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# Experience with posttransplant lymphoproliferative disorders in solid organ transplant recipients

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**Abstract:** Nearly 6000 solid organ transplants have been performed at the University of Pittsburgh since 1981. Posttransplant lymphoproliferative disorders (PTLD) have occurred in 131 patients, at a frequency of 2.2%. The majority of cases manifest within 6 months following allograft, but individual lesions may arise several years thereafter. From 1981 to 1989, cyclosporine-A (CsA) served as the primary immunosuppressant in this population. In March of 1989, FK506 was introduced for clinical trials. Since that time, 1421 patients have received FK506 either for primary immunosuppression or as rescue therapy. The frequency of PTLD in this subpopulation is 1.5%. PTLD arising under FK506-containing regimens have clinicopathologic features similar to those arising with CsA immunosuppression. The frequency of PTLD at this point in time is approximately 1% in kidney allograft patients, 2.7% in liver, 3.3% in heart and 3.8% in heart/lung or lung recipients. An understanding of the range of histologic appearance is important for the diagnosis of PTLD, especially when it involves the allograft itself. Immunoglobulin heavy chain gene analysis shows that lesions with no rearrangements or with a rearrangement in only a small proportion of cells are more likely to respond to reduced immunosuppression than are those with clonal rearrangement involving a high proportion of cells. However, this distinction is not absolute, and a trial of reduced immunosuppression appears to be indicated regardless of clonal status.

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## Introduction

Lymphomas and lymphoproliferative disorders arise in a small but significant minority of organ allograft recipients (1). Penn's analysis of over 5000 neoplasms arising in transplant patients has provided a framework for understanding this phenomenon (2). Post-transplant lymphoid tumors are most often of B-cell origin and they are frequently preceded by infection with the Epstein-Barr virus. The lesions tend to be extranodal, may involve the allograft organ and may occur within a short time after transplantation. The opportunistic nature of this disorder has been underscored by the well-described phenomenon of tumor regression following a reduction of immunosuppression (1). Ap-

proximately 15% of tumors are of non-B cell origin, raising additional questions regarding the etiology, pathogenesis and behavior of this category of lesions (2).

Despite the recent rapid strides in our understanding of this disease, much remains to be learned. Although primary EBV infection, heavy immunosuppression, and type of allograft have all been identified as relative risk factors for development of posttransplant lymphoproliferative disorders (PTLD), there is no way to predict who will and who will not develop such a disorder. Although many PTLD respond to a reduction of immunosuppression, there are no precise pathologic criteria to diagnose those lesions which progress under this regimen. The continuing evolution of clinical immunosuppression and of new transplantation procedures requires constant surveillance of untoward side-effects, including lymphomas. The relationship of PTLD to conventional lymphoma is

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only beginning to be understood, and no adequate hypothesis yet exists to guide a therapeutic approach to EBV-negative, non-B cell lymphoproliferations in this population.

Our current state of knowledge mandates an open exchange of information regarding individual experience in the diagnosis and treatment of this life-threatening but potentially curable condition. This report updates features of PTLD as seen in the transplant patient population at the University of Pittsburgh.

## Patients and methods

### Patients

The organ transplant program at the University of Pittsburgh Medical Center was initiated in 1981. As of May 1991, a total of 3019 liver, 2057 renal, 583 heart, 79 heart/lung, and 51 lung transplant procedures had been performed. In addition, 79 procedures had involved the allograft of liver and other organs, and several had involved multivisceral transplants (liver, pancreas, bowel). The multivisceral transplant procedure has been modified into a cluster operation in which liver, a small portion of bowel, and pancreatic islets are transplanted. As of December 1990, a single small bowel transplant had been performed. Thus, a total of 5873 transplant procedures were performed during this period. The retransplant frequency for liver and kidney is less than 10%, and that for thoracic transplant recipients is essentially nil. Bone marrow transplants are performed at a separate institute and are not considered in this report. The figures are derived from the Transplant Database, which is maintained and continuously updated within the Division of Transplantation Surgery.

