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Posttransplantation Lymphoproliferative Disorders in Renal Transplant Recipients: Report of Over 20 Years of Experience

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ABSTRACT

Introduction. Despite the benefits of immunosuppressive medications to improve graft function, they have several adverse effects, such as development of neoplasms in renal transplant recipients. Posttransplantation lymphoproliferative disorders (PTLDs) are not uncommon complications, so we conducted a study to evaluate the characteristics of affected patients.

Methods. We enrolled 2117 kidney recipients from June 1984 to March 2004 in order to find pathological and clinical evidence of neoplasms. We collected and analyzed all data on PTLD patients.

Results. Overall there were 46 recipients with different types of neoplasms, among which the most common types were diseases of the skin (24 cases, 52.2%), Kaposi's sarcoma (15 cases, 32.6%), and PTLD (14 cases, 30.4%). The mean (± SD) age of PTLD patients at the time of transplantation was 37.86 ± 9.67 years and 42.8% were women. Median and mean (± SD) time interval to PTLD diagnosis were 38.5 and 50.35 ± 41.7 months, respectively (range 1 to 146 months). Types of PTLD in these patients were kidney lymphoma (14.3%); gastrointestinal (14.3%); brain lymphoma; tonsils; palatine; Hodgkin's lymphoma, large cell lymphoma, and acute lymphoblastic lymphoma (each 7.1%), with 28.6% unspecified types. The 1-, 5-, and 10-year patient survival rates after transplantation were 71.4%, 51.4%, and 44.3%, respectively. Despite discontinuing immunosuppressive therapy in PTLD patients, five of six surviving had graft function up to a mean time of 105.4 ± 57.6 months after transplantation.

Conclusion. Our findings showed that the prevalence of PTLD was 0.66%, which was less than reports from Western countries. The fact that there were surviving grafts for a considerable time despite discontinuing immunosuppressive therapy is of great importance.

RENAL TRANSPLANTATION in patients with end-stage renal disease can improve their survival and quality of life. Despite the benefits of immunosuppressive medications to improve graft function and duration, they may have several adverse effects, such as development of neoplasms.[1–3] Secondary malignancies are the most important long-term complications of transplantation. The risk of malignancy is 100 times greater among transplant patients than the general population.[1–7]

The most frequent cause of posttransplantation lymphoproliferative disease (PTLD) is Epstein-Barr virus (EBV) in EBV-immortalized B-cell lines continue to proliferate with increased random genetic damage.[5] Although the role of each individual agent is unclear, the degree of overall suppression can be a major determinant of the development of a lymphoproliferative disorder.[1–3] Skin cancer is the most common malignancy[1,3,7] followed by PTLD.[1–6] The 1% to

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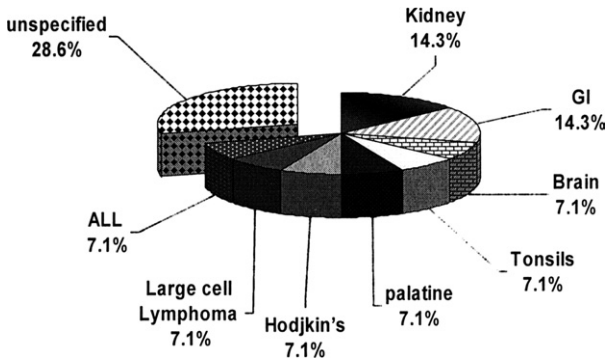

Fig 1. Frequency of different types and locations of posttransplantation lymphoma.

3% rate of lymphoma after renal transplantation is about 30 to 50 times higher than the general population.[3–7] Non-Hodgkin's lymphoma (NHL) accounts for 65% of lymphomas in the general population compared with 93% among transplant recipients.[4] Guz reported that the average time for the appearance of NHL was 15 months, while that for Kaposi's sarcoma (KS) was 20 months.[3,4,7]

The optimal treatment for these patients involves reduction or withdrawal of immunosuppression, antiviral medications, radiation therapy, surgical debulking, chemotherapy, alpha interferon, and cell-line treatment.[1–7] Lymphoproliferative disorders are among the most serious and potentially fatal complications of chronic immunosuppression in organ transplant recipients, so that a delay in diagnosis or treatment often leads to a fatal outcome.[3,4,7] We conducted this study to evaluate the characteristics of patients with PTLD and its correlation with various factors including patient and graft survival.

