Spectrum of Mycobacterial Infections: Tuberculosis and Mycobacterium other than Tuberculosis in Dialysis Patients

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Abstract

Background: Patients with end-stage renal disease are at high risk of mycobacterial infection.

Objectives: To analyze the difficulties in reaching an accurate diagnosis of tuberculosis in dialysis patients.

Methods: We conducted a retrospective follow-up of patients who attended our peritoneal and hemodialysis units during the 10 year period 1995–2005.

Results: Our dialysis unit diagnosed 10 cases of tuberculosis caused by *Mycobacterium tuberculosis* and 9 cases of Mycobacterium other than tuberculosis. In the former group, five patients had *Mycobacterium* in the sputum, which was diagnosed by intraabdominal mass biopsy in one, culture of the gastric juices in one, and pleural fluid culture or pleural biopsy in three. One of these patients was suffering from pleural TB as well as Potts disease. Of the patients with Mycobacterium other than tuberculosis, five were diagnosed by sputum cultures, three by urine cultures and one in peritoneal fluid. Differences in treatment and outcome were also reviewed.

Conclusions: The diagnosis of TB in dialysis patients should be approached with a high index of suspicion. It is clear that extensive diagnostic procedures are required to ensure an accurate diagnosis of the disease. Tuberculosis incurs a significant added burden due to the need for isolation of infected patients within the dialysis unit. Treatment of patients with Mycobacterium other than tuberculosis should be addressed individually.

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Infection remains one of the major causes of morbidity in patients with uremia. The impaired immunity of patients on dialysis puts them at greater risk to develop tuberculosis, as evidenced by both a 15-fold increase in the incidence of TB among patients with advanced renal failure compared with the general population and higher mortality due to this complication [1-3].

In dialysis patients the clinical course and presentation of TB is frequently atypical and associated with extra-pulmonary involvement. Possibly due to impaired immunity there is less caseation and cavernous TB is less frequent. On the other hand, uremia, which is commonly associated with general weakness, malnutrition and other non-specific complaints, may mimic the clinical course of TB, making the diagnosis of TB in dialysis patients more difficult [4,5]. This often leads to a delay in accurate diagnosis and therapy, sometimes resulting in death.

The present study is a retrospective analysis of 10 patients with TB and 9 patients with Mycobacterium other than TB who were treated in our dialysis unit since 1995. We discuss their clinical features, pulmonary versus extra-pulmonary involvement, diagnostic procedures, and management problems.

TB = tuberculosis

Patients and Methods

We have been monitoring patients with TB in our dialysis unit since 1995. Several significant epidemiological factors were taken into account as our dialysis population includes many immigrants from endemic areas for tuberculosis, such as the former Soviet Union, India, Ethiopia, as well as Bedouin patients living in deprived conditions with poor hygiene and without a clean water supply.

We collected data from the TB patients' records, which included socioeconomic background and demographic parameters (age, gender, etiology of uremia, duration of dialysis). Clinical history was obtained, including concomitant diseases, albumin level, hepatitis B vaccination status, chest X-ray, sputum, urine or gastric juice for M. *tuberculosis*, pleural fluid culture for M. *tuberculosis*, pleural biopsy, peritoneal biopsy, lymph node biopsy, and paravertebral mass biopsy. Table 1 provides data on all cases of tuberculosis found during the period of our survey. Table 2 shows the incidence of Mycobacterium other than TB and the site of infection. Table 3 illustrates TB localization (pulmonary versus extra-pulmonary TB).

Patients with TB

In the group of TB patients M*ycobacterium* was found in the sputum of five patients: three patients required pleural fluid or pleural biopsy, one case was diagnosed by paravertebral mass biopsy as well as pleural biopsy, one case by intraabdominal mass biopsy discovered incidentally during the insertion of a Tenckhoff catheter with caseating granuloma on histological examination, and one by culture of gastric juice (this patient subsequently died from respiratory failure and emaciation).

Although extra-pulmonary TB in dialysis patients is frequently reported, most of the patients (6 of 10) in our dialysis unit were suffering from pulmonary TB often with atypical presentation, as described in Table 3. According to the literature pleural TB is an extra-pulmonary form of tuberculosis most probably because of its hematogenous mode of dissemination [6].

