



Alexey Bobylev. *Autumn Overture*, 2005. Oil mounted on cardboard, 50 × 70 cm. Courtesy of the St. Petersburg Art Salon, Russia.

*New agents and prospective, randomized trials are needed to improve the poor outcome of patients with peripheral T-cell neoplasms.*

# The Diagnosis, Management, and Role of Hematopoietic Stem Cell Transplantation in Aggressive Peripheral T-Cell Neoplasms

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**Background:** *Peripheral T-cell neoplasms (PTCNs) comprise a group of uncommon and heterogeneous lymphoid malignancies. They are more difficult to diagnose and treat and have a worse prognosis than B-cell lymphomas. Although PTCNs initially show a significant degree of chemosensitivity, the outcome of treatment with conventional dose chemotherapy remains poor.*

**Methods:** *We reviewed the literature on the diagnosis, treatment, and collective transplant reports regarding PTCNs.*

**Results:** *The correct diagnosis of peripheral T-cell lymphoma requires a combination of clinical presentation, morphology, immunophenotype, and molecular study. While no specific treatment other than conventional dose chemotherapy is currently available for aggressive PTCN, histone acetylase inhibitors and monoclonal antibodies such as anti-CD7 and anti-CD52 are being studied in T-cell malignancies. The role of autologous and allogeneic transplantation is being investigated for high-risk, relapsed, and refractory PTCNs with some promising results.*

**Conclusions:** *Access to hematopathology expertise in a tertiary care setting may lead to earlier and more accurate diagnoses of these diseases. PTCNs comprise a heterogeneous group of diseases with no widely accepted standard of care, and accurate determination of their histologic subtypes correlates with prognosis. Patients in first complete remission with poor risk features and patients with relapsed and refractory disease should be considered for bone marrow transplant due to the poor outcomes obtained with conventional chemotherapy.*

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**Abbreviations used in this paper:** PTCN = peripheral T-cell neoplasm, NK = natural killer, PTCL-u = peripheral T-cell lymphoma, unspecified, EBV = Epstein-Barr virus, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, AITL = angioimmunoblastic T-cell lymphoma, HSCT = hematopoietic stem cell transplantation.

## Introduction

Peripheral T-cell neoplasms (PTCNs) are an uncommon and heterogeneous group of lymphoid malignancies. According to the International Lymphoma Study Group, PTCNs account for only 12% of all lymphomas,<sup>1</sup> yet they are more difficult to treat and diagnose, and they carry worse prognosis than B-cell lymphomas.<sup>2,3</sup> In contrast to lymphoblastic lymphoma (derived from T-cell precursor cells), most T-cell lymphomas arise from postthymic cells (mature T cells) and are collectively called PTCNs. Based on pathogenesis and clinical features, several subtypes of PTCNs are recognized (Table 1), including anaplastic large T/null-cell lymphoma, mycosis fungoides, T-cell prolymphocytic leukemia, adult T-cell leukemia/lymphoma, angioimmunoblastic T-cell lymphomas, hepatosplenic T-cell lymphomas, T-cell prolymphocytic leukemia, enteropathy-associated T-cell lymphoma, and others. Natural killer (NK)-cell malignancies are also included in this group. Any mature T-cell lymphoma that is not included in these previous categories (not belonging to a defined entity) is considered a peripheral T-cell lymphoma, unspecified (PTCL-u). PTCL-u is the most common subtype of T-cell lymphoma in Europe and North America, representing approximately 4% of all lymphomas. It is possible that new entities will eventually be defined within this broad category, thus allowing the “unspecified” designation to disappear. Herein, we included the diagnostic criteria and the treatment with emphasis on the role of hematopoietic stem cell transplantation.

## Peripheral T-Cell Lymphoma, Unspecified

**Definition:** PTCL-u represents a distinct category of T-cell lymphomas with a variety of morphologic subtypes that do not resemble the more identifiable subtypes. It is the most common subtype of PTCNs in Western countries. This heterogeneous category requires further study; as more entities are identified, the need for the PTCL-u category will diminish.

**Pattern of Infiltration:** On lymph nodes biopsies, PTCL-u shows diffuse infiltration with effacement of the normal lymph node architecture.

**Cytomorphology:** Cytologically, many different patterns can be present, such as large cells, mixed small and large cells, diffuse small cleaved cells, and immunoblastic cells. Nuclei are irregular and pleomorphic, with prominent nucleoli and frequent mitotic figures. A common characteristic is an inflammatory polymorphous background with small lymphocytes, eosinophils, plasma cells, and clusters of epithelioid histiocytes. The term *lymphoepithelioid cell lymphoma* (Lennert's lymphoma) refers to cases with numerous clusters of epithelioid cells. In the T zone variant, an interfollicular growth pattern with hyperplastic follicles is seen.

