Pulmonary tuberculosis in patients with chronic renal failure at Zagazig University Hospitals

Abdelreheem I. Yousef 1, Mohamad F. Ismael 2, Ashraf E. Elshora *, Heba E. Abdou 3

Chest Department, Faculty of Medicine, Zagazig University, Egypt

Received 4 October 2013; accepted 11 November 2013
Available online 5 December 2013

Abstract The incidence of active TB and attendant mortality is increased in patients with impaired cellular immunity, such as HIV infected patients, solid organ and stem cell transplant recipients and patients with end-stage renal failure. The relative risk for TB varies with the type of immunodeficiency and mortality rates may be as high as 75%. End-stage renal disease (ESRD) and particularly uraemia is a known contributor to immunosuppression.

The aim of this work: The aim of this work was to evaluate the increasing risk of pulmonary tuberculosis among patients with chronic renal failure and the impact of hemodialysis.

Patients and methods: This study was carried at both Nephrology Unit and Chest Department, Zagazig University Hospitals during the period from April 2012 to Jan 2013. The study included a total number of 140 patients with chronic renal failure (92 males and 48 females), with mean age of 49 ± 6.4 years. Patients were classified to three groups: Group 1: Included 40 Patients with chronic renal failure and not on dialysis. Group 2: Included 50 Patients with chronic renal failure and on regular hemodialysis three sittings per week for less than 1 year. Group 3: Included 50 Patients with chronic renal failure and on regular hemodialysis three sittings per week for more than 1 year. All patients were subjected to: history taking and medical evaluation including general and local
Introduction

The incidence of active TB and attendant mortality is increased in patients with impaired cellular immunity, such as HIV infected patients, solid organ and stem cell transplant recipients, and patients with end-stage renal failure. The relative risk for TB varies with the type of immunodeficiency and mortality rates may be as high as 75% [1]. This emphasizes the particular importance of the cellular arm of the adaptive immune response for efficient control of Mycobacterium tuberculosis [1–4]. Moreover, the presence of M. tuberculosis-specific CD4+ T-cell immunity is used as a surrogate marker for a previous contact [5]. Despite the availability of highly efficacious treatment for TB, it remains a major global health problem. In 1993, the World Health Organization (WHO) declared TB a global public health emergency, at a time when an estimated 7–8 million cases and 1.3–1.6 million deaths occurred each year. In 2010, there were an estimated 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people). TB is the second leading cause of death from an infectious disease worldwide (after HIV, which caused an estimated 1.8 million deaths in 2008 [6].

It is likely that TB will be seen more frequently in patients with chronic kidney disease (CKD) as people from the areas of the world with high background levels of TB are also at increased risk of CKD [7]. Active TB in immuno-compromised patients can pose a number of challenges. Due to the impaired immune response, patients maybe clinically oligosymptomatic in the beginning of active disease, and its diagnosis is often delayed due to atypical presentations and more frequent extra-pulmonary dissemination. Active TB is further aggravated by a significantly higher morbidity due to a more fatal course in the face of a weakened immune system [1]. In addition, treatment is frequently complicated due to complex drug interactions and altered pharmaco-kinetics [2,4]. End-stage renal disease (ESRD) and particularly uraemia is a known contributor to immuno-suppression. The causative factors of the immunosupression are complex and disrupt the cell-mediated immune functions which include identification and killing of intracellular pathogens such as M. tuberculosis [8].

The aim of this work was to evaluate the increasing risk of pulmonary Tuberculosis among patients with chronic renal failure and the impact of hemodialysis.

Patients and methods

This study was carried at both Nephrology Unit and Chest Department, Zagazig University Hospitals during the period from April 2012 to Jan 2013. The study included a total number of 140 patients with chronic renal failure (92 males and 48 females), with mean age of 49 ± 6.4 years. Patients were classified to three groups:

- **Group 1**: Included 40 Patients with chronic renal failure and not on dialysis.
- **Group 2**: Included 50 Patients with chronic renal failure and on regular hemodialysis three sittings per week for less than 1 year.
- **Group 3**: Included 50 Patients with chronic renal failure and on regular hemodialysis three sittings per week for more than 1 year.

