Posttransplant Lymphoproliferative Disorders in Kidney Transplant Recipients

An Iranian Multicenter Experience

Behzad Einollahi,[1] Mahboob Lessan-Pezeshki,[2] Mohammad Hossein Nourbala,[1] Nasser Simforoosh,[3] Vahid Pourfarziani,[1] Eghlim Nemati,[1] Mohsen Nafar,[3] Abbas Basiri,[3] Fatemeh Pour-Reza-Gholi,[3] Ahmad Firoozan,[3] Mohammad Hassan Ghadiani,[1] Khadijeh Makhdoomi,[4] Ali Ghafari,[4] Pedram Ahmadpour,[3] Farshid Oliaei,[5] Mohammad Reza Ardalan,[6] Atieh Makhlough,[7] Hamid Reza Samimagham,[8] Jalal Azmandian,[9] Efat Razeghi,[2] Heshmatollah Shahbazian[10]

[1]Nephrology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2]Department of Nephrology, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Kidney Transplant, Shahid Beheshti University (MC), Tehran, Iran
[4]Department of Nephrology, Urmia University of Medical Sciences, Urmia, Iran
[5]Department of Nephrology, Babol University of Medical Sciences, Babol, Iran
[6]Department of Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran
[7]Department of Nephrology, Sari University of Medical Sciences, Sari, Iran
[8]Department of Nephrology, Hormozgan University of Medical Sciences, Bandarabbas, Iran
[9]Department of Nephrology, Kerman University of Medical Sciences, Kerman, Iran
[10]Department of Nephrology, Ahwaz University of Medical Sciences, Ahwaz, Iran

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Introduction. Limited data with adequate sample size exist on the development of posttransplant lymphoproliferative disorder (PTLD) in living donor kidney recipients. We conducted a retrospective cohort study on the data of 10 transplant centers to identify the incidence of PTLD in Iran.

Materials and Methods. Data of 9917 kidney transplant recipients who received their kidneys between 1984 and 2008 were reviewed. Fifty-one recipients (0.5%) who developed PTLD were evaluated with a median follow-up of 47.5 months (range, 1 to 211) months.

Results. Patients with PTLD represented 24% of all posttransplant malignancies (51 out of 211 cases). There was no relationship between PTLD and sex ($P = .20$). There were no statistically significance differences considering the age at transplantation between patients with and without PTLD. The late-onset PTLD (70.6%) occurred more frequently compared to the early form. There was no signification relationship between early-onset and late-onset groups in terms of clinical course and outcome. In patients who received azathioprine, PTLD was more frequent when compared to those who received mycophenolate mofetil ($P < .001$). The lymph nodes were the predominantly involved site (35.3%), followed by the gastrointestinal tract, brain, kidney allograft, lung, ovary, vertebrae, and palatine. Age at diagnosis and the time from transplantation to diagnosis were comparable for various involvement sites of PTLDs. The overall mortality in this series of patients was 51.0%.

Conclusions. Posttransplant lymphoproliferative disorder is a rare but devastating complication and long-term prognosis can be improved with early recognition and appropriate therapy.

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INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) is an uncommon but potentially fatal complication affecting 1% to 3% of kidney transplant recipients.[1] Its incidence in kidney allografts is lower than that in heart, lung, and liver transplant organs.[1] Posttransplant lymphoproliferative disorder, however, is a more frequent tumor than other hematopoietic tumors following solid organ transplantation, comprising up to 15% of all neoplasms.[2] Its mortality rate has approached 60% in some reports.[2]

Although few reports on cancers from transplant registries are available, we previously showed that the pattern of cancer development in Iran was different from that in the Western countries; Kaposi sarcoma was the most common malignancy, followed by PTLD.[3-6] It is difficult to accurately ascertain the incidence of most malignancies and to compare their rates of occurrence with those in the general population, using data from small single-center studies.[7] On the other hand, the majority of the reports on PTLD are derived from deceased transplant recipients. There are no major studies reporting the occurrence and characteristics of PTLD after living donor kidney transplantations. We have previously reported the experiences of 3 transplant centers with PTLD in Iran.[8] Then, we conducted the largest retrospective cohort study on the data of 10 transplant centers, the report of which is reported hereby, to identify the incidence of PTLD in the Iranian kidney transplant recipients between 1984 and 2008.

MATERIALS AND METHODS

Patients

We conducted a retrospective cohort study on the data of 10 kidney transplant centers in Iran to identify all cases of PTLD following transplantation. A total of 9917 patients (37% women and 63% men), receiving a kidney between October 1984 and August 2008, were surveyed for the development of PTLD. The time to tumor onset was defined as the period between kidney transplantation and the first signs of PTLD. In all cases, the diagnosis of PTLD was based on histologic examination of the biopsy specimens from various involved organs. Early-onset and late-onset PTLDs were distinguished based on their occurrence before and after the first year of transplantation.

