T-Cell and NK-Cell Posttransplantation Lymphoproliferative Disorders

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Abstract

Posttransplantation lymphoproliferative disorders (PTLDs) of T-cell or natural killer (NK)-cell origin are an uncommon heterogeneous group of lymphoid proliferations that fulfill the criteria for one of the T- or NK-cell lymphomas/leukemias. This report summarizes 130 T/NK-cell PTLDs reported in the literature or presented at the Society for Hematopathology/European Association for Haematopathology Workshop on T/NK-cell malignancies. The T/NK-cell PTLDs occur at a median of 66 months following transplantation and are usually extranodal. The most common types reported are peripheral T-cell lymphoma, unspecified, and hepatosplenic T-cell lymphoma. Approximately one third are Epstein-Barr virus (EBV)+. The median survival is 6 months. EBV+ cases have a significantly longer survival than EBV– cases, even when indolent T-cell large granular lymphocytic leukemias are included among the EBV– cases. Many T/NK-cell PTLDs have been treated with chemotherapy, often together with decreased immunosuppression, but there are infrequent patients who have done well without chemotherapy or radiation.

Posttransplantation lymphoproliferative disorders (PTLDs) represent a heterogeneous group of lymphoid and plasmacytic proliferations that occur following solid organ or bone marrow or stem cell transplantation and for which there is no other known explanation. Categorization of PTLD is important for prognostic and therapeutic purposes. The World Health Organization (WHO) classification of hematopoietic and lymphoid tumors includes a separate classification for PTLDs. As indicated, T-cell PTLDs are included as one of the major types of monomorphic PTLDs. PTLDs are classified as being of T-cell type when they fulfill the criteria for a T-cell leukemia or lymphoma. Once designated, they are further classified based on the specific type of T-cell neoplasm they most closely resemble. This review also includes the rare PTLDs of natural killer (NK)-cell origin, even though they are not specifically listed in the 2001 WHO classification. Although not always documented, T/NK-cell PTLDs should be clonal proliferations that are not acceptable for a reactive disorder. Thus, there are no PTLDs of “early” or polymorphic type that would be considered T-cell PTLD. A simple T-cell predominance, as one can see, in particular, in some polymorphic or early PTLDs, is insufficient to diagnose a PTLD as being of the T-cell type. Furthermore, in contrast with the monomorphic PTLDs of B-cell origin that are recognized because they are composed of numerous transformed cells or, less often, homogeneous sheets of plasma cells, monomorphic T-cell PTLDs are not necessarily composed of numerous transformed-appearing cells nor are they necessarily monomorphic-appearing.

It is in part for these reasons, together with, as discussed subsequently, the rarity of T/NK-cell PTLDs and their frequent
lack of associated Epstein-Barr virus (EBV) infection that they may be more difficult to diagnose than their B-cell “counterparts.” The single case illustrated herein emphasizes the importance of immunophenotypic and, in selected cases, genotypic studies in the workup of potential T/NK-cell PTLDs. The histopathologic subtleties and the important role of ancillary studies in the recognition and classification of the many different types of T-cell neoplasms that can manifest as T/NK-cell PTLDs are discussed in other 2005 Society for Hematopathology/European Association for Haematopathology Workshop articles published in the April, May, and June 2007 issues of the Journal.

This discussion is based on a comprehensive but incomplete review of the T-cell and NK-cell PTLD cases that have been reported,2-79 together with those presented at the Workshop (not known to have been published). With rare exceptions, the cases will not be further referenced in this article.

The descriptions of these 130 cases help elucidate the spectrum of T/NK-cell PTLDs and their clinical associations; however, the analysis should be interpreted with some caution because it is flawed for several reasons. First, it is skewed because most of it is based on cases that were considered to be worth reporting. Second, there may be artificial geographic biases, eg, based on how many reports were derived from human T-cell lymphoma/leukemia virus-type 1 endemic vs nonendemic regions. Third, the degree of detail and the extent of ambiguities in the reports vary widely, as do the methods used to work up each case of PTLD. I have not tried to rigorously differentiate, for example, between EBV positivity documented by EBV small-encoded RNA in situ hybridization analysis vs the less sensitive EBV latent membrane protein type 1 immunohistochemical stains. I excluded cases in which it seemed ambiguous if the lesions reported were truly PTLDs, but I did not exclude cases even if the information provided about them was incomplete or the precise classification not completely convincing. Nor did I attempt to dissect each reported case in detail. The possibility that some cases are included twice cannot be completely excluded. Fourth, some cases required some translation into more conventional terms, although I tried to do this as little as possible. Finally, I have added some artificiality to the numeric analyses owing to some vagaries in some of the reports and in my translation sometimes of years into months. I will not burden the reader with additional shortcomings of this endeavor.

