Thoracic Presentations of Posttransplant Lymphoproliferative Disorders*

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Background: Posttransplant lymphoproliferative disorders (PTLDs) are rare complications following transplantation. Although organ-specific cases have been reported, primary presentation in the thoracic cavity has not been fully characterized.

Methods: Eleven cases of PTLD with a primary thoracic presentation were identified among 3,085 solid-organ transplant patients and 1,662 bone marrow transplant patients from 1990 to 2001.

Results: There were eight men and three women with a mean age of 49 years. Transplanted organs included lungs (three patients), kidneys (three patients), kidney/pancreas (two patients), allogeneic bone marrow (two patients), and heart (one patient). The time to presentation ranged from 1 to 97 months (median time, 8 months). Six patients developed PTLD within 1 year of undergoing transplantation. Pretransplant serology for Epstein-Barr virus (EBV) and cytomegalovirus was negative in 80% and 78% of cases, respectively. Radiographic evaluation revealed mediastinal adenopathy in 45% of patients, and pulmonary parenchymal lesions in 55%. Fifty-five percent of patients also had extrathoracic involvement. Diagnosis was achieved by CT-guided transthoracic needle biopsy in eight patients, and by open biopsy in three patients. Pathologic analysis revealed monomorphic PTLD (ie, diffuse large B-

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References

cell lymphoma) in seven patients, polymorphic PTLD in two patients, anaplastic large cell lymphoma in one patient, and Hodgkin lymphoma in one patient. Eighty-four percent of the specimens evaluated for EBV were determined to be positive by in situ hybridization and/or immunohistochemistry. All patients were initially treated with a reduction in immunosuppression therapy, and six patients (55%) received adjuvant chemotherapy. The overall mortality rate was 64%. Four patients died from complications of PTLD (kidney, two patients; heart, one patient; bone marrow, one patient), and three patients (all lung transplant recipients) died from rejection or infectious complications. The median interval from diagnosis to death was 13 months (range, 1 to 42 months).

Conclusions: Thoracic PTLD can occur in any transplant patient and must be regarded as a potentially fatal complication in the immunosuppressed patient. Heart and lung allograft recipients have the worst prognosis because of the mortality that accompanies rejection with subtherapeutic immunosuppression therapy. Earlier diagnosis and improvements in immunosuppression and chemotherapy may improve survival for these inherently high-risk patients.

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Key words: Epstein-Barr virus; immunosuppression; posttransplant lymphoproliferative disorder; transplantation

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; PTLD = posttransplant lymphoproliferative disorder; TTNBx = transthoracic needle biopsy; VCA = viral capsid antigen

Posttransplant lymphoproliferative disorders (PTLDs) are rare complications following solid-organ and bone marrow transplantation. Prevalence ranges from 0.6 to 20%, depending on the allograft and the reporting center. These disorders encompass the broad spectrum of clinical syndromes that are associated with lymphoproliferation, ranging from benign posttransplant infectious mononucleosis to malignant lymphoma.

Risk factors have been identified in the transplant population that increase the probability of developing PTLD. Among these, primary Epstein-Barr virus (EBV) infection is one of the most powerful predisposing factors for the early development of PTLD. Although the reactivation of EBV from latently infected cells can result in PTLD, most cases occur in patients without prior immunity or exposure. In 30% of cases, PTLD involves the transplanted allograft, although this number may be higher with early onset PTLD. Nonetheless, PTLD can present within the CNS, thoracic or abdominal cavities, or extravisceral lymphoid tissue. While there have been numerous reports documenting the various clinical, radiologic, and pathologic aspects of PTLDs, few have been devoted to the presentations of this disorder within the thorax. In this study, we describe a series of patients with various intrathoracic manifestations of PTLDs to elucidate some of the problems in diagnosing and managing this potentially fatal complication of transplantation.

Materials and Methods

We retrospectively reviewed the medical records from the Department of Anatomic Pathology at Emory University Hospital for cases of PTLD using the keywords “lymphoma,” “malignancy,” and “PTLD.” In addition, transplant coordinators from each respective organ-specific program were contacted for information about patients who developed PTLDs or other malignancies between January 1990 and December 2001. Information collected from our databases was correlated with that from the United Network for Organ Sharing database. Specific medical, radiologic, and pathologic data were extracted from the medical records of these patients. Follow-up information was obtained through medical record review and by contacting referring physicians. This study was approved by the Emory University School of Medicine Institutional Review Board.

