T-cell Prolymphocytic Leukemia

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**Background:** T-cell prolymphocytic leukemia (T-PLL) is a post-thymic T-cell malignancy with aggressive clinical course. Although T-PLL has been referred to under different designations, it is a distinct clinicobiological entity and should be distinguished from other T-cell disorders.

**Methods:** The literature on T-PLL is reviewed. Experience on the clinical and laboratory features, differential diagnosis, and therapy on a large series of T-PLL patients is presented.

**Results:** T-PLL affects adults and occurs more frequently in men. The principal disease characteristics are organomegaly, skin lesions, and a raised lymphocyte count. Immunological markers show a post-thymic T-cell phenotype (CD5− CD2+ CD5+ CD3+) with strong expression of CD7. A CD4+ CD8− phenotype is seen in two thirds of cases. CD4+ and CD8− are coexpressed in 25%, and a CD4− CD8+ phenotype is rare. Cytogenetics show a recurrent abnormality inv(14)(q11;q32) that is always associated to other aberrations (particularly iso8q or trisomy 8). Differential diagnosis between T-PLL and other T-cell malignancies is based on a constellation of clinical and laboratory features. Generally, T-PLL patients are refractory to the therapy used in lymphoid disorders. Median survival is short but is improving with the use of 2-deoxycoformycin and the humanized monoclonal antibody, anti-CDw52 (Campath-1H).

**Conclusions:** T-PLL is a distinct T-cell disorder with characteristic clinical and laboratory features and a poor prognosis. A precise diagnosis of this disease is important in determining patient management and treatment.

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**Introduction**

T-cell prolymphocytic leukemia (T-PLL) is a mature post-thymic T-cell malignancy with distinct clinical and laboratory features and an aggressive clinical course.

The disease was first recognized in 1973 in a single patient presenting with a leukemic picture similar to that of B-cell PLL but in whom the cells were shown to be E-rosette positive. B-PLL and T-PLL are distinct disease entities with different clinical and laboratory features. In the 1980s, several single case reports were described either as T-PLL or as other designations such as T-cell chronic lymphocytic leukemia (T-CLL). The morphologic variation and cytogenetic characteristics in a series of patients with T-PLL were also documented, and in the early 1990s, the clinical and laboratory features in 78 patients with T-PLL were reported. T-PLL currently is recognized as a distinct T-cell malignancy that is included in the French-American-British (FAB) classification. Both B- and T-PLL are rare diseases when considering the spectrum of lymphoproliferative disorders. Within the post-thymic T-cell disorders that evolve from leukemia, T-PLL is frequent and accounts for one third of cases seen at our institution.

**Clinical Features**

T-PLL affects adults and occurs slightly more often in men. The median age in a series of 135 patients seen at our institute was 65 years (range = 33 to 91 years) and the man:woman ratio was 1.37. Main disease features at presentation are splenomegaly, lymphadenopathy hepatomegaly, skin lesions, and marked lymphocytosis (Table 1). Although palpable lymphadenopathy is seen in half of the patients, computed tomography scans show that most patients have enlarged lymph nodes - a feature that differentiates T-PLL from B-PLL. Patients with cutaneous lesions present with a maculopapular rash, nodules or, rarely, erythrodermia. Other manifestations that are rare at the onset of the disease but are common in the evolution are pleural effusions, ascites, and/or central nervous system involvement. In a small proportion of cases, the disease evolves with a slowly progressive lymphocytosis, and the diagnosis is made through a routine blood test. As a rule, these patients will show disease progression during the following months. Such cases, particularly those with small cells, are often misdiagnosed as chronic lymphocytic leukemia (CLL).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percent of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>79%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>46%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>39%</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>23%</td>
</tr>
<tr>
<td>Effusions</td>
<td>15%</td>
</tr>
<tr>
<td>White blood cell count (&lt;100 x 10^9/L)</td>
<td>72%</td>
</tr>
<tr>
<td>Platelets (&lt;100 x 10^9/L)</td>
<td>44%</td>
</tr>
<tr>
<td>Hemoglobin (&lt;100 g/L)</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Data from a series of 135 patients.*

**Table 1. -- Clinical Features of T-PLL**

The peripheral blood counts in T-PLL show a consistent raised white blood cell count, usually >100 x 10^9/L or greater, with more than 90% of lymphoid cells having the features of prolymphocytes. This is characteristic of both B- and T-PLL, albeit the degree of leukocytosis is more marked in T-PLL. Anemia and
thrombocytopenia may be present in one third of cases, which may result from bone marrow failure due to lymphoid infiltration and/or hypersplenism. Features of autoimmune disease have not been described thus far. Serum immunoglobulins and renal biochemistry, including calcium levels, are normal, and liver function tests may show a mild impairment. Hyperuricemia and a slightly raised lactate dehydrogenase (LDH) are common features. Serum antibodies to the human T-cell leukemia virus (HTLV)-I and -II have not been detected, even in patients originating from regions endemic to HTLV-I. DNA analysis using the polymerase chain reaction with primers to detect all HTLV-I and -II sequences (LTR, gag, env, pol, tax/rex) do not show involvement of these retroviruses in T-PLL, even when studies are performed following cell culture. Therefore, the occasionally previously reported HTLV-positive T-PLL case might represent detection of endogenous sequences or technical artifacts.

