Hematopathology / T-PLL IN VolVING EXTRAMEDULLARY SITES

T-Cell Prolymphocytic Leukemia Involving Extramedullary Sites

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Abstract

T-cell prolymphocytic leukemia (T-PLL) can involve extramedullary sites, but the diagnosis is usually established by examination of blood and bone marrow. As a result, the histologic findings at extramedullary sites are poorly documented in the literature. We describe 19 extramedullary biopsy specimens from 14 patients with T-PLL. Skin (n = 10) was the most common site biopsied. T-PLL surrounded dermal blood vessels and appendages (n = 6), diffusely replaced dermis (n = 3), or formed a subcutaneous mass (n = 1). Other extramedullary sites included liver and lymph nodes (3 each) and spleen, lung, and cecum (1 each). In liver and lymph nodes, the neoplasm predominantly involved portal tracts and paracortex, respectively. Cytologically, the T-PLL cells were round (n = 16) or Sézary cell–like (n = 3). Nucleoli were observed in a subset of cells in 8 specimens and were prominent in 3 specimens. Immunostaining for T-cell leukemia–1 (TCL-1) was positive in specimens from 9 (64%) of 14 patients. We conclude that the prolymphocytoid features of T-PLL cells can be difficult to detect in routinely stained sections of extramedullary biopsy specimens. TCL-1 expression can aid in diagnosis at extramedullary sites.

T-cell prolymphocytic leukemia (T-PLL) is the most common type of mature T-cell leukemia and is characterized by a rapidly rising peripheral blood lymphocyte count, bone marrow involvement, and splenomegaly.1 The disease in most patients follows an aggressive clinical course, but a subset of patients initially can have an indolent clinical course, up to approximately 25% in 1 study.2 In peripheral blood or bone marrow aspirate smears, T-PLL cells are slightly larger than normal lymphocytes, and, commonly, each cell has a prominent nucleolus, irregular nuclear contours, and moderately abundant, nongranular and basophilic cytoplasm with protrusions or blebs.1,2 However, small cell and cerebriform cell variants of T-PLL also are described.2 Immunophenotypically, T-PLL cells are of mature T-cell lineage, positive for T-cell markers, and negative for terminal deoxynucleotidyl transferase (TdT). The neoplastic cells usually are positive for CD4, although cases positive or negative for both CD4 and CD8 also are reported.1

Previous studies of T-PLL have emphasized the clinical characteristics of this disorder and the morphologic findings in peripheral blood and bone marrow.3,4 Few reports have focused on the histologic findings of T-PLL involving extramedullary sites. In this study, we describe the pathologic findings of T-PLL involving 19 extramedullary biopsy specimens obtained from 14 patients.

Materials and Methods

Case Selection

During the last 6 years, 41 patients with T-PLL have been evaluated at The University of Texas M.D. Anderson Cancer
Center, Houston. The criteria used to establish the diagnosis of T-PLL are those specified in the World Health Organization classification.  

From this group, we identified 14 patients who underwent biopsy of 1 or more extramedullary sites.

At the time of initial diagnosis, all patients had involvement of peripheral blood and bone marrow by small lymphocytes with cytologic and immunophenotypic features consistent with T-PLL. The peripheral blood WBC count ranged from 17,000 to 350,000/µL (17.0–350.0 × 10⁹/L). Bone marrow aspiration and biopsy showed involvement by T-PLL representing 20% to 80% of the total cellularity. All patients received single or multiagent chemotherapy, immunotherapy (anti-CD52 monoclonal antibody, CAMPATH-1H), or both.

Flow cytometry immunophenotypic analysis was performed on bone marrow aspirate material from all cases with an extensive panel of antibodies as previously described. All neoplasms expressed T-cell antigens and were negative for TdT. Twelve neoplasms were CD4+/CD8−, 1 was CD4+/CD8+ (case 14), and 1 was CD4−/CD8− (case 10).

