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Mycobacterium Tuberculosis Infection Following Kidney Transplantation

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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 alones 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. Reccurence 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*

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1. Introduction

Tuberculosis (TB) is an opportunist infectious disease with obligatory declaration, caused by Mycobactérium 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 becames 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 one of its multiple alternatives (Jensen, Coletsos...).

The histological analysis was the presence of a giganto-cellular 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, couph, impairment of general state), urine exam, biology (cratininemia, biological inflammatory syndrome, and complete blood count), chest radiograph patterns, organ involvement, diagnostic methods, administration of anti-TB therapy and mortality.

Radiographic patterns were classified as normal findings, miliary pattern, pleural effusion, parenchymal cavitation, nodules, pulmonary infiltrate and hilar or mediastinal lymphadenopathy. As the association of radiagraphic patterns is possible, this makes that the sum of the frequencies of radiographic patterns to be more than 100% [7,8].

A search for coïnfections with candida albicans, pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter haemolyticus, cytomegalovirus and / or aspergillus was done.

Interval between diagnosis of TB and date of kidney transplantation and circumstances of discovery of TB for each patient were recorded.

Mendel–Mantoux skin testing was carried out by the intracutaneous inoculation of purified protein obtained from vaccine BCG and called Tuberkulin into the volar surface of the forearm [7]. The test is read after 72 hours and is positif if induration is ≥ 10 millimetres.

A disseminated TB was defined when 2 organs were involved.

Results were analyzed using Statview.5.0 software. Values were expressed as mean ± standard deviation.

Our 16 patients were compared with 29 controls who were matched for age, sex, type of dialysis and who were transplanted at the same period.

The groups were compared as for time spite on dialysis, allograft dysfunction and number of acute rejection.

The characteristics of the 2 groups (TB group and control group) were summarized in Table 1.

Table 1. Characteristics of TB and control groups

	TB group	Control group	p
Donor age (years)	32,5	28,7	0,2843
Recipients sex ratio (M/F)	14/2	26/3	>0,9999
Type of dialysis	PD=2 HD=12 HD_PD= 2	PD=4 HD=24 HD_PD= 1	0,5072

HD: haemodialysis, F: female, M: male, PD: peritoneal dialysis, TB: tuberculosis.

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

Name	sex	age	previous history of TB and direct contact with a TB carrier	Nephropathy	Time spent on dialysis (years)	Donor	Immunosuppressive regimen	AR	Ttt of AR	HC	Diabetes	Creat µmo/l
1- A M	F	14	-	unknown	39,688	Cadaver38 years	CS+MMF	1	ALS+CS	Non	Non	178
2- A H	M	32	-	interstitial	25,068	Mother 61 years	CS + AZT	0	-	Non	Non	140
3- Z A	M	42	-	glomeular	39,951	Brother50 years	CS+AZT	1	ALS +CS	Non	Non	164
4- Gh N	F	34	husband	interstitial	23,359	Mother 65 years	CS+AZT	1	ALS +CS	Non	Non	157
5- D Y	M	60	-	diabetic	25,823	Wife 54 years	CS+MMF	0	-	Non	Oui	150
6- H O	M	22	-	lupic	14,324	Sister39 years	CS+ MMF	0	-	Non	Non	128
7- D M	M	34	-	glomerular	13,996	Sister 32 years	CS+ ciclo+AZT	0	-	Non	Non	90
8- H A	M	22	-	interstitial	31,836	Mère 57 ans	CS+tacrolimus+MMF	0	-	Non	Non	128
9- M A	M	51	Urogenital	unknown	99,745	Brother 30 years	CS+ciclo	0	-	Oui	Non	96
10- M F	M	27	-	hypertension	17,018	Mother 46 years	CS+AZT	2	ALS +CS CS	Non	Non	520
11- H Dh	M	13	-	interstitial	25,462	Cadaver 27 years	CS+ciclo+MMF	0	-	Non	Non	118
12- M A	M	19	brother	unknown	20,337	Mother 40 years	CS + MMF	0	-	Non	Non	90
13- J K	M	37	-	unknown	188,386	Sister 43 years	CS+tacrolimus+MMF	1	SAL+CS EP	Oui	Non	142
14- Ch N	M	39	-	glomerular	18,957	Brother 34 years	CS+AZT	1	ALS +CS	Non	Non	113
15- B F	M	36	-	glomerular	18,858	Sister 30 years	CS+ciclo+ AZT	1	ALS +CS	Oui	Oui	111
16- J H	M	38	-	glomerular	22,045	Sister 36 years	CS+MMF	0	-	Oui	Oui	187

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.