Studied Parameters

The studied parameters were patient age, sex, induction and maintenance immunosuppressive therapy, posttransplant latency period, sites of lymphoma involvement, simultaneous neoplastic or infectious problems, the treatment modalities, graft function at the time of diagnosis and the last follow-up, rejection episodes, clinical presentation, therapeutic responses, and outcome of the disease.

At diagnosis of PTLD, immunosuppressive regimens consisted of various combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil (MMF), and antithymocyte/antilymphocyte globulin (ATG/ALG). Before 2000, the patients used to receive maintenance immunosuppression with prednisone and azathioprine or triple therapy with cyclosporine, prednisone, and azathioprine. Thereafter, the majority of the patients received cyclosporine, prednisone, and MMF. Rejection episodes not responding to steroid pulse therapy were treated with ATG/ALG in the majority of the recipients. For induction therapy, ATG/ALG was used in highly sensitized patients, recipients of kidneys from deceased donors, poorly matched living donor kidney recipients, and recipients of a second or third transplant. None of the patients received OKT3.

There is no uniform approach to PTLD and treatment of the tumor is difficult and challenging. However, the first step in the majority of our patients with PTLD was promptly reduced or withdrawal of cyclosporine and azathioprine/MMF. All of the patients had taken ATG/ALG and received prophylactic antiviral therapy, ganciclovir, for a minimum of 1 month after transplantation. Changing cyclosporine to sirolimus, chemotherapy and/or radiotherapy were of other therapeutic measures. Outcome was assessed by response to therapy, remission duration, and survival.

Statistical Analyses

The SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA) was used for data analyses. Categorical data and continuous variables were reviewed using the relative frequency and the mean value ± standard deviation, respectively. Continuous data of the two groups of with and without PTLD were compared by the Student *t* test, and nonparametric data were

analyzed by the Mann-Whitney U test. Categorical data were analyzed using the chi-square or Fisher exact tests. The Spearman rho correlation coefficient test was used to evaluate the strength of association between continuous variables. Patient and graft survivals (noncensored for death) were defined as the time from diagnosis of the PTLD to death and graft loss, respectively. The survival rate was calculated using the Kaplan-Meier method, and comparisons were made with the log-rank test. Statistical significance was defined as a probability value less than .05.

RESULTS

Fifty-one recipients (0.5%) had developed PTLD following kidney transplantation, representing 24% of all posttransplant malignancies (51 out of 211 cases). In addition, 1 patient had Kaposi sarcoma. They were retrospectively evaluated with a median follow-up of 47.5 months (range, 1 to 211 months). The characteristics of the patients with PTLD are summarized in Table 1.

Data on Epstein-Barr virus and cytomegalovirus serostatus was available only in 25 recipients from 2 centers, and all of them were positive for immunoglobulin G and negative for immunoglobulin G regarding both viruses. Cytomegalovirus infection was found in 3 patients who had PTLD, and there was no significant relationship between developing of PTLD and cytomegalovirus infection.

There was no relationship between developing of PTLD and sex distribution (P = .20). There was no statistically significance differences considering the age at transplantation between patients with and without PTLD (mean age, 35 ± 13 years versus 37 ± 15 years, respectively; P = .30; Table 2). The

Table 1. Characteristics of Kidney Transplant Recipients With Posttransplant Lymphoproliferative Disorders

Characteristic	Value
Median recipients' age at diagnosis, y	40 (12 to 66)
Recipients' sex distribution	
Male	28 (54.9)
Female	23 (45.1)
Median time from transplantation to diagnosis, mo	47.5 (1 to 211)
Median follow-up after transplantation, mo	60.0 (1.5 to 214.0)
Median follow up after diagnosis, mo	5.5 (0.5 to 108.0)
PTLD types	
Early-onset	15 (29.4)
Late-onset	36 (70.6)
Lesions in patients with NHL	
Nodal	18 (38.3)
Extranodal	29 (61.7)
Treatment modalities	
Withdrawal of immunosuppressants	40 (78.4)
Reduction of immunosuppressants	4 (7.8)
Change to sirolimus	5 (9.8)
Ganciclovir	2 (3.9)
Chemotherapy	47 (92.2)
Radiotherapy	7 (13.7)
Surgical excision of the lesions	9 (17.6)
No treatment	4 (7.8)
Response to treatment	
Yes	24 (47.1)
No	26 (51.0)
Missed	1 (2.0)
Outcomes	
Overall mortality	26 (51.0)
1-year patient survival, %	46
5-year patient survival, %	41
1-year graft survival, %	39
5-year graft survival, %	35

*Values in parentheses are percentages for reports of frequency and range for median values. PTLD indicates posttransplant lymphoproliferative disorders and NHL, non-Hodgkin lymphoma.