Conventional cytogenetic studies were performed on 9 cases using methods previously described, and the results are summarized in Table 1.

Definition of Disease Progression

All extramedullary biopsy specimens were obtained at the time of disease progression. The term disease progression, as used in the present study, includes development of disease relapse after complete clinical remission or uncontrolled peripheral blood lymphocytosis or growth of disease at an extramedullary site (eg, new-onset lesions or expansion of preexisting lesions) despite standard therapy.

Immunohistochemical and Molecular Methods

Each biopsy specimen was fixed in formalin, processed routinely, and H&E-stained slides were prepared. Immunohistochemical studies were performed on all specimens using fixed, paraffin-embedded tissue sections and a variable panel of antibodies, including CD3, CD4, CD5, CD8, CD20, CD57, S-100, T-cell leukemia–1 (TCL-1), and TdT as described previously. Flow cytometry immunophenotypic studies (see “Case Selection”) were performed on cell suspensions of 4 specimens.

In 4 biopsy specimens from 3 patients (cases 2, 5, and 10), molecular studies to assess for clonality of the T-cell receptor (TCR) chain gene were performed using fixed, paraffin-embedded tissue samples from extramedullary biopsy sites. In case 2, the TCRγ chain gene was assessed using denaturing gradient electrophoresis and staining with ethidium bromide as described by Theodorou et al. In cases 5 and 10, the TCRγ chain gene was assessed using fluorescently labeled consensus variable region primers, unlabeled joining region primers, and a polymerase chain reaction method followed by capillary electrophoresis and GeneScan (PE/Applied Biosystems, Foster City, CA) analysis as described previously.

In 1 patient (case 5), conventional cytogenetics studies (see “Case Selection”) were performed on a cell suspension of tissue obtained from a subcutaneous tissue mass on the right thigh.

Results

Clinical Findings

The study group included 8 women and 6 men with a mean age of 65.4 years (range, 49-77 years). At the time of initial diagnosis, all 14 patients (100%) had clinical evidence of extramedullary disease, including lymphadenopathy (n = 9), maculopapular skin lesions (n = 7), splenomegaly (n = 4), pleural effusion (n = 3), ascites (n = 1), hepatomegaly (n = 1), and a paraspinal mass (n = 1). However, none of these sites was biopsied at the time of diagnosis because the diagnosis was established at the time of relapse. All peripheral blood and bone marrow specimens were obtained at the time of initial diagnosis.

Table 1

Results of Conventional Cytogenetics in 9 Cases of T-Cell Prolymphocytic Leukemia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Specimen Type</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Bone marrow</td>
<td>Hypodiploid clone 43-45,XX,del(1)(p34),del(3)(p13p23),add(9)(q33),add(11)(q24),inv(14)(q11q32),−16,−17,−18,−22,+3-6mar[cp5]</td>
<td></td>
</tr>
<tr>
<td>5 Subcutaneous tissue</td>
<td>Pseudodiploid clone 46,XX,−3,del(4)(q12q23),−14,inv(14)(q11q32)+2mar[5]</td>
<td></td>
</tr>
<tr>
<td>6 Bone marrow</td>
<td>add(14)(q32),−12,−13,−14</td>
<td></td>
</tr>
<tr>
<td>8 Bone marrow</td>
<td>Hypodiploid clone 42-50,XX,add(1)(p36.2),+2,+3,add(4)(p16),+del(6)(q22q25),i(7)(q10),i(8)(q10),del(10)(q24),−14,−15,del(16)(q25),−17−20,add(21)(p11.1),+1-2mar[cp15]</td>
<td></td>
</tr>
<tr>
<td>10 Peripheral blood</td>
<td>Normal diploid clone 46,XY</td>
<td></td>
</tr>
<tr>
<td>11 Bone marrow</td>
<td>Normal diploid clone 46,XX</td>
<td></td>
</tr>
<tr>
<td>12 Bone marrow</td>
<td>Hypodiploid clone 42-45,X−X,−add(4)(q35),−5,add(7)(q36),add(8)(p23),−11,−13,−14,add(14)(q32.3),add(15)(q26),−17−20,add(21)(p11),+3-mar[cp15]</td>
<td></td>
</tr>
<tr>
<td>13 Bone marrow</td>
<td>Hypodiploid clone 45,X,Y[4]</td>
<td></td>
</tr>
<tr>
<td>14 Bone marrow</td>
<td>Hypodiploid clone 44X,psu dic(8;6)(p23;q13),−11,inv(14)(q11q32),add(15)(p12.2),der(17)(t(6;17)(q13;p13),+19,add(21)(q22),−22[cp7],idem,−19,+</td>
<td></td>
</tr>
</tbody>
</table>