All patients were subjected to the following:

1. **History taking and medical evaluation including general and local examinations.**
2. **Laboratory investigations:**
   - Serum creatinine & blood urea.
   - ALT & AST & serum bilirubin & serum albumin.
   - Complete Blood Count (CBC).
   - Erythrocyte Sedimentation Rate (ESR).
   - Fasting & post prandial blood glucose level.
3. **Plain chest X-ray:** Postero-anterior and lateral views for all patients.
4. **Sputum Ziehl–Neelsen staining and Sputum induction in patients who had chest X-ray suspecting pulmonary TB without expectoration.** The patient was considered suspect for pulmonary tuberculosis if there were signs or symptoms consistent with pulmonary tuberculosis and had radiological picture of the chest consistent with pulmonary tuberculosis (apical infiltrations, cavitations, calcifications or hilar lymphadenopathy) with –ve sputum ZN for acid fast bacilli [9].
5. **Tuberculin skin testing (TST).**
6. **Bronchoscopy to obtain BAL for bacteriological examination for acid fast bacilli in 10 cases in whom Plain**
chance X-ray is suspect of pulmonary TB while there is no sputum production and induction of sputum failed to produce proper sample.

(7) Pleural fluid aspiration and full chemical, bacteriological and cytological examination in patients presented by pleural effusion. Abram pleural biopsies were performed in 4 patients and pleural biopsies were taken by thoracoscopy in 2 patients.

(8) Excisional cervical lymph node biopsies in 2 cases presented by cervical lymphadenopathy and sent for cytological examination.

Statistical analysis

Statistical analysis was performed with SPSS version 19 software package (SPSS, Inc. Chicago). *P* value < 0.05 was considered significant.

Results

Table 1 shows that 16 patients (11.4%) were proved to have pulmonary tuberculosis by +ve sputum ZN for acid fast bacilli in 13 patients and +ve ZN in BAL in 3 patients, 28 patients (20%) were suspected to have pulmonary tuberculosis by radiological suspension and –ve sputum ZN for acid fast bacilli, 6 patients (4.3%) were proved to have extra-pulmonary TB while 90 patients (64.3%) were free from pulmonary tuberculosis.

Table 2 shows that there were no significant differences among different groups with sputum ZN +ve but there were significant differences among suspected cases in different patient groups (*P* < 0.05). 14 patients (28%) in group III were pulmonary TB suspects, 10 patients (20%) in group II were pulmonary TB suspects and 4 patients (10%) in group I were pulmonary TB suspects.

Table 3 shows that 1 patient (2.5%) in group I had TB cervical lymphadenitis and another in the third group also had TB cervical lymphadenitis. As regards pleural effusion there were 2 patients (5%) in group I versus 1 patient in group II and another in group III.

Table 4 shows that there were 15 patients out of 140 (10.7%) diagnosed to have pleural effusion. 4 Patients out of 15 (26.7%) were tuberculous pleural effusion and 11 patients (73.3%) were non tuberculous.

Table 5 shows the frequency of each symptom in the three studied groups. The most common symptom in group I was weight loss followed by cough and haemoptysis. The most common symptom in group II was fever followed by weight loss and cough. The most common symptoms in group III was cough and haemoptysis followed by weight loss and fever.

There were highly significant differences between the three groups as regards, fever, haemoptysis and weight loss as *P* ≤ 0.001 but there were non significant differences between the three groups as regards cough.

Table 6 shows that there were no significant differences among different groups of patients with sputum ZN +ve as regards chest X-ray. In group I there was one patient (16.6%) with normal plain chest X-ray, two patients (33.3%) with mild lesion, two patients (33.3%) with moderate lesion and one patient (16.6%) with far advanced lesion. In group II there were two patients (50%) with mild lesion and two patients (50%) with lesion infection. In group III there was one patient (16.6%) with normal plain chest X-ray, two patients (33.3%) with mild lesion, two patients (33.3%) with moderate lesion and one patient (16.6%) with far advanced lesion.