Between January 1990 and December 2001, 3,085 solid-organ transplants (heart, 343 transplants; lung, 83 transplants; kidney, 1,573 transplants; kidney-pancreas, 371 transplants; and liver, 715 transplants) were performed at Emory University Hospital. From 1990 to 2001, 1,662 bone marrow transplants (allogeneic transplants, 673; autologous transplants, 989) were performed at Emory University Hospital. From 1990 to 2001, 1,662 bone marrow transplants (allogeneic transplants, 673; autologous transplants, 989) were performed using the methods described, we identified a total of 38 cases (0.80%) of PTLD (liver, 11 cases; kidney, 9 cases; heart, 5 cases; bone marrow, 5 cases [5 of 5 allogeneic transplants]; lung, 4 cases; and kidney-pancreas, 4 cases). Of the total number of cases of PTLD, 11 demonstrated a primary thoracic presentation (heart, 1 of 5 cases; lung, 3 of 4 cases; kidney, 3 of 9 cases; kidney-pancreas, 2 of 4 cases; liver, 0 of 11 cases; and bone marrow, 2 of 5 cases) [Table 1].

Demographic variables and patient characteristics were iden-

### Table 1—Transplant and PTLD Cases

<table>
<thead>
<tr>
<th>Organ Transplanted</th>
<th>Transplants, No.</th>
<th>Total PTLDs, No.</th>
<th>Thoracic PTLDs, No.</th>
<th>Mean Time to Thoracic Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>343</td>
<td>5</td>
<td>1</td>
<td>&lt; 1 yr 1 yr 0</td>
</tr>
<tr>
<td>Lung</td>
<td>83</td>
<td>4</td>
<td>3</td>
<td>2 1</td>
</tr>
<tr>
<td>Kidney</td>
<td>1,573</td>
<td>9</td>
<td>3</td>
<td>1 2</td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>371</td>
<td>4</td>
<td>2</td>
<td>0 2</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1,662*</td>
<td>5</td>
<td>2</td>
<td>0 2</td>
</tr>
<tr>
<td>Liver</td>
<td>715</td>
<td>11</td>
<td>0</td>
<td>6 5</td>
</tr>
<tr>
<td>Total</td>
<td>4,747</td>
<td>38</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

*Allogenic transplants, 673.
of the patients with thoracic PTLDs, EBV serology was available for 10 of 11 pretransplant patients and 8 of 11 posttransplant patients. Pretransplant and posttransplant EBV serologic titers included IgG and IgM antibodies to viral capsid antigen (VCA). The presence of any antibody (ie, IgG or IgM) defined EBV seropositivity. EBV seroconversion was defined as conversion from negative IgG VCA or IgM VCA to positive any time following transplantation. Pretransplant CMV status was also available in 9 of 11 patients, with seropositivity defined as the presence of IgG or IgM antibody to CMV. Seroconversion was defined as conversion from negative CMV antibody to positive at any time after transplantation.

Biopsy material, either from paraffin-embedded cell blocks obtained during transsthoracic needle biopsy (TTNBx) or open biopsy, was reviewed by an experienced hematopathologist. Using a combination of light microscopy, flow cytometry, immunohistochemistry for lymphoid markers, and EBV testing, the PTLD was classified according to criteria established by the World Health Organization International Agency for Research on Cancer,12 as follows: (1) reactive plasmacytic hyperplasia or infectious mononucleosis-like PTLD; (2) polymorphic PTLD; (3) monomorphic lymphoma, which includes B-lineage and T-lineage lymphomas; and (4) Hodgkin lymphoma.

