Mycobacterium Tuberculosis Infection Following Kidney Transplantation

Karima Boubaker*, Ezzedine Abderrahim, Taieb Ben Abdallah, Adel Kheder

Internal Medicine Department, Charles Nicole Hospital, Tunis
*Corresponding author: ranou04@yahoo.fr

Received June 05, 2013; Revised August 16, 2013; Accepted October 16, 2013

Abstract Tuberculosis (TB) is one of the major causes of morbidity and mortality worldwide. Post-transplant TB is a problem in successful long-term outcome of renal transplantation recipients. It is a life-threatening opportunistic infection that is frequently encountered, but the diagnosis is often delayed. With the emergence of newer potent immunosuppressive regimens and an increased incidence of TB in the general population, post-transplant TB among transplant recipients can be anticipated. Our objective was to describe the pattern and risk factors of TB infection, and the prognosis in our transplant recipients. This study was a retrospective review of the records of 491 renal transplant recipients in our hospital during the period from January 1986 to December 2009. The demographic data, transplant characteristics, clinical manifestations, diagnostic criteria, treatment protocol, and long-term outcome of this cohort of patients were analyzed. 16 patients (3.2%) developed posttransplant TB with a mean age of 32.5 ± 12.7 (range: 13-60) years and a mean post-transplant period of 36.6 months (range: 12.3 months – 15.9 years). The forms of the diseases were pulmonary in 10/16 (62.6%), disseminated in 3/16 (18.7%) and extrapulmonary in 3/16 (18.7%). All patients initially received 4-drug combination therapy. Because of drug interaction, an increase in the dose of calcineurium inhibitor and steroid was done in 2 cases and in steroids alone in 1 case. Graft dysfunction was observed in 7 cases (43.7%) with tissue-proof acute rejection in 3 cases and loss of the graft in 4 cases. Hepatotoxicity developed in 3 patients (18.7%) during treatment. Recurrence were observed in 4 cases after early stop of treatment. Two patients (12.5%) died. Extrapulmonary and disseminated tuberculosis were observed in third of our patients. More than 9 months of treatment may be necessary to prevent recurrence.

Keywords: kidney transplantation, tuberculosis

Cite This Article: Karima Boubaker, Ezzedine Abderrahim, Taieb Ben Abdallah, and Adel Kheder, “Mycobacterium Tuberculosis Infection Following Kidney Transplantation.” American Journal of Medical Sciences and Medicine 1, no. 5 (2013): 75-82. doi: 10.12691/ajmsm-1-5-1.

1. Introduction

Tuberculosis (TB) is an opportunistic infectious disease with obligatory declaration, caused by Mycobacterium tuberculosis discovered by German Robert Koch in 1882 from where name bacillus of Koch (abbreviation BK).

TB is the most important infectious disease in humans and is endemic in many developing countries [1,2], with a prevalence estimated at 27.07/100 000 inhabitants in 1995 in Tunisia [3]. In situations wherein the immune system becomes impaired such as acquired human deficiency syndrome (AIDS), chronic renal failure or organ transplant recipients treated by immunosuppressive drugs, TB is a major problem and the key to controlling is rapid detection.

The TB incidence in kidney recipient patients is 20 to 74 times greater than that among the general population [4]. This is due to iatrogenic immunosuppression in transplant recipients which accounts for a progressive impairment in cellular immune function allowing the development of BK which is an intracellular germ [5,6]. Post-transplant TB is a problem in successful long-term outcome of kidney transplant recipients and is a life-threatening infection. However, its diagnosis is often delayed.

With the emergence of newer potent immunosuppressive regimens and an increased incidence of TB in the general population, TB among kidney transplant recipients can be anticipated.

This study tried to examine the prevalence, course, and outcome of TB in our kidney transplant recipients.

2. Patients and Methods

2.1. Patients

In this retrospective study, we reviewed medical records of 491 renal transplant recipients in our department from June 1986 date of the first kidney transplantation to December 2009.

The criteria of exclusion were onset of tuberculosis before kidney transplantation or after 3 months of the return in dialysis.

