True T-Cell Chronic Lymphocytic Leukemia: A Morphologic and Immunophenotypic Study of 25 Cases

By J.D. Hoyer, C.W. Ross, C.-Y. Li, T.E. Witzig, R.D. Gascoyne, G.W. Dewald, and C.A. Hanson

We studied 25 T-cell chronic lymphocytic leukemia (T-CLL) cases collected over a 15-year period. Immunophenotypic analysis was performed in each case; 12 cases were evaluated by cytogenetics, and gene rearrangement studies were performed in 14 cases. The median age was 57 years with a male predominance (M:F, 15:10). The median presenting lymphocyte count was 36.3 x 10^9/L (range, 3.9 to 438 x 10^9/L). Fourteen patients (56%) had shotty adenopathy and ten (40%) had mild-to-moderate splenomegaly at presentation; four (16%) had erythematous skin lesions. The lymphocytes were predominantly small; some cases had a minor component of medium-sized cells (<10%). The nuclear:cytoplasmic ratios were uniformly high with round to oval nuclei; however, a wide spectrum of nuclear outlines could be found, ranging from minimally to markedly convoluted. Nucleoli were either absent or small and inconspicuous. These lymphocytes did not have the morphology of prolymphocytes and did not contain cytoplasmic granules. Bone marrow infiltration was generally in an interstitial pattern; the degree of involvement ranged from 15% to 90%. Immunophenotyping showed that the lymphocytes were mature T-cells with a predominant CD4+ immunophenotype. Three cases displayed a CD8+ immunophenotype. The patients were treated with a variety of chemotherapeutic regimens with only a minimal response observed in two of 20 patients. We conclude that T-CLL is an uncommon chronic lymphoproliferative disorder (CLPD) that can be morphologically similar to B-CLL, is distinct from T-prolymphocytic leukemia, and has an aggressive clinical course that is refractory to therapy. It may also be difficult to distinguish T-CLL from other T-CLPD, especially the leukemic phase of peripheral T-cell lymphomas and some cases of Sézary syndrome.

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Peripheral Blood, Bone Marrow (BM), and Tissue Samples

Peripheral blood and BM aspirate smears were stained by either Wright’s or Wright-Giemsa stains using standard techniques. BM trephine biopsies were fixed in B5 fixative, processed by standard decalcification techniques, and stained using hematoxylin-eosin.

Lymph node biopsies from two cases were fixed in 10% formalin and/or B5 fixative; skin biopsies from two cases were fixed in 10% formalin. Both tissues were stained by standard hematoxylin-eosin techniques.

Immunophenotyping

Immunophenotyping was performed on peripheral blood using flow cytometric analysis (16 cases), immunocytochemical stains of air-dried smears (seven cases), or by immunoperoxidase studies on paraffin sections (two cases). Flow cytometric analysis was performed on either a FACS IV or FACSScan Analyzer (Becton Dickinson, Mountain View, CA), using standard techniques. The immunocytochemical technique on air-dried slides used either an alkaline phosphatase-antialkaline phosphatase method with fast red violet as the chromogen or a labeled streptavidin-biotin method using aminoethylcarbazole as the chromogen. The following antibodies were used with either flow cytometry or immunocytochemical techniques: CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD19, CD20, CD56, CD57, and HLA-DR.

Two cases were identified before the availability of immunophenotyping. A T-cell phenotype of the lymphocytes was presumed by detecting T-rosette formation and focal, punctate α-naphthyl acetate esterase (ANAE) staining. Retrospectively, the BM biopsy blocks in these two cases were retrieved and paraffin section immunostaining using a labeled streptavidin-biotin method with aminoethylcarbazole as the chromogen was performed. The following antibodies were used for these two paraffin block studies: CD2 (L26), CD3, CD4, CD5, CD7, CD8, CD16, CD19, CD20, CD56, CD57, and HLA-DR.

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CD45RO (UCHL-1, OPD4), CD43 (Leu-22), CD3 (polyclonal), and CD57 (Leu-7).

Cytogenetics

Chromosomal analysis was performed on either peripheral blood (nine cases), BM aspirates (two cases), or both (one case). Specimens collected before 1984 were processed using standard direct and short-term unstimulated culture methods. Specimens collected after 1984 were cultured and procured using a standard direct technique and an in situ unstimulated culture method. Metaphases were stained by either Giemsa stain with trypsin pretreatment (GTG-banding) or fluorescent staining with quinacrine mustard (QFQ-banding). Photomicrographs of representative metaphases were taken in all cases for documentation purposes. The cytogenetic results were recorded in accordance with the standard rules for the International System for Human Cytogenetic Nomenclature (ISCN).