RESULTS

Presentation and Diagnosis

Patients with thoracic PTLDs included eight men and three women with a mean age of 49 years (age range, 19 to 61 years). The median time interval from transplantation to diagnosis of a thoracic PTLD was 5 months, with a range of 1 to 97 months (Table 2). Patients receiving heart, lung, or bone marrow transplants had a median time to presentation of 5 months (range, 1 to 14 months), compared to 75 months (range, 5 to 97 months) for the kidney and kidney/pancreas transplant patients. The extrathoracic manifestations of PTLD in those patients with primary thoracic presentation are listed in Table 2. Of the 27 patients without thoracic presentations of PTLD, the primary site of involvement was identified according to the allograft transplanted, as follows: heart, two patients with mesenteric lymphadenopathy, and two patients with peripheral lymph node disease; lung, one patient with peripheral lymph node involvement; liver, five patients with primary intestinal lymphoma or mesenteric lymphadenopathy; three patients with hepatic (allograft) lymphoma, and three patients with peripheral lymph node or bone marrow disease; bone marrow, two patients with cervical lymph node involvement, and one patient with gastric lymphoma; kidney, two patients with mesenteric lymphadenopathy, one patient with splenic PTLD, two patients with CNS disease, and one patient with hepatic lymphoma; and kidney-pancreas, one patient with mesenteric lymphadenopathy and one patient with CNS lymphoma. Although eight patients were symptomatic, diagnosis was suspected in three asymptomatic patients based on abnormal chest radiograph findings alone. Clinical abnormalities or abnormal plain radiograph findings prompted further radiologic evaluation with a subsequent biopsy. On CT scanning, six patients presented with pulmonary masses or nodules (Fig 1), five patients had mediastinal lymphadenopathy, and one patient had a mediastinal mass. Six patients (54.5%) also had extrathoracic involvement. CT scan-guided TTNBx was successful in eight patients, but three patients required an open biopsy procedure. Of the transplant patients who presented with thoracic PTLDs, eight of nine solid-organ recipients, but none of the bone marrow recipients, had histologic evidence of rejection or graft-vs-host disease. The occurrence of acute and/or chronic rejection is listed in Table 2.

EBV/CMV Status and Pathology

Pretransplant EBV status was available in eight of the nine solid-organ transplant patients (89%) who developed thoracic PTLD (Table 3). All eight patients were EBV-negative prior to transplantation. Both bone marrow recipients were EBV-positive prior to transplantation. In addition, both patients receiving bone marrow transplants received allografts from matched sibling donors. All eight of the solid-organ and bone marrow recipients who had undergone posttransplant EBV serologic follow-up were positive for PTLD. Of the six patients who had EBV analysis performed on biopsy tissue, five were EBV-positive by in situ hybridization and/or immunohistochemistry (Fig 2). Similarly, only two of nine patients (22%) with pretransplant CMV data were positive for PTLD, and six of nine patients (67%) were positive for PTLD after transplantation. Seven patients had monomorphic B-cell lymphoma (Fig 3), two patients had polymorphic PTLD (Fig 4), one patient had anaplastic large cell lymphoma, and one patient had Hodgkin lymphoma.

Treatment

In all patients who presented with thoracic PTLD, the initial treatment consisted of a reduction of immunosuppression therapy. Other treatment modalities were implemented according to the discretion of the treating physician. These included traditional chemotherapy for non-Hodgkin lymphoma and anti-CD20 monoclonal antibody therapy.

The various immunosuppression regimens used by the different Emory University transplant programs are included in Table 2. In heart and lung allograft patients, only modest reductions were possible in order to avoid the risk of acute or chronic rejection. In kidney, kidney/pancreas, and bone marrow recipients, however, aggressive reduction or even discontinuation of immunosuppression therapy was standard. Six patients were treated with chemotherapy based on non-Hodgkin lymphoma protocols with the exception of one patient with Hodgkin disease. Two patients declined further treatment and died shortly thereafter, and two patients had remissions of PTLD with the reduction of immunosuppression therapy alone. In addition, anti-CD20 monoclonal antibody therapy was administered to two patients.
Table 2—Individual Patient Characteristics