**Immunophenotype:** T-cell-associated antigens are variably expressed with CD4+, CD8-, CD3 +/-, CD5 +/-, or CD7 -/+. CD4 is expressed more often than CD8, and tumor might be CD4- and CD8-. One of the mature T-cell antigens, commonly CD5 or CD7, is usually lost. Some tumors might have reactive bystander Epstein-Barr virus (EBV) positive B-cells morphologically similar to Reed-Sternberg cells.

**Cytogenetics and Molecular Studies:** The T-cell receptor gene is usually but not always rearranged. Until recently, no recurrent chromosomal translocations in PTCL were reported. Streubel et al<sup>4</sup> identified a novel recurrent translocation t(5;9)(q33;q22) in a subset of PTCL-u. This translocation results in the fusion of two nonreceptor tyrosine kinases, *ITK* in chromosome 5 and *SYK* in chromosome 9, with the likely result of constitutive activation of *SYK* through overexpression. Complex karyotypes are common in large-cell tumors, while trisomy 3 is common in the lymphoepithelioid (Lennert) variant. Other mutations described are *K-ras* mutations, *c-kit* genes, and *B-catenin* genes. Patients in whom tumors express p53 have a worse prognosis.

**Treatment:** A prospective, randomized, multi-institutional trial confirmed CHOP therapy, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone, as the standard of care for aggressive lymphoma. This trial did not make any differentiation between T- or B-cell lymphomas.<sup>5</sup> Despite this, CHOP therapy has remained the most common regimen for the treatment of aggressive PTCL.<sup>6</sup>

Other anthracycline-based regimens have been used with relatively poor results. In the LNH87 protocol, patients with PTCL (including unspecified and other subtypes) were treated prospectively with four different anthracycline-based chemotherapy regimens.

Table 1. — Mature T-Cell Neoplasms

<b>Leukemic or Disseminated</b>	T-cell prolymphocytic leukemia T-cell granular lymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell lymphoma/leukemia
<b>Extranodal</b>	Extranodal NK/T-cell lymphoma, nasal type Enteropathy type T-cell lymphoma Hepatosplenic T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma
<b>Cutaneous</b>	Blastic NK-cell lymphoma Mycosis fungoides/Sézary syndrome Anaplastic large-cell lymphoma, T/null cell, primary cutaneous
<b>Nodal</b>	Peripheral T-cell lymphoma, unspecified Angioimmunoblastic T-cell lymphoma Anaplastic large-cell lymphoma, T/null cell, primary systemic type

Adapted from Jaffe ES, Harris NL, Stein H, et al, eds. *World Health Organization Classification of Tumours — Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press: Lyon, France; 2001. Reprinted with permission.

Among patients with PTCN, 54% achieved complete remission and 41% were alive at 5 years. Patients with anaplastic large T-cell lymphoma fared better, with a 5-year overall survival rate of 64%. PTCN other than anaplastic large T-cell lymphoma had a poor outcome, with a 5-year overall survival rate of 35% and an event-free survival rate of 32%.<sup>3</sup>

Given the poor prognosis with CHOP-like chemotherapy, new agents have been studied in small trials. Nucleoside analogs have shown activity in PTCN. Pentostatin has been used in patients with PTCL-u with variable responses. Tsimberidou et al<sup>7</sup> reported a response rate of 54%, with a complete response rate of 14% but a median duration of response of only 4.3 months. This report included several types of PTCN. Experience with other purine analogs is even more limited.

Denileukin diftitox is a genetically engineered fusion protein comprising the enzymatically active domain of diphtheria toxin and the full-length sequence of interleukin (IL)-2 that targets malignancies expressing the IL-2 receptor. In a single-institution phase II trial, 14 patients with different subtypes of PTCN were treated and evaluable. The overall response rate was 50%, complete remission was achieved in 14%, and partial remission occurred in 36%. The median time of response was not reported.<sup>3</sup> Alemtuzumab, an anti-CD52 monoclonal antibody, was studied in a phase

II multi-institutional trial in 14 patients with advanced PTCN. The overall response rate was 36%, with complete and partial remission in 3 and 2 patients, respectively. Toxicity included opportunistic infections and hemophagocytic syndrome.<sup>8</sup>

New medications and prospective trials are needed to improve the generally poor outcome of patients with PTCL-u.

## Angioimmunoblastic T-Cell Lymphoma

**Definition:** Angioimmunoblastic T-cell lymphoma (AITL) is characterized by a systemic disease with a polymorphous infiltrate involving lymph nodes, with a prominent proliferation of high endothelial venules and follicular dendritic cells as well as the presence of polymorphous collection of lymphocytes, plasma cells, and immunoblasts. AITL can present in many extranodal locations, including the skin.