Table 7 shows that there were no significant differences among different groups of pulmonary tuberculosis patients.

<table>
<thead>
<tr>
<th>Table 1 Percentage distribution of all studied patients according to their infection by <em>Mycobacterium tuberculosis</em>.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (140)</strong></td>
</tr>
<tr>
<td>Pulmonary TB</td>
</tr>
<tr>
<td>Suspect pulmonary TB</td>
</tr>
<tr>
<td>Extra-pulmonary TB</td>
</tr>
<tr>
<td>Free from TB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 Percentage distribution of proved and suspected pulmonary TB cases in different patients groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI 40</strong></td>
</tr>
<tr>
<td>Tuberculous (ZN + ve)</td>
</tr>
<tr>
<td>Suspect (ZN – ve)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3 Percentage distribution of extra-pulmonary TB in different patient groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI 40</strong></td>
</tr>
<tr>
<td>Cervical lymphadenitis (2)</td>
</tr>
<tr>
<td>Plural effusion (4)</td>
</tr>
</tbody>
</table>
as regards blood urea but there were highly significant differences ($P < 0.001$) as regards serum creatinine levels with the highest value in GIII.

Table 8 shows that there were no significant differences among different groups of all studied according to their co-morbidity. The most common co-morbidity in all groups was diabetes mellitus as in group I there were 11 patients (27.5%) who were diabetics, in group II there were 14 patients (28%) who were diabetics and in group III there were 15 patients (30%) who were diabetics and these results are statistically significant ($P < 0.05$). As regards hepatic diseases there were 7 patients (17.5%) in group I, 13 patients (26%) in group II and 12 patients (24%) in group III. As regards cardiac diseases there were 4 patients (10%) in group I, 6 patients (12%) in group II and 8 patients (18.2%) in group III.

Table 9 shows that there were significant differences between different groups as regards co-morbidity with DM and hepatic affection. In group I there were 4 patients (66.6%) who were diabetics and 1 patient (16.7%) was having hepatic disease. In group II there were 2 patients (50%) who were diabetics and 1 patient (25%) was hepatic. In group III there were 3 patients (50%) who were diabetics and 2 patients (33.3%) hepatic. There were non significant differences between the three groups as regards cardiac co-morbidity. Diabetes mellitus was the most common co-morbid disease in all patient groups followed by hepatic then cardiac co-morbidity.

### Discussion

Patients with End Stage Renal Disease (ESRD) undergoing chronic dialysis are 6–25 times more likely to develop tuberculosis (TB) than the general population, mainly because of the impaired cellular immunity characteristic of this condition. Nosocomial transmission of TB has also been reported in hemodialysis (HD) centers. In a US Renal Data System (USRDS) retrospective analysis, age, unemployement, smoking, reduced body mass index, low serum albumin, ischemic heart disease, and anemia were all significant risk factors for HD patients to develop TB [10]. End-stage renal disease (ESRD) and particularly uraemia is a known contributor to immuno-suppression. The causative factors of the
immunosuppression are complex and disrupt the cell-mediated immune (CMI) response. T-cells are primarily responsible for CMI and their functions include identification and killing of intracellular pathogens such as \textit{M. tuberculosis}. It is the delayed type hypersensitivity response of the CMI system that is responsible for the reaction to the tuberculin skin test. Therefore, while new methods for determining infection with TB are developed, identifying risk factors for TB among this population may aid in developing appropriate counseling and more targeted screening [8]. There is a 10% increased risk of TB in the chronic renal failure patients on hemodialysis. It is likely that the proximity of the patients to each other during frequent contacts, suboptimal isolation and screening limited to tuberculin skin test (TST) and chest X-ray (CXR) contribute to this risk [11].