Table 2. Comparison of Kidney Recipients With and Without Posttransplant Lymphoproliferative Disorders

Parameter	PTLD Group (n = 51)	Non-PTLD Group (n = 9866)	*P*
Mean age at transplantation, y	35 ± 13	37 ± 15	.30
Males	23	6211	.20
Donor Source			
Living related	10 (19.6)	949 (9.6)	
Living unrelated	36 (70.6)	7975 (80.8)	
Deceased	1 (2.0)	169 (1.7)	
Unknown	4 (7.8)	773 (7.8)	.05
Immunosuppressive regimen			
Mycophenolate mofetil-based	11 (21.6)	6357 (64.4)	
Azathioprine-based	38 (74.4)	3509 (35.6)	< .001

*Values in parentheses are percents. PTLD indicates posttransplant lymphoproliferative disorder.

late PTLD had occurred more frequently compared to the early form of disease (Table 2). There was no signification relation between the early-onset and late-onset groups in terms of clinical course and outcome. Posttransplant lymphoproliferative disorder had occurred more frequently among patients who had received azathioprine compared to those with MMF ($P < .001$).

The majority of the patients with non-Hodgkin lymphoma (61.7%) had extranodal tumor sites (Table 1), and there was no significant relation between extranodal involvement and mortality ($P = .90$). The sites of PTLD involvement are shown in Figure 1. Lymph nodes were the predominantly involved site (35.3%), followed by the gastrointestinal tract, brain, kidney allograft, lung, ovary, vertebral, and palatine. The age at diagnosis and the time from transplantation to diagnosis are listed for PTLDs in Table 3. Two patients had Hodgkin lymphoma.

Of the 51 recipients with PTLD, 11 had received ATG/ALG. Changing cyclosporine to sirolimus had been successfully done in 5 recipients. Chemotherapy and/or radiotherapy had been performed in 47 cases, and 5 patients had died before receiving any treatment. Two patients presented with kidney dysfunction. None of the 5 patients who treated by sirolimus experienced rejection, which means that kidney function was preserved when immunosuppression was changed to sirolimus, and all of them reached complete remission. Withdrawal of immunosuppression was associated more graft loss when compared to reduction of immunosuppressive therapy ($P = .001$).

Twenty-five patients enjoyed remission, responding to chemotherapy or radiotherapy. However, 26 (51.0%) died of the disease. The main cause of mortality was sepsis. Figures 2 and 3

Table 3. Comparison of Age at Diagnosis and Time From Transplantation to Diagnosis in Patients With Posttransplant Lymphoproliferative Disorders

Involvement Site	Mean Age at Diagnosis, y	Mean Time From Transplantation to Diagnosis, mo
Lymph nodes	39 ± 13	48 ± 52
Gastrointestinal tract	38 ± 10	101 ± 59
Brain	44 ± 11	40 ± 49
Kidney	52 ± 9	18 ± 6
Lung	46 ± 19	117 ± 47
Ovary	41 ± 7	93 ± 28
Vertebrae	29 ± 7	9 ± 0
Palatine	44	27
Acute lymphoblastic leukemia	22 ± 14	46 ± 4