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 nephropathy 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 associated anti-lymphocyte serum in 10 cases and steroids in all cases. Maintenance immunosuppressive regimen associated before diagnosis of TB, steroids in all cases, ciclosporine in 4 cases, tacrolimus in 2 cases, mycophenolate mofetil in 7 cases and azathioprine in 7 cases.

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 pulmonar 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 coïnfection 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 3. Interval between tuberculois diagnosis and kidney transplantation, clinical and paraclinical picture, proof and localization

Name	Interval KT / TB (years)	circumstances of discovery and clinical picture	Biology	Creat µmo/l	Radiology	Proof	Localization (s)
1- A M	9,561	Fever Sweat Low bak pain	BIS	227	spondylodiscitis L5	0	vertebra
2- A H	13,339	Fever Impairment of general state	ARF	170	Pulmonary infiltrate pleuretic effusion	Bacteriological	Urinary and pulmonar
3- Z A	253,503	Fever	ARF	500	Pulmonary infiltrate	Bacteriological	pulmonar
4- Gh N	62,489	Fever, Impairment of general state PleurItic syndrom	BIS	134	Miliary Pleuretic effusion	histological	pulmonar
5- D Y	28,452	-	BIS	147	nodules	histological	pulmonar
6- H O	9,396	Fever, Impairment of general state PleurItic syndrom	BIS	115	Pleuretic effusion	histological	pleural
7- D M	6,505	Fever	pancytopenia	100	normal	histological	Lymph nodes
8- H A	7,984	Feve Chest pain PleurItic syndrom	BIS ARF	164	Pleuretic effusion	histological	pulmonar
9- M A	3,154	fever Impairment of general state sweat	BIS Sterile leukocyturia	98	Hilar calcification	Bacteriological	urinary
10- M F	164,271	Fever, Sweat Chest pain	SIB	472	Pulmonary infiltrate	Bacteriological	Pulmonar and meningeal
11- H Dh	2,825	Fever	SIB anemia	101	Nodule Pulmonary infiltrate Mediastinal lymphadenopathy	Bacteriological	pulmonar
12- M A	79,047	Fever, couph, sweat Impairment of general state	SIB	114	Pleuretic effusion	0	pleural
13- J K	1,544	Fever	Sterile leukocyturia ARF, BIS	177	normal	Bacteriological	Pulmonar and urinairy
14- Ch N	117,257	Fever	ARF	288	Mediastinal lymphadenopathy	Bacteriological	pulmonar
15- B F	3,811	Fever Couph pulmonary infection resistant to AB	BIS	112	Nodule miliary	Bacteriological	pulmonar
16- J H	93,700	Fever	BIS	400	cavern Pulmonary infiltrate	Bacteriological	pulmonar

AB: antibiotics, ARF: acute renal failure, BIS: biological inflammatory syndrome, Creat: cretininemia, KT: kidney transplantation, TB: tuberculosis