Sixteen patients received treatment for TB. Diagnosis of TB was made on bacteriological, histological and/or therapeutic proof, or in front of the association of clinical, biological and/or radiological elements of presumption.
2.2. Methods
The bacteriological analysis included using direct light microscopy to reveal acid-fast-bacilli (AFB) in at least 1 Ziehl-Neelsen-stained respiratory tract secretion, urine or other biological liquid sample or positive cultures for the etiologic pathogen on a special medium of Löwenstein or other biological liquid sample or positive cultures for the TB therapy and mortality.

The histological analysis was the presence of a gigantocellular granuloma with necroses caseous on the liquid of puncture or a fragment coming from an organ biopsy.

The following data were obtained from each patient’s medical record: patient demographics (age and sex), presence of another comorbid disease or pre-existing risk-factors for TB infection, symptoms (Fever, cough, impairment of general state), urine exam, biology factors for TB infection, symptoms (Fever, couph, puncture or a fragment coming from an organ biopsy. cellular granuloma with necroses caseous on the liquid of presence of another comorbid disease or pre-existing risk factors, medical record: patient demographics (age and sex), ALS: anti-lymphocyte serum, AR: acute rejection, AZT: azathioprin, ciclo: ciclosporine, Creat: creatininemia, CS : steroids, F: female, HC: hepatitis C infection, M: male, MMF : mycophenolate mofetil, TB: tuberculosis, Ttt: Treatment.

Table 2. Epidemiological, clinical and biological characteristics of TB kidney recipients patients before diagnosis of TB

<table>
<thead>
<tr>
<th>Name</th>
<th>sex</th>
<th>age</th>
<th>previous history of TB and direct contact with a TB carrier</th>
<th>Nephropathy</th>
<th>Time spent on dialysis (years)</th>
<th>Donor</th>
<th>Immunosuppressive regimen</th>
<th>AR</th>
<th>Tit of AR</th>
<th>HC</th>
<th>Diabetes</th>
<th>Creat µmo/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- A M</td>
<td>F</td>
<td>14</td>
<td>-</td>
<td>unknown</td>
<td>39,688</td>
<td>Cadaver 38 years</td>
<td>CS+MMF</td>
<td>1</td>
<td>ALS</td>
<td>CS</td>
<td>Non</td>
<td>Non</td>
</tr>
<tr>
<td>2- A H</td>
<td>M</td>
<td>32</td>
<td>-</td>
<td>interstitial</td>
<td>25,068</td>
<td>Mother 61 years</td>
<td>CS + AZT</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>140</td>
</tr>
<tr>
<td>3- Z A</td>
<td>M</td>
<td>42</td>
<td>-</td>
<td>glomerular</td>
<td>39,951</td>
<td>Brother 50 years</td>
<td>CS+AZT</td>
<td>1</td>
<td>ALS</td>
<td>+CS</td>
<td>Non</td>
<td>Non</td>
</tr>
<tr>
<td>4- Gh N</td>
<td>F</td>
<td>34</td>
<td>husband</td>
<td>interstitial</td>
<td>23,359</td>
<td>Mother 65 years</td>
<td>CS+AZT</td>
<td>1</td>
<td>ALS</td>
<td>+CS</td>
<td>Non</td>
<td>Non</td>
</tr>
<tr>
<td>5- D Y</td>
<td>M</td>
<td>60</td>
<td>-</td>
<td>diabetic</td>
<td>25,823</td>
<td>Wife 54 years</td>
<td>CS+MMF</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Oui</td>
<td>150</td>
</tr>
<tr>
<td>6- H O</td>
<td>M</td>
<td>22</td>
<td>-</td>
<td>lupic</td>
<td>14,324</td>
<td>Sister 39 years</td>
<td>CS+ MMF</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>128</td>
</tr>
<tr>
<td>7- M D</td>
<td>M</td>
<td>34</td>
<td>-</td>
<td>glomerular</td>
<td>13,996</td>
<td>Sister 32 years</td>
<td>CS+ ciclo+AZT</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>90</td>
</tr>
<tr>
<td>8- H A</td>
<td>M</td>
<td>22</td>
<td>-</td>
<td>interstitial</td>
<td>31,836</td>
<td>Mère 57 ans</td>
<td>CS+tacrolimus+MMF</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>128</td>
</tr>
<tr>
<td>9- M A</td>
<td>M</td>
<td>51</td>
<td>-</td>
<td>Urogenital</td>
<td>99,745</td>
<td>Brother 30 years</td>
<td>CS+ciclo</td>
<td>0</td>
<td>-</td>
<td>Oui</td>
<td>Non</td>
<td>96</td>
</tr>
<tr>
<td>10- M F</td>
<td>M</td>
<td>27</td>
<td>-</td>
<td>hypertension</td>
<td>17,018</td>
<td>Mother 46 years</td>
<td>CS+AZT</td>
<td>2</td>
<td>ALS</td>
<td>+CS</td>
<td>CS</td>
<td>Non</td>
</tr>
<tr>
<td>11- H Dh</td>
<td>M</td>
<td>13</td>
<td>-</td>
<td>interstitial</td>
<td>25,462</td>
<td>Cadaver 27 years</td>
<td>CS+cielo+MMF</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>118</td>
</tr>
<tr>
<td>12- M A</td>
<td>M</td>
<td>19</td>
<td>brother</td>
<td>unknown</td>
<td>20,337</td>
<td>Mother 40 years</td>
<td>CS + MMF</td>
<td>0</td>
<td>-</td>
<td>Non</td>
<td>Non</td>
<td>90</td>
</tr>
<tr>
<td>13- J K</td>
<td>M</td>
<td>37</td>
<td>-</td>
<td>unknown</td>
<td>188,386</td>
<td>Sister 43 years</td>
<td>CS+tacrolimus+MMF</td>
<td>1</td>
<td>SAL+CS</td>
<td>EP</td>
<td>Oui</td>
<td>Non</td>
</tr>
<tr>
<td>14- Ch N</td>
<td>M</td>
<td>39</td>
<td>-</td>
<td>glomerular</td>
<td>18,957</td>
<td>Brother 34 years</td>
<td>CS+AZT</td>
<td>1</td>
<td>ALS</td>
<td>+CS</td>
<td>Non</td>
<td>Non</td>
</tr>
<tr>
<td>15- B F</td>
<td>M</td>
<td>36</td>
<td>-</td>
<td>glomerular</td>
<td>18,858</td>
<td>Sister 30 years</td>
<td>CS+ciclo + AZT</td>
<td>1</td>
<td>ALS</td>
<td>+CS</td>
<td>Oui</td>
<td>Oui</td>
</tr>
<tr>
<td>16- J H</td>
<td>M</td>
<td>38</td>
<td>-</td>
<td>glomerular</td>
<td>22,045</td>
<td>Sister 36 years</td>
<td>CS+MMF</td>
<td>0</td>
<td>-</td>
<td>Oui</td>
<td>Oui</td>
<td>187</td>
</tr>
</tbody>
</table>