In our study we have found that 16 patients (11.4\%) proved to have pulmonary tuberculosis by +ve sputum ZN for acid fast bacilli and 28 patients (20\%) were suspected to have pulmonary tuberculosis by radiological suspension and –ve sputum ZN for acid fast bacilli and 6 patients (4.3\%) proved to have extra-pulmonary TB (Table 1 and 2). The sex patients with extra-pulmonary TB were diagnosed as cervical lymphadenitis (2 patients) and pleural effusion (4 patients) (Table 3).

In ESRD, the diagnosis of TB disease is often difficult because of prevailing extrapulmonary involvement and nonspecific symptoms. Extrapulmonary TB has been reported in as many as 60–80\% of cases, either alone or associated with pulmonary TB. The most common forms of presentation are lymphadenitis, gastrointestinal, bone, genitourinary, peritoneal, pleural effusion, pericardial effusion, military TB, and pyrexia of unknown origin [12]. In immunocompromised hosts, the presentation of Extrapulmonary TB is often different compared to immuno-competent hosts. Dissemination of the disease is more common and clinicians should be aware of other localizations. Dissemination is more likely because ill-formed granulomata are more common in immunocompromised hosts [13].

Hussein et al. 2003, reported that TB is generally diagnosed in the first year after beginning dialysis, and this is attributed to the seriously impaired host defense mechanism in these patients during the initial dialysis period [14].

In our study there were no significant differences among different groups with sputum zn +ve but there were significant differences among suspected cases in different patient groups \((P < 0.05)\) as the numbers of suspected TB cases were more in group three in whom dialysis was performed for more than 1 year (Table 2).

Atypical manifestations of the disease are observed in 20–22\% of cases [15].

In our study there were highly significant differences between different groups as regards, fever, haemoptysis and weight loss as \(P < 0.001\) but there were non significant differences between the three groups as regards cough. The most common symptom in group I were weight loss followed by cough and haemoptysis. The most common symptom in group II was fever followed by weight loss and cough. The most common symptoms in group III were cough and haemoptysis followed by weight loss and fever (Table 5).

The possibility of TB should always be considered in any patient with a chronic cough, unexplained weight loss or night sweats, a cloudy peritoneal dialysate, lymphadenopathy or chronic site-specific symptoms.Appearances on a chest radiograph should be compared with previous films and, if new abnormalities are present, advice should be sought from a respiratory physician. Every effort should be made to obtain a specimen for culture and sensitivity. Histological Appearances of granulomata, with or without caseation or necrosis, are helpful [16]. Uremia is commonly associated with fatigue, mal-nutrition, and other nonspecific complaints, possibly concealing the course of an underlying TB disease. This atypical presentation may often lead to a delay in accurate diagnosis and therapy, sometimes resulting in patient death. Therefore, nephrologists should always have a high degree of suspicion and consider the possibility of TB whenever confronted with an ESRD patient presenting with general symptoms such as fever, weight loss, and/or lymphadenopathy. The diagnosis would then require the isolation of acid-fast bacilli, the finding of typical caseating granuloma on biopsy, or the recovery of tubercle bacilli from the culture of the biopsy material [17].

TB progress insidiously in ESRD patients. The most common symptoms are non specific and mimic uraemia (such as fever, malaise and weight loss) [14].

We have found in our study one patient in group I and another one in group III with normal plain chest X-ray and sputum ZN +ve for acid fast bacilli (Table 6). Pulmonary TB in the presence of a normal chest X-ray has been reported previously [18]. A normal chest radiograph has a high negative predictive value for the presence of active TB. However, the frequency of false-negative examinations is approximately 1\% in the adult immunocompetent population and increases to 7–15\% in HIV-seropositive individuals [19]. Darcy et al., had found that the incidence of smear-positive pulmonary TB with a normal chest radiograph was \(\leq1\%\) in the period from 1988 to 1989 and steadily increased to 10\% in the period from 1996 to 1997 [20].

Conclusion

Patients with chronic renal failure are at increased risk for pulmonary and extra pulmonary tuberculosis and should be screened routinely and carefully for early detection of TB infection.

Conflict of interest

None declared.

References