**Clinical Presentation:** Patients typically have a systemic disease characterized by generalized lymphadenopathy, fever, weight loss, hepatosplenomegaly, ascites, proteinuria, and a polyclonal gammopathy. Other manifestations include serositis, positive antiglobulin test, and hypoalbuminemia. Skin manifestations include a maculopapular rash.<sup>9</sup> Prognosis is poor, with a median survival of less than 3 years.<sup>10</sup> Infectious complications are common. Most patients are EBV seropositive, but this does not correlate with outcome.

**Epidemiology:** Elderly individuals are affected (median age 67 years), with a male:female of ratio 2.2:1.<sup>9</sup>

**Pattern of Infiltration:** The lymph node is often effaced by a diffuse paucicellular infiltrate with prominent arborizing blood vessels (Fig 1A) with eosinophils and plasma cells, as well as islands of cells with “clear” cytoplasm with pleomorphism and scattered immunoblasts (Fig 1B). The vessel walls may be thickened or hyalinized and may stain positively with periodic acid-Schiff stain. There is also perivascular grouping of a spectrum of atypical lymphocytes and expansion of follicular dendritic cell networks. Occasional Reed-Sternberg-like cells are noted. When germinal centers are present, they are often atrophic and involuted. In the skin, a dermal infiltrate of atypical lymphocytes is accompanied by similar patterns of arborizing small vessels with involvement of skin appendages and the upper dermis. The histologic features range from mild to dense infiltrate, with an occasional report of granulomatous inflammation mimicking sarcoidosis. Diagnosis in lymph nodes is more straightforward but may be challenging in skin because of wide histologic patterns. Martel et al<sup>11</sup> classified skin biopsies ranging from a non-specific pattern of mild perivascular infiltrates of eosinophils and lymphocytes with no atypia in the superficial dermis associated with capillary hyperplasia to dense

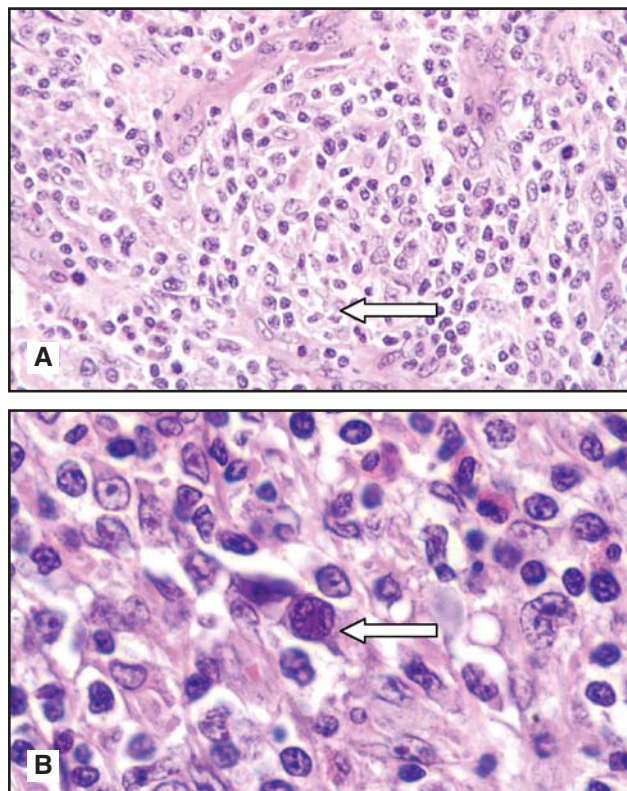


Fig 1A-B. — (A) Angioimmunoblastic T-cell lymphoma (AITL) is characterized by a systemic disease with a polymorphous infiltrate involving lymph nodes, with a prominent proliferation of high endothelial venules (arrow). (B) AITL is shown with atypical immunoblasts (arrow).

pleomorphic infiltrate composed of atypical lymphocytes in the superficial and deep dermis, suggestive of cutaneous lymphoma.

**Immunophenotype:** The neoplastic cells are usually positive for CD4, CD2, CD5, CD45RO, CD10, CXCL13<sup>12</sup> and usually negative for CD8 and CD56. Expanded follicular dendritic cell clusters (CD21+) are present around proliferated venules. CD10, normally associated with B cells, is characteristically coexpressed in the T-cell population in this type of T-cell lymphoma.<sup>13</sup>

**Cytogenetic and Molecular Alterations:** T-cell receptor genes are rearranged. Immunoglobulin heavy chains may be rearranged in 10%, corresponding to expanded B-cell clones. Trisomy 3 and/or 5 and +3 are common translocations.<sup>14</sup> EBV is frequently detected in infiltrating polyclonal B cells but not in T cells. The role of EBV is unclear in the pathogenesis of this disease.<sup>15</sup>