**Morphology**

A key diagnostic test in T-PLL is a well-stained peripheral blood film. The blood picture is homogeneous, with the predominant cell being a medium-sized lymphocyte with either a regular or an irregular nuclear outline and a single nucleus. The cytoplasm is scanty, agranular, deeply basophilic, and often irregular with protrusions (Fig 1). There are no obvious differences between B and T prolymphocytes except the size (B prolymphocytes are larger) and the degree of cytoplasmic basophilia (more marked in T prolymphocytes). In addition, the nucleus is usually regular in B prolymphocytes and irregular in half of the T-PLL cases. The nuclear irregularities of T prolymphocytes are seen as several short indentations and, very rarely, cells show a polylobated nucleus (as in adult T-cell leukemia lymphoma [ATLL]) or display a cerebriform configuration (as in Sezary cells). In 20% of T-PLL cases, the cells are small and have more condensed chromatin. The nucleus is visible by light microscopy in only a proportion of cells, though it can be visualized by electron microscopy in most of the cells. This group has been designated as the small-cell variant of T-PLL, and likely corresponds to most of the cases described as “knobby-type” T-PLL or T-CLL. The clinical and laboratory features, including cytogenticites of the small-cell T-PLL, are identical to the typical cases, although whether to consider them as a variant of T-PLL is controversial. Therefore, this is a strong argument to consider them within the spectrum of T-PLL.

Electron microscopy studies in T-PLL are useful to confirm that cells in the small-cell T-PLL have similar features to the typical prolymphocytes. These studies also help to identify structures not visualized by light microscopy, such as clustered cytoplasmic granules that contain acid phosphatase and other hydrolases, as well as well-developed rough endoplasmic reticulum and clusters of ribosomes that account for the cytoplasmic basophilia. Ultrastructural studies also can be useful in cases that present diagnostic problems with Sezary cell-like leukemia.

**Histology**

Infiltration by lymphocytes in the bone marrow aspirates ranges from 30% to 100%, and the cell morphology is identical to that of the circulating blood cells. However, the cytologic details are defined more clearly in the peripheral blood films. The pattern of infiltration in the bone marrow trephine biopsy is variable, the most common being a mixed pattern (diffuse and interstitial) of infiltration and thus similar to that seen in B-PLL. Reticulin fibrosis is almost always present. Spleen histology shows expansion of the white and red pulp with infiltration by nucleolated lymphoid cells and atrophy of the follicular centers. Lymph node histology is available in few cases; the nodal infiltration is diffuse and, in some cases, the paracortical areas are expanded.

The pattern of skin involvement in T-PLL is different from that of the cutaneous T-cell lymphomas and Sezary syndrome, even in T-PLL cases that present with erythrodermia. As a rule, the epidermis is not involved, while infiltrates in the dermis (Fig 2) sometimes extend to the subcutaneous fat. The infiltrates tend to be arranged around the skin appendages.

**Immunological Markers**

Membrane marker studies show that cells from all T-PLL cases have a mature post-thymic T-cell phenotype and do not express CD1a and terminal deoxynucleotidyl transferase (TdT). The monoclonal antibodies CD2 and CD5 are usually positive, and CD7 is strongly expressed in most cases. The number of CD7 antigenic determinants estimated by the antibody-binding capacity is higher in T-prolymphocytes compared with normal T cells or cells from other mature T-cell malignancies, and it is similar or close to that of T-cell acute lymphoblastic leukemia (T-ALL). In contrast to CD7, cells from approximately 20% of T-PLL cases do not express CD3 in the membrane, although they are cytoplasmic CD3-positive. Other cases may be negative, with antibodies against the T-cell receptor (TCR)-alpha/beta chain genes without correlation between the negative findings with CD3 and anti-TCR-alpha/beta. Despite this, the TCR-beta and/or -gamma chain genes are always found in a rearranged configuration in T-PLL. Regarding the expression of CD4 and CD8, there is no pattern unique to this disease, the most common being a CD4+ CD8− phenotype. Findings in 128 patients at our center showed that 61% had a CD4+ CD8− phenotype, the cells coexpressed CD4 and CD8 in 25%
Markers linked to T-cell activation such as CD25, CD38, and class II HLA-DR determinants are variably expressed, while those against natural killer (NK) cells (eg, CD56 and CD16) are negative as a rule. Other monoclonal antibodies such as TIA-1 that detect granular structures in T lymphocytes and are positive in most cases of large granular lymphocytic leukemia are negative in T-PLL, including cases whose cells express CD8.19

