Tanaffos (2006) 5(1), 19-24

Risk Factors and Laboratory Diagnostics for Post Renal Transplant Tuberculosis: A Case-Controlled, Country-Wide Study on Definitive Cases

A Basiri [1],SM Hosseini Moghaddam [2], N Simforoosh [1], B Einollahi [3], M Hosseini [4], A Firouzan [5], F Pourrezagholi [6], M Nafar [6], MA Zargar [7], G Pourmand [7], A Tara [6], H Mombeni [4], MR Moradi [8], A Taghizadeh[9], HR Gholamrezaee [10], A Bohlouli [11], H Nezhadgashti [12], A Akbarzadehpasha [13], E Ahmad [14], M Salehipour [15], M Yazdani [16], A Nasrollahi [6], A Shamsa [17],R Mahdavi[17], N Oqbai [1], R Esmaeili Azad [1], Z Mohammadi [1]

[1] Department of Urology, Urology Nephrology Research Center (UNRC), Shaheed Beheshti University of Medical Sciences and Health Services, [2] Department of Infectious Diseases, UNRC, [3] Department of Nephrology, UNRC, Baqiyatallah Medical University, [4] Department of Urology, UNRC, Ahwaz University of Medical Sciences and Health Services, [5] Department of Nephrology, UNRC, Islamic Azad University of Medical Sciences, [6] Department of Nephrology, UNRC, Shaheed Beheshti University of Medical Sciences and Health Services, [7] Department of Urology, UNRC, Iran University of Medical Sciences and Health Services, [8] Department of Urology, UNRC, Kermanshah University of Medical Sciences and Health Services, [9] Department of Urology, UNRC, West Azarbaiejan, Uremia University of Medical Sciences and Health Services, [10] Department of Urology, UNRC, Chamran Hospital, [11] Department of Urology, UNRC, East Azarbaiejan University of Medical Sciences and Health Services, [12] Department of Nephrology, UNRC, Iran University of Medical Sciences and Health Services, [13] Department of Urology, UNRC, Babol University of Medical Sciences and Health Services, [14] Department of Urology, UNRC, Shiraz University of Medical sciences and health Services, [15] Department of Nephrology, UNRC, Shiraz University of Medical sciences and health Services, [16] Department of Urology, UNRC, Isfahan University of Medical Sciences and Health Services, [17] Department of Urology, Mashhad University of Medical Sciences and Health Services, UNRC, TEHRAN-IRAN

ABSTRACT

Background: *Tuberculosis (TB) is a common cause of morbidity and mortality in renal transplant recipients. It is usually misdiagnosed because of lack of medical awareness and its infrequency in renal transplant recipients.*

Materials and Methods: *44 cases (0.3%) with post-transplant TB out of 12820 patients who had renal transplants performed between 1984 to 2003 were found from the hospital records of 12 major kidney transplantation centers in Iran. These cases were compared with 184 healthy transplant subjects whose transplants were performed by the same surgical team as the controls.*

Results: *The mean age of cases and controls was 37.7 (13-63) and 35.6 (8-67) years (p=0.3), respectively. The mean duration of pre-transplantation hemodialysis was 30.3 (3-168) months in cases and 18.2(1-180) months in controls (p=0.03). A past history of tuberculosis was detected in 2 cases and 1 control (p=0.3). The mean doses of initial and maintenance immunosuppressive drugs in cases and controls were not significantly different. A total of 25 cases (56.8%) and 60(32.6%) controls had rejection prior to diagnosis of TB (p=0.004; OR=2.7, $CI_{95\%}$: 1. 3-5.6).*

Conclusion: *To our knowledge, this is the first study that demonstrated increasing risk of post-transplant TB by extending the duration of pre-transplant hemodialysis and the number of post-transplant rejection episodes. Further study is needed to clarify our new findings specifically in respect of different immunosuppressive regimens.* ***(Tanaffos 2006; 5(1): 19-24)***

Key words: *Kidney Transplantation, Tuberculosis, Risk factors*

Correspondence to: Basiri A
Address: UNRC, No 44, Boustan 9th, Pasdaran Ave., Tehran-Iran.
PO.Box: 1666679951
Email address: h_sasan@hotmail.com

INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end stage renal disease (ESRD).