Despite the aforementioned cautions, these cases paint a reasonable picture of T/NK-cell PTLDs and, I hope, assist in their recognition. Because of the significant differences between EBV+ and EBV– PTLDs,54,80 this review will also analyze cases based on their EBV status.

### How Frequent Are T/NK-Cell PTLDs Compared With Other PTLDs?

Most Western studies report that T-cell PTLDs constitute about 7% to 15% of all PTLDs following solid organ transplantation with at least 1 report describing only 2%.14,15,40,81-84 One Japanese study, however, reported a T-cell origin for 42% of the PTLDs following renal transplantation.29

### In Whom Do T/NK-Cell PTLDs Occur?

T/NK-cell PTLDs occur in patients of all ages, with a range of 2 to 75 years and a median of 43.5 years. EBV– cases show a slightly older but not significantly different median age vs EBV+ cases (45.5 vs 41.5 years). When known, the male/female ratio is 2.4 for EBV– cases and an inexplicably high 4.4 for EBV+ cases. The former is most similar to PTLDs as a whole.

For patients with T-cell PTLDs and available information, 69% had received kidney transplants (including several who also received pancreas or other organs), 20% had received heart or heart-lung transplants, 5% liver transplants, 6% bone marrow or peripheral blood stem cell transplants, and 1 a multivisceral transplant. This is in contrast with our experience in which PTLDs are more common in liver transplant recipients.85

### When and Where Do T/NK-Cell PTLDs Occur?

T/NK-cell PTLDs are among the “late” occurring PTLDs. The median time from transplantation to development of PTLD was 66 months, although 15% occurred during the first posttransplantation year (1-312 months). A significant difference between the time to development of EBV+ vs EBV– cases could not be demonstrated (median, 51 vs 67.5 months).

Extranodal sites were involved in approximately 91% of cases, together with lymph node involvement in 19%. The
14-year-old boy 76 months following cardiac transplantation and 6 years following a polymorphic PTLD. Two initial needle core biopsy specimens were considered not to be diagnostic of a PTLD. Supporting the diagnosis in this pulmonary wedge biopsy specimen were the histopathologic features, the dim CD3 expression by flow cytometric immunophenotypic analysis, and the documented T-cell clonality by Southern blot (T-cell receptor [TCR]β) and polymerase chain reaction (TCRγ) studies. The patient did not respond to alemtuzumab (Campath 1H) and went into remission only after 2 different chemotherapeutic regimens. Note the mass lesion in the lung (A) composed predominantly of pale areas surrounding scattered follicles (B, H&E, ×4). The follicles often were regressively transformed (C, H&E, ×40). The infiltrate included many small lymphocytes with irregular nuclear contours (D, H&E, ×100). There were also foci with large transformed cells that were CD20+ (E, H&E, ×100; inset, CD20 immunostain with hematoxylin counterstain, ×40). Only infrequent Epstein-Barr virus+ cells were identified. Case contributed by S.H. Swerdlow and S.A. Webber.

**Image 1** This pulmonary T-cell posttransplantation lymphoproliferative disorder (PTLD), further classified as peripheral T-cell lymphoma, unspecified type, occurred in a...
PTLD often involved more than 1 extranodal site. The more common extranodal sites included the peripheral blood (22%), bone marrow (30%), spleen (28%), skin (19%), liver (18%), gastrointestinal tract (14%, most often in the small intestine and including 1 case with involvement of the allograft), and lung and pleura or pleural cavities (12%). Renal involvement (7%) often represented disease in the allograft. Other sites included the brain (5%); heart, pericardium, or pericardial fluid (5%, including 2 cases with involvement of the allograft); multiple unspecified sites (4%); nose or pharynx (3%); pancreas (3%, including 2 of 3 cases involving an allograft); and mediastinum (not clearly lymph nodes, 2%). Fewer than 1% of cases involved the breast, gallbladder, thymus, salivary gland, a pelvic mass, abdominal fluid, or muscle.

