RESEARCH COMMUNICATION

Posttransplant Malignancies in Renal Transplant Recipients: 22-years Experience from a Single Center in Pakistan

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Abstract

Objective: To study the incidence, types and distribution pattern of malignant tumors in renal transplant recipients at a single center in Pakistan. Materials and methods: This retrospective study was conducted at Sindh Institute of Urology and Transplantation (SIUT) and included all transplant patients on regular follow-up from November 1986 to December 2008. The original biopsy reports and case files of all patients who developed posttransplant malignancies were reviewed and relevant demographic, clinical, radiological, and histopathological data were retrieved and analyzed. SPSS version 10.0 was used for statistical analysis. Results: Over 22 years of study period, 1816 renal transplants were carried out at our center. Among these, 44 patients developed malignancies constituting an overall incidence rate of 2.4%. All patients in this study were males with a mean age of 34.9±9.5 years (range: 9 to 60 years). The most common type of malignancy was lymphoma (27 patients, 61.4%), followed by Kaposi's sarcoma (11 patients, 25%) and skin malignancies (3 patients, 6.8%). One case each of adenocarcinoma of the gallbladder, acute myeloid leukemia (AML), conjunctival carcinoma-in-situ and seminoma were also diagnosed. Conclusion: Posttransplant malignancies occurring in our renal transplant recipients show different incidence rates and patterns as compared with western studies.

Keywords: Kaposi's sarcoma - lymphoma - posttransplant malignancies - renal transplant - skin tumors

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Introduction

Solid organ and bone marrow transplant recipients are at an increased risk of developing malignant tumors. When compared with the age-matched general population, the frequency of malignancies is increased 100 times (Honda et al., 1990), which is partly attributed to the improvement of long-term survival of the transplant patients with improved immunosuppressive regimens. Iatrogenic immunosuppression and chronic viral infections are the major risk factors predisposing these patients to a spectrum of malignancies, particularly to posttransplant lymphoproliferative disorders (PTLD) (Caillard et al., 2006), in addition to many other risk factors involved, which also include genetic and geographical factors. The incidence of development of lymphoproliferative disorders is 1.4% according to US Renal Data System (USRDS) (1996-2001) (Caillard et al., 2005), whereas, other studies have reported it to be as high as 15-25% (Boubenider et al., 1997), depending on the type of organ transplant and the immunosuppression protocol (Boubenider et al., 1997).

In kidney transplantation, the risk for PTLD was found to be about 40 times greater than in the general population (Pen, 1998; Pen, 2000; Kasiske et al., 2004). Once this complication develops, it is associated with a significantly high morbidity and mortality rate, as evidenced by literature, which shows that death occurs in more than 50% of patients (Opelz and Dohler, 2004). Hence, an early diagnosis and treatment of posttransplant malignancies is important.

With regard to the types and distribution of tumors in transplanted patients, these characteristics of tumors in this population are also different from those occurring in general population, as evidenced by a common occurrence of very uncommon tumors like Kaposi sarcoma in these subjects (Yilderim et al., 2006). We have earlier reported the incidence and the pattern of posttransplant malignancies in 1000 renal transplant recipients at our center (Kazi et al., 2001). The present is an extended follow-up study of the previous preliminary report with the inclusion of more patients as well as the prolongation of the follow-up period to gain further and a better insight into this important complication in renal transplant patients.

Materials and Methods

This retrospective study was carried out at SIUT, which is the biggest renal transplant institute in Pakistan. In this study, all transplanted patients (n=1816) were included from November 1986 to December 2008 (22 years). Only

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first transplants were included. The original biopsy reports and case files of all patients who developed posttransplant malignancies were reviewed and relevant demographic, clinical, radiologic and histopathologic data was retrieved and analyzed.

Routine immunosuppression

The immunosuppressants used in all these patients were cyclosporine, azathioprine, and corticosterods, as described in detail in our previous report (Kazi et al., 2001). Briefly, prednisolone was given in the starting dose of 0.5 mg/kg/day, tapered to 0.2 to 0.3 mg/kg/day. Azathioprine was given in a dose of 1.5 mg /kg/day and cyclosporine was administered at a dose of 8 mg/kg/day in divided doses.

Treatment of rejection

This was carried out according to standard guidelines and as described in our previous report (Kazi et al., 2001). Briefly, T-cell mediated rejection was treated with 3 to 5 intravenosu boluses of methyl prednisolone (500 mg each): in steroid-resistant rejections, antilymphocyte sera were given. OKT3 was also used in selected cases. Doses of biological agents were monitored according to CD3 lymphocyte count by flow cytometry (Kazi et al., 2001).

Statistical analysis

Statistical analysis was performed by SPSS for Windows version 10.0 (SPSS, Chicago, IL, USA). Simple descriptive statistics such as mean ± SD were used for continuous variables such as age and numbers (percentages) were used for categorical variables.