One patient on routine immunosuppressive therapy after kid-

Table 1. Patients with tuberculosis in the dialysis unit, 1995–2005

Patient no.	Gender	Origin	Mode of dialysis	Cause of end-stage kidney disease	Samples taken	Outcome	Therapy
1	M	Bedouin	Hemodialysis	Diabetes	Sputum culture	Died from TB	Conventional antibiotics
2	M	Bedouin	Hemodialysis	Diabetes	Sputum culture	Recovered	Anti-TB drug
3	F	Bedouin	Hemodialysis	Unknown	Sputum culture	Recovered	Anti-TB drug
4	M	USSR	Hemodialysis	Diabetes	Pleural biopsy, paravertebral mass biopsy	Recovered	Anti-TB drug
5	F	India	Peritoneal dialysis	Diabetes	Gastric juice on autopsy	Died from TB	Conventional antibiotics
6	M	Austria	Peritoneal dialysis	Membrano-proliferative glomerulo-nephritis	Sputum culture	Recovered	Anti-TB drug
7	M	Bedouin	Peritoneal dialysis	Diabetes	Sputum culture	Recovered, died in an accident	Anti-TB drug
8	F	India	Hemodialysis	Diabetes	Granulomae in mass biopsy	Recovered	Anti-TB drug
9	F	Morocco	Hemodialysis	Diabetes	Pleural fluid & pleural biopsy	Recovered	Anti-TB drug
10	F	India	Peritoneal dialysis	Unknown	Pleural biopsy	Died from stroke	Anti-TB drug

Table 2. Cases of Mycobacterium other than TB in dialysis patients

	Positive for M. *tuberculosis*				
Patient no.	Sputum	Urine	Peritoneal fluid	Mycobacterium other than TB	M. *avium-intracellulare*
1	+			+	
2	+			+	
3	+			+	
4	+			+	
5	+			+	
6		+		+	
7		+		+	
8		+			+
9			+	+	

Table 3. Clinical characteristics of patients with different TB localization

	Pulmonary TB (n/%)	Extra-pulmonary TB (n/%)
Total no. of patients	6	4
Male to female ratio	4:2	1:3
Mode of dialysis (PD vs. HD)	3:3	3
Immigrants from endemic countries	2	4
Bedouin patients	4	–
Previous kidney transplant	2	–
Diabetes mellitus	4	4
Side effects of anti-TB therapy	Peripheral neuropathy in 1 patient	Peripheral neuropathy and depression

PD = peritoneal dialysis, HD = hemodialysis

ney rejection presented with lung infiltrate and prolonged fever. After repeated sputum samples and bronchoscopy the patient was treated accordingly. The fever returned to normal and the infiltrate resolved. One patient suffered from lymphoma and began chemotherapy; tuberculosis was diagnosed by pleural biopsy and in the pleural fluid. This suggests that the immunosuppressive regimen in patients on dialysis may well predispose the patient to developing TB.

Only 5 of the 10 TB patients presented with fever. Two of our patients had been treated for respiratory failure and lung infiltrate or destructive pneumonia by conventional antibiotics and only at autopsy were sputum and gastric juices found positive for TB.

Patients with Mycobacterium other than TB

Of these patients, five were diagnosed by sputum cultures, three by urine cultures and one from culture of the peritoneal fluid (M*ycobacterium fortuitum* peritonitis). Overall, nine patients were diagnosed with Mycobacterium other than TB – M. *cansasii*, M. *fortuitum*, M. *avium-intracellulare* – between the years 1995 and 2005.

Asymptomatic patients were not treated. Only two patients were symptomatic for Mycobacterium other than TB and were specifically treated for this condition. The first patient (no. 1) was a 69 year old man who, several years after kidney transplantation and ensuing immunosuppressive medication, presented with prolonged fever and progressive weight loss. Kidney graft biopsy revealed polyoma virus and the graft was subsequently removed. When the fever persisted further tests revealed M*ycobacterium cansasii* in the sputum and right lung pulmonary consolidation by chest X-ray. Treatment with clarythromycin, rifampicin and etambutol was instituted. The fever resolved and the patient's nutritional status improved substantially.

The second patient (no. 9) was a 74 year old woman treated by peritoneal dialysis who presented with peritonitis resistant to conventional antibiotic therapy. M*ycobacterium fortuitum* was found in peritoneal fluid cultures. The Tenckhoff catheter was removed and the patient was transferred to hemodialysis. Appropriate antibiotic treatment (clarythromycin, amikacin, cefipime) was introduced followed by a full clinical recovery.