**Treatment:** Anthracycline-based combination chemotherapy results in complete remission rates of up to 70%, but most patients eventually relapse.<sup>16</sup> Patients with relapsed AITL may respond to immunosuppressive therapy such as low-dose methotrexate, prednisone, and cyclosporine, purine analogs, and denileukin diftitox.<sup>17</sup>

Retrospective data from the European Group for Blood and Marrow Transplantation from 29 patients who received high-dose therapy followed by autologous stem-cell support demonstrated an increase in the rate of complete remission from 45% before high-dose chemotherapy to 76% after. The probability of 5-year overall survival and event-free survival was 44% (95% CI, 22% to 66%) and 37% (95% CI, 17% to 57%), respectively. AITL seems to be susceptible to high-dose chemotherapy.<sup>18</sup>

## T-Cell Prolymphocytic Leukemia

**Definition:** T-cell prolymphocytic leukemia is a rare disorder with an adverse prognosis. It is a progressive disease that includes rapidly increasing leucocytosis and splenomegaly. Patients usually have a high white blood cell count (frequently  $>100.0 \times 10^9/L$ ). Marrow, spleen, liver, and lymph nodes may be involved. It was previously known as “knobby” type of T-cell leukemia.<sup>19</sup>

**Clinical Presentation:** The main disease features, in order of frequency, are splenomegaly, lymphadenopathy, hepatomegaly, skin lesions, and a high leukocyte count (greater than  $100 \times 10^9/L$  in 75%) with prolymphocytes. A variant form with small, less typical cells was recognized in 19%.<sup>20</sup> Skin manifestations include a diffuse infiltrative erythema or as nodules. Lesions most often present on the face or ears. Median survival is 7.5 months.<sup>20</sup>

**Epidemiology:** This rare condition accounts for 2% of all cases of small lymphocytic lymphoma/chronic lymphocytic leukemia. It typically presents in adults over 30 years of age, with a median age of 57 years.

**Cytomorphology:** Lymphocytes are variable, some medium in size with a large amount of cytoplasm and showing prominent nucleoli. However, some cases present with smaller nuclei with “knobby” nuclear irregularity with protrusion and “blebby” cytoplasm<sup>20</sup> (Fig 2). Spleen shows both red and white pulp infiltration. Paracortical infiltration is noted in lymph nodes.

**Immunophenotype:** Nearly all cases have a CD4 T-helper phenotype with rare CD8. CD2, CD3, CD5, and CD25 are usually positive and CD7 expression may be lost.

**Cytogenetics:** Inversion (14)(q11;q32) or, less frequently, t(14;14)(q11;q32) can lead to activation of TCL-1, and deletions in 11q22-11q23 affect the ataxia telangiectasia-mutated (*ATM*) gene. Other recurrent karyotypes such as inv(8q)/t(8;8), del(13q14), del(12p13), del(6q) and dup(6p) have been reported.<sup>20</sup>

**Differential Diagnosis:** These include B-cell chronic lymphocytic leukemia with prolymphocytic transformation, T-cell chronic lymphocytic leukemia (although this entity is questionable), B-cell prolymphocytic leukemia, and peripheralized lymphomas.

**Treatment:** This condition is not curable with conventional treatment. Deoxycoformycin<sup>21</sup> and alemtuzumab have been used as treatment options. Pawson et al<sup>22</sup> initiated a study using alemtuzumab administered 3 times weekly for up to 12 weeks. Complete response was achieved in 23 patients (59%) and partial response was seen in 6 patients (15%). The median overall survival from the start of alemtuzumab treatment was 10 months — 18 months in patients who had achieved a complete response. The toxicity in this trial was acceptable, and the response was better than with pentostatin. Alemtuzumab is not curative but may allow patients to progress to autologous or allogeneic stem cell transplantation. Transplantation should be considered early in first remission. Before alemtuzumab, only pentostatin provided an improved survival.

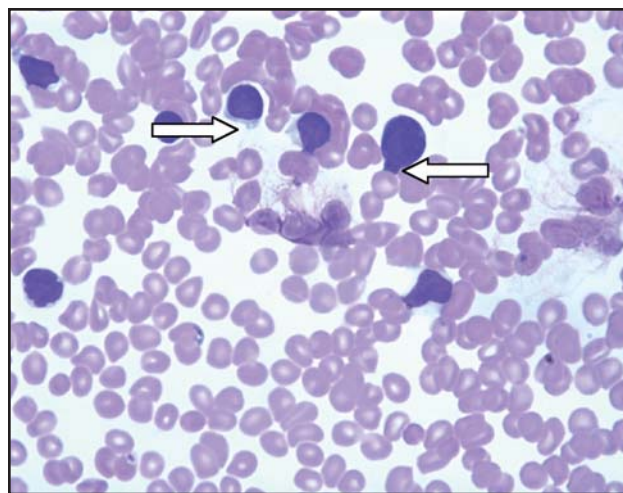


Fig 2. — Peripheral blood with “knobby” variant of T-cell prolymphocytic leukemia. Note the cytoplasmic bleb (arrows) and protrusion.