What Types of T/NK-Cell PTLDs Are There, and How Often Are They Associated With the EBV?

T/NK-cell PTLDs include many types of T- and NK-cell neoplasms [Table 2].45,86 In general, the criteria for subclassifying the monomorphic T-cell PTLDs are those for T-cell neoplasms occurring in immunocompetent patients, although some cases are reported with diagnoses that are not easily translatable and others are reported using prior classifications.87,88

The largest category includes cases that would most likely be classified as peripheral T-cell lymphoma, unspecified (PTCL-U) type (36%). This is a heterogeneous category that seems to include some subsets of more homogeneous clinicopathologic entities that are difficult to precisely categorize. Hanson et al7 described a series of T-PTLDS that resembled acute leukemia and appeared similar to the cases of aggressive NK-like T-cell malignancy with leukemic presentation described by Natkunam et al.52 The neoplastic cells appear blastoid, including at least some with azurophilic granules, and have been described as resembling monoblasts or as blast-like granular lymphocytes; however, they have a variably aberrant mature T-cell phenotype. Most cases tested are CD56+. These cases may also bear a relationship to other cases of NK-like T-cell PTLDs. In addition to the T/NK-cell PTLD described subsequently, at least 14 of the PTCL-U cases were cytotoxic T-cell neoplasms, and many were not tested. One intravascular T-cell lymphoma has been reported.

It is important to distinguish cases such as those described by Hanson et al27 and Natkunam et al52 from the typically much more indolent T-cell large granular lymphocytic leukemias (T-LGLs), which are also leukemic and are composed of cytotoxic T cells that express NK cell–associated antigens and have cytoplasmic granules.27,52 It is not clear that this has always been done. Of the 9 cases of T-LGL included in this review, 4 were found in bone marrow transplant recipients. All were proven to be monoclonal and, when tested, were CD57+. The order of diagnoses and terminology is that of the World Health Organization Classification of Hematopoietic and Lymphoid Tumors (as much as possible).

### Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>Positive</th>
<th>Negative</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-lymphoblastic leukemia/lymphoma</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
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<td>T-cell large granular lymphocytic leukemia</td>
<td>9</td>
<td>0</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NK-cell lymphoma(eu)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Extramedullary NK/T-cell lymphoma, nasal type</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>18</td>
<td>1</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Subcutaneous panniculitides-like T-cell lymphoma</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mycosis fungoides/Sézary syndrome</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td>47</td>
<td>19</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>T-cell lymphoma, not further specified7</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NK-like T-cell lymphoma(\text{NK/T, nodal})</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Angiotropic T-cell lymphoma (intravascular)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PTLD, T-cell, not further specified4</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK+</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Anaplastic large cell lymphoma, other6</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>40</td>
<td>67</td>
<td>23</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; NK, natural killer; PTLD, posttransplantation lymphoproliferative disorder.

1. The order of diagnoses and terminology is that of the World Health Organization Classification of Hematopoietic and Lymphoid Tumors (as much as possible).
2. Most like peripheral T-cell lymphoma, unspecified, except was CD1a+.
3. These cases of Macon et al\(^{46}\) were considered hepatosplenic T-cell lymphoma (1 case) or aggressive T-cell large granular lymphocytic leukemia/lymphoma (2 cases) by Jaffe.86
4. These were called polymorphic/polyclonal or were not specifically designated as any of the T-cell lymphomas.
5. ALK negative or not done.
When considering this diagnosis, one should be aware that large clonal CD8+ T-cell expansions are reported with infectious mononucleosis, and major oligoclonal CD8+/CD57+ T-cell expansions with restricted \( \gamma\delta \) gene usage are reported following bone marrow transplantation.

The second most commonly reported T/NK-cell PTLD is hepatosplenic T-cell lymphoma (HSTCL; 14%). In fact, a review of the literature from several years ago reported that about 15% of HSTCLs were found in patients following transplantation. The Workshop also included a case of HSTCL occurring after immunosuppression for ulcerative colitis. In the transplantation setting, at least 14 cases were definitely of the \( \gamma\delta \) type, with 2 probably of the \( \gamma\delta \) type, 1 of the \( \alpha\beta \) type, and 1 uncertain. The characteristic iso7(q) was present in 7 of 10 cases with 1 additional case that showed del7. Trisomy 8 was present in 5 of 6 cases.