3. Results

Sixteen patients (3.2%) developed posttransplant TB. The overall incidence of TB was 72/100 kidney transplant recipient/year (Table 2).

They were 14 men and 2 women. Mean age was 32.5 ± 12.7 (range: 13 - 60) years. Median age was 34 years and 62% of patients were aged more than 30 years.

A previous history of urogenital TB was found in 1 case and direct contact with a TB carrier in 2 cases. Blood group was A in 2 cases, B in 1 case, AB in 3 cases and O in 10 cases.

Causes of end stage renal stage were glomerulonephritis in 5 cases, diabetic nephrpathy in 1 case, lupus nephritis in 1 case, interstitial nephritis in 4 cases, hypertension in 1 case and unknown in 4 cases. Time spent on dialysis was 38.6 months (10.3 months- 21.1 years). It is significantly higher than controls (38.6 years Versus 27.4 years, p=0.27). Initial immunosuppressive regimen a ssociated higher than controls (38.6 years Versus 27.4 years, p=0.27).

Diabetes was observed in 3 cases and hepatitis C in 4 cases. Seven patients presented an acute rejection before diagnosis of TB. There was only one episode of acute rejection in 5 cases and 2 episodes in 1 case. TB patients were not significantly different from controls by means of diabetes and acute rejection.

Mean interval between kidney transplantation and TB diagnosis was 36.6 months (range: 12.3 months - 15.9 years) with median of 23.6 months.

Clinical picture associated unexplained and moderate fever in 15 cases (93.7 %), pleuritic syndrome in 3 cases and a pulmonary infection resistant to antibiotics in 1 case.