### Immunosuppression

From 1981 to 1989, cyclosporine-A (CsA) was the primary immunosuppressant used in all organ transplant groups at the University of Pittsburgh. In March 1989 the macrolide immunosuppressant FK506 was introduced for human use (3). As of May 1991, a total of 1421 patients had received FK506, either as primary immunosuppression or as rescue therapy. Prophylactic OKT3 or RATG was utilized in cardiothoracic transplants until October 1989, and was discontinued when FK506 therapy was initiated in this group.

### Diagnosis of lymphomas and lymphoproliferative disorders

The diagnosis of post-transplant lymphoproliferative disorder (PTLD) is used at our facility to refer to the entire spectrum of atypical lymphoprolifera-

tions arising within the organ transplant population. PTLD are subdivided into polymorphic and monomorphic subtypes on the basis of histologic appearance (1). Further evaluation includes phenotypic and genotypic analysis of clonal status, DNA analysis for the presence of EBV and for study of the clonal status of EBV, as previously described (3). A total of 133 patients received the diagnosis of PTLD or lymphoma during the period 1981–May 1 1991 at the University of Pittsburgh. Two patients had been previously transplanted at the University of Colorado and are excluded from this study.

## Results

### 1. Frequency of PTLD development and influence of allograft

The 131 cases of PTLD constitute approximately 2.2% of the transplant population for this period. The annual frequency has remained relatively constant, ranging from 0.7% to 3.4% per yr. No trends of increased or decreased frequency have been uncovered during this time interval.

To date, 83 PTLDs have been identified in liver allograft recipients, for an approximate frequency of 2.7%. Two cases of PTLD have occurred when livers have been transplanted in association with other organs (2.5%). Heart allograft recipients have a 3.3% incidence of PTLD (19 cases) whereas heart/lung recipients and lung recipients as a group have an incidence of 3.8% (5 cases). Following the occurrence of PTLD in 2 patients who underwent multivisceral transplantation, this operation has been discontinued. PTLD has not complicated the course of any patient who underwent intestinal transplantation, including those transplanted outside of the study interval.

### 2. Influence of immunosuppressive medication

FK506 was introduced into clinical use at the University of Pittsburgh in March, 1989. Since that time, 1421 patients have been immunosuppressed with this drug. There have been 16 cases of PTLD occurring in patients primarily immunosuppressed with FK506, and 5 cases of PTLD in patients who were switched to FK following CsA immunosuppression. Thus, 21 of 1421 patients, or 1.6%, have developed PTLD while on FK506 immunosuppression. Eight additional patients were switched to FK506 at varying times following the diagnosis of CsA-associated PTLD. None of these patients has developed recurrent PTLD to date.

### 3. Influence of OKT3

Twenty-five of the 131 PTLD patients (19%) received OKT3 at some time during their course.

Data regarding the entire population of patients who received OKT3 are currently being collected and will form the basis of a subsequent report.

#### 4. Time of onset of PTLT

The majority of cases continue to occur within 6 months following transplantation. The mean time to tumor onset in the subpopulation of patients treated with FK506 was 4 months. The mean time of onset for PTLT in association with CsA in this group has been calculated at 6.4 months, with a median of 4.4 months (4). The time of onset for the entire PTLT population ranges from 0.7 to 162 months.

#### 5. Pathology studies of PTLT

Lesions demonstrate the range of histopathology as previously described (4). Results of immunoglobulin heavy chain gene rearrangement analysis have been graded 0–3+ in 48 specimens to date (see Methods Section). Of these 48, 35% have been nonclonal (polyclonal), 19% have had minor (1+) rearranged subpopulations, 33% have had more significant percentages of rearranged cells within the lesions, and 13% appear to have been composed almost entirely of clonal outgrowths of cells. In 2 cases in which Ig gene rearrangement studies were nonclonal, subsequent analysis of the terminal repeat region of EBV revealed a clonal pattern.

