the 925 patients screened, this study is the largest scaled one among the studies performed in our country. There were 9976 hemodialysis patients in Istanbul in 2009 according to the statistical reports of local health authorities. But due to the dynamic nature of these patients and the presence of acute cases, it is very difficult to determine the exact number of patients who fulfill the criteria for inclusion in the study at the time of analysis. We have screened about 9.27% of the hemodialysis population in the city. The percentage of patients with a diagnosis of tuberculosis (3.35%) was lower when compared with previous studies, which reported rates between 5.7% and 23.6%, with the highest number of patients screened as 296.[1,3,7–9]

Table 2 Side effects related to antituberculosis drugs

Side effect	Percentage/number
Transaminitis	6.5/2
Neuropathy	6.5/2
Visual disturbance	6.5/2
Others[a]	22.6/7

[a]Pruritus, dryness, and redness of the skin, etc.

The lower incidence of tuberculosis in the present study may be related to the differences in the diagnostic criteria of tuberculosis. We only included patients with histopathological or microbiological evidence, but not those who were treated empirically due to suspicion of clinical and radiological findings. There is not enough proof for following a route from response to treatment to diagnosis in the absence of microbiological or pathological proof.

In the hemodialysis population, the diagnosis is often difficult due to nonspecific symptoms like fever, fatigue, loss of weight, and, frequently, an anergic skin test (due to blunted lymphocyte functions and cytokine expression in uremia). Presentation of tuberculosis may be different in dialysis patients compared with the general population, pulmonary involvement being still at the first place.[3] In Turkey, the percentage of extrapulmonary tuberculosis in 2007 was 30.5% according to the report of the Ministry of Health. Extrapulmonary involvement has been reported to be high in both Turkey (38–77%) and other countries (up to 50%) among the dialysis population,[1,2,4,5,7–12] and it was 48.39% in the present study. These difficulties lead to a delayed diagnosis, sometimes postmortem. For these reasons, hemodialysis patients are checked annually by chest X-ray.

There is a wide variation in the prevalence of the disease in different reports from different regions of the country. According to the 2009 statistical reports of Ministry of Health, Istanbul is the city with the highest values for both the incidence and the prevalence of tuberculosis (50.8/100,000 population). But this must be considered carefully because Istanbul is the city with the highest rate of immigration from other cities due not only to socioeconomic reasons but also health problems. It is not unexpected for a patient receiving hemodialysis treatment in a peripheral city to move into a large city when faced with a chronic health problem that cannot be solved. This fact may be responsible for the high incidence and prevalence of tuberculosis in hemodialysis patients in Istanbul. To minimize the effect of this factor, we included only patients who had started and continued their dialysis program in Istanbul.

Another factor that may influence the statistics may be the timing of diagnosis. Patients may have been infected before the dialysis therapy but may have been diagnosed after the onset of dialysis possibly due to more frequent

visits. This is why we excluded patients who were diagnosed within the first 3 months of dialysis treatment.

Another factor for the increased rate of tuberculosis in the dialysis population may be related to the sociocultural status. According to the data of the National Statistics Institute at 2009, among the total population in Istanbul above the age of 15, 44.72% had graduated from elementary school, 28.18% from high school, 11.15% from university, 9.3% were not educated at all, and 6.65% were unrecorded. With the figures obtained in our study (70.97% had graduated from elementary school, 6.45% from high school, 3.2% from university, and 19.35% were not educated at all), it can be seen that dialysis patients were clearly less educated than the general population.

Both the incidence and the prevalence of tuberculosis seem to have decreased in recent years all over the world.[13] The EuroTB 2009 Report has proposed that the incidence of tuberculosis in Turkey reached a peak in 2006 and then started to decline. According to the reports of the Ministry of Health, the prevalences of tuberculosis in 2006 and 2007 were 20.526 (28.1/100,000) and 19.694 (27.9/100,000), respectively.[13] A program named "Directly Observed Treatment Strategy" has been used for tuberculosis patients as proposed by the World Health Organization since 2000; i.e., all patients were observed taking the drugs for each dose by a dedicated medical staff.[14] This program was in parallel with other modifications in strategies related to the medical staff and budget. They all resulted in the highest rate of microbiological diagnosis and the lowest rate of discontinuation of treatment in 2008. The incidence of tuberculosis was reported to be 23.6% in hemodialysis patients in a study carried out in 1996,[3] which is considerably higher than our report of 3.35%. This difference provides another clue of the decrease in the incidence of tuberculosis in our country.

In a previous study in our country by Sen et al.,[8] 18 patients (5.2%) among 343 dialysis (both hemodialysis and peritoneal dialysis) patients screened and 14 patients (4.9%) among 285 hemodialysis patients were reported to have active tuberculosis infection. They involved patients who had empirical antituberculosis treatment without prompt evidence in contrast to our study. The time period between the start of dialysis and the diagnosis of tuberculosis (19.5 ± 26 months) was similar to our results.