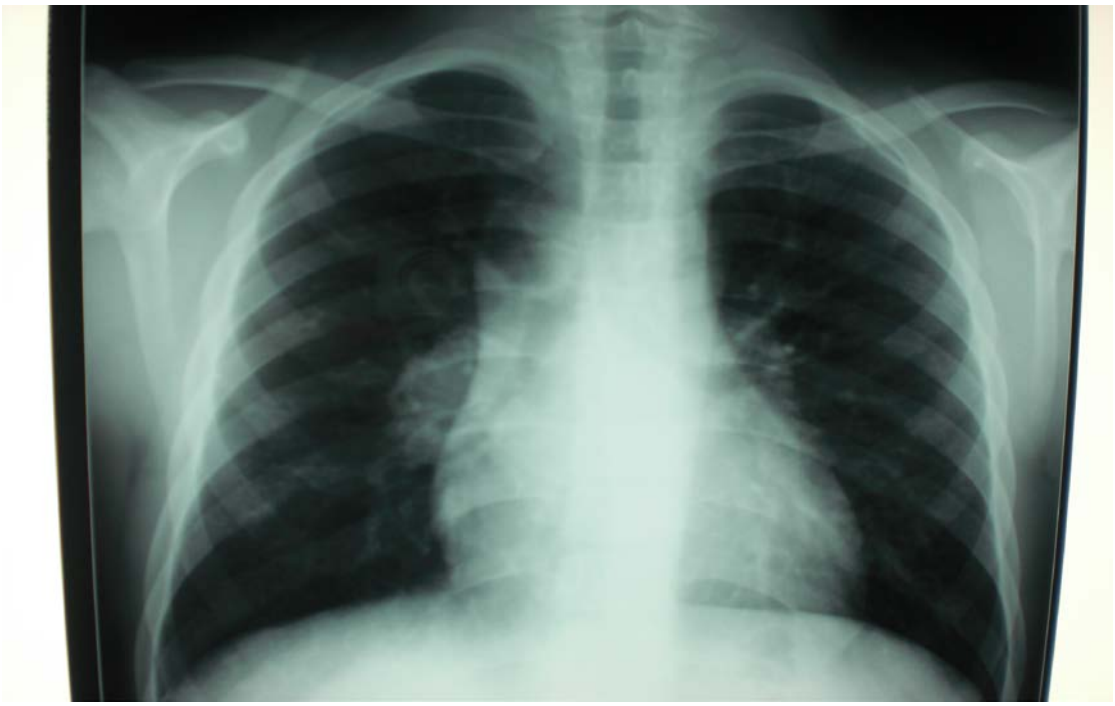

Figure 1. Chest X ray showing mediastinal enlargement

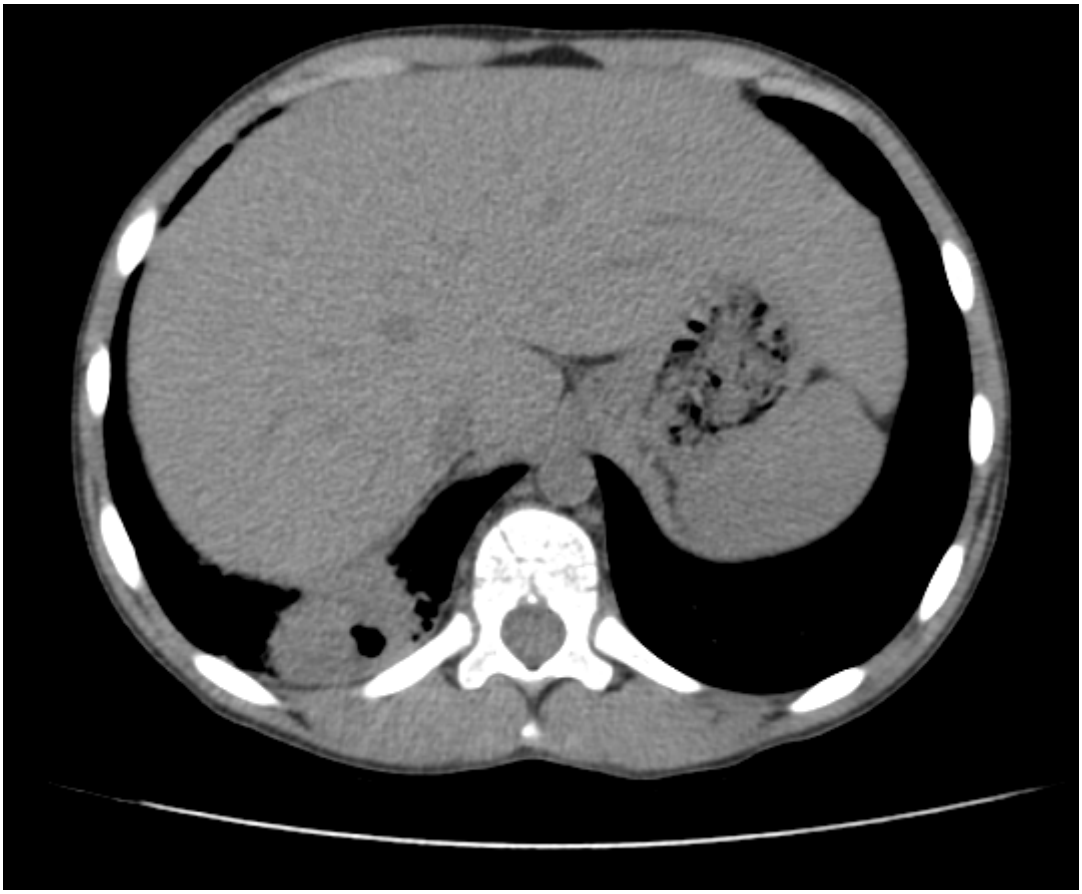

Figure 2. Chest computed tomography showing cavitations of the left lung

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 alones in 1 case (Table 4).

All patients were followed up. After a mean follow up of 291,3 months (88- 755 months), recorvery 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.

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

Reccurence of TB was observed in 4 cases after early stop of treatment (Table 4).

Table 4. AntiTB treatment and course of patients

Name	Duration of ttt antitbc (months)	Course	Reccurence of TB	Interval between stop of TB ttt and recurrence	Duration of resumption of antiTB treatment (months)	Follow-up (months)	Course
1- A M	6	ARF, DCG Loss of graft	Lumbar pain and radiologic abnormalities		12	9,363	HD
2- A H	12	hepatotoxicity hyperuricemia	Lymph nodes TB		12	213,717	Recovery
3- Z A	12	ARF CAD	-		-	11,992	HD
4- Gh N	12	-	meningeal and vertebral TB after stop of ttt		-	23,918	Death
5- D Y	10	ARF, CAD	-		-	26,809	CAD
6- H O	12	-	-		-	1,150	Recovery
7- D M	6	Hepatotoxicity	Lymph nodes TB, 6 months after stop of ttt		12	149,881	Recovery
8- H A	12	ARF	-		-	20,337	Recovery
9- M A	10	Hepatotoxicity Hyperuricemia	-		-	58,251	Recovery
10 -M F	1	CAD	-		-	1,577	Death
11-H Dh	9	-	-		-	9,626	Recovery
12- M A	12	Hyperuricemia	-		-	16,657	Recovery
13- J K	12	ARF CAD	-		-	35,055	CAD
14- Ch N	12	CAD	-		-	47,441	HD
15- B F	17	ARF	-		-	173,602	Recovery
16- J H	10	hyperuricemia ARF CAD	-		-	18,201	HD

ARF: acute renal failure, AR: acute rejection, CAD: Chronic allograft dysfunction HD: hemodialysis, ttt: TB treatment, TB: tuberculosis.

4. Disscussion

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 hyperuicemia (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 prevelence 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].

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. Rareley, in less than five percent of patients, TB is caused by nosocomial acquisition or donor transmission [12,13].

Mean age of our patients was 32,5 years, versus data of the literature which is 37,7 years [14]. No difference in age or gender between kidney transplant recipients with or without TB is described [14].

Time spent on dialysis was 38,6 months versus data of the literature which is 30,3 months and it is significantly higher compared to kidney transplant recipients without TB [14].

Half of our patients developed TB before the end of their second year of transplantation. In fact, the peak incidence is after the first year of transplantation [15,16].

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 dysfuction with creatininemia higher than 1.5 mg/dl [14,19].

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

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 spondilodiscitis [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 antiTB 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) shoud be improved and time spent on dialysis shoud 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 urines 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 coïnfection 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. Oher coïnfections with pseudomonas aeruginosa, staphylococcus aureus and acinetobacter haemolyticus 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 monitorated.

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.

Hoxewer, 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].

Hepatoxicity 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-nourrished 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.

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