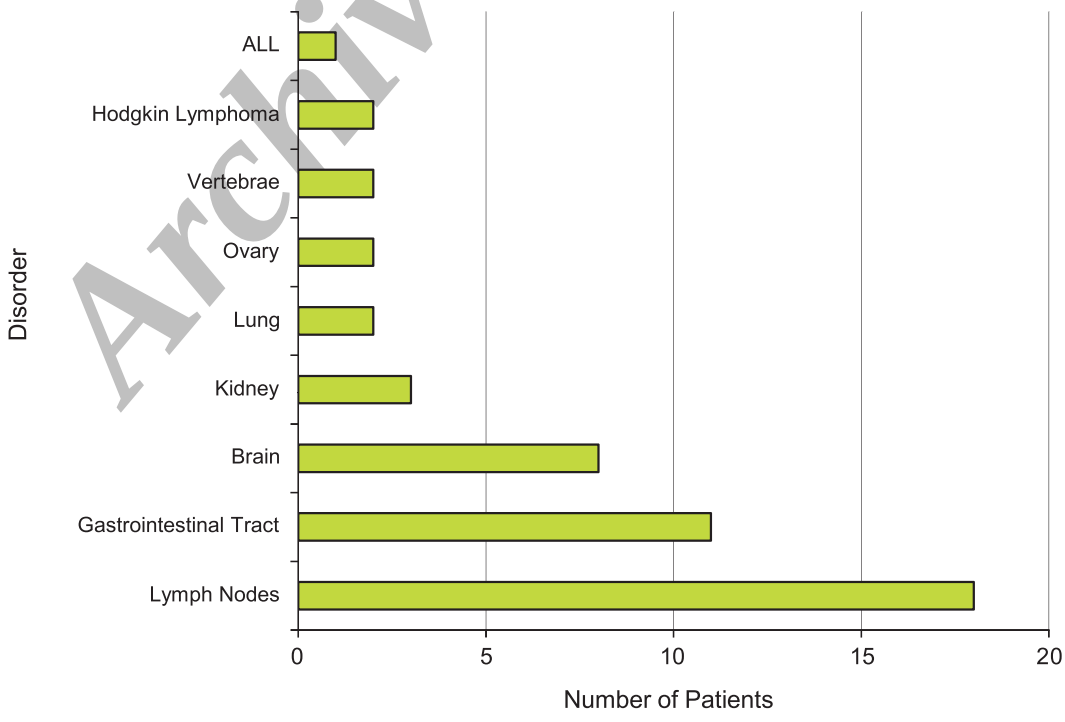

Figure 1. The sites of posttransplant lymphoproliferative disorder involvement. ALL indicates acute lymphoblastic lymphoma.

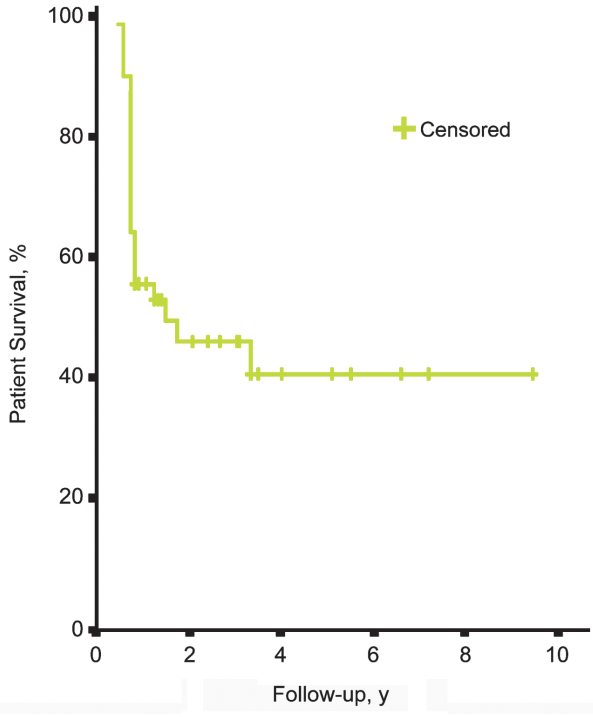

Figure 2. Patient survival since diagnosis of posttransplant lymphoproliferative disorder.

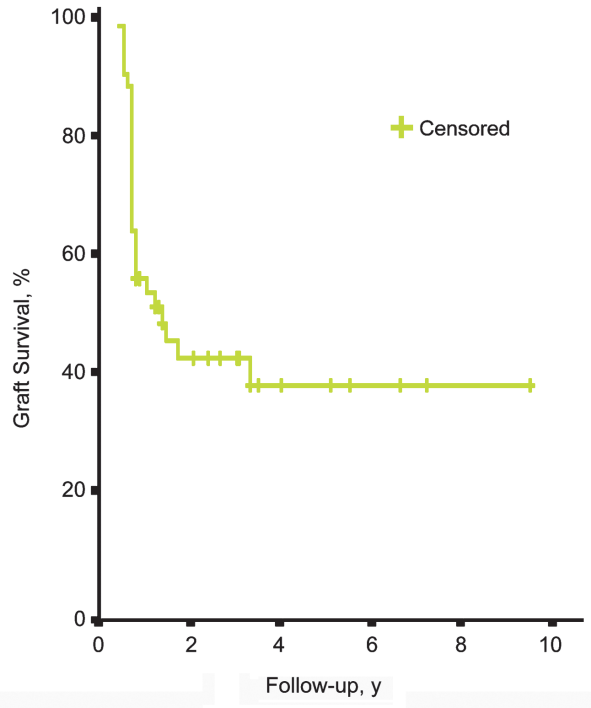

Figure 3. Kidney allograft survival (noncensored for death) diagnosis of posttransplant lymphoproliferative disorder.

shows the patient and graft survival rates since PTLD diagnosis. Twenty-one patients were living with a functioning graft, and 2 were on dialysis at the end of the follow-up period. The mortality rate was not significantly differences in terms of sex (P = .10) and early-onset versus late-onset PTLD (P = .70). Patient and graft survival rates since the time of PTLD onset were not significantly different in terms of the age, sex, and the time of presentation since transplantation (P = .60, P = .90, and P = .08 for patient survival, and P = .50, P = .20, and P = .60 for graft survival, respectively).