At biology, sterile leukocyturia was noted in 2 cases, graft dysfunction in 5 cases, biological inflammatory syndrome in 12 cases and pancytopenia in 1 case.

Bacteriological analysis confirmed TB diagnosis in 9 cases (AFB at direct light microscopy in 7 cases, positive culture in 9 cases).

A coinfection with candida albicans was found in 1 case, with cytomegalovirus in 1 case and with aspergillus in another case.

Tuberculin skin test done in 5 cases was positive in 2 cases.

Radiographic patterns showed abnormalities in all cases with miliary pattern in 3 cases, pleural effusion in 5 cases, cavitation in 1 case, nodules in 2 cases, pulmonary infiltrate in 6 cases, mediastinal lymphadenopathy in 2 cases and spondylodiscitis L5 in 1 case.

Diagnosis of tuberculosis was confirmed only in 14 cases, on bacteriological proof in 9 cases and on histological proof in 5 cases.

<table>
<thead>
<tr>
<th>Name</th>
<th>Interval KT / TB (years)</th>
<th>circumstances of discovery and clinical picture</th>
<th>Biology</th>
<th>Creat µmol/l</th>
<th>Radiology</th>
<th>Proof</th>
<th>Localization (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-A M</td>
<td>9,561</td>
<td>Fever, Low bak pain</td>
<td>BIS</td>
<td>227</td>
<td>Pulmonary infiltrate</td>
<td>Bacteriological</td>
<td>Urinary and pulmonary</td>
</tr>
<tr>
<td>2-A H</td>
<td>13,339</td>
<td>Fever, Impairment of general state</td>
<td>ARF</td>
<td>170</td>
<td>Pleuritic effusion</td>
<td>histological</td>
<td>pulmonary</td>
</tr>
<tr>
<td>3-Z A</td>
<td>253,503</td>
<td>Fever</td>
<td>ARF</td>
<td>500</td>
<td>Pulmonary infiltrate</td>
<td>Bacteriological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>4-Gh N</td>
<td>62,489</td>
<td>Fever, Impairment of general state</td>
<td>BIS</td>
<td>134</td>
<td>Miliary</td>
<td>Pleuritic effusion</td>
<td>histological</td>
</tr>
<tr>
<td>5-D Y</td>
<td>28,452</td>
<td>Fever</td>
<td>BIS</td>
<td>147</td>
<td>Nodules</td>
<td>histological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>6-H O</td>
<td>9,396</td>
<td>Fever, Impairment of general state</td>
<td>BIS</td>
<td>115</td>
<td>Pleuritic effusion</td>
<td>histological</td>
<td>Pleural</td>
</tr>
<tr>
<td>7-D M</td>
<td>6,505</td>
<td>Fever, pancytopenia</td>
<td></td>
<td>100</td>
<td>normal</td>
<td>histological</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>8-H A</td>
<td>7,984</td>
<td>Fever, Chest pain Pleuritic syndrom</td>
<td>BIS ARF</td>
<td>164</td>
<td>Pleuritic effusion</td>
<td>histological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>9-M A</td>
<td>3,154</td>
<td>fever Impairment of general state</td>
<td>BIS Sterile leukocyturia</td>
<td>98</td>
<td>Hilar calcification</td>
<td>Bacteriological</td>
<td>Urinary</td>
</tr>
<tr>
<td>10-M F</td>
<td>164,271</td>
<td>Fever, Chest pain</td>
<td>SIB</td>
<td>472</td>
<td>Pulmonary infiltrate</td>
<td>Bacteriological</td>
<td>Pulmonary and meningeal</td>
</tr>
<tr>
<td>11-H Dh</td>
<td>2,825</td>
<td>Fever</td>
<td>SIB anemia</td>
<td>101</td>
<td>Nodule Pulmonary infiltrate Mediastinal lymphadenopathy</td>
<td>Bacteriological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>12-M A</td>
<td>79,047</td>
<td>Fever, cough, Impairment of general state</td>
<td>SIB</td>
<td>114</td>
<td>Pleuritic effusion</td>
<td>0</td>
<td>Pleural</td>
</tr>
<tr>
<td>13-J K</td>
<td>1,544</td>
<td>Fever</td>
<td>Sterile leukocyturia ARF, BIS</td>
<td>177</td>
<td>normal</td>
<td>Bacteriological</td>
<td>Pulmonary and urinary</td>
</tr>
<tr>
<td>14-Ch N</td>
<td>117,257</td>
<td>Fever</td>
<td>ARF</td>
<td>288</td>
<td>Mediastinal lymphadenopathy</td>
<td>Bacteriological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>15-B F</td>
<td>3,811</td>
<td>Fever, Cough pulmonary infection resistant to AB</td>
<td>BIS</td>
<td>112</td>
<td>Nodule miliary</td>
<td>Bacteriological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>16-J H</td>
<td>93,700</td>
<td>Fever</td>
<td>BIS</td>
<td>400</td>
<td>cavern Pulmonary infiltrate</td>
<td>Bacteriological</td>
<td>Pulmonary</td>
</tr>
</tbody>
</table>