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Allograft</th>
<th>Maintenance Immunosuppression</th>
<th>Months to PTLD</th>
<th>Primary Site</th>
<th>Extrathoracic PTLD</th>
<th>Presentation</th>
<th>EBV Status</th>
<th>Pathology</th>
<th>Episode of Rejection</th>
<th>Time to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>Heart</td>
<td>Cyclosporine, prednisone, mycophenolate mofetil</td>
<td>5</td>
<td>Mediastinum both lungs</td>
<td>Liver</td>
<td>Fever, fatigue, headache</td>
<td>Negative</td>
<td>Positive</td>
<td>Monomorphic B-cell, EBV+</td>
<td>Acute grade II</td>
</tr>
<tr>
<td>19</td>
<td>Bilateral lung</td>
<td>Azathioprine, prednisone, cyclosporine, mycophenolate mofetil</td>
<td>8</td>
<td>Mediastinum</td>
<td>None</td>
<td>No symptoms</td>
<td>Negative</td>
<td>Positive</td>
<td>Polymorphic, EBV+</td>
<td>Acute grade II</td>
</tr>
<tr>
<td>60</td>
<td>Left lung</td>
<td>Azathioprine, prednisone, cyclosporine, mycophenolate mofetil</td>
<td>3</td>
<td>Left lung (donor)</td>
<td>None</td>
<td>No symptoms</td>
<td>Negative</td>
<td>Positive</td>
<td>Monomorphic B-cell</td>
<td>Acute grade IV and OB</td>
</tr>
<tr>
<td>42</td>
<td>Right lung</td>
<td>Azathioprine, prednisone, cyclosporine, mycophenolate mofetil</td>
<td>14</td>
<td>Left lung (native)</td>
<td>None</td>
<td>No symptoms</td>
<td>Negative</td>
<td>Unknown</td>
<td>Monomorphic B-cell</td>
<td>Acute grade II and OB</td>
</tr>
<tr>
<td>40</td>
<td>Bone marrow allograft</td>
<td>Prednisone, cyclosporine</td>
<td>4</td>
<td>Left and right lung</td>
<td>None</td>
<td>Pleuritic chest pain</td>
<td>Positive</td>
<td>Positive</td>
<td>Polymorphic, EBV+</td>
<td>No</td>
</tr>
<tr>
<td>65</td>
<td>Bone marrow allograft</td>
<td>None</td>
<td>1</td>
<td>Mediastinum</td>
<td>Abdomen</td>
<td>Fever</td>
<td>Positive</td>
<td>Positive</td>
<td>Monomorphic B-cell, EBV+</td>
<td>No</td>
</tr>
<tr>
<td>55</td>
<td>Kidney/pancreas</td>
<td>Cyclosporine, prednisone, mycophenolate mofetil</td>
<td>36</td>
<td>Right lung</td>
<td>None</td>
<td>Cough, fever, anorexia</td>
<td>Negative</td>
<td>Positive</td>
<td>Monomorphic B-cell</td>
<td>Acute grade II, pancreas</td>
</tr>
<tr>
<td>50</td>
<td>Kidney/pancreas</td>
<td>Cyclosporine, prednisone, azathioprine</td>
<td>76</td>
<td>Mediastinum</td>
<td>Right axilla</td>
<td>Fever, weight loss, anorexia</td>
<td>Negative</td>
<td>Positive</td>
<td>Hodgkin lymphoma, EBV+</td>
<td>Acute grade III, kidney</td>
</tr>
<tr>
<td>57</td>
<td>Kidney</td>
<td>Cyclosporine, prednisone, azathioprine</td>
<td>75</td>
<td>Right lung</td>
<td>Bone marrow, cutaneous</td>
<td>Fever, sepsis</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Monomorphic B-cell</td>
<td>Chronic rejection at autopsy</td>
</tr>
<tr>
<td>53</td>
<td>Kidney</td>
<td>Cyclosporine, prednisone, azathioprine</td>
<td>97</td>
<td>Mediastinum</td>
<td>Paraaortic lymph nodes</td>
<td>Fever, weight loss, anorexia</td>
<td>Negative</td>
<td>Unknown</td>
<td>Anaplastic T-cell, EBV−</td>
<td>No</td>
</tr>
<tr>
<td>42</td>
<td>Kidney</td>
<td>Cyclosporine, prednisone, azathioprine</td>
<td>5</td>
<td>Mediastinum</td>
<td>Abdomen, cervical nodes, CNS</td>
<td>Fever, weight loss</td>
<td>Negative</td>
<td>Positive</td>
<td>Monomorphic B-cell</td>
<td>Acute grade IV and chronic</td>
</tr>
</tbody>
</table>