## Hepatosplenic T-Cell Lymphoma

**Definition:** Hepatosplenic T-cell lymphoma is a distinct clinicopathologic entity with hepatosplenomegaly at presentation without lymphadenopathy, as well as peculiar sinusoidal pattern of infiltration of the spleen, liver, and bone marrow.

**Clinical Presentation:** Presenting features include hepatomegaly, splenomegaly, and marked thrombocytopenia and leukocytosis. No significant lymphadenopathy is found in most patients. Presenting features also include B symptoms and abdominal pain. Median survival is 12 to 14 months.<sup>23</sup>

**Epidemiology:** Young male adults (median age 34 years) are affected, comprising less than 5% of all PTCNs. This type of lymphoma may be more common in immunosuppressed individuals.<sup>24,25</sup>

**Pattern of Infiltration:** The spleen and liver are both involved in a diffuse manner with no discrete masses. General architecture of the spleen is preserved with marked hyperplasia (expansion) of the red pulp and atrophy of the white pulp. Lymphoma cells infiltrate the cords of Billroth and often pack the sinuses (Fig 3). In the liver, neoplastic lymphoid cells infiltrate variably dilated sinusoids (Fig 4). Bone marrow is usually involved, often hypercellular, and exhibits a selective sinusal infiltrate that is difficult to observe. Lymph nodes are seldom involved, and peripheral blood involvement is seen late in the course of the disease.

**Cytomorphology:** Lymphoma cells are usually monomorphic, small- to medium-sized, with round or oval nuclei showing slightly dispersed chromatin and scant to moderate cytoplasm admixed with histiocytes. Hemophagocytosis is common.

**Immunophenotype:** Neoplastic cells display a nonactivated cytotoxic profile with strong granular cytoplasmic staining for TIA1 with no perforin and granzyme B expression<sup>26,27</sup> and no EBV genome. They usually are CD3+/CD5-/CD56+/p53-/CD4-/CD8-. The T-cell receptors are usually gamma-delta, but alpha-beta types have been reported.

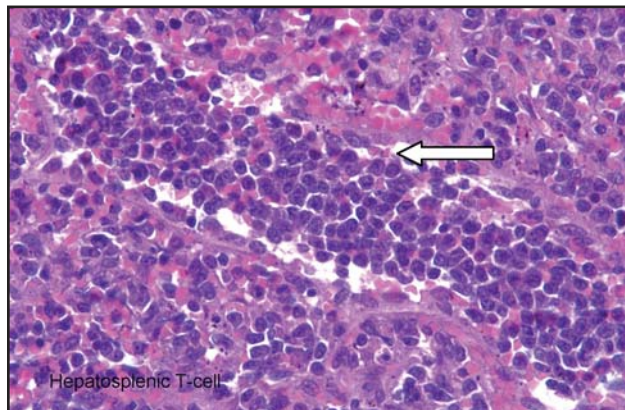


Fig 3. — Sinusoidal (arrow) dense infiltrate of hepatosplenic lymphoma.

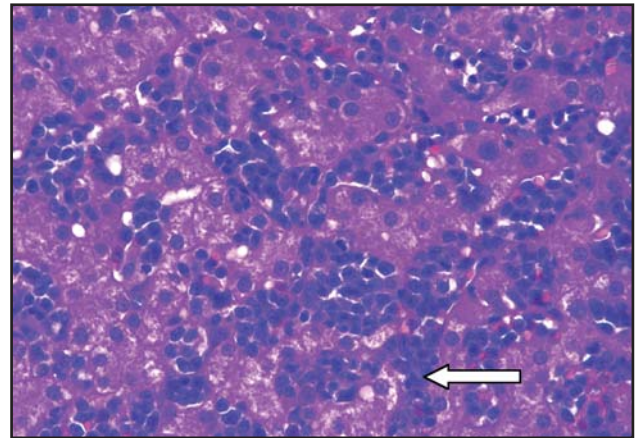


Fig 4. — Sinusoidal (arrow) hepatic infiltration of hepatosplenic lymphoma.

**Cytogenetics:** The characteristic aberrations are isochromosome 7q and trisomy 8,<sup>28</sup> but the functional consequences of these changes have yet to be determined.

**Pathogenesis:** Mutations of the *ATM* gene — a frequent occurrence in T-cell prolymphocytic leukemia — may be involved in the initiation of the malignant process.<sup>28</sup> A subsequent gain or activation of the T-cell lymphoma-1 (TCL-1) gene may lead to proliferation and further modifications to the aggressive character of the disease.<sup>29</sup>

**Treatment:** CHOP or CHOP-like first-line regimens with salvage high-dose therapy with autologous transplant have been ineffective. Allogeneic transplantation has induced durable remission in several cases of hepatosplenic lymphoma.<sup>23</sup>

## Enteropathy-Associated T-Cell Lymphoma

**Definition:** This rare neoplasm comprises approximately 1% of all lymphoma cases and about 5% of gastrointestinal lymphomas. It is aggressive and in most cases arises in the setting of celiac disease. In rare cases, the lymphoma arises in extraintestinal sites.