Although advances in immunosuppressive therapy have led to the increased survival of renal transplant recipients, there are greater risks of developing infectious complications. Because of its infrequency and the lack of medical awareness, tuberculosis may be misdiagnosed (1). Physicians usually consider *Mycobacterium tuberculosis* in the differential diagnoses of fevers of an unknown source after renal transplantation.

Tuberculosis (TB) is a major cause of morbidity and mortality in renal transplant recipients. It is likely that the patients are infected prior to transplantation and the disease reactivates after the procedure. Moreover, the possible contribution made by mycobacterial infection or anti-TB drugs to the incidence of graft rejection or renal dysfunction remains unclear.

The incidence of tuberculosis (TB) has been increasing, especially in immunocompromised patients. It was reported that the overall incidence of TB in solid-organ transplant recipients is 0.8% (2). In endemic areas and developing countries, tuberculosis could prove to be fatal if not recognized and treated early.

In this report we present the latest results of our case-control study comparing patients with post-transplant TB and healthy post transplant subjects.

MATERIALS AND METHODS

We conducted this case-control study at fifteen university teaching hospitals in Tehran, Shiraz, Mashhad, Babol, Urmia, Tabriz, Isfahan, Kermanshah, and Ahwaz. We reviewed the hospital records of 12820 cases of renal transplantation who were operated on between 1984 and 2003. Additionally, we conducted an "in-depth" interview with nephrologists who interviewed the patients after transplantation. We found 44 patients with confirmed diagnoses of post-transplant TB during the period of study. We selected 184 patients who had their transplantation performed by the same surgical team at the same time as controls. All kidneys were harvested from living donors in our study.

Patients' clinical and hospital records were studied for confirmation of TB according to our diagnostic criteria, demographic information, degree of immunosuppression, previous history of tuberculosis, time to development of tuberculosis , clinical presentation, laboratory data, radiographic and pathologic features, sites of involvement of tuberculosis infection, methods for diagnosis, TB treatment protocol, and number of rejection episodes prior to tuberculosis.

According to WHO recommendations, Iran is using the internationally recommended strategy to TB control referred to as DOTS. Therefore "Once patients with infectious TB (bacilli visible in a sputum smear) have been identified using microscopy services, health and community workers or trained volunteers observe patients swallowing the full course of the correct dosage of anti-TB medicines" (3). In our national health system, all patients receive isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and ethambutol (ETM) for two months and subsequently, INH and RMP for 4 months. Although cases with positive smears are diagnosed as TB and receive anti-TB drugs in Iran, in this study, we present our findings including cases with confirmed diagnosis of TB. The diagnosis of tuberculosis was considered certain if either pulmonary, extrapulmonary, or disseminated (miliary) TB were present if M.TB was cultured from any clinical sample, or if polymerase chain reaction (PCR) was positive for (M.TB).

Cases with probable diagnosis of TB- including patients whose radiographic and non-specific laboratory data were supportive for diagnosis of TB and whose clinical pictures were highly suggestive of tuberculosis that resolved with specific antituberculous treatment -were not included in this study. Immunosuppressive regimens varied according to the hospitals and the year of

transplantation. Triple therapy with cyclosporine (CsA), azathioprine, and steroids was used during the study period by the majority of centers, and some patients received mycophenolate mofetil (MMF) instead of azathioprine. Doses of CsA were adjusted to obtain plasma levels of 200-400 ng/ml (as determined by radioimmunoassay) during the first month and 100-200 ng/ml thereafter. Rejection episodes were usually treated with boluses of steroids and in the case of steroid-resistant rejection antilymphocyte antibodies-antilymphocyte globulin, antithymocyte globulin, or OKT3- was administered. Since 1985, pretransplantation HIV screening has been performed routinely in all centers.

We compared the demographic characteristics, clinical, and laboratory variables between the control group and kidney transplant recipients with TB. All statistical associations were analyzed using either Mann-Whitney or two-tailed *t* tests for quantitative variables and the chi-square or Fisher's exact test for qualitative variables. P-values of <0.05 were statistically significant. We calculated the odd's ratio for all risk factor variables analyzed in this study.