Pulmonary localization of TB was the most frequent observed in 62.6% of cases. (Figure 1, Figure 2).

Extrapulmonary localization was observed in 3 cases (18.7%) and disseminated TB in 3 cases (18.7%) (Table 3).

All patients initially received 4-drug combination therapy which associated Isoniazid, Rifampicin, Ethambutol and Pyrazinamide during 2 months relayed then by a daily therapy by isoniazid and the rifampicine. The average total duration of the treatment was 10.3 ± 3.5 months (1 - 17 months) (Table 4).

Because of drug interaction, an increase in the dose of calcineurium inhibitor and steroid was done in 2 cases and in steroids alone in 1 case (Table 4).

All patients were followed up. After a mean follow up of 291.3 months (88- 755 months), recovery of TB was obtained in 8 cases, graft dysfunction in 7 cases (43.7%)
with tissue-proof acute rejection in 3 cases and loss of the graft in 4 cases (Table 4).

Hepatotoxicity observed in 3 cases and hyperuricemia in 4 cases were reversible after stop of treatment (Table 4).

Death was observed in 2 patients (12.5%) and was related to TB complications.

Post transplantantion TB is predominantly the result of reactivation of an earlier quiescent TB focus [11] with an exsudative form during the early post-transplantation period [2]. Then, chronic renal failure patients who are awaiting transplantation should be carefully evaluated for previous TB anamnesis and family history. Rarely, in less than five percent of patients, TB is caused by nosocomial acquisition or donor transmission [12,13].

Risk factors of TB transmission to kidney transplant recipients are direct contact with a TB carrier (17), Blood group AB (18), hepatitis C (19), and allograft dysfunction with creatininemia higher than 1.5 mg/dl [14,19].

Prolonged duration of pretransplant hemodialysis is associated with increased risk of developing TB because