**Epidemiology:** Middle-aged to elderly individuals are usually affected (median age 57 years), with a male:female ratio of 3:1. The odds ratio for coeliac disease is 19.2 (95% confidence interval, 7.9–46.6).

**Pattern of Infiltration:** The most common location is the jejunum, and it presents as a single tumor or multiple tumors. Tumor forms circumferential ulcers in the bowel wall. The adjacent small intestine usually shows edema. Enlargement of the mesenteric nodes is invariably present (edema and reactive changes). A large population of inflammatory cells diffusely infiltrate the tumor and occasionally mask the tumor cell population. Histology of the small intestine remote from the site of the tumor is important because this

usually shows celiac appearances,<sup>30</sup> with villous atrophy, crypt hyperplasia, plasmacytosis in the lamina propria, and an increase in intraepithelial lymphocytes. Mucosal change is usually maximal proximally; the lower jejunum and ileum may appear normal.

**Cytomorphology:** Features include highly pleomorphic, blastic lymphocytes, usually with rounded vesicular nuclei and a single nucleolus or numerous bizarre, multinucleated forms. An intestinal lymphoma that is CD30+ and has features consistent with enteropathy-type T-cell lymphoma should not be considered an anaplastic large-cell lymphoma despite having a similar morphological appearance.

**Immunophenotype:** In half of these cases, CD3, CD7, CD103, TIA1, perforin, granzyme B, CD45RO and CD8 are positive and CD4 is negative. Positive staining with the monoclonal antibody human mucosal lymphocyte-1 (CD103) is characteristic. In cases in which large immunoblast-like cells predominate, CD30 expression is characteristic and can be a useful marker to distinguish tumor cells in an inflammatory background. EBV is negative.<sup>31</sup>

**Cytogenetics:** The characteristic feature is monoclonal T-cell receptor beta and gamma gene rearrangement. Chromosomal gain at chromosome 9q is common.

**Differential Diagnosis:** Extranodal NK/T cell, nasal type commonly involves the gastrointestinal tract and must be ruled out based on clinical presentation and expression of CD103 in enteropathy-associated T-cell lymphoma.

**Clinical Presentation:** Presenting symptoms are abdominal pain, weight loss, diarrhea, and vomiting. Malabsorption is commonly found in most patients. Small-bowel perforation, small-bowel obstruction, and abdominal masses have been reported. B symptoms (sweats and fevers) may be present. The poor prognosis of this disease is heightened by complications such as peritonitis and malnutrition, and later by intestinal recurrences. Therefore, only about 50% of patients are amenable to chemotherapy, and only a small proportion of those are able to finish the treatment as scheduled. The 5-year failure-free survival rate is 3%. Early diagnosis is crucial and should be considered in all patients who present with celiac disease and in those who later become resistant to a gluten-free diet. Having a proportion of patients with no preceding celiac history makes diagnosis more difficult.

**Treatment:** Following diagnosis of enteropathy-associated T-cell lymphoma, chemotherapy should be considered for all patients. A variety of regimens, including CHOP, have been used, but other combinations warrant investigation in an attempt to improve the poor prognosis of these patients. Prognosis, in part, reflects late diagnosis and poor performance status at the time of presentation. High-dose therapy with autologous stem cell transplant has been tried.<sup>32</sup>

## Treatment and Prognosis of Aggressive PTCN

With the notable exception of anaplastic large-cell lymphoma (ALCL), the clinical outcome of aggressive PTCNs is poor. When compared with diffuse large B-cell lymphoma, patients with PTCNs typically present at a more advanced stage and have lower performance status, more frequent B symptoms, abnormal LDH, and extranodal disease. They also have higher International Prognostic Index (IPI) scores at diagnosis.<sup>33</sup> Anthracycline-based chemotherapy has remained the most commonly used initial treatment. In patients with ALCL treated with this type of regimen, long-term survival is achieved in 60% to 80% of cases.<sup>34</sup> In contrast, in patients with other subtypes of PTCNs, long-term survival is poor, with a 5-year overall survival rate of 30% or less.<sup>35</sup> Differences in overall survival according to the IPI are also significant; the IPI score is useful to stratify the patient's risk and modify therapy accordingly.<sup>36</sup> Reiser et al<sup>32</sup> emphasized that in T-cell lymphomas, the histologic subtype and risk factors may be more relevant for the estimation of prognosis than the T-cell phenotype alone. Monoclonal antibodies and other therapies are now being studied. Because of the heterogeneity of stage-specific T-cell differentiation and antigen expression, antibody treatment may be applicable in only a limited number of T-cell tumors. Since the alpha chain of IL-2 receptor (CD25) or CD30 is expressed on only a subset and the pan-T CD3 antibodies are not reactive in all PTCL, as some have aberrant CD3 loss, the treatment must be personalized. In addition, the use of anti-CD3 in transplant medicine has suggested that even low doses are likely to be associated with severe side effects. Most PTCLs express the CD7 antigen, with the notable exception of CTCL. Data on a CD7-*Pseudomonas* exotoxin suggest that the CD7 antigen might be a target.<sup>37</sup> Other monoclonal antibody therapy in T-cell lymphomas such as anti-CD2 and anti-CD4 are also in various clinical trials.