Results

Since 1995 we have treated 1384 patients with hemodialysis and peritoneal dialysis in our dialysis unit. We found that certain ethnic groups were at particular risk for TB, including Bedouins and immigrants from the former Soviet Union and India.

To date 10 patients have been diagnosed, 2 of whom presented in 2004 and 1 in 2005. We diagnosed 10 cases of

tuberculosis caused by M*ycobacterium tuberculosis* (5 males and 5 females) and 9 cases of Mycobacterium other than tuberculosis. The mean age of the TB patients was 64.4 (range 41–75 years). Of the 10 TB patients, 7 fully recovered, 2 died due to TB and 1 died from stroke [Table 1].

Management

Anti-tuberculosis therapy protocols were adopted according to the recommendations of the TB specialist, based on internationally accepted guidelines of the American Thoracic Society and the U.S. Centers for Disease Control. Anti-tuberculosis medication was administered to the hemodialysis patients during dialysis sessions by the medical team in order to ensure compliance.

Severe side effects were observed in patients when the anti-tuberculosis regimen was introduced, mostly depression and painful peripheral neuropathy despite supplements of vitamin B6.

The Mantoux test is not routinely used for the diagnosis of tuberculosis among patients in our dialysis unit, but is applied to patients who are candidates for kidney transplantation. We routinely perform the tuberculin skin test on our nurses, doctors and technicians. One case of seroconversion was revealed in our unit. Because of risk factors this staff member was treated for half a year according to the guidelines.

For newly diagnosed patients with pulmonary TB we instituted disposable mask isolation during a 1 month period after the anti-tubercular regimen was introduced.

Discussion

Over the past two decades there has been a significant rise in the number of tuberculosis cases worldwide. The increasing incidence of human immunodeficiency virus, easy travel access between countries, and ethnic factors all contribute to the spread of the disease [7]. Statistics show that the frequency of TB among dialysis patients is significantly higher than among the general population [1]. During the decade 1995 to 2005 the annual incidence of TB among dialysis patients in our unit was 72/100,000 patients and the annual incidence of Mycobacterium other than TB was 65/100,000 patients. By comparison, from the statistics provided by the U.S. Centers for Disease Control the incidence of tuberculosis in the general population in 1995 was 7.09/100,000 in Israel, 7.44/100,000 in the United States, and 15.31/100,000 (average) in Europe.

The paucity of clinical signs and non-specific manifestations of tuberculosis in dialysis patients highlight the limitations of conventional diagnostic methods (sputum samples) for such patients. Extra-pulmonary TB is not an uncommon occurrence in dialysis patients, as demonstrated by Fang et al. [4] who recently reported a high 51% incidence of extra-pulmonary TB among dialysis patients in a Taiwan hospital. Caseating necrosis is often reduced and thus caverna is not seen [8]. Decreased cellular immunity may be due to a defect in the co-stimulatory function of antigen-presenting cells, which is caused by the uremia as well as by the dialysis treatment or malnutrition, and to immunosuppressive regimens in cases of previous kidney transplantation and progressive renal failure [9-11].

Despite the high incidence of anergy in dialysis patients, the tuberculin skin test is recommended but is not widely used for screening [4]. The data provided by Sester and colleagues [12] showed that among hemodialysis patients 51.4% tested positive compared to 85.7% among the healthy controls. Wauters et al. [9] used three consecutive boosters of purified protein derivative. The combination of the tuberculin skin test with a chest X-ray proved to be an efficient method for detecting M. *tuberculosis*. The difficulty in diagnosis and the high level of anergy require aggressive intervention. Early tissue aspiration from possible infectious sites should be performed in cases where TB cannot be excluded.

In our dialysis unit most of the patients were suffering from pulmonary TB (6 of our 10 patients). Since a number of patients were sputum smear-negative (5 of 10 patients) further tests such as pleural biopsy or pleural fluid cultures were required. One of the patients presented with respiratory failure or signs of respiratory infection resembling pneumonia and was treated with conventional antibiotics for respiratory infection. The results of the cultures of gastric juices taken from the patient on her admission were found to be positive for M. *tuberculosis* only after the patient died.