Results

Patient characteristics

Among 1816 renal transplant recipients, 44 patients developed malignancies after renal transplantation (Table 1). The mean age of 44 patients was 34.9±9.5 years (range: 9-60 years). Interestingly, all 44 patients were males. Almost all patients except two received kidneys from live related donors. Most of these patients received kidneys from first degree related donors (parents, brother or sister) with at least one haplotype and two antigen match. The time period of development of malignancy after transplantation varied from 3 months to 149 months (Mean: 68.0±47.0 months).

Posttransplant malignancies

Among 44 renal transplant recipients, PTLD formed the bulk of posttransplant malignancies, found in 27 patients, among which, 24 had non-Hodgkin's lymphoma (NHL), and three had Hodgkin's disease (Table 1). Eleven patients had Kaposi's sarcoma, 3 patients had skin cancer, while one patient each was found to have gall bladder carcinoma, acute myeloid leukemia (AML), and seminoma (Table 1).

Regarding the primary site of localization, the gastrointestinal tract (GIT) was the most favored site for NHL in these patients (21 patients constituting 77% of all lymphomas and 91% of NHL), as shown in Table 2. Out of these, 14 involved small or large bowel or both and the bowel is the most common site of involvement. One of the patients developed NHL of stomach, four patients developed mesenteric masses, two patients had liver masses, while central nervous system (CNS) involvement occurred in only one patient.

Table 1. Incidence and Types of Malignancies Found in 44 Renal Transplant Patients.

S. No.	No. of patients	% in all transplant patients (n=1816)	% of all malignant tumour (n=44)
Type of malignancy			
1	Lymphoma (PTLD)		
	27	1.48	61.36%
2	Kaposi's Sarcoma (KS)		
	11	0.6	25.00%
3	Non-melanotic skin cancer (NMSC)		
	3	0.16	6.80%
4	Adenocarcinoma of gall bladder		
	1	0.05	2.20%
7	Carcinoma-in-situ of conjunctiva		
	1	0.05	2.20%
8	Acute myeloid leukemia		
	1	0.05	2.20%
9	Seminoma		
	1	0.05	2.20%

Table 2. Primary Sites of Lymphoma in 27 Renal Transplant Recipients

Type of lymphoma	System involved	Patients
Non-Hodgkin's Lymphoma		
	Gastrointestinal system	
	Small or large intestine or both	14
	Mesentery	4
	Liver	2
	Stomach	1
	Duodenum	1
	Lymph Nodes (LN)	
	Retroperitoneal LN	1
	CNS	
	Corpus callosum and periventricular white matter	1
Total		24 (88.8%)
Hodgkin's Disease		
	Cervical lymph node	3
Total		3 (11.1%)

Discussion

An increased incidence of malignant tumors in transplant recipients was recognized in 1970's and their association with immunosuppressive medications has also been described as early as 1976 (Pen, 1976; Pen, 1977). Development of cancer is one of the most common causes of death in transplant patients after cardiovascular disease, infections and liver failure (Yilderim et al., 2006; Chapman and Campistol, 2007). Malignancies in transplant recipients can develop de novo, as recurrent malignancies in the recipients, or even transmission of malignancy from the donor (Morath et al., 2004).

Extensive research has been carried out on this subject and many risk factors have been identified for the development of malignancies in renal transplant recipients which include immunosuppression, chronic viral infections, genetic factors, geographical factors and transplantation with cytotoxic agents like cyclophosphamaide (Morath et al., 2004).

During a span of 22 years, a total of 1816 renal transplants were carried out at SIUT. Among these, 44 patients developed posttransplant malignancies of different types constituting an overall incidence of 2.4 % in our patients, which is comparable to other reported studies (Pen, 1978; Pen, 1979). This figure is almost similar to that (2.5%) found in our previous study, implying that there is no significant increase in the incidence rate of this complication (Kazi et al., 2001).

Interestingly, all the transplant patients who developed malignancies were males, a finding that has never been reported in other studies, although a male preponderance has been described by many reasearchers (Honda et al., 1990; Yilderim et al., 2006; Sandhu et al., 2005). Our previous report also found all patients with posttransplant malignancies to be males (Kazi et al., 2001).

In the present analysis, the most common malignancies encountered included PTLD, which occurred in 27 patients, constituting 61.3% of all malignancies, followed by Kaposi's sarcoma in 11 patients (25 % of all malignancies), and non-melanotic skin cancers (NMSCs) in 3 patients, comprising 6.8 %. In addition, one patient (2.2%) each developed squamous cell carcinoma of conjunctiva, adenocarcinoma of gallbladder, seminoma and acute myeloid leukemia (AML). This distribution of types of posttransplant malignancies is unique to this part of the world and is comparable to the distribution noted in an Indian study, carried out at Dayanand Medical College and Hospital, Ludhiana, which found PTLD as the commonest malignancy (75%) in renal transplant recipients (Sandhu et al., 2005). Our distribution pattern is different from the Western pattern as well as the pattern described from Mediterranean countries. According to the results that have been concluded in the Duke University Medical Center of North Carolina, NMSCs constituted upto 82% of malignancies in organ transplant recipients while PTLD constituted 1-11 % and 6% patients developed Kaposi sarcoma (Zafar et al., 2008). In comparison to this, the results from a study conducted at the Baskent University, Turkey, the most common malignancy was Kaposi sarcoma, found in 32.2%, followed by lymphomas, in 27.1%, and skin cancers in 22% (Yilderim et al., 2006).