RESULTS

44(0.3%) out of 12820 cases of renal transplantation who were operated on between 1984 and 2003 had a confirmed diagnosis of tuberculosis. The mean interval between transplantation and expression of first symptoms or diagnosis of TB was 25.1 months (0.5-78 months) or 18.5 months (0.5-78 months), respectively. Major findings and comparisons between cases and controls are given in table-1. The frequencies of prolonged fever, complaint of chronic cough (more than three weeks), sputum production, night sweating, hemoptysis, weight loss in cases with TB were :39 (88.6%), 26 (59.1%), 29 (65.9%), 18 (40.9%), 4 (9.1%),16(36.4%), respectively. No subjects in the control group complained of these problems.

Table 1. Clinical Characteristics of Kidney Transplant Recipients with Tuberculosis Comparing with Controls

Variable	Case (n=44)	Control(n=184)	P-value	OR
Mean Age ,year(range)	37.7 (13-63)	35.6 (8-67)	0.3	
Sex(M/F)	22/22	116/68	0.1	0.58 $CI_{95\%}$:0.3-1.1
Weight	54.9(26-81)	56.7(19-92)	0.5	
Living in Rural Areas	7(15.9%)	15(8.3%)	0.1	2.13 $CI_{95\%}$:0.73-6.09
Type of Tuberculosis				
Pulmonary	26(59%)			
Extrapulmonary	9(20.5%)			
Disseminated	9 (20.5%)			
History of Prior Renal Transplantation	0	10(5.4%)	0.1	0.00 $CI_{95\%}$:0.00-2.17
Rejection Prior to Diagnosis of TB	25(56.8%)	60(32.6%)		
One episode	12(27%)	44(23.9%)		
Two episodes	9(20.5/%)	12(6.5%)	0.004	2.7 $CI_{95\%}$: 1. 3-5.6
Three episodes	2(4.5%)	3(1.6%)		
Four episodes	0	1(0.5%)		
Five episodes	2(4.5%)	0		
History of Tuberculosis in Patient	2	1	0.3	4.3 $CI_{95\%}$:0.42-44.6
in First Relatives	3	3	0.05	4.4 $CI_{95\%}$:0.68-28.6
Mean Time (Months) of Being on Hemodialysis Prior to Transplantation	30.3(3-168)	18.2(1-180)	0.03*	

* Mann-Whitney U test

At the time of diagnosis of TB, both the mean percentage of basophils and lymphocytes in peripheral blood smear were higher in cases than in controls (1.83% vs. 0.85%, p=0.02; 29% vs.21% cell/µL, p=0.01). Similarly erythrocyte sedimentation rate at the first hour was considerably higher in cases of TB(82.6 vs. 47.4, p=0.00).

All patients in both groups received prednisolone with similar mean maintenance doses (0.43 vs. 0.49 mg/Kg, p=0.46; OR: 1.2, $CI_{95\%}$:0.13-10.5). Ten cases (22.7%) and 27 subjects in the control group (14.7%) received MMF (p=0.2; OR: 1.7 $CI_{95\%}$:0.75-3.8) with similar mean maintenance doses (13.3 mg/Kg vs.17.8 mg/kg, p=0.5).CsA was received by 41 cases (93.2%) and 172 controls (93.5%, p=0.5 OR: 0.95 $CI_{95\%}$:0.26-3.5) with similar mean maintenance doses (4.03 vs. 4.2 mg/Kg, p=0.17). Thirty-four cases (77.3%) and 135 controls (73.4%, p=0.6; OR: 1.2 $CI_{95\%}$:0.57-2.6) received azathioprine with similar mean doses (1.4 vs. 1.5 mg/Kg , p= 0.6). According to our protocol, all cases with transplant rejection receive pulses of methyl prednisolone and rarely if needed ATG (no case and 2 controls i.e.0% vs. 1.1%) or ALG (1 case and 7 controls, 2.3 % vs.3.8 %, p=0.6;OR=0.59 ,$CI_{95\%}$:0.03 - 4.97).

No HIV-positive patients were found in this study. Aside from pleural effusion in 12 cases, 17 cases had typical feature of TB in CXR. No patients in the control group had radiological evidence of tuberculosis (p=0.0). Table 2 shows radiological features of CXR in cases with TB.