*OB = obliterative bronchiolitis; Pre = before transplant; Post = after transplant; HD = hemodialysis.
Outcomes

The median length of follow-up was 24 months (range, 1 to 144 months) and was complete in all patients. In general, survival was poor, with an overall 1-year survival rate of 64%, and a 5-year survival rate of 36%. Of the PTLD patients who presented without thoracic involvement, the 5-year survival rate was comparable at 33.3%. None of the heart or lung transplants afflicted with thoracic PTLDs survived 5 years. On the contrary, kidney, kidney/pancreas, and bone marrow recipients had a 5-year survival rate of 57%. Four of seven deaths (57.1%) were directly attributable to PTLD; however, the three lung transplant recipients died from complications of chronic rejection or infection (Table 4). The mean interval from diagnosis to death was 13 months (range, 1 to 42 months).

Discussion

Chronic rejection and opportunistic infections are the major obstacles that limit the success of solid-organ and bone marrow transplantation. The development of novel prevention strategies and highly specific immunosuppression regimens may reduce the incidence of these complications. PTLD is a rare complication that develops in transplant patients. This potentially lethal lymphoproliferative process is causally related to several factors, including the type of transplanted allograft, pretransplant seronegative EBV status, the intensity of immunosuppression, and the incidence and frequency of acute rejection episodes.2,5–7,13,14 At our institution from 1990 to 2001, PTLD developed in < 1% of all solid-organ and bone marrow transplant recipients. The incidence was highest in lung allograft recipients (4.8%), and was lowest in renal allograft recipients (0.57%).

Primary presentation within the chest occurred in 29% of our PTLD cases. Thoracic presentations of PTLD occurred more often in lung transplant recipients, but also occurred in heart, bone marrow, kidney, and kidney-pancreas recipients. Thoracic presentations of PTLD have been reported,11,15,16 but these studies usually focused on heart and lung allograft recipients. Thoracic PTLD did not occur in any of our liver transplant patients, although Dodd and colleagues11 reported a higher incidence among liver transplant recipients. However, Ben-Ari and colleagues17 documented no intrathoracic PTLD cases in their cohort of 422 liver transplant patients.

Table 3—EBV and CMV Status*

<table>
<thead>
<tr>
<th>Status</th>
<th>Pretransplant</th>
<th>Posttransplant</th>
<th>Tissue Pathology†</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>2/10</td>
<td>8/8</td>
<td>0/8</td>
</tr>
<tr>
<td>CMV</td>
<td>8/10</td>
<td>0/8</td>
<td>6/9</td>
</tr>
</tbody>
</table>

*Values given as No. of patients with condition/total No. of patients. †EBV plus biopsy tissue.

Figure 2. Photomicrograph of monomorphic B-cell lymphoma with immunohistochemistry stain positive for EBV (original ×63).

Figure 3. Photomicrograph of monomorphic B-cell lymphoma (hematoxylin-eosin, original ×63).
ancy in intrathoracic PTLD among liver transplant patients may be partly related to the overall low incidence of this complication in the transplant population.

This study emphasized the importance of acknowledging the unusual intrathoracic presentations of this disorder. The most common radiologic findings in this series were isolated or multiple discreet pulmonary nodules and enlarged mediastinal lymph nodes. Patchy airspace disease, pleural effusion, and thymic PTLD also have been described but were not present in our patients.11 Although the presence of a pulmonary lesion in a transplant patient may be suggestive of PTLD, these anomalies often can be mistaken as manifestations of infection. Therefore, achieving an accurate diagnosis requires tissue biopsy of parenchymal lesions or enlarged mediastinal nodes. CT scan-guided TTNBs, which has been confirmed as a sensitive diagnostic tool,18 successfully diagnosed PTLD in 8 of 11 cases.