Posttransplant lymphoma was the commonest malignancy in renal transplant recipients in this study. A total of 27 patients had PTLD in this series (1.48% of all 1816 transplanted patients), which constituted 61.3% of all malignancies in this study. Among these, 24 were NHL, which was the commonest type of lymphoma constituting 88.8 % of all lymphomas, while 3 patients had Hodgkin's disease (11.1 %). In our series, lymphomas developed 5 months to 156 months (13 yrs) after transplantation, with a mean posttransplant period of 66 months (5.5 yrs), which is contrary to USRDS 2001 database, according to which highest observed rates of lymphoma were in the first 12 months, after which the rate of lymphoma diagnosis decreased (Smith et al., 2006). Compared to our own previous study, the incidence of PTLD increased while that of Kaposi's sarcoma declined over 22 years of the study period (Kazi et al., 2001). In our previous analysis, the incidence rates of PTLD and Kaposi's sarcoma were almost similar, where as in the present study, the incidence rate of PTLD has more than doubled the rate of Kaposi's sarcoma.

The mean age of renal transplant patients in our study was 34.9 years, while according to USRDS, highest rates of posttransplant lymphomas were in the younger (<25 yrs) or older (≥ 60 yrs) age groups (Smith et al., 2006). The mean age of our renal transplant patients with posttransplant malignancies has remained more or less similar to our previous report (Kazi et al., 2001).

The gastrointestinal tract (GIT) is the most favored site for NHL in these patients (21 patients constituting 77% of all lymphomas and 91% of NHL), as shown in table 2. Out of these, 14 involved small or large bowel or both and the bowel is the most common site of involvement. One of the patients developed NHL of stomach, four patients developed mesenteric masses, two patients had liver masses, while central nervous system (CNS) involvement occurred in only one patient. These findings are in keeping with the predominant extranodal origin of lymphomas in transplant recipients contrary to the lymphomas occurring in the general population. This extranodal preference has been noted in all other major studies on this subject (Pen, 1990; Pen, 1991; Opelz and Handerson, 2003).

Kaposi's sarcoma is the second most common malignancy in our renal transplant recipients. A total of 11 patients developed Kaposi's sarcoma which constitutes 0.6 % of all transplant recipients and 25 % of all malignancies among these patients. This incidence is slightly higher than that reported in the western studies but is much lower than that reported in Mediterranean, Jewish, Arabic, Middle Eastern, Caribbean and African ethnic groups, where the majority of cases of Kaposi's sarcomas occur and the incidence reported in transplant recipients has been as high as 500 times that in healthy individuals (Mendez and Paya, 2000; Euvrard et al., 2003). The prevalence of Kaposi's sarcoma varies in different ethnic groups and has marked geographical variation and ranges from 0.5% in USA to 5.3% in Saudi Arabia (Euvrard et al., 2003). Kaposi's sarcoma is the commonest malignancy according to Turkish study where it constituted 32 % of all malignancies (Yilderim et al., 2006). Even higher relative frequency of this tumor (41.6%) has been reported in Tunisian study (Hazrallah et al., 2008). In our study, visceral involvement of Kaposi's sarcoma (7 patients; 63.6%) was more common than cutaneous involvement which occurred in 4 patients (27.2%). This distribution of lesions is different from the results of other studies. GIT is the most commonly affected system including esophagus, stomach, duodenum, colon and liver, and the stomach and colon were the commonest sites (two patients each). Lung lesions were seen in three patients and three patients had lymphadenopathy. In one patient, Kaposi's sarcoma presented as a primary tongue lesion. Interestingly, one of

the patients developed both cutaneous Kaposi's sarcoma and primary NHL of the liver. Simultaneous development of both malignancies is extremely rare and only few cases have been reported in the literature (Sabeel et al., 1998; Yaich et al., 2010).

In our patients, skin malignancies were present in three patients (0.16% among transplanted patients and 6.8% of all malignancies) and constituted the 3rd most common malignancies. Among the three, one had squamous cell carcinoma, the second basal cell carcinoma, and the third had sebaceous carcinoma. The skin tumors developed 1.58 years to 7 years after transplantation and were treated adequately and are all alive.

Seminoma, AML, adenocarcinoma of the gall bladder and conjunctival carcinoma were the uncommon tumors in our transplanted population and were diagnosed in single patient each

In conclusion, the incidence and the pattern of malignancies occurring in Pakistani renal transplant recipients are unique as compared to Western, Middle Eastern, Arabic and African populations but are in agreement with the other regional studies. Although the overall incidence of posttransplant malignacies has remained the same, as compared with our previous report, the incidence of Kaposi's sarcoma has declined markedly. To reduce the morbidity and mortality among the transplanted patients, early diagnosis and treatment of malignancies is important and prevention of malignancies is a challenge which can be accomplished by identification of risk factors in our population.

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