* The subcutaneous tissue specimen was obtained at the time of relapse. All peripheral blood and bone marrow specimens were obtained at the time of initial diagnosis.
was established by examination of peripheral blood and bone marrow samples.

At the time of biopsy of an extramedullary site, all patients had clinical evidence of disease progression, following complete or partial clinical remission \table{2}. At this time, the WBC count ranged from 2,100 to 286,000/µL (2.1-286.0 × 10⁹/L); 12 patients had an elevated WBC count. T-PLL was persistent in a diffuse pattern in the bone marrow in 11 of 13 patients assessed. However, in 2 patients (cases 3 and 5), there was no morphologic evidence of disease in peripheral blood or bone marrow samples, although extramedullary sites of disease were proven by biopsy. In 1 patient, bone marrow was not assessed; this patient had a WBC of 230,000/µL (230.0 × 10⁹/L). Clinically, 9 patients had peripheral lymphadenopathy, 8 had hepatomegaly, and 6 had splenomegaly. Pleural effusions were present in 6 patients, and 1 patient had ascites.

Clinical follow-up data were available for all 14 patients. Nine were alive at the time of last follow-up, with a mean survival of 22.5 months. Five patients (cases 1-3, 9, and 10) died by the time this study was completed, with a mean survival of 13.6 months from the time of diagnosis. The causes of death were sepsis and multiorgan system failure (case 1); overwhelming sepsis due to Aspergillus fumigatus infection with extensive residual T-PLL involving bone marrow, liver, spleen, lymph nodes, lungs, and colon (case 2); sepsis with multiorgan system failure due to Aspergillus fumigatus infection (case 10); and disease progression in 2 patients (cases 3 and 9). One patient (case 3) had skin tumors and lymphadenopathy, and fine-needle aspiration of a cervical lymph node immediately preceding death demonstrated T-PLL. This patient did not have peripheral blood lymphocytosis or bone marrow involvement. In case 9, no additional details of the clinical findings at time of death are available.

\textbf{Histopathologic Findings}

The most common anatomic site biopsied was skin: 10 specimens obtained from 7 patients. One patient (case 5) had 4 skin biopsy specimens. In this subgroup, the pattern of involvement in 6 biopsy specimens (from 4 patients) consisted of an infiltrate of atypical lymphocytes in the superficial dermis, with a perivascular and perinodal distribution \image{1}. Other histologic features in these cases included a variable degree of stromal edema surrounding blood vessels with minimal endothelial damage and a few scattered extravasated erythrocytes. In 3 biopsy specimens, the neoplasm infiltrated the dermis in a diffuse pattern \image{2}, and in 1 biopsy specimen (case 5), T-PLL cells formed a subcutaneous mass \image{3}. The latter patient also had 3 other skin lesions with dermal perivasculary and perinodal involvement as mentioned. A subset of 2 skin biopsy specimens had foci of epidermotropism, one with a dermal perivascular and perinodal pattern (case 10) and the other with diffuse dermal involvement (case 12) \image{4}. The epidermis was otherwise unremarkable except for the presence of parakeratosis and hyperkeratosis in 2 specimens (cases 3 and 12).