#### 6. Treatment of PTLT

Reduction of immunosuppression combined with acyclovir and surgery for symptomatic lesions continues to be employed in all patients following the diagnosis of PTLT.

#### 7. Behavior of PTLT

Current follow-up was available from 62 patients for this report. Resolution of PTLT occurred in 69% of patients. A somewhat higher rate of resolution (81%) was seen in patients who developed PTLT in the setting of prior renal transplantation.

Twenty-five patients with recent follow-up had tumor clonality categorized on a 1–3 scale. Of 8 patients with nonclonal PTLT, resolution was seen in 6 (75%). Resolution was observed in all 3 patients with a 1+ clonal component. Four of 8 (50%) patients had resolution when the highest grad of clonality was 2+. In the setting of 3+ PTLT, only 2 of 6 (33%) patients showed resolution of disease.

## Discussion

Posttransplant lymphoproliferative disorder continues to complicate immunosuppressive regimens used for organ transplantation in approximately 2% of cases. This report indicates that this incidence also occurs in the FK506-containing regimen used at our institution. A recent report has generated concern regarding the incidence of PTLT occurring with the use of prophylactic OKT3 in cardiac allograft recipients (5). Prophylactic immunosuppression with OKT3 has not been used at the University of Pittsburgh since late 1989 (6), when the use of FK506 was initiated in this allograft group. Armitage et al. have summarized the thoracic transplant data prior to that time (mss. in preparation). Five of 352 patients (1.4%) who received rabbit anti-thymocyte globulin subsequently developed PTLT, whereas none of 77 patients who received OKT3 developed this disorder.

The frequency data for individual organ allograft subpopulations show small differences among the various groups. However, these differences do not appear to be as marked as earlier reports would indicate (1). Somewhat higher frequencies may also be generated depending upon the method of analysis. For example, if the patients who expire within a perioperative period of 30 d are censored from analysis, the frequency for lung and heart/lung patients rises to 7.9% (Armitage et al., mss. in preparation). In this report, such an approach was not taken, since some PTLT arose prior to 30 d.

The data presented here continue to support the hypothesis that PTLT encompasses a range of nonclonal to clonal proliferations (7). Preliminary evidence suggests that there may be some relationship between the extent of rearrangement and the ability of the tumor to persist despite a reduction of immunosuppression. We cannot advocate using the clonal status of these lesions to define treatment modalities; at present all patients are given a trial of reduced immunosuppression, usually with acyclovir. The individual response of the patient must be gauged clinically. The fact that patients with a clonal component often respond to such treatment supports the hypothesis, raised by recent phenotypic studies, that PTLT more closely resemble EBV-induced lymphoblastoid cells than they do fully malignant B lymphocytes of a Burkitt lymphoma type (8).

One concern in reducing immunosuppression as part of initial therapy is the fear of graft rejection. In renal recipients, loss of the graft is usually preferable to continued growth of the tumor. Histologic rejection is often, but not always, seen in liver allografts. In most cases, the graft can be preserved. Titration of immunosuppressive dosage may oc-

asionally be difficult, but is the main option at present. Although histologic rejection can be seen in heart and heart/lung recipients in such cases, no grafts have ever been lost as a result of this approach (Griffith B., personal communication).

Our current concepts of EBV-related lymphoproliferations do not adequately categorize other forms of lymphoproliferative disease which may occur in this population. One patient not detailed in this report had Hodgkin's disease which did not respond to reduced immunosuppression. The tumor was not related to EBV. The patient remains free of disease following radiation therapy. A more recent case of non-Hodgkin's lymphoma proved to have clonal rearrangement of the T-cell receptor, without evidence of EBV. Early follow-up indicates that the lesion appears to have regressed following reduction of immunosuppression. It is clear that the full range of this intriguing group of lesions is still being uncovered. Application of the lessons so far learned will allow us to identify variant tumors that may shed light on mechanisms entirely different from those currently thought to be operative in the Epstein-Barr virus-related lymphoproliferations.

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