The next most common category includes the anaplastic large cell lymphomas: anaplastic lymphoma kinase–positive and anaplastic lymphoma kinase–negative systemic-type cases and primary cutaneous anaplastic large cell lymphoma. As reviewed elsewhere, PTLDs of mycosis fungoides and Sézary syndrome type are also well described. Subcutaneous panniculitis-like T-cell lymphomas also occur in this setting, with at least 2 of 3 reported cases of the \( \alpha\beta \) type, fulfilling the current WHO–European Organization for Research and Treatment of Cancer criteria for this diagnosis. Of the cases reviewed of adult T-cell leukemia/lymphoma, which can also involve the skin, 1 patient was from the Caribbean area and the remainder were from Japan.

The very rare true NK-cell PTLDs include cases from several variably well-defined categories. Of the reported extra-nodal NK/T-cell lymphomas, nasal type, 1 case was of the \( \alpha\beta \) T-cell type and the others of the NK or probably NK type. Only 3 had nasal or pharyngeal involvement. The others involved the breast, allograft pancreas and associated lymph nodes, and 1 the liver and spleen (but was not thought to be HSTCL).

Four cases of precursor T-lymphoblastic leukemia/lymphoma were reported in solid organ transplant recipients. When occurring in the setting of bone marrow or peripheral blood stem cell transplantation for acute leukemia, a relationship to the original leukemia may be difficult to exclude even if there are some phenotypic differences. Finally, there are some cases described as T-cell PTLD that are not further specified because resemblance to a specific lymphoma was not documented. Some of these cases that were reported to be polyclonal or polymorphic may be better thought of as T-cell–rich cases of other types of PTLDs.

Of the cases with documented EBV studies, about 37% of the T/NK-cell PTLDs were EBV+ (Table 2). All of the extra-nodal NK/T-cell lymphomas, nasal type, were EBV+, as were almost half of the PTCL-U cases. In contrast, almost all of the HSTCLs were EBV−, and, in some categories, such as T-LGL, all cases were EBV− (where EBV status was documented). Some EBV-associated cases were found in perhaps unexpected circumstances, such as among the anaplastic large cell lymphomas of all types. The EBV+ cases may bear some relationship to the clinically aggressive T-cell lymphoproliferative disorders that are reported to occur in patients with acute or chronic EBV infections who have not received transplants.

Although speculative, it has been suggested that EBV− T-cell PTLDs may be the result of chronic antigenic stimulation rather than being driven by a virus.

What Happens to Patients With T/NK-Cell PTLDs, and How Have the Diseases Been Treated?

The overall survival for T/NK-cell PTLDs is only 6 months \( \text{Figure 11} \). A T/NK-cell origin for a PTLD is considered an adverse prognostic indicator. Despite the fact that the more indolent LGL T-cell PTLDs are EBV−, patients with EBV− T-cell PTLDs had a significantly shorter overall survival (median, 6 vs 18 months; \( P = .0347; \text{log-rank test} \)). The median survivals for the more common types of T-cell PTLD are given in \( \text{Figure 21} \). The median survival for the 3 largest groups, illustrated in \( \text{Figure 31} \). The T-LGL group stood out as being very indolent, although the relatively small extra-nodal NK/T cell lymphoma, nasal type, group also had a median survival that had not been reached, with 3 of 5 alive at 36 to 45 months. The median survival for the other groups with 5 or more cases ranged from 3 to 18 months, with none being significantly different from the 3-month median survival for patients with PTCL-U.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure11.png}
\caption{Overall survival for T-cell/natural killer cell posttransplantation lymphoproliferative disorder with available data. Patients who died even without known disease are included as deaths.}
\end{figure}
Of the patients, 60 received chemotherapy, often together with decreased immunosuppression, and sometimes other therapies. Two patients received skin-based therapy for mycosis fungoides, 4 were treated with radiation therapy with or without decreased immunosuppression, and for 20 patients, the therapy was unknown. No chemotherapy or radiation was received by 44 patients, including at least 16 treated with decreased immunosuppression with or without antiviral agents. In this group, 10 patients were alive when their cases were reported, including 3 without known disease (1 anaplastic large cell lymphoma, 1 T-PTLD also treated with surgery, and 1 enteropathy type T-cell lymphoma treated with surgery alone). It has been suggested that patients with localized T-cell PTLD may have a better prognosis. In 4 other patients, the disease status was uncertain (1 adult T-cell leukemia/lymphoma, 1 PTCL-U with recurrent adenopathy, and 2 T-LGLs), and 3 had known disease, including 2 with T-LGL. One additional patient with PTCL-U who died had a complete remission with decreased immunosuppression and died without evidence of PTLD.