Although definitive data are lacking regarding factors that influence outcomes in patients with PTLD, a more thorough understanding of its etiology now exists. Probably the most influential is the role of EBV infection in pretransplant seronegative patients.7 It is important to note, however, that EBV-negative PTLD has been reported to account for 10 to 20% of PTLD cases.19 Furthermore, the intensity of immunosuppression also has been implicated as a major risk factor and may explain why lung transplants may be more susceptible to early presentations of PTLD.20 Although risk factors have been identified that may predispose a patient to PTLD, no individual risk factor can solely account for its pathogenesis.

Because of the infrequency of this complication, large trials reporting the outcomes of this disorder are limited to single-institution experiences. In our lung transplant patients who developed PTLD, 75% had intrathoracic involvement. In both heart and lung allograft recipients, PTLD occurred within 14 months after transplantation. Compared to the heart and lung recipients, those receiving kidney and pancreas allografts usually had delayed presentations, with 80% presenting > 1 year after transplant. The higher 5-year survival rate of kidney and pancreas allograft recipients suggests improved survival with delayed presentations, but this may reflect the overall expected higher long-term survival among kidney and pancreas recipients compared to lung recipients. Although some studies have suggested that the timing of PTLD development may reflect its malignant potential,21 our results suggest that the intensity of the organ-specific immunosuppression regimen and the concomitant extrathoracic involvement may be more significant. Although all of our lung and heart transplant patients with thoracic PTLD presented early after undergoing transplantation, the lung recipients ultimately died of complications of chronic rejection or of unremitting infection. On the contrary, the patients who presented with disseminated disease had a high mortality rate, irrespective of the timing, primary location, treatment strategy, or transplanted allograft. Our heart, kidney, pancreas, and bone marrow transplant patients who presented with disseminated disease fared poorly, while those with isolated thoracic involvement responded well to immunosuppression therapy changes and chemotherapy.

It is intuitive to state that patients with disseminated disease have a worse prognosis, but these data suggest that survival among heart and lung transplant recipients with isolated thoracic PTLD may correlate more to the inability of these patients to tolerate reductions in immunosuppression once a diagnosis is achieved rather than to the timing or site of development of the PTLD. Both pancreas and renal allograft recipients rely on adequate immunosuppression therapy for graft function but can survive with the

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reduction of Immunosuppression</th>
<th>Monoclonal Antibody to CD-20</th>
<th>Survival</th>
<th>Complications of PTLD</th>
<th>Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapy</td>
<td>Chemotherapy</td>
<td>1 yr</td>
<td>5 yr</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>0/1</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>3/3</td>
<td>2/3</td>
<td>0/3</td>
<td>3/3</td>
<td>0</td>
</tr>
<tr>
<td>Kidney</td>
<td>3/3</td>
<td>1/3</td>
<td>0/3</td>
<td>1/3</td>
<td>2</td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>2/2</td>
<td>2/2</td>
<td>1/2</td>
<td>2/2</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2/2</td>
<td>0/2</td>
<td>1/2</td>
<td>1/2</td>
<td>1</td>
</tr>
<tr>
<td>Total patients</td>
<td>11/11</td>
<td>6/11</td>
<td>2/11</td>
<td>7/11 (64%)</td>
<td>4/11 (36%)</td>
</tr>
</tbody>
</table>

*Values given as No. of patients with condition/total No. of patients unless otherwise indicated.
allograft dysfunction that accompanies rejection. In contrast to our series, others have reported\cite{15,21,22} the cause of death in lung transplants to be directly attributable to complications of PTLD. It is more likely that a combination of factors, including primary EBV infection, intensity and duration of immunosuppression therapy, and type of allograft each contribute to the development of PTLD.

In contrast to solid-organ recipients, PTLD in bone marrow allograft recipients is almost always of donor origin\cite{23} because the host immune system is exclusively of donor origin. Moreover, they usually present early after transplantation\cite{24} and often present with disseminated disease.