The second most commonly biopsied sites were liver (n = 3) and lymph node (n = 3). The pattern of infiltration in 3 liver needle biopsy specimens was mostly periportal.

\table{2}

<table>
<thead>
<tr>
<th>Case No.</th>
<th>WBC Count (× 10⁹/L)²</th>
<th>Skin†‡</th>
<th>L†‡</th>
<th>H†‡</th>
<th>S†‡</th>
<th>Lung†‡</th>
<th>PE‡</th>
<th>Biopsy Site</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.2</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Liver</td>
<td>Dead, 18</td>
</tr>
<tr>
<td>2</td>
<td>24.4</td>
<td>+, rash</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Cecum and LN</td>
<td>Dead, 8</td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>+, rash</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Skin</td>
<td>Dead, 17</td>
</tr>
<tr>
<td>4</td>
<td>9.18</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Liver and spleen</td>
<td>AWD, 16</td>
</tr>
<tr>
<td>5</td>
<td>3.4</td>
<td>+, rash</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Subcutaneous mass and skin (n = 4)</td>
<td>AWD, 72</td>
</tr>
<tr>
<td>6</td>
<td>153.0</td>
<td>+, rash</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Skin</td>
<td>AWD, 10</td>
</tr>
<tr>
<td>7</td>
<td>32.2</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Liver</td>
<td>AWD, 32</td>
</tr>
<tr>
<td>8</td>
<td>286.0</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Lung</td>
<td>AWD, 4</td>
</tr>
<tr>
<td>9</td>
<td>230.0</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>LN</td>
<td>Dead, 16</td>
</tr>
<tr>
<td>10</td>
<td>57.0</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>LN</td>
<td>Dead, 9</td>
</tr>
<tr>
<td>11</td>
<td>64.4</td>
<td>+, rash</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Skin</td>
<td>AWD, 30</td>
</tr>
<tr>
<td>12</td>
<td>12.3</td>
<td>+, rash</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Skin</td>
<td>AWD, 30</td>
</tr>
<tr>
<td>13</td>
<td>48.4</td>
<td>+, rash</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Skin</td>
<td>AWD, 3</td>
</tr>
<tr>
<td>14</td>
<td>22.3</td>
<td>+, rash and nodules</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Skin</td>
<td>AWD, 6</td>
</tr>
</tbody>
</table>

AWD, alive with disease; H, hepatomegaly; L, lymphadenopathy; LN, lymph node; PE, pleural effusion; S, splenomegaly; T–PLL, T–cell prolymphocytic leukemia; +, present or yes; –, absent or no.

² To convert WBC count values to conventional units (µL), divide by .001.

† Detected by physical examination.

‡ Detected by imaging studies.

§ Ascites also was present.
cases with less extensive disease, T-PLL was confined predominantly to portal tracts, with minimal portal tract expansion or sinusoidal involvement \( \text{Image 5} \). Blood vessels within portal tracts were distended by T-PLL cells in 1 of these specimens. In the third liver biopsy specimen, there was extensive involvement and expansion of portal tracts by T-PLL with disruption of the limiting plates. Obvious sinusoidal involvement also was present, although to a lesser degree. Nonspecific histologic features in these specimens included edema and cholestasis in all 3 cases, with the degree of these changes correlating with the amount of involvement by neoplasm.

In the 3 lymph node biopsy specimens, T-PLL had a diffuse pattern and subtotally replaced the normal architecture in a paracortical distribution. In all cases, a few residual lymphoid follicles and patent sinusoids were identified \( \text{Image 6} \). The T-PLL cells were monomorphous in 2 specimens but showed some variability in size in 1 specimen (case 10) \( \text{Image 7} \). Mitotic figures were identified easily in all 3 specimens, ranging from 1 to 2 mitoses per 10 high-power fields (×400) to greater than 10 mitoses per 10 high-power fields (case 9).