Another relatively large-scale study, again in our country, performed by Erkoc et al.[9] reported the number of patients having tuberculosis (with/without microbiological or histopathological evidence) to be 30 (10.5%) among 287 dialysis patients screened (223 hemodialysis, 64 peritoneal dialysis). Fifty-seven percent of these cases had extrapulmonary disease.

The demographic parameters (age, gender) and the primary kidney disease of the patients in our study were quite similar to the average dialysis population in Turkey according to the registry reported by the Turkish Society of Nephrology in 2008. This is why with our results we cannot address a subpopulation in the hemodialysis population that has additional risk factors for tuberculosis. Diabetic patients did not have an increased incidence compared with nondiabetic ones as opposed to previous studies reporting a higher incidence in diabetic patients.[15,16]

The disease has different characteristics in hemodialysis patients regarding the drugs used. It is well known that they have more side effects in this population. We reported the rate of side effects other than skin reactions as 19.3%, which prompts more frequent visits.

CONCLUSION

Although the rates of tuberculosis have begun to decline, it is still higher in hemodialysis patients than in the general population. It is important to prevent and diagnose early tuberculosis in hemodialysis patients due to the atypical course of the disease and the relatively high rate of side effects. Thus, we recommend routine screening of hemodialysis patients, especially those with a previous history of tuberculosis, and treat these patients effectively with close monitoring.

Manuscript received January 2010; revised June 2010.

REFERENCES

1 Taskapan H, Utas C, Oymak FS, Gülmez I, Ozesmi M. The outcome of tuberculosis in patients on chronic hemodialysis. *Clin Nephrol*. 2000; **54**:134–137.
2 Zahiri K, Ramdani B, Hachim K, Benghanem MG, Fatihi E, Zaid D. Tuberculosis in hemodialysis. *Nephrologie*. 1997; **18**:303–306.
3 Cengiz K. Increased incidence of tuberculosis in patients undergoing hemodialysis. *Nephron*. 1996; **73**:421–424.
4 Woeltje KF, Mathew A, Rothstein M, Seiler S, Fraser FJ. Tuberculosis infection and anergy in hemodialysis patients. *Am J Kidney Dis*. 1998; **31**:848–852.
5 Smirnoff M, Patt C, Seckler B, Adler JJ. Tuberculin and anergy skin testing of patients receiving long-term hemodialysis. *Chest*. 1998; **113**:25–27.
6 Serdengecti K, Suleymanlar G, Altiparmak MR, Seyahi N. *Registry of the nephrology, dialysis and*

transplantation in Turkey; Registry 2008. Metris Press, 2009. pp. 5–6.
7 Ekim M, Tumer N, Bakkaloğlu S. Tuberculosis in children undergoing continuous ambulatory peritoneal dialysis. *Pediatr Nephrol*. 1999; **13**:577–579.
8 Sen N, Turunc T, Karatasli M, Sezer S, Demiroglu YZ, Oner Eyuboglu F. Tuberculosis in patients with end-stage renal disease undergoing dialysis in an endemic region of Turkey. *Transplant Proc*. 2008; **40**:81–84.
9 Erkoc R, Dogan E, Sayarlioglu H, et al. Tuberculosis in dialysis patients, single centre experience from an endemic area. *Int J Clin Pract*. 2004; **58**:1115–1117.
10 Kürşat S, Ozgür B. Increased incidence of tuberculosis in chronic hemodialysis patients. *Am J Nephrol*. 2001; **21**:490–493.
11 Kaul KL. Molecular detection of *Mycobacterium tuberculosis*: Impact on patient care. *Clin Chem*. 2001; **47**:1553–1558.
12 Nagesh BS, Sehgal S, Jindal SK, Arora SK. Evaluation of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in pleural fluid. *Chest*. 2001; **119**:1737–1741.
13 World Health Organization. *World Health Organization Global TB Report, The World and Turkey in 2009 (WHO/HTM/TB/2009.411)*. Geneva, Switzerland: WHO; 2009.
14 World Health Organization. *WHO Tuberculosis Programme: Framework for Effective Tuberculosis Control WHO/TB/94.179*. Geneva, Switzerland: WHO.
15 Shohaib SA, Scrimgeour EM, Shaerya F. Tuberculosis in active dialysis patients in Jeddah. *Am J Nephrol*. 1999; **19**:34–37.
16 Moore DA, Lightstone L, Javid B, Friedland JS. High rates of tuberculosis in end-stage renal failure: The impact of international migration. *Emerg Infect Dis*. 2002; **8**:77–78.