Molecular Genetics

T-cell receptor (TCR) and Ig gene rearrangement studies were performed on either peripheral blood (13 cases) or both BM aspirate and peripheral blood (one case) using standard methods. The TCR/β chain region probes used were either a Jβ3 (0.7-kb XbaI fragment)/Jβ2 (4.4-kb EcoRI fragment) probe mixture (four cases) or a Cβ1 (0.7-kb EcoRI fragment) (five cases) or a Cβ1 (3.5-kb HindIII fragment) (five cases). The TCRγ chain region probe used was a 0.7-kb EcoRI/Hind III fragment (four cases). Ig gene rearrangements were evaluated with the following DNA probes: Jκ (1.8-kb SacI fragment); CA (1.06-kb BamHI fragment); Cμ (1.3-kb EcoRI fragment); and Jκ (2.5-kb Sau3A fragment) (14 cases). The restriction enzymes used for the Southern blot analysis included: (1) EcoRI for Jβ3/Jβ2, TCRγ, and CA; (2) BamHI for Cμ and Jκ; (3) Bgl II, BamHI, and HindIII for Jκ; and (4) EcoRI, BamHI, and HindIII for Cβ1.

RESULTS

Patient Profiles/Laboratory Findings

The median age range of the patients was 57 years (range, 26 to 80 years) with a male predominance (M:F, 15:10). The median white blood cell count at presentation was 48.1 × 10^9/L (range, 10.9 to 488.0 × 10^9/L), with a median absolute lymphocyte count of 36.3 × 10^9/L (range, 3.9 to 438.0 × 10^9/L). Twelve patients had a marked lymphocytosis exceeding 100.0 × 10^9/L at some point in the course of their disease, with the highest lymphocyte count recorded being 762.0 × 10^9/L. Six patients presented with both anemia and thrombocytopenia, three patients with anemia alone, and two patients with thrombocytopenia alone. In those patients with anemia and/or thrombocytopenia, the hemoglobin values ranged from 7.1 to 12.6 g/dL and platelet counts from 42 to 135 × 10^9/L. None of the patients had an absolute neutropenia. Ten patients showed elevated serum liver function tests at some time in the course of their disease, usually manifested as a mild elevation of both alkaline phosphatase and aspartate aminotransferase with or without mild elevation of lactate dehydrogenase. One patient had an elevation of lactate dehydrogenase to 750 U/L. None of the patients had significant hypercalcemia or hyperproteinemia. One patient had a small monoclonal gammapathy by immuno electrophoresis, which was not clinically significant. Ten patients had serologic testing for HTLV-1; all were serologically negative.

Physical Findings

Fourteen patients had mild lymphadenopathy at presentation, characteristically with small shotty nodes (<1 cm) in multiple lymph node chains; two cases underwent lymph node biopsies. Ten patients presented with mild-to-moderate splenomegaly and two others with mild-to-moderate hepatosplenomegaly. Two additional patients developed hepatosplenomegaly later in their clinical course. Three patients presented with a maculopapular rash and one patient with erythematous plaques over the trunk.

Morphology

Peripheral blood. The peripheral blood smears in all cases showed a predominant small lymphocytic proliferation (Fig 1). In eight cases, there was a minor component of medium-sized lymphocytes, comprising less than 10% of the lymphoid cells. The small lymphocytes were characterized by a high nuclear:cytoplasmic ratio, with scant pale-blue cytoplasm. Cytoplasmic granulation was absent in all cases. In four specimens, the lymphocytes displayed cytoplasmic blebs. The malignant lymphocytes exhibited a wide variety of nuclear shapes and contours. In 16 of the cases the lymphocytes were round to oval and exhibited only mild nuclear irregularity, consisting of a slight indentation to one side of the nucleus. Two cases in this group had a minor component of lymphocytes with a more pronounced indentation almost resembling a cleaved cell. The remaining nine exhibited moderate nuclear irregularity with the nuclear membranes being either folded or undulated. In these cases, a minority of lymphocytes were markedly convoluted. In all cases the nuclear chromatin was condensed, with nucleoli either absent or small and inconspicuous. The medium-sized lymphocytes displayed a lower nuclear:cytoplasmic ratio with pale-blue cytoplasm, had irregular nuclear outlines, and had identifiable, but not prominent, nucleoli.