Other anatomic sites involved by T-PLL were single biopsy specimens obtained from 3 patients. One patient with splenomegaly developed splenic rupture and underwent splenectomy. The spleen weighed 832 g, and T-PLL cells diffusely infiltrated the white pulp with lesser involvement of the red pulp. The neoplasm in the red pulp had a vaguely nodular pattern. A second patient had bilateral pleural effusions and interstitial infiltrates in the lung shown by radiologic studies. A transbronchial biopsy specimen showed small, discrete aggregates of T-PLL in the bronchial mucosa. A third patient had persistent diarrhea that led to endoscopy of the colon. Endoscopy showed superficial ulcers in the cecum and small, discrete aggregates of T-PLL in the lamina propria; no lymphoepithelial lesions were identified \( \text{Image 8} \).

In all biopsy specimens, the T-PLL cells were small to medium-sized. Nuclear contours were relatively round in 16 specimens and highly irregular or Sézary cell–like in 3 specimens.

\( \text{Image 2} \) \( \text{Image 11} \)

\( \text{Image 2} \) \( \text{Image 11} \) (Case 11) T-cell prolymphocytic leukemia involving skin. \( \text{A, In this case, the neoplasm diffusely infiltrated the dermis (H&E, ×200).} \text{ B, High-power magnification revealed that the neoplastic cells had slightly irregular nuclear contours and a subset of cells had distinct nucleoli (H&E, ×1,000).} \)
All 3 specimens with Sézary cell–like cells were obtained from the skin. Nucleoli were identified in at least a subset of cells in 11 biopsy specimens, and nucleoli were prominent in virtually all cells in 3 specimens. In these 3 specimens, the nucleoli could be observed at ×400 magnification. In the remaining biopsy specimens with nucleoli, ×1,000 (oil immersion) magnification was required to adequately detect the nucleoli in the T-PLL cells. The 8 biopsy specimens in which nucleoli were not prominent included skin (n = 4), liver (n = 2), lymph node (n = 1), and cecum (n = 1).

Additional histologic material was reviewed from an autopsy performed on 1 patient (case 2). Multiple organs showed extensive involvement by T-PLL. The bone marrow was involved in an interstitial and diffuse pattern. There was
extensive infiltration of the lungs in a perivascular and peribronchial distribution, associated with interstitial edema, and perihilar lymph nodes were infiltrated diffusely. The spleen was congested markedly and depleted of lymphocytes. However, T-PLL cells were observed in the residual white pulp around blood vessels. In the liver, discrete periportal infiltrates with minimal sinusoidal involvement were observed. Patchy atypical lymphoid aggregates were observed within the lamina propria of the colon. No other sites were involved.

Immunohistochemical Results

Immunohistochemical studies were performed on fixed, paraffin-embedded tissue sections of all extramedullary biopsy specimens. However, the antibody panel used was limited and highly variable. In each specimen, the neoplasm was shown to be of T-cell lineage. All biopsy specimens assessed were positive for CD3 (n = 18), CD4 (n = 9), and CD5 (n = 8) and negative for CD20 (n = 14), CD8 (n = 9), and TdT (n = 5). S-100 protein was negative in all 10 biopsy specimens assessed.

TCL-1 expression was assessed in 12 extramedullary biopsy specimens (cases 1, 2, 4, 5, 7-14); 6 were positive. As part of an earlier study by Herling and colleagues, bone marrow biopsy specimens of many of these patients (cases 1-8 and 11-14) also were assessed, and 7 were positive for TCL-1. In sum, TCL-1 was positive in at least 1 biopsy specimen from 9 (64%) of 14 patients.

Other Data

Flow cytometry immunophenotypic studies were performed on cell suspensions prepared from extramedullary biopsy specimens from 4 patients. In each specimen, the neoplastic cells had a mature T-cell immunophenotype similar to that determined on bone marrow aspirate specimens at the time of initial diagnosis.