Table 2. Radiological Features of CXR in cases with TB

Feature	Frequency	Percent
Apical infiltration and calcification	8	27.6
Pleural effusion	12	41.4
Apical cavitations	6	20.7
Miliary pattern	3	10.3
Total	29	100

DISCUSSION

The frequency of primary infection or reactivation of latent infection caused by *Mycobacterium tuberculosis* is considerable among Iranians (4). This microorganism is a dormant pathogen that may restore the ability to function in renal transplant recipients (5). The world-wide incidence of this disease causes a high index of suspicion among physicians, to try to promote screening methods, and initiates INH prophylaxis in recipients at high risk for reactivation of latent TB (6).

A new finding in this study was that patients on hemodialysis for a long duration of time prior to transplantation are at greater risk for post transplantation TB. This phenomenon can be described by taking into account the immunosuppressive effects of ESRD and hemodialysis. Moreover, we found new diagnostic tools using simple CBC for making the diagnosis of TB. Although lymphocytosis is a well-known, nonspecific finding indicator for diagnosis of TB, basophilia was found for the first time in our study that could be a new parameter for making diagnosis in renal transplant subjects.

A retrospective study among renal transplant patients in China was performed in 2004 and 23 cases of TB were diagnosed (7). In this report the interval between renal transplantation and the development of tuberculosis ranged from 3 to 127 months with a median of 46 months. There were 18 cases of pulmonary tuberculosis, two cases of pulmonary plus laryngeal tuberculosis, two cases of disseminated tuberculosis, and one case of tuberculosis involving the urinary tract. Diagnosis was established by a positive culture for *Mycobacterium tuberculosis* in 21 patients and response to empirical anti-TB treatment in two patients. In our study the median interval between renal transplantation and the development of TB was 18 months (ranged from 0.5 to 78 months). This

means our patients may face more severe environmental exposure or have a higher degree of immunosuppression. Although patients in both study received the same drugs we have no information of doses of immunosuppressive drugs in Lui's study.

Although both rejection and receiving ATG or ALG as well as pulses of methyl prednisolone may facilitate the development of TB in kidney transplant recipients, the risk factors for tuberculosis in transplant patients are currently poorly defined. Though the impact of on increase in intensity of immunosuppression on the function of a graft with insufficient performance seems to be crucial, the probability of infectious processes like TB enhances as well. Episodes of rejection per se or via antilymphocyte globulines used for treatment enhance the probability of post transplant TB. Specifically, ATG or ALG by tapering the function of cell mediated immunity to a slender point may help reactivate dormant infections. Invasion and multiplication of pathogenic microorganisms strongly affect the nature and/ or the course of events affecting the renal allograft performance. Paying attention to deleterious effects of chronic infectious processes and making the diagnosis in a timely manner help physicians to manage a patient's problems appropriately.

Although our study had some limitations, to our knowledge, this is the first comparative case - control study on confirmed cases of post- transplant TB and controls (healthy kidney transplant subjects). This study has better acquainted us with post transplant TB and its risk factors. Basophilia, apart from lymphocytosis and elevation of ESR, was found in our study as another non-specific test that could be helpful for making the diagnosis of TB in kidney allograft recipients.

Since our patients have received all the necessary anti-TB medications under DOTS strategy (4), conventional treatment using this scheme appears to be appropriate for renal transplant recipients with TB. Our study was not designed to measure the side effects of anti-TB drugs, or specific drug interactions like rifampin and CsA. Considering significant frequency of TB in Iran, we think other studies can be undertaken for surveying treatment complications. Aside from treatment modalities, multi-drug resistant tuberculosis (MDR-TB) is a new emerging problem facing health care professionals and globally, about three per cent of all newly diagnosed patients have MDR-TB (8). Since HIV enhances the MDR-TB (9) and prevalence of both HIV infection and drug resistant M.TB is increasing in our geographic region, conducting further studies to understand whether immunosuppression caused by renal transplantation like HIV infection increases the incidence of MDR-TB is crucial. MDR-TB has been reported in liver (3), heart (10) and lung (11) transplantation.

We conclude that the frequency of TB is noticeable among Iranian kidney transplant recipients and we should make a high index of suspicion for TB among kidney allograft recipients to ensure a prompt start of DOTS treatment.

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