BM. BM aspiration and biopsy samples were available from 17 of the 25 patients. The BM aspirate smears showed an increase in small lymphocytes similar in appearance to that seen on the peripheral blood smears. No abnormalities were seen in the myeloid, erythroid, or megakaryocytic cell lines. Four of the 17 BM biopsy samples were normocellular with the rest being hypercellular. The degree of lymphocytic involvement ranged from 15% to 90%, with two cases showing a nodular pattern, 12 an interstitial pattern, and three a diffuse pattern of infiltration (Fig 2). The lymphocytic infiltrate had a homogeneous appearance in all but one case; in most cases, slight-to-moderate nuclear irregularity of the small lymphocytes could be appreciated. In one case, a small (10%) component of larger cells was present. Nucleoli were absent and mitoses were not seen. Only one case had prominent vascularity within the lymphoid infiltrate. None of the cases had associated necrosis, granulomas, or plasma cell/eosinophilic infiltrates.

Other specimens. Lymph node biopsy samples were available for review in two cases. Both cases showed effacement of the normal lymph node architecture by a monomor- phous population of small lymphocytes. Small, sometimes sclerotic vessels were prominent in both cases. One case was...
characterized by small lymphocytes with minimal nuclear irregularity. There were occasional small clusters of larger cells present. In the other case, prominent nuclear irregularity in the small lymphoid cells was noted. In two of the cases with skin involvement, skin biopsy samples were available for review (neither of these had lymph node biopsies performed); both showed a perivascular lymphocytic infiltrate without epidermotropism. The patient with the erythematous plaques did not undergo a biopsy; these plaques regressed after initial treatment.

**Immunophenotyping**

All cases showed a mature T-cell immunophenotype (Table 1). No aberrant expression or loss of pan-T-cell antigens was identified. In 20 cases, the lymphocytes were CD4⁺; however, three cases displayed a CD8⁺ phenotype. These three cases were morphologically indistinguishable from the CD4⁺ cases, did not have a LGL morphology, and were CD16⁻, CD56⁻, and CD57⁻.

The two cases identified before the availability of immunohistochemical studies showed positive E-rosettes and focal ANAE staining, in a pattern shown to be common in T-lymphocytes. Retrospective immunohistochemical studies performed on the BM biopsy sample paraffin sections showed a lymphocytic infiltrate composed of T-lymphocytes that were positive for CD3 and weak CD45RO (both UCHL-1 and OPD4). These lymphocytes were CD20⁻, CD43⁻, and CD57⁻.

**Treatment/Survival**

Complete follow-up information was available on 20 of the 25 patients; partial information was available for the
Table 1. Summary of Immunophenotypic Results

<table>
<thead>
<tr>
<th>Antigen</th>
<th>No. Positive/No. Tested</th>
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<tbody>
<tr>
<td>CD2</td>
<td>16/16</td>
</tr>
<tr>
<td>CD3</td>
<td>21/21</td>
</tr>
<tr>
<td>CD4</td>
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<tr>
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<td>0/10</td>
</tr>
<tr>
<td>CD57</td>
<td>0/11</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>0/14</td>
</tr>
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</table>

Table 2. Summary of Cytogenetic and Molecular Genetic Studies

<table>
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<tr>
<th>Cytogenetics (n = 12)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Chromosome abnormality*</td>
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</tr>
<tr>
<td>inv(14)(q11.2;q32)</td>
<td>2</td>
</tr>
<tr>
<td>t(14;14)(q32;q11)</td>
<td>1</td>
</tr>
<tr>
<td>t(X;14)(q28;q11)</td>
<td>1</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>1</td>
</tr>
<tr>
<td>7p15 abnormality</td>
<td>1</td>
</tr>
<tr>
<td>Complex abnormalities involving chromosomes</td>
<td></td>
</tr>
<tr>
<td>7p15 and 14q11</td>
<td>1</td>
</tr>
<tr>
<td>Isochromosome 8q</td>
<td>2</td>
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<tr>
<td>Deletion 8q</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular Genetics (n = 14)</th>
<th>No. of Rearranged</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell receptor β chain</td>
<td>14/14</td>
</tr>
<tr>
<td>Ig heavy &amp; light chains</td>
<td>0/14</td>
</tr>
<tr>
<td>T-cell receptor γ chain</td>
<td>2/4</td>
</tr>
</tbody>
</table>

* Some cases had more than one of these abnormalities, i.e., i(18q) and inv(14)(q11.2;q32). Many cases also displayed additional random abnormalities not listed here.