## The Role of Hematopoietic Stem Cell Transplantation in PTCN

Although PTCNs show a significant degree of chemosensitivity, the outcome of treatment with conventional-dose chemotherapy remains poor, as noted above. Hematopoietic stem cell transplantation (HSCT) has been explored as part of the primary therapy and also in patients with relapsed and refractory disease. Several small case series have been published,<sup>37-44</sup> but no prospective, randomized trials have been done. Case series include different entities, different types of transplants (autologous vs allogeneic),<sup>45</sup> status of disease (relapsed vs primary refractory vs first complete

remission), and different regimens. It is difficult to arrive at definitive conclusions, and the exact role of HSCT remains undefined.

### Autologous Hematopoietic Stem Cell Transplantation

Several investigators have added HSCT as consolidation after primary chemotherapy in an attempt to decrease the risk of relapse or to use as salvage in patients with relapsed and refractory disease (Table 2).<sup>37-41,43,44,46</sup> Series including a large fraction of patients with anaplastic large cell lymphoma have reported a better outcome when compared with series including mostly other subtypes of PTCN.<sup>46,47</sup>

Transplant-related mortality has fluctuated between 0 to 18%, but in most series it is less than 10%. Complete remission is achieved in 80% to 100% of patients. Those undergoing transplants in first remission seem to have the best outcome — a 76% disease-free survival rate at 15 months — as reported by Reimer et al.<sup>48</sup> Patients with relapsed or refractory disease have a disease-free survival rate of 23% to 47% at 3 to 5 years. The most commonly used conditioning regimens are BEAM (a combination of BCNU, etoposide, Ara-C, and melphalan) and BEAC (BCNU, etoposide, Ara-C, and cyclophosphamide).

Several prognostic factors at the time of the transplant have emerged as good predictors for overall survival.<sup>46</sup> They are similar to those described in B-cell lymphomas (Table 3).

**Table 3. — Prognostic Factors That Influence Overall Survival Following Autologous HSCT for PTCL**

Age	
B symptoms	
Extranodal disease	
Histology (anaplastic large cell lymphoma vs other PTCL)	
Pretransplant International Prognostic Index (IPI) score	
Pretransplant lactic dehydrogenase (LDH) level	
Disease status (clinical remission 1 vs relapsed vs refractory)	
Modified from Majhail NS, Burns LJ. Hematopoietic stem cell transplantation in the treatment of peripheral T-cell lymphomas. <i>Curr Hematol Rep.</i> 2005;4:252-259. Reprinted with permission by Current Science, Inc, Philadelphia, Pa.	

Patients with anaplastic large-cell lymphoma in first complete remission have the best outcome, particularly with Alk+ disease, with an event-free survival rate as high as 87% at 5 years.<sup>41</sup> However, given the overall good response of this type of lymphoma to CHOP-like chemotherapy, intensification with HSCT in first complete remission may not be indicated.

Patients with AITL and enteropathy-associated T-cell lymphomas have such a poor prognosis after primary chemotherapy that the use of intensification with HSCT is favored by some investigators.<sup>18,49</sup>

PTCL-u is the most common subtype of PTCN in the Western world and seems to have a worse outcome than aggressive B-cell lymphomas when treated with CHOP-like chemotherapy. Although transplantation is

**Table 2. — Selected Studies of Hematopoietic Stem Cell Transplantation in Different Subtypes of Peripheral T-Cell Lymphomas, Published in the Last 6 Years**