### Table 4. AntiTB treatment and course of patients

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of antiTB (months)</th>
<th>Course</th>
<th>Recurrence of TB</th>
<th>Interval between stop of TB and recurrence</th>
<th>Duration of resumption of antiTB treatment (months)</th>
<th>Follow-up (months)</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- A M</td>
<td>6</td>
<td>ARF, DCG Loss of graft</td>
<td>Lumbar pain and radiologic abnormalities</td>
<td></td>
<td>12</td>
<td>9,363</td>
<td>HD</td>
</tr>
<tr>
<td>2- A H</td>
<td>12</td>
<td>hepatotoxicity hyperuricemia</td>
<td>Lymph nodes TB</td>
<td></td>
<td>12</td>
<td>213,717</td>
<td>Recovery</td>
</tr>
<tr>
<td>3- Z A</td>
<td>12</td>
<td>ARF CAD</td>
<td>meningeal and vertebral TB after stop of ttt</td>
<td></td>
<td>-</td>
<td>1,150</td>
<td>Recovery</td>
</tr>
<tr>
<td>4- Gh N</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>26,809</td>
<td>CAD</td>
</tr>
<tr>
<td>5- D Y</td>
<td>10</td>
<td>ARF, CAD</td>
<td>-</td>
<td></td>
<td>-</td>
<td>23,918</td>
<td>Death</td>
</tr>
<tr>
<td>6- H Q</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>26,809</td>
<td>CAD</td>
</tr>
<tr>
<td>7- D M</td>
<td>12</td>
<td>Hepatotoxicity</td>
<td>Lymph nodes TB, 6 months after stop of ttt</td>
<td></td>
<td>12</td>
<td>149,881</td>
<td>Recovery</td>
</tr>
<tr>
<td>8- H A</td>
<td>12</td>
<td>ARF</td>
<td>-</td>
<td></td>
<td>-</td>
<td>20,337</td>
<td>Recovery</td>
</tr>
<tr>
<td>9- M A</td>
<td>10</td>
<td>Hepatotoxicity Hyperuricemia</td>
<td>-</td>
<td></td>
<td>-</td>
<td>58,251</td>
<td>Recovery</td>
</tr>
<tr>
<td>10- M F</td>
<td>1</td>
<td>CAD</td>
<td>-</td>
<td></td>
<td>-</td>
<td>1,577</td>
<td>Death</td>
</tr>
<tr>
<td>11-H Dh</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>9,626</td>
<td>Recovery</td>
</tr>
<tr>
<td>12- M A</td>
<td>12</td>
<td>Hyperuricemia</td>
<td>-</td>
<td></td>
<td>-</td>
<td>1,657</td>
<td>Recovery</td>
</tr>
<tr>
<td>13- J K</td>
<td>12</td>
<td>ARF CAD</td>
<td>-</td>
<td></td>
<td>-</td>
<td>35,055</td>
<td>CAD</td>
</tr>
<tr>
<td>14- Ch N</td>
<td>12</td>
<td>CAD</td>
<td>-</td>
<td></td>
<td>-</td>
<td>47,441</td>
<td>HD</td>
</tr>
<tr>
<td>15- B F</td>
<td>17</td>
<td>ARF</td>
<td>-</td>
<td></td>
<td>-</td>
<td>173,602</td>
<td>Recovery</td>
</tr>
<tr>
<td>16- J H</td>
<td>10</td>
<td>hyperuricemia ARF CAD</td>
<td>-</td>
<td></td>
<td>-</td>
<td>18,201</td>
<td>HD</td>
</tr>
</tbody>
</table>


### 4. Discussion

TB in the kidney transplant recipients in our department displayed the following characteristics:

High incidence within a short time after transplantation with 50 % of patients were diagnosed within the first 2 years post-transplant, high co-infection rate (18,7%). Fever was the most common clinical manifestation (93,7%). Graft dysfunction (43,7%), liver function damage (18,7%) and hyperuricemia (25%) were the main adverse effects of anti-TB treatment. Mortality of patients reached up to 12,5 %.

We found that prevalence of TB was 3,2%, lower to the prevalence observed in developing countries (11,8 to 13,3%) [4,8]. Prevalence of latent tuberculosis is even higher [9].

TB incidence was 72/100 kidney transplant recipient/year, 25 fold higher than among the Tunisian population (17 /100 000 inhabitant /year) (10). It reaches the incidence observed in developing countries which is 20 to 74 fold higher than among the general population [4,8].

Annual incidence of TB is 0.47% among kidney transplant recipients [4].

TB patients were not significantly different from controls by means of graft and patient survival (Table 4).

Recurrence of TB was observed in 4 cases after early stop of treatment (Table 4).
uremia altere phagocytosis, bactericidal activity and lymphocyte transformation. However, it was not been found as a risk factor in our study.

Previous history of TB is controverse in the development of post kidney transplantation TB [14,17]. However, in some studies, 9.5% to 13.5% of kidney transplant recipients had previous history of TB [4,20].

Diabetes and more than 3 episodes of acute rejection were not been found as risk factors of TB in our study.

Immunosuppressive drugs used in these patients explain the increased incidence of TB [14]. Higher doses of steroids prescribed for long course [21], mycophenolate mofetil more than one year [2] in switch to azathioprine [22], Tacrolimus [18,23] and anti-lymphocyte serum [21] are associated with high risk of TB. However, Campath (alemtuzumab) does not increase the incidence of TB [24].

The clinical features of TB can be unusual and may be masked by the blunted response to infection. Common clinical abnormalities include pyrexia, pulmonary infiltrates, exudative pleural effusion, and exudative ascites. In our study, moderate and permanent fever of unknown origin was observed in 93.7% of cases versus 71% to 82.9 % in literature [4,25,26,27]. Impairment of the general state was observed in 31.2% patients in our study versus 40 % in literature [27,28].