PATIENTS AND METHODS

In this retrospective and case series study, we enrolled 2117 renal transplant recipients from June 1984 to March 2004. We found 14 rare cases of neoplasms in our study. Survival time was defined as the interval from the time of diagnosis of malignancy to death; if there were no death report, survival time was defined as the interval from the time of malignancy diagnosis to the time the patient was last known to be alive. In this study, we reviewed patients with survival times greater than 6 months after grafting. We used SPSS 11/5 for data analysis evaluating dispersion and central tendency for descriptive analyses, and Kaplan-Meier for survival time analysis.

RESULTS

There were overall 46 recipients with various neoplasms, among which 82.9% of all types were skin neoplasms (24 cases, 52.2%), KS (15 cases, 32.6%), and PTLD (14 cases, 30.4%). The prevalence rate of PTLD was 0.66% (14/2117). The mean (±SD) age of PTLD patients at the time of transplantation was 37.86 ± 9.67 years and 42.8% were women. Median and mean (±SD) time intervals from transplant to PTLD diagnosis were 38.5 and 50.35 ± 41.7 months, respectively (ranging from 1 to 146 months). Types of PTLD in these patients were kidney lymphoma (14.3%), gastrointestinal (14.3%), brain lymphoma, tonsils, palatine, Hodgkin's lymphoma, large cell lymphoma, and acute lymphoblastic lymphoma (ALL) (each 7.1%), and finally 28.6% of unspecified types (Fig 1).

Five cases were diagnosed with radiography and biopsy together, three cases with radiography alone, four cases with biopsy, and one case with laparotomy. One case was a 43-year-old man who died 32 days after transplant with a brain mass reported as the possible cause of death. Ten cases (71.4%) had extranodal involvement. The 1-, 5-, and 10-year patient survival rates after transplantation were 71.4%, 51.4%, and 44.3%, respectively (Fig 2). Despite discontinuing immunosuppressive therapy in PTLD patients among surviving patients (6 out of 14) over the time, five surviving patients had functioning grafts was at a mean time of 105.4 ± 57.6 months after transplantation.

DISCUSSION

Our study showed that our 0.66% prevalence of lymphoproliferative disorders was less than other reports in Western counties (1% to 3%). Lymphoproliferative disorders formed 30.4% of all neoplasms, a figure similar to previous studies.[8] Lymphoproliferative disorders were the most common types of neoplasm after those of the skin. KS with 32.6% (15/24) was the most common type of skin neoplasm, which is consistent with similar studies.[1–7] The risk rates of K,S and PTLD were increased 400 and 30 to 50 times, respectively.[3] Mean age of patients with PTLD at the time of transplant was 37.8 ± 9.67 years. Since we did not have a control group in our study, we were not able to obtain the average age at which PTLD developed; neither were we able to make a comparison with general population.[6] But in comparison with similar studies (33.5 ± 10.1 years), our patients were older.

The mean interval from transplant to PTLD diagnosis was 50.35 ± 41.7 months, while in similar studies it was between 26.3 and 55.6 months.[5,6] Of patients with PTLD, 57.1% (8/14) died despite discontinuation of drugs, while in similar studies the figure is about 66.7%.[5] Penn reported that despite surgical therapy, chemotherapy, and radiotherapy, 80% of patients died.[9] According to this report, it is apparent that clinical progression after transplantation is more malignant and invasive than in general population as

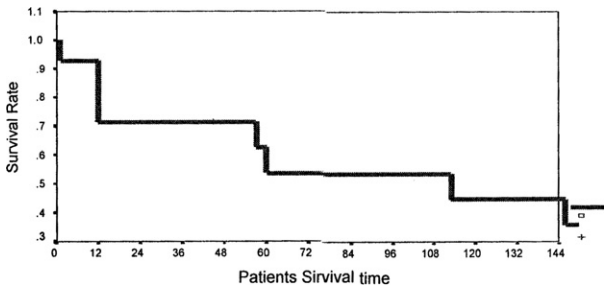

Fig 2. Kaplan-Meier survival rate of PTLD patients (n = 14).

the fatality rate due to PTLD is 48 times higher than among the general population.[9]

External nodal involvement was 71.4% (10/14), which confirms similar studies more than 50% in one study and in another about 70%.[8–10] Central nervous system involvement was 7.1%, which was lower than other studies reporting 20% to 25% involvement.[11] Kidney involvement was 14.2%, which was similar to the Opelz and Henderson report (14.2%).[11]

In conclusion, Iran, lymphoproliferative disorders are the most common type of neoplasm after skin tumors.

Because of the high risk of death and invasion, we recommend to decrease or withdraw immunosuppression, especially cyclosporine, as early as PTLD was diagnosed, since it can help to increase tumor regression. The fact that five out of six patients survived a considerable time despite discontinuation of immunosuppressive therapy was remarkable.

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