Author	No. of Patients	Disease Status	Conditioning Regimen	Median Follow-up (mos)	Complete Response Rate	Overall Survival Rate	Treatment-Related Mortality Rate
Blystad et al <sup>38</sup>	40	Mixed	BEAM (autologous) BEAC	36	80%	58% at 3 yrs	8%
Rodriguez et al <sup>39</sup>	29	Relapsed/ refractory	Various (autologous)	43	86%	39% at 3 yrs	7%
Kahl et al <sup>40</sup>	10	Mixed	Various (autologous)	12	70%	58% at 1 yr	10%
Angelopoulou et al <sup>41</sup>	35	Relapsed/ refractory	Various (autologous)	33	N/A	33% at 5 yrs	3%
Rodriguez et al <sup>42</sup>	115	Mixed	BEAM (autologous), BEAC	37	91%	56% at 5 yrs	8%
Song et al <sup>43</sup>	36	Relapsed/ refractory	Mel/VP16 ±TBI (autologous)	42	N/A	48% at 3 yrs	17%
Jantunen et al <sup>44</sup>	37	Mixed	BEAM (autologous), BEAC	24	81%	63% at 5 yrs	11%
Corradini et al <sup>45</sup>	17	Relapsed/ refractory	Thiotepa, fludarabine, cyclophosphamide (allogeneic)	28	76%	81% at 3 yrs	6%
Reimer et al <sup>48</sup>	21	First complete remission	BEAM (autologous)	15	100%	76% at 15 mos	0%
Modified from Majhail NS, Burns LJ. Hematopoietic stem cell transplantation in the treatment of peripheral T-cell lymphomas. <i>Curr Hematol Rep.</i> 2005;4:252-259. Reprinted with permission by Current Science, Inc, Philadelphia, Pa.							

commonly used in patients with relapsed or refractory disease, it may have a role in first complete remission, particularly in patients with poor risk features (eg, intermediate or high IPI score).<sup>44,46</sup>

The effectiveness of the use of HSCT in less common subtypes of PTCL, such as hepatosplenic T-cell lymphoma and extranodal NK/T-cell lymphoma, is limited to a few case reports. Allogeneic HSCT has induced durable remission in several cases of hepatosplenic lymphoma.<sup>50</sup>

The role of HSCT in patients with primary refractory PTCL (defined as failure to achieve a complete response after primary chemotherapy) was explored by the Grupo Espanol de Linfomas/Trasplante Autologo de Medula Osea (GEL-TAMO) Spanish registry in a retrospective review of 35 patients from their registry. Approximately one third of patients with PTCL who do not achieve a complete response to the first chemotherapeutic regimen can be rescued with HSCT and become long-term survivors.<sup>42</sup>

HSCT has a promising but still undefined role in the therapy of PTCL. Patients with relapsed and refractory disease should be offered high-dose chemotherapy and HSCT, particularly in the setting of chemosensitive disease. Patients with poor risk features at diagnosis may also be candidates for intensification with HSCT after achieving first complete response with primary chemotherapy. Prospective randomized trials are needed to clarify the role and the appropriate timing of HSCT.

### Allogeneic Hematopoietic Stem Cell Transplantation

The published experience with allogeneic HSCT is limited to a few studies that included small numbers and selected patients. Conventional myeloablative allogeneic transplant has been associated with a high transplant-related mortality rate, ranging from 40% to 50%, which has limited the use of this procedure.<sup>44,46</sup> Corradini et al<sup>45</sup> used a reduced-intensity conditioning regimen in 17 patients with relapsed and refractory PTCL with a low nonrelapse mortality of 6% at 2 years. The estimated 3-year overall and progression-free survival rates were 81% and 64%, respectively. Donor lymphocyte infusions induced responses in 2 patients who relapsed following transplant. These data suggest that allogeneic transplantation after a reduced-intensity conditioning regimen is feasible, has a low mortality, and seems to be a promising strategy for relapsed and refractory PTCL. It also suggests the existence of a graft vs T-cell lymphoma effect.

HSCT has an undefined and evolving role in the management of PTCL. The available data come from small, uncontrolled, and mostly retrospective studies. Despite these limitations, a significant number of patients seem to benefit from this intensive approach. Autologous or even allogeneic transplantation should be offered in patients with relapsed and refractory dis-

ease as it is probably the most effective therapy in that setting. Patients in first complete remission with poor risk features should also be considered for this approach since their prognosis with conventional chemotherapy remain poor. Prospective studies are needed to better define the role of HSCT in PTCL. Because these are uncommon malignancies, only multi-institutional trials will answer all these questions.

## Conclusions

PTCNs constitute an uncommon and heterogeneous group of lymphoid malignancies arising from postthymic T cells. Several defined entities have been included in this family, and others not classifiable are defined as PTCL-u. They share a diffuse pattern of infiltration of nodal and extranodal tissues, systemic symptoms, and advanced clinical stage at presentation. They have an aggressive clinical behavior with poor response to standard anthracycline-based chemotherapy. Immunotherapy with denileukin diftitox or alemtuzumab has shown some activity in clinical trials. Given the poor outcome with conventional therapies, high-dose chemotherapy followed by autologous or allogeneic HSCT has emerged as a potential curative treatment in patients with high-risk or relapsed and refractory disease. New agents and prospective, randomized trials are needed to improve the poor outcome of PTCNs.

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