Other markers such as CD52, although not lymphoid specific, are expressed at a higher density in T prolymphocytes than in normal T cells.20 This might explain in part the good response of T-PLL to anti-CD52 therapy.

Cyto genetics

Chromosome abnormalities are detected in most T-PLL cases after cell culture with mitogens (eg, phytohemagglutinin and phorbol esters). These have demonstrated a recurrent chromosomal abnormality, inv(14) (q11;q32), which is present in more than two thirds of cases.8,9 Few patients may have tandem translocations between the two chromosomes 14 involving the same breakpoints than in the inv(14), such as t(14;14) (q11;q32). It has been suggested that inv(14) results in the juxtaposition of a putative oncogene, TCL-1, located at 14q32, a region centromeric to the immunoglobulin heavy chain locus, with the gene coding for the TCR-alpha chain at 14q11 resulting in the expression and activation of TCL-1.21 In T-PLL, this is not seen as a single aberration but rather is associated with other abnormalities.

Abnormalities of chromosome 14 identical to those seen in T-PLL have been documented in T-cell clones from patients who have ataxia telangiectasia without leukemia but have an increased risk to develop leukemias, particularly T-PLL.22 In addition, the 1.3 kb TCL-1 transcript has been expressed in cases of ataxia telangiectasia with lymphoplasies or in patients who have developed a T-cell leukemia.23,24 When the leukemia develops in ataxia telangiectasia, additional abnormalities always are documented as in T-PLL. In a series of T-PLL at our center, one patient had a t(X;14)(q28;q11) and t(8;22) (q24;q11).9 Therefore, such data indicate that inv(14) is likely a primary abnormality and that other events are required for the lymphoid cell to become leukemic.

Trisomy 8 and iso8q are also common in T-PLL and found in 55% of cases, while abnormalities of the short arm of chromosome 8 occur less frequently. Although rearrangement of c-myc has not been demonstrated, cells from T-PLL cases with trisomy 8 or iso8q overexpress the c-myc protein as estimated by flow cytometry analysis.25 It is then possible that a high expression of c-myc plays a role in disease progression as a secondary event.

Abnormalities involving chromosome 11, including some with 11q23 breakpoints where the ataxia telangiectasia-mutated gene is located, have also been reported in T-PLL.9 Studies are underway to investigate whether this gene is disrupted or mutated in T-PLL.

Differential Diagnosis

The differential diagnosis of T-PLL with B-PLL can be established by immunological markers; also, some clinical features (eg, the presence of lymphadenopathy and skin lesions) are found only in T-PLL. The differential diagnosis with other T-cell malignancies must be based on a constellation of laboratory features that includes cell morphology, histology, and immunological markers. T-PLL and T-ALL can be distinguished on cell morphology and immunological markers. In T-ALL, the cells are lymphoblasts and express TdT, while TdT is negative in T-PLL. In addition, the clinical features are different from T-PLL; for example, T-ALL affects mainly children and young adults and may present with a mediastinal mass. Regarding the post-thymic T-cell disorders, T-PLL can be distinguished from the other type of primary T-cell leukemia -- large granular lymphocytic leukemia -- on the basis of cell morphology, immunological markers, and clinical features (Table 2). Differential diagnosis between T-PLL and Sezary syndrome or ATLL may arise in some cases. T-PLL presenting with cutaneous manifestations has other clinical features (eg, widespread disease and marked leukocytosis) not seen in Sezary syndrome. In addition, the cell morphology and skin histology are different in these two diseases. Distinction between T-PLL and ATLL is based on clinical features (eg, hypercalcemia in ATLL), cell morphology, and HTLV-I status.