TB infection is more frequent in diabetic patients than in any other underlying disease [8]; in fact 8 of our 10 TB patients were suffering from diabetes mellitus and its complications.

An unusually high incidence of Mycobacterium other than TB (nine cases) diagnosed by sputum, urine and peritoneal fluid cultures was observed in our dialysis unit over the 10 year period under survey. These species are distributed widely in the environment. Isolation of Mycobacterium other than TB from a clinical specimen may represent true infection, colonization, or environmental contamination. Treatment is required only if there is clinical or radiological evidence of the disease [13]. Only two of our patients met these criteria and were treated for Mycobacterium other than TB, which manifests as prolonged fever, right lung pulmonary consolidation and peritonitis.

Conclusions

The diagnosis of TB in dialysis patients should be approached with a high index of suspicion. Risk factors that should be taken into consideration and immigrants from countries known to be at high risk for TB should be thoroughly investigated [7]. Minimal clinical signs and malnutrition commonly found in dialysis patients are sometimes the only evidence of the disease [14,15]. This would indicate the need for Mantoux testing and a method of temporary isolation until sputum for tuberculosis is found to be negative. The diagnosis of extra-pulmonary TB may be the most difficult to determine and requires tests such as pleural biopsy or pleural fluid cultures. New cases of TB present a further burden for the medical team and dialysis population due to the close proximity to the carrier of the disease.

In order to improve patient compliance, the required medication should be administered by the clinical staff during the dialysis session according to the literature. However, it is not always recommended to treat patients suffering from Mycobacterium

other than TB, and in asymptomatic patients no treatment should be given.

References

1. Chou KJ, Fang HC, Bai KJ, HWANG SJ, Yang WC, Chung HM. Tuberculosis in maintenance dialysis patients. *Nephron* 2001;88: 138–43.
2. Ahmed AT, Karter AJ. Tuberculosis in California dialysis patients. *Int J Tuberc Lung Dis* 2004;8:341–5.
3. Tuberculosis transmission in a renal dialysis center – Nevada, 2003. MMWR *Morb Mortal Wkly Rep* 2004;53(37):873–5.
4. Fang HC, Chou KJ, Chen CL, et al. Tuberculin skin test and anergy in dialysis patients of the tuberculosis endemic area. *Nephron* 2002;91:682–7.
5. Ko YC, Lee CT, Cheng YF, et al. Hypercalcaemia and haemophagocytic syndrome: rare concurrent presentations of disseminated tuberculosis in a dialysis patient. *Int J Clin Pract* 2004;58: 723–5.
6. Ravilione MC, O'Brien RJ. Tuberculosis. In: Harrison's Principles of Internal Medicine. 16th edn. New York: McGraw-Hill, 2005:953–66.
7. Fogazzi GB, Castelnovo C. Maintenance dialysis in patients from developing countries: the experience of an Italian center. *J Nephrol* 2004;17:552–8.
8. Tuberculosis in compromised hosts. *Kekkaku* 2003;78:717–22. (No authors listed)
9. Wauters A, Peetermans WE, Van den Brande P, et al. The value of tuberculin skin testing in haemodialysis patients. *Nephrol Dial Transplant* 2004;19:433–8.
10. Vanholder R, De Smet R, Waterloos MA, et al. Mechanisms of phagocyte reactive species production: characterization of the role of p-crezol. *Kidney Int* 1995;47:510–17.
11. Chervu I, Kiersztejn M, Alexiewicz JM, Fadda GZ, Smogorzewski M, Massry SG. Impaired phagocytosis in chronic renal failure is mediated by secondary hyperparathyroidism. *Kidney Int* 1992;41: 1501–5.
12. Sester M, Clauer P, Heine G, et al. Tuberculin skin testing underestimates a high prevalence of latent tuberculosis infection in hemodialysis patients. *Kidney Int* 2004;65:1826–34.
13. Fordham von Rein C. Nontuberculous mycobacteria. In: Harrison's Principles of Internal Medicine. 16th edn. New Cork: McGraw-Hill, 2005:972–6.
14. Korzets A, Gafter U. Tuberculosis prophylaxis for the chronically dialysed patient – yes or no? *Nephrol Dial Transplant* 1999;14:2857–9.
15. Leventhal Z, Gafter U, Zevin D, Turani H, Levi J. Tuberculosis in patients on hemodialysis. *Isr J Med Sci* 1982;18:245–7.

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