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Post-transplant lymphoproliferative disorder after lung transplantation: A review of 35 cases

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BACKGROUND: Post-transplant lymphoproliferative disorder (PTLD) is a complication of organ transplantation. The risk of developing PTLD varies depending on a number of factors, including the organ transplanted and the degree of immunosuppression used.

METHODS: We report a retrospective analysis of 35 patients with PTLD treated at our center after lung transplantation. Of 705 patients who received allografts, 34 (4.8%) developed PTLD. One patient underwent transplantation elsewhere and was treated at our center.

RESULTS: PTLD involved the allograft in 49% of our patients and the gastrointestinal (GI) tract lumen in 23%. Histologically, 39% of tumors were monomorphic and 48% polymorphic. The time to presentation defined the location and histology of disease. Of 17 patients diagnosed within 11 months of transplantation, PTLD involved the allograft in 12 (71%) and the GI tract in 1 ($p = 0.01$). This "early" PTLD was 85% polymorphic ($p = 0.006$). Conversely, of the 18 patients diagnosed more than 11 months after transplant, the lung was involved in 5 (28%) and the GI tract in 7 (39%; $p = 0.01$). "Late" PTLD was 71% monomorphic ($p = 0.006$). Median overall survival after diagnosis was 18.57 months. Overall survival did not differ between all lung transplant recipients and those who developed PTLD.

CONCLUSIONS: PTLD is an uncommon complication after lung transplantation, and its incidence declined remarkably in the era of modern immunosuppression. We report several factors that are important for predisposition toward, progression of, and treatment of PTLD after lung transplantation.
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Post-transplant lymphoproliferative disorder (PTLD) is a serious complication of solid organ and hematopoietic stem cell transplantation that is linked to immunosuppression, the Epstein-Barr virus (EBV), and cytomegalovirus (CMV).[1–4] Although PTLD has been described after transplantation of all solid organs, its incidence varies depending on the organ transplanted; studies have reported rates between 2.5% and 8% in lung transplant recipients.[5–8] One explanation for this variability lies in the increased immunosuppression requirements for lung transplantation compared with other organs due to the higher risk of graft rejection.[9,10] Although individual regimens vary, immunologic management of lung transplantation is twofold: induction in the peri-operative period to deplete T cells or inhibit T-cell proliferation, followed by maintenance immunosuppression with daily agents.

PTLD is a highly variable disease in its clinical presentation as well as in its pathologic characteristics. Clinically, PTLD can affect virtually any organ system and can present with nodal and extranodal involvement. The clinical presentation can vary from simple lymphoid hyperplasia to aggressive disease that closely resembles non-Hodgkin's lymphoma.[11] Pathologically, there are 2 major subtypes of

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PTLD. Polymorphic PTLD is characterized morphologically by a plethora of monoclonal B cells in all stages of maturation as well as reactive T cells.[3] Monomorphic PTLD is a sub-type of non-Hodgkin's lymphoma that appears as homogeneous sheets of transformed, monoclonal B cells, often with cytogenetic abnormalities.[3,11] The etiologic factors that underlie these different sub-types, as well as the implications for differential therapy and survival, are unknown.

Owing to the rarity of this disease, no formal multicenter double-blinded trials have been performed to determine the ideal regimen for treating PTLD. The disease is closely linked to pharmacologic manipulation of the immune system, so reduction of immunosuppression (RI) remains the cornerstone of treatment.[10,12–15] Rituximab has become standard for CD20-expressing tumors in many centers and has significantly increased the response rate of therapy.[16–18] Other chemotherapeutic regimens have been used with some success.[10,19] All of these treatments, however, come with risks as a result of direct toxicity of the treatments as well as the risk of organ rejection that arises from RI.

In this report, we describe our experience evaluating and treating PTLD in lung transplant recipients at the Hospital of the University of Pennsylvania (HUP) and present a retrospective analysis of 35 patients. Our objectives were to identify key characteristics that link these patients and describe our methods and outcomes in treating this disease.