DISCUSSION

It is well-documented that kidney transplant recipients are at increased risk of developing lymphoproliferative disorders. The kidney recipient has a relative risk of developing PTLD that is 10 times greater than that in the general population.[9] We, however, were not able to make a comparison with the general population. Our study showed that the incidence of lymphoproliferative disorders (0.5%) was less than that in other reports from the Western counties (1% to 3%).[10] Posttransplant lymphoproliferative disorders (24% of all tumors) were the most common types of neoplasms after Kaposi sarcoma (34.5% of all cancers) in kidney transplant recipients, which is consistent with the previous studies.[3,5] Their greater incidence occurs in the first posttransplant months or years, and then gradually, it declines with time.[11] However, in our study, late-onset PTLD was more prevalent than its early-onset form. Lymphoproliferative disorders can present as early as less than a month to as late as several years after transplantation. In our study, the earliest case was observed 1 month and the latest case occurred 17.5 years following transplantation.

Non-Hodgkin lymphoma was the most common variant, accounting for more than 92% of our cases, and was predominantly extranodal presenting in the gastrointestinal tract or in the central nervous system. On the contrary to the lymphomas in the general population, which predominantly affect lymph nodes, the PTLD occurs in extranodal sites in 65% of the cases in the current study and 70% in another study.[12]

Epidemiologic studies in patients receiving azathioprine and prednisone immunosuppression confirm a 20- to 50-fold increase in relative risk of PTLD by comparison with the general population.[13,14] Furthermore, our results revealed the

incidence of PTLD was also significantly increased in patients receiving azathioprine when compared to patients receiving mycophenolate mofetil ($P < .001$); this finding is in contrast with previous reports, in which a triple immunosuppressive regimen including mycophenolate mofetil was considered to have the highest imposing impact on the post-transplant malignancies.[15]

Although some studies showed that early-onset PTLD frequently have a favorable outcome and late-onset PTLD behave more alike aggressive lymphoma with long latency period responds poorly to treatment and has worse prognosis,[16] we did not find signification relation between early- and late-onset groups in terms of clinical course and outcome.

Among the factors that increase the incidence of PTLD are the EBV status and the strength of immunosuppression.[17] An increased risk for PTLD has been associated with EBV seronegativity at the time of transplantation.[18] This risk is strengthened if the patients are seronegative for cytomegalovirus and the donors are seropositive for this virus.[19] Recipient EBV and CMV serostatus was not available for all patients. Thus, we could not examine the relationship between EBV and CMV with occurrence of PTLD in the current study.

Posttransplant lymphoproliferative disorder are recognized as a significant and morbid complication of solid-organ tranplantation.[20] Unlike lymphomas occurring in immunocompetent patients, PTLD often do not respond to chemotherapy, but a reduction or a withdrawal of the immunosuppressive treatment may be followed by a regression of the lymphoma.[21] Of patients with PTLD, 51.0% (26 of 51) died despite discontinuation of drugs and receiving the treatment, while in similar studies the figure is about 66.7%, and Penn reported that despite surgical therapy, chemotherapy, and radiotherapy, 80% of patients died.[22,23] Therefore, we have better outcomes in our patients compared to other studies.

Some studies have found a linkage between antilymphocytic agent treatment, and PTLD[24], but only 11 of our PTLD cases had ATG/ALG and none of our patients had OKT3. Opelz and Henderson demonstrated that the use of ATG/ALG or OKT3 in the kidney transplant recipients increases risk of PTLD 1.8 times.[25] They observed that treatment with ATG/ALG OKT3 increased the risk of lymphoma only during the first year after transplant, whereas the risk was similar to that in non-antibody-treated patients in subsequent years.[26]

CONCLUSIONS

Posttransplant lymphoproliferative disorder is a rare but devastating complication after kidney transplantation, and long-term prognosis can be improved with early recognition and appropriate therapy. However, immunosuppression, particularly azathioprine, is the leading factor in kidney transplant recipients.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Behzad Einollahi, MD
Nephrology Research Center, Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran, Iran
Fax: +98 21 8803 7673
E-mail: einollahi@bmsu.ac.ir

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