Cytogenetics

Cytogenetic studies were performed on 12 cases (Table 2). Recurring structural abnormalities involving bands 14q11 and 14q32, because of either translocation or inversion, were identified in six cases. Two cases also had abnormalities involving band 7p15. Three cases had abnormalities involving the long arm of chromosome 8; two of these were iso-

other five. The patients were treated with a variety of chemotherapeutic regimens, the most common being chlorambucil (or cyclophosphamide) plus prednisone. Other regimens included CHOP, CVP, m-BACOD, CVB, PROMACE, COPA, CAP-BOP, VP-16, fludarabine, and pentostatin. One patient was treated with intrathecal methotrexate, prednisone, and whole brain irradiation (3,000 rads) because of suspected meningeal involvement (bilateral seventh nerve palsies). Two patients received allogeneic BM transplantation.

Seventeen of the 20 patients with available follow-up information have died as a result of their disease (Fig 3). The median survival of those who died was 13 months (range, less than 1 month to 6 years). In this group, only two patients showed minimal responses to chemotherapy; all others were refractory. Currently three patients are still alive (9 to 14 months after diagnosis). One of these patients received a BM transplantation and is alive 9 months after diagnosis.

Molecular Genetics

Gene rearrangement studies were performed in 14 cases. In all instances there was rearrangement of the TCRβ chain without rearrangement of the Ig heavy or light chain. Rearrangement of the TCRγ chain was also detected in two cases. Interestingly, there were two cases that had cytogenetic abnormalities involving 14q32 that also had molecular genetic studies performed. These two cases did not show rearrangement of the Ig heavy chain gene.

DISCUSSION

The results from this multi-institutional study show that T-CLL is an uncommon entity with features distinct from other T-CLPD. Based on the total number of cases seen at our institutions, T-CLL accounts for less than 1% of all CLPDs. T-CLL is characterized by a marked lymphocytosis of primarily small, mature T-lymphocytes having some degree of nuclear irregularity, and inconspicuous nucleoli that do not meet the diagnostic criteria for prolymphocytes. Lymphadenopathy and splenomegaly are uncommonly found and, when present, are always mild to moderate without striking organomegaly. The immunophenotype is that of a mature T-cell that is usually CD4+, but may occasionally be CD8+. The patients from our study did poorly; a number of different chemotherapeutic agents were administered with only a minimal response being obtained in a minority of patients.

A number of CLPDs enter into the differential diagnosis of T-CLL, including: T-PLL, leukemic phase of peripheral T-cell lymphoma (PTCL), mycosis fungoides/Sézary syn-
drome, adult T-cell leukemia/lymphoma (ATL), LGL leukemia, as well as B-CLPDs. The distinction of T-CLL from these various CLPDs can at times be difficult and depends on an accurate morphologic assessment and correlation with morphologic, immunophenotypic, and clinical features.

T-PLL is a well-published entity that shares many clinical and hematologic features with T-CLL; namely, both may present with a marked lymphocytosis and both usually, but not always, display a CD4+, mature T-cell immunophenotype.17-21 As opposed to T-CLL, patients with T-PLL often have striking splenomegaly with or without concurrent lymphadenopathy or hepatomegaly. In T-PLL cases, the lymphoid cells have characteristics of prolymphocytes, being intermediate in size, having a nuclear/cytoplasmic ratio that is lower than T-CLL with moderately condensed chromatin, and, as a hallmark, a single, prominent central nucleolus. Although in eight of our cases a small subpopulation (<10% of cells) of medium-sized cells could be identified, true prolymphocytes were infrequent. Morphologically, T-PLL was not a consideration when these cases were initially detected because of the homogeneous small lymphocyte appearance and lack of observable nucleoli. Significantly, in the largest published series of T-PLL,21 ~20% of T-PLL cases were termed the “small cell variant,” of T-PLL in which the nucleolus was not obvious by light microscopy and visible only by electron microscopy. It would appear that the cases we have termed T-CLL comprising our series probably correspond to this so-called small cell variant of T-PLL.