Pulmonary TB was observed in 62.6% of our patients. It continues to be the most common form in kidney transplant recipients [29]. Pulmonary signs were observed in 37.5% of the cases particularly coughing (12.5 % of the patients) versus 56.1% in literature accompanied by spittles in 39 % of the cases [26]. No case of hemoptysis was reported in our study while they are observed in 20 % in other studies [30].

Chest X-ray is abnormal in 81.2% of our patients showing pulmonary infiltrates in 37.5% of cases versus 60% in literature, nodules, cavities in 6,2% of cases versus 10% in literature, miliary pattern, pleural effusion, mediastinal lymphadenopathy and/or spondiolodiscitis [4,31].

Extrapulmonary presentations of TB are more frequent in kidney transplant recipients compared to immunocompetent patients, observed in 18,7% of cases in our study versus 28.6 to 50% in other studies [4,32,33]. Extra pulmonary symptoms are sometimes atypical such as an unusual gastro-intestinal symptomatology, skin lesions not improved by antibiotics and/or dissemination [16,31,34].

Genitourinary TB that occurs after kidney transplantation is uncommon and appears to present differently than genitourinary TB in the non-transplant population [31,35,36]. It has a different clinicoradiological presentation with predominance of systemic symptoms, disseminated TB, multiple parenchymatous renal foci, and lower frequency of lesions of the collecting system [31].

Predominantly parenchymatous renal involvement was more frequent in immunocompromised patients, who also had lower frequency of stenosis of the collecting system and contracted bladder [31,37].

Genitourinary symptoms are more likely to be found in immunocompetent patients with TB of the renal system than in immunocompromised hosts. Our 2 kidney transplant recipients with genitourinary TB did not presented with urinary symptoms. They had only fever and sterile leukocyturia.

TB localized to the renal allograft is an unusual presentation of TB may be the cause of graft rejection and loss [38]. The allograft biopsy is helpful when other investigations are inconclusive with symptoms of allograft dysfunction [2]. Histology shows, in this form, granuloma suggestive of TB [2,25,39].

Cerebral TB can be revealed by an intracranial haemorrhage [40]. In our case of meningeal TB, the patient presented confusion.

Disseminated TB is 3 times more frequent in kidney transplant recipients compared to patients without immunosuppression, accounting for 18,7% of cases in our study and 23.8 to 62.5% of cases in other studies [4,5,31,38]. This increased frequency of disseminated TB is explained by the fact that, in the context of immunosuppression, TB behaves as a severe bacterial infection, with bacteremia and visceral metastatic foci [31].

75% of our patients had biological inflammatory syndrome. The measurement of C Reactive protein which is a protein of the inflammation levels may be a useful tool for differentiating bacterial or TB infection from CMV infection in kidney transplant recipients. Patients with TB and bacterial infection presented lower levels of CRP than patients with CMV disease [41].

In our study, a bacteriological or histological confirmation was obtained in 75% of the cases. A treatment with quinolones, which is a second line anti-TB drugs, can negative AFB at Ziehl-Neelsen- stained smear using direct light microscopy [2].

Indeed, only a positive culture of BK confirms the diagnosis of TB in 35.71% of the cases [42] because we can not differentiate between AFB (Acid Fast Bacilli) and atypical mycobacterium at Ziehl-Neelsen- stained smear. However, only one AFB in only one field is enough with the startup to the anti-TB treatment while waiting for the culture.

Tuberculin skin test is not helpful in the majority of patients because it has low sensitivity and specificity. Low sensitivity of 50% for predicting post-transplant TB is explained by anergy due to deterioration of cellular immunity particularly in poor-nourished and anaemic patients, males, elderly, smokers, patients with hepatic pathology, peptic ulcer and/or prolonged duration of pretransplant hemodialysis [43,44,45,46]. Sensitivity of skin-test increases to 75% in kidney transplant recipients after exclusion of patients with anergy [9,26,34]. The sensitivity of the skin-test is not affected by Bacillus-Calmette - Guerin (BCG) vaccine [43]. Low specificity of 52% for predicting post-transplant TB is explained by higher positivity of the test in the endemic countries [9,26,43].