The majority of cases of thoracic PTLD in this report were classified as monomorphic B-cell lymphoma. The patients with less aggressive polymorphic cases of PTLD had better outcomes, as expected. PTLD of T-cell origin is less common than B-cell morphology and is more likely to be EBV-negative.\cite{20}

The reduction or discontinuation of immunosuppression therapy is the cornerstone of therapy for PTLD. The majority of patients in this series experienced the regression of disease with these changes. Chemotherapy based on non-Hodgkin lymphoma protocols was administered with varying success. The patient with Hodgkin histopathology was treated with a doxorubicin-based protocol. Success also was achieved with anti-CD20 monoclonal antibody therapy, with both patients achieving long-term survival after its administration. Unfortunately, our overall outcomes were disappointing, with only 64% and 36% of thoracic PTLD patients, respectively, surviving to 1 and 5 years.

In conclusion, thoracic PTLD represents a realistic threat to solid-organ and marrow allograft recipients. Although more likely to occur in lung transplant recipients, heart, abdominal organ, and bone marrow transplant patients are also susceptible. Presentation in the thorax can occur at any time in the posttransplant period and does not necessarily portend a worse prognosis. As we have demonstrated in this series, patients who present with isolated thoracic PTLD, even with malignant morphology, have a better prognosis than those with disseminated disease. The higher mortality rate in lung and heart transplant recipients reflects the fatal sequela of chronic rejection that occurs with inadequate immunosuppression therapy. An increased awareness of this complication, earlier diagnosis and intervention, and enhanced treatment modalities may improve the outcome of these inherently high-risk patients.

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REFERENCES

Endoscopic and Endobronchial Ultrasound Real-time Fine-Needle Aspiration for Staging of the Mediastinum in Lung Cancer*

Robert C. Rintoul, PhD; Kristopher M. Skwarski, MD; John T. Murchison, MD; Adam Hill, MD; William S. Walker, MD; and Ian D. Penman, MD

Mediastinal lymph node metastases in patients with non-small cell lung cancer are a critical determinant of operability. Mediastinoscopy is invasive, requires general anesthesia, and carries appreciable morbidity. The development of minimally invasive techniques for the pathologic staging of lung cancer is important. We report a one-stop minimally invasive method for the pathologic diagnosis and staging of the majority of the mediastinum under conscious sedation using a novel prototype endobronchial ultrasound probe with real-time fine-needle aspiration (FNA) facility in combination with conventional endoscopic ultrasound FNA.

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Key words: endobronchial ultrasound; endoscopic ultrasound; fine-needle aspiration; lung cancer; mediastinal lymphadenopathy

Abbreviations: EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; FNA = fine-needle aspiration; NSCLC = non-small cell lung cancer; TBNA = transbronchial needle aspiration

In the absence of distant metastases, mediastinal lymph node metastases in patients with non-small cell lung cancer (NSCLC) are a critical determinant of operability, occurring in up to 38% of cases at diagnosis.1 Until now, mediastinoscopy has been the investigation of choice for the diagnosis and staging of middle mediastinal lymph nodes, but it is invasive, requires a general anesthetic, and has a complication rate of 1 to 3%.2 The development of minimally invasive techniques for the pathologic staging of the mediastinum offers increased patient safety as well as potential savings in time and cost. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA), while extremely effective for biopsies of posterior and inferior mediastinal lymph node stations, does not allow access to stations anterior and superior to the trachea or main bronchi.3

Here, we describe the use of a novel prototype linear array endobronchial ultrasound (EBUS) probe with a fine-needle biopsy facility for real-time imaging and aspiration biopsy of pretracheal, peritracheal, and hilar lymph nodes, which, when used in combination with EUS-FNA, allows the minimally invasive diagnosis and staging of the majority of the mediastinum with the patient under conscious sedation.

Case Reports

Case Report 1

A 68-year-old ex-smoker presented with a short history of lethargy. A CT scan of his chest revealed right paratracheal (station 4R) and subcarinal lymphadenopathy (station 7), although no primary mass lesion was apparent. Under conscious sedation, the pretracheal, peritracheal, subcarinal, and hilar lymph node stations (stations 1, 2, 3, 4, 7, and 10) were examined using a novel prototype linear array ultrasonic bronchoscope (model XBF-UC280F-OL8; Olympus Ltd; Tokyo, Japan) [Fig 1]. The instrument, which is similar to a standard fiberoptic bronchoscope, has a maximum outer

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22019/ on 06/26/2017)