Materials and methods

The records of all lung transplant patients treated for PTLD at the HUP Abramson Cancer Center were reviewed. All patients received induction immunosuppression with anti-thymocyte globulin (ATG), daclizumab, or basiliximab. Maintenance immunosuppression regimens included a combination of prednisone, a calcineurin inhibitor (cyclosporine or tacrolimus) and an anti-proliferative agent (azathioprine, mycophenolate mofetil [MMF], or sirolimus).

The presence of disease was confirmed in all patients by biopsy specimen. Most patients were sub-classified by histologic sub-type as polymorphic, monomorphic, or other morphology. Immunohistochemical staining for CD20 and in-situ hybridization for EBV-encoded RNA (EBER) were performed as indicated.

Serum chemistries and computed tomography (CT) scans of the chest, abdomen, and pelvis were obtained in all patients. The disease was staged according to the Ann Arbor staging system.[20] Repeat imaging was performed to monitor the clinical progression of the disease. Response to treatment was defined by the Response Evaluation Criteria in Solid Tumors criteria.[21]

Treatment modalities included RI, rituximab infusion, surgical resection, radiotherapy, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or temozolomide-based chemotherapy regimens. In most cases, RI involved the discontinuation of the anti-proliferative agent and reduction in the dose of the calcineurin inhibitor. Steroids were continued unchanged. Patients treated with rituximab or CHOP as additional therapies received standard doses and courses.

Survival analysis was performed using the Kaplan-Meier method to estimate overall survival and progression-free survival. Comparison of expected vs observed data for time of presentation was performed using the Fisher's exact test. Grey's test was used to compare the cumulative incidence of PTLD before and after 2000. Death without PTLD was considered a competing risk. The Cox proportional hazards model was used to estimate the effect of PTLD on survival of lung transplant recipients. PTLD was treated as a time-dependent variable for this analysis.

Results

Patient characteristics

Between December 1991 and March 2011, 705 patients underwent lung transplantation at the HUP and PTLD developed in 34 (4.8%). One additional patient underwent transplantation at another institution but was treated for PTLD at HUP. Characteristics of our PTLD population are summarized in Table 1. The median age of patients at transplantation of 52 years (range, 21–65 years), and 17 (49%) were women. The most common indication for transplantation was chronic obstructive pulmonary disease, occurring in 17 (49%), followed by cystic fibrosis in 6 (17%). No significant differences were observed in the demographic characteristics and indications for transplantation between transplant recipients who did and did not develop PTLD (data not shown). In addition, there was not a significant relationship between age at transplantation and diagnosis of PTLD, using the median age at transplant as the cutoff ($p = 0.11$).

Incidence of disease

The cumulative incidence of PTLD was 5.87% ± 1.18% at 5 years after transplantation. The median time from transplant to diagnosis was 11 months (range, 11 days–15 years). PTLD incidence decreased between 1991 and 2011 (Figure 1). Although the number of patients diagnosed each year did not change dramatically (Figure 1A), plotting incidence against the year of transplantation demonstrated that 31 of the 35 PTLD patients (89%) underwent transplantation in the first 10 years of the program and 25 (71%) underwent transplantation between 1991 and 1996 (Figure 1B). Furthermore, because the annual number of transplants increased year-by-year, the percentage of patients who developed PTLD annually also decreased dramatically (Figure 1C). In 4 of the years studied, between 1991 and 1996, PTLD subsequently developed in >20% of the patients who received allografts that year. Conversely, between 2001 and 2011, the annual incidence of PTLD as a fraction of the total number of transplantations ranged from 0% to 3%.

The ability to diagnose PTLD partly depends on the length of follow-up since transplantation. In addition, there is a lag between transplantation and the onset of disease. Individuals who underwent transplantation before 2000 have had a longer follow-up than those who received allografts more recently. To account for the longer follow-up for patients who underwent transplantation before 2000, the cumulative incidence of PTLD was calculated separately for