In all 4 extramedullary biopsy specimens (from 3 patients) assessed by polymerase chain reaction, monoclonal TCRγ chain gene rearrangements were identified. In 1 biopsy specimen, 2 discrete bands were identified on the ethidium-stained gel. Vγ family use was not determined. In 2 skin biopsy specimens from the same patient, 2 identical monoclonal rearrangements that used the VγI family were identified. In another biopsy specimen, a single monoclonal band that used the VγII family was detected.

Conventional cytogenetics analysis was performed on peripheral blood (n = 1) or bone marrow (n = 7) aspirate material at the time of initial diagnosis in 8 patients and on 1 extramedullary biopsy specimen (the subcutaneous mass) at the time of disease progression. Three neoplasms had the inv(14)(q11q32), and 3 neoplasms had complex karyotypes with chromosome 14 abnormalities, including add(14)(q32) and monosomy 14. In the remaining 3 neoplasms assessed, 2 had a normal karyotype and 1 showed loss of the Y chromosome (case 13), a common finding in elderly men that is thought not to be of clinical significance. The complete karyotypes are listed in Table 1.
### Discussion

Although the clinical and morphologic features of T-PLL have been reported previously, most of these studies have addressed the morphologic characteristics of this disease in the peripheral blood and bone marrow. The morphologic features of T-PLL involving extramedullary sites are poorly documented in the literature. The goal of this study was to focus on the pathologic findings of T-PLL involving extramedullary sites. To achieve this goal, we collected 19 biopsy specimens obtained from extramedullary sites in 14 patients, all whom had well-documented T-PLL at the time of initial diagnosis.

In the present study, none of the extramedullary biopsy specimens were obtained at the time of initial diagnosis; all were obtained later, at the time of disease progression. Presumably, extramedullary sites are not biopsied at the time of initial diagnosis because the diagnosis is established by examination of peripheral blood or bone marrow specimens. Nevertheless, most patients with T-PLL have extramedullary sites of involvement at the time of initial diagnosis, most often involving the spleen, liver, lymph nodes, and skin. In a review of 175 patients with T-PLL by Matutes and Catovsky, splenomegaly was present in 74%, hepatomegaly in 55%, lymphadenopathy in 26%, and skin lesions in 25%. These sites also were involved in the 14 cases we report, although the frequency differed somewhat at the time of initial diagnosis; lymphadenopathy (69%) and skin lesions (46%) were more common, and hepatosplenomegaly was less common. At the time of disease progression when an extramedullary site was biopsied, skin lesions and hepatomegaly (both 57%) were relatively more common (Table 2).

The skin was the anatomic site most commonly biopsied in this study group (10 specimens from 7 patients). Although other extramedullary sites were also commonly involved in these patients, presumably the skin was most often biopsied in our study group because it is readily accessible. In our review of the literature, we found surprisingly few reports describing the pathologic findings of T-PLL involving the skin. The largest study by Mallet et al described 9 skin biopsy specimens obtained from 92 patients with T-PLL (including 26 patients who had clinical evidence of skin disease). Other pathologic studies of T-PLL involving skin have been case reports.

Histologically, skin lesions involved by T-PLL have been described as atypical lymphoid infiltrates of variable density surrounding blood vessels and skin appendages with no epidermotropism. Patients with skin nodules have had diffuse dermal involvement. Thus, the cases in the present study are in agreement with the literature. However, case 5 in this study is unusual. We are not aware of another patient with T-PLL described in the literature who had a large subcutaneous mass. Two other biopsy specimens (cases 12 and 13) also are of interest because the skin biopsy specimens had foci of epidermotropism. This has not been emphasized adequately in earlier reports of skin involvement by T-PLL. In fact, 1
biopsy specimen had epidermotropism and epidermal changes, the latter including hyperkeratosis and parakeratosis. These changes raise the differential diagnosis with mycosis fungoides/Sézary syndrome. In addition, in 3 of the skin biopsy specimens we studied, the neoplastic cells had irregular or Sézary-like nuclear contours, as described by others. However, the clinical setting of well-established T-PLL in the cases included in the present study prevented potential misdiagnosis.