**Figure 2** Overall survival for patients with Epstein-Barr virus (EBV)+ T-cell/natural killer cell posttransplantation lymphoproliferative disorder (T/NK-cell PTLD; open squares) was significantly better than for patients with EBV− T/NK-cell PTLD (closed squares), even with the EBV− indolent T-cell large granular lymphocytic leukemia cases included ($P = .0347$).

**Figure 3** Overall survival curves for the 3 most common types of T-cell posttransplantation lymphoproliferative disorder (PTLD). The patients with T-cell large granular lymphocytic leukemia (circles) had a significantly better survival than patients with peripheral T-cell lymphoma, unspecified (triangles) or hepatosplenic T-cell lymphoma (squares) ($P = .004$).

**Table 3** Median Survival for Major Types of T/NK-Cell PTLD

<table>
<thead>
<tr>
<th>Type of T/NK-cell PTLD</th>
<th>No. of Cases With Survival Data</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell large granular lymphocyte leukemia</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Mycosis fungoides/Sézary syndrome</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>6</td>
<td>2.5</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>5</td>
<td>NR</td>
</tr>
</tbody>
</table>

NK, natural killer; NR, not reached; PTLD, posttransplantation lymphoproliferative disorder.

*The only group with a survival statistically different from the peripheral T-cell lymphoma, unspecified group was the T-cell large granular lymphocyte leukemia group ($P = .004$).

**Do T/NK-Cell PTLDs Occur in Association With B-Cell PTLDs?**

Variably well-defined synchronous or metachronous T-cell PTLDs have been reported to occur with B-cell PTLDs. Although in some cases the “mixed” nature may relate to ambiguous genotypic studies or genotypically defined T-cell clones in the peripheral blood without clear-cut morphologic-phenotypic correlation, other cases clearly have 2 well-documented components. A case of Sézary syndrome in which a lymph node biopsy specimen during the course of the disease showed a B-cell PTLD has been described, as has a case in which PTCL-U developed at about the same time as a clonal plasma cell–rich B-cell PTLD that over time became the dominant lesion. Other cases are described in which polymorphic (clonal) B-cell PTLD/EBV+ B-cell hyperplasia, infectious mononucleosis–like reactivated EBV episode, or Burkitt-like PTLD have preceded a T-cell PTLD by months to years, including 1 case in which the polymorphic B-cell PTLD recurred when an HSTCL-like PTLD developed. This is analogous to cases such as the one in which EBV+ mononucleosis that remitted developed in a 58-year-old man; however, an EBV− pleomorphic T-cell lymphoma developed 8 months later.
What Should I Remember About T/NK-Cell PTLDs?

T/NK-cell PTLDs typically occur much later than many other PTLDs, especially compared with EBV+ PTLDs. They are often EBV−, usually do not respond to a simple decrease in immunosuppression, and have an adverse prognosis. However, exceptions to each of these generalizations must be kept in mind. Some T/NK-cell PTLDs occur shortly after transplantation, almost 40% are EBV+, rare cases go into complete remission without chemotherapy or radiation, and some patients have an extended survival. Most cases occur in renal transplant recipients, and, like other PTLDs, they are usually extranodal. Their diagnosis may be a challenge so that a high index of suspicion is needed when any type of lymphoid proliferation is identified in a transplant recipient, even if the cells are relatively small or very polymorphic, a clonal B-cell population is not identified, and there is an absence of EBV. It is important that these cases are sufficiently worked up so they can be classified as precisely as possible for therapeutic and prognostic purposes.

References


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