<table>
<thead>
<tr>
<th>Feature</th>
<th>T-PLL</th>
<th>LGL Leukemia</th>
<th>Sezary Syndrome</th>
<th>ATLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>prolymphocyte</td>
<td>LGL</td>
<td>cerebriform</td>
<td>flower cell</td>
</tr>
<tr>
<td>Phenotype</td>
<td>CD4+ CD8-</td>
<td>CD8+ CD4-</td>
<td>CD4+ CD8+</td>
<td>CD4+ CD8+</td>
</tr>
<tr>
<td></td>
<td>CD4+ CD8+</td>
<td>natural killer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD7+</td>
<td>markers+</td>
<td></td>
<td>CD25+</td>
</tr>
<tr>
<td>Histology:</td>
<td>spleen</td>
<td>red/white pulp</td>
<td>red pulp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>skin</td>
<td>dermal</td>
<td>dermal and epidermal</td>
<td>dermal and epidermal</td>
</tr>
<tr>
<td></td>
<td>HTLV-1</td>
<td>negative</td>
<td>negative*</td>
<td>positive</td>
</tr>
<tr>
<td>Clinical course</td>
<td>aggressive</td>
<td>indolent</td>
<td>chronic</td>
<td>aggressive</td>
</tr>
</tbody>
</table>

Establishing a differential diagnosis of T-PLL and Sezary cell-like leukemia, a rare form of T-cell leukemia, can be difficult.20 Patients with Sezary cell-like leukemia present a leukemic picture with cells that are indistinguishable morphologically from Sezary cells by light and electron microscopy but, unlike Sezary syndrome, the skin is not involved. The clinical course of these patients is similar to that of T-PLL, and cytogentic, so far available in few cases, shows similarities with T-PLL (eg, inv [14]) and with Sezary syndrome (eg, 17q).27 Therefore, whether to consider this disease as a separate entity or a "cerebriform" variant of T-PLL is uncertain.

Natural History and Prognosis

T-PLL is an aggressive T-cell disorder that always progresses, even in cases evolving with mild lymphocytosis and in which the disease is discovered by chance. Left untreated, patients die shortly after the diagnosis is made.9 Thus, the outlook is very different compared with that of large granular lymphocytic leukemia. Patients with
bulky disease may have a poorer prognosis, but this is not influenced by the immunophenotype (whether typical T-PLL or small-cell variant) or by other parameters such as the degree of lymphocytosis.

**Treatment and Survival**

The overall survival of patients with T-PLL is short. In the series of 78 patients reported in 1991,9 the median survival was seven months, similar to that of ATLL. As a rule, patients treated with alkylating agents such as chlorambucil are either resistant to this therapy or achieve only partial and short-lived responses. Approximately one third of patients may respond to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy, but most responses are partial and few are complete as judged by clinical features (Table 3). The disease eventually recurs in all of these patients.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Patients</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agent</td>
<td>52</td>
<td>0%</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>CHOP</td>
<td>15</td>
<td>6%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>2'-deoxycoformycin</td>
<td>55</td>
<td>9%</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Campath-1H</td>
<td>14</td>
<td>57%</td>
<td>14%</td>
<td>71%</td>
</tr>
<tr>
<td>CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone</td>
<td>Data from Matutes,9 Mercieca,30 and Pawson.31</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. -- Response to Treatment in T-PLL

Complete or partial responses have been documented in single case reports using mediastinal or abdominal irradiation and the purine analog 2’-deoxycoformycin.28,29 Our experience indicates that this drug is one of the best agents for the treatment of T-PLL when used on a schedule of 4 mg/m² per week until a maximal response is achieved. We have documented partial or complete responses in 45% of patients treated with this drug as a single agent.9,30 Most patients were refractory to other therapies. The drug was well tolerated, and responses were rapid as judged by the decrease in the leukocyte count. No differences in response rates were seen between previously treated and untreated patients. This translated to an improvement in survival in the responders (median survival = 17.5 months) and even in nonresponders (9 months) compared with the historical series.9

More recently, Campath-1H has been shown to be highly effective in T-PLL.31 Responses to Campath-1H have been seen in more than two thirds of patients, including those who were resistant to 2’-deoxycoformycin or who achieved only a partial response.

Both agents are well tolerated, and the principal management problem is immunosuppression, particularly with Campath 1H. Therefore, an effective schedule for treatment of T-PLL is 2’-deoxycoformycin followed by Campath-1H in patients who achieve only partial responses or are refractory to 2’-deoxycoformycin. An alternate approach is Campath-1H as first-line therapy. These strategies allow harvesting of peripheral blood stem cells and proceeding to high-dose chemotherapy with an autograft in young patients with T-PLL with the possibility of cure.

**Conclusions**

T-PLL is a rare post-thymic T-cell malignancy characterized by splenomegaly, lymphadenopathy, hepatomegaly, and a poor prognosis. No ideal treatment exists, although some success has been seen with 2’-deoxycoformycin or Campath-1H. Further clinical investigation is needed to establish a more effective treatment approach for this rare disorder.

**References**