The biopsy specimens in the present study show that the cytologic features of T-PLL in routinely stained tissue sections are heterogeneous. The typical description of T-PLL in peripheral blood or bone marrow smears, that being a mononuclear population of medium-sized prolymphocytes with prominent central nucleoli, was not common in the cases we report. The T-PLL cells in 3 biopsy specimens, 2 skin and 1 lymph node, were monotonous with virtually all cells having a prominent nucleolus that could be observed readily at routine high-power magnification (×400). In 8 additional biopsy specimens, a subset of T-PLL cells had prominent nucleoli, although these cells initially were better detected at ×1,000 (oil immersion) magnification. In the remaining biopsy specimens, nucleoli were not prominent, even at ×1,000 magnification. The latter cases might correspond to the small cell variant of T-PLL described in blood and bone marrow.

A number of chromosome abnormalities have been reported in T-PLL. The most distinctive cytogenetic abnormality known to occur is the inv(14)(q11q32), or the rare t(14;14)(q11;q32) and t(X;14)(q28;q11). In the inv(14) and t(14;14), the tcl-1 oncogene is juxtaposed with the promoter/enhancer of the TCRαδ locus at 14q32, resulting in TCL-1 overexpression. Similarly, in the t(X;14) the metp-1 gene on chromosome Xq28 is juxtaposed with the TCRαδ locus. Overexpression of TCL-1 is reported to be present in 80% to 90% of cases of T-PLL. In TCL-1-negative cases, other genes in proximity at 14q32, such as tcl-1b, may also be involved.

In the present study, we demonstrated TCL-1 overexpression using immunohistochemical methods in biopsy specimens from 9 (64%) of 14 patients. In an earlier study, Herling and colleagues demonstrated that TCL-1 expression is restricted to T-PLL among mature T-cell neoplasms, and, thus, TCL-1 expression can be useful in distinguishing this neoplasm from other T-cell neoplasms. However, TCL-1 immunostaining did not detect all cases of T-PLL in the present study. Furthermore, TCL-1 is not specific for T-PLL. By using immunohistochemical methods, Narducci et al assessed TCL-1 expression in 194 cases, including neoplastic B- and T-cell lymphomas and reactive specimens. In reactive tissue, TCL-1 is expressed in most pre-germinal center B cells and some germinal center B cells but not in post-germinal center B cells, plasma cells, or mature T cells. TCL-1 also is expressed in many B-cell neoplasms, including cases of precursor B-cell lymphoblastic lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, and primary cutaneous B-cell lymphoma. Taken together, our results show that TCL-1 immunostaining in neoplasms known to be of T-cell lineage is a specific but not sensitive marker of T-PLL. These results, however, also suggest that T-PLL, as currently defined in the WHO classification, is not a completely homogeneous entity.

In summary, we describe the histologic findings of T-PLL involving 19 biopsy specimens obtained from extramedullary sites in 14 patients. Skin involvement was the most common extramedullary site biopsied, followed by liver and lymph nodes. At our institution, extramedullary sites of involvement, although present, were not biopsied at the time of initial diagnosis, presumably because peripheral blood and bone marrow are more appropriate and accessible for establishing the diagnosis. Instead, extramedullary sites of disease in patients with T-PLL at our institution were biopsied subsequently, to support the clinical impression of disease progression. Disease involving these extramedullary sites may have been less responsive to the therapy, because peripheral blood and bone marrow samples were negative or minimally involved in some of the patients.

In addition, we found the cytologic features of T-cell prolymphocytes difficult to recognize in routine H&E-stained tissue sections in many specimens. Thus, recognition of T-PLL involving extramedullary sites often requires morphologic evaluation at ×1,000 magnification and usually needs additional workup using ancillary methods. TCL-1 expression, assessed immunohistochemically, is a useful marker for documenting T-PLL involving extramedullary sites. However, absence of TCL-1 expression does not exclude involvement by T-PLL.

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References