Being given that we are an endemic country of TB and to increase sensitivity and specificity, it is necessary to increase doses of tuberkulin at 10 units [7], repeat the skin-test if the first injection or the reading is nonsatisfactory [47]. Nutritional status (haemoglobin, albumin and creatinine) should be improved and time spent on dialysis should be reduced [43]. Moreover, to increase the skin-test specificity by distinguishing between latent TB infection from BCG-induced reactivity, T-cell reactivity towards early secretory antigenic target-6 (ESAT-6), a protein specific for mycobacterium tuberculosis but absent from the BCG-vaccine strain, is found in 52.9% of all individuals with purified protein-derivative (PPD)-reactivity in vitro [9].
The diagnosis of genitourinary TB is made by urine cultures done for the detection of mycobacteria. Because of the delay inherent in diagnosis by culture, rapid testing methods for identification of mycobacterium tuberculosis such as Polymerase Chain reaction analysis of the ureines which made diagnosis of TB in 17.86% of the cases or DNA probing of urine should be employed [29,42].

Aggressive investigations must be done in patients with pyrexia, pulmonary abnormalities, scanty sputum, and weight loss and whose diagnosis was not confirmed by bacteriology [11,48]. X-ray and computed tomography scan with puncture and/or biopsy of the chest should be done in such cases.

A coinfection with candida albicans, cytomegalovirus and aspergillus was observed in 18,7% of cases versus to the data of literature which is of 19, 5% of cases. Other coinfections with pseudomonas aeruginosa, staphylococcus aureus and acinetobacter haemolytics are also observed [26,49,50].

The treatment of TB in kidney transplant recipients should be the same as in the general population [11,42,51,52]. However, the use of rifampicin must be undertaken with caution because of its frequent interaction with immunosuppressive drugs, and blood levels of immunosuppressive drugs should be monitored. Prolonged follow-up should be provided. Patients can show good clinical and radiological responses under therapy but complications are possible related to either to TB or to side effects of anti-bacterial drugs [21].

Six Patients (37,5%) were successfully treated with quadruple anti-TB therapy for 12 months (9-17 months). Anti TB treatment can induce a successful management with reduction of allograft nephropathy, graft nephrectomy and mortality [2,25,53,54]. Response to antiTB treatment should be considered to make a diagnosis among patients highly suspected of TB infections.

However, several complications of antiTB treatment can appear.

Acute rejection is observed in 29,3% of cases [11]. It can be seen even after the stop of the anti TB treatment [21]. To avoid acute rejection, blood levels of calcineurin inhibitors should be monitored closely with an increase in doses in 53,57% to 100% and anti-lymphocyte globulin can be used as anti-rejection prophylaxis (11,21,28,30,42).

Chronic allograft nephropathy is a serious complication observed in 65% of the cases and has a negative impact on the graft survival [20,34,39,55].

Hepatotoxicity is a considerable risk of treatment observed in 17.1% to 42,8% of the cases, as a result of additive toxic effects of immunosuppressive drugs particularly Isoniazid [20,28,42]. Hepatitis need close observation because of the frequent occurrence of viral hepatitis in such cases.

Recurrence of TB is a frequent complication among kidney transplant recipients [33]. More than 9 months of treatment may be necessary to prevent recurrence [21,42,53,56,57,58].

Two patients (12,5%) died due to TB-related complications in our study and 12,9% to more than 22 % of cases in other studies [21,26,55]. Mortality is higher when TB occurs during the first year after kidney transplantation, among poor-nourished patients, treated with steroids and having hypoxia [59].

Prophylaxis is recommended for high-risk patients with previous history of TB before kidney transplantation and direct contact with a TB carrier. It associated isoniazid at a daily dose of 300 mg for patients weighing more than 35 kg and 5 mg/kg in patients weighing less than 35 kg, and Pyridoxin at the dose of 50 mg daily for 1 year [11,17,48,55].

5. Conclusion

Tunisian kidney transplant recipients face a high risk of TB because of their immuno-compromised state and epidemiological prevalence of the disease. Its clinical presentation is atypical with a high frequency of the extra pulmonary and disseminated localizations observed in third of cases in our patients. Therefore, attention should be given to this differential diagnosis in clinical practice.

To prevent recurrence of TB, which was frequent (18,7% of cases), prolonged antiTB treatment for at least 9 months is recommended.

References