Matutes et al22 have advocated using the term T-PLL to encompass both of these entities, with commentaries from other authors strongly discouraging the use of the term T-CLL.23 The rationale presented has been that subdividing these T-cell disorders will discourage a further understanding of this group of mature T-cell processes and hinder development of effective treatments. Furthermore, it has been feared that using the term “CLL” to describe the small cell variant of T-PLL may cause clinicians to underestimate the aggressive nature of these cases. However, it is our contention that the mature T-cell classification system should have a category for T-CLL that is based on the morphologic finding of a small lymphocyte proliferation.

Equally important is the distinction of T-CLL from the leukemic phase of PTCL.22,23 Both entities may present with varying degrees of lymphadenopathy and blood and marrow lymphocytosis.24 Similar to T-PLL, the majority of PTCL cases express a CD4+ immunophenotype. The morphology of circulating PTCL cells is usually more variable than in T-CLL. These lymphoma cells can be large to intermediate in size, with irregular nuclei, reticular nuclear chromatin, and may have prominent nucleoli. In our two cases in which lymph node biopsies were obtained, the morphology was that of a small lymphocytic lymphoma. As with other entities, such as B-cell small lymphocytic lymphoma/B-CLL, T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, or Burkitt’s lymphoma/leukemia, the distinction between a leukemic phase of lymphoma versus a marrow-derived leukemia can be an exercise in semantics without an obvious answer. It would appear appropriate that, analogous to B-CLL and B-cell small lymphocytic lymphoma, the designation T-CLL be used (as in our cases) in primarily marrow-based processes with significant involvement of the peripheral blood and BM by a small immature lymphocyte population and with only minimal secondary involvement of other organs such as lymph nodes or spleen. Conversely, the finding of prominent lymphadenopathy without marrow replacement would be more consistent with the diagnosis of a PTCL.

Morphologic confusion of T-CLL with the small cell variant of mycosis fungoides/Sézary syndrome is certainly possible.25 The lymphocytes from both T-CLL and Sézary syndrome can exhibit nuclear convolutions. Furthermore, a small subset of patients with T-CLL can present with erythematous skin rashes. In these cases, a skin biopsy may be critical in making the distinction between T-CLL and Sézary syndrome. In our study, those cases in which skin biopsy samples were obtained showed a perivascular lymphocytic infiltrate and not the characteristic epidermotropism seen in mycosis fungoides/Sézary syndrome.

The distinction of T-CLL from other entities in the differential diagnosis (ATL, LGL disorders, and B-CLPDs) should not be difficult. Each of these has morphologic, immunophenotypic, or serologic characteristics that usually permit their distinction from T-CLL.26-28 The identification of cytoplasmic granules in LGLs and their absence in T-CLL should override any concern with an uncommon CD8+ immunophenotype that can occasionally be encountered in T-CLL.

The cytogenetic results from our study are consistent with other reports of T-CLPDs.29-31 A recurring chromosomal abnormality in patients with these T-cell malignancies involves 14q11, the site of the T-cell receptor a and d chain genes, and 14q32. Other cases had abnormalities involving 7p15, the site of the TCRy chain gene. Although some authors have claimed that inv(14) and t(14;14) abnormalities are specific for T-PLL,21,33 it appears more likely that these findings are common to T-cell proliferations in general, including T-CLL,34-37 PTCL,38-41 T-cell acute lymphoblastic leukemia,42-43 T-cell lymphoblastic lymphoma,40 ATL,44 and Sézary syndrome.45 Although 14q32 is the location of the Ig heavy chain gene, it may not be intimately involved in inv(14)(q11;q32) or t(14;14)(q11;q32).12,13 This concept is supported by two of our cases in which simultaneous cytogenetic and molecular genetic studies were performed. In both cases, the 14q32 locus was involved and yet no Ig heavy chain gene rearrangements were detected by molecular studies, implying that the breakpoint on band 14q32 is outside the Ig heavy chain gene locus detected by commonly used probes.

Studies in the literature have reported an association between ataxia telangiectasia and T-CLPDs35,36,46-48; our series included such one patient. Early chromosome studies on this patient before the T-CLL diagnosis showed a t(14;14)(q11;q32), but with no additional chromosomal abnormalities and a normal white blood cell count and differential. She continued to have a protracted clinical course; 8 years later, a repeat karyotype showed numerous complex abnormalities in addition to the t(14;14). She subsequently entered a more aggressive stage of her disease, was diagnosed with a T-CLL, and died within 2 years. This case...
supports the theory previously presented that 14q11 abnormalities may represent a precursor event in ataxia telangiec-tasia, and that additional cytogenetic abnormalities signal the development of a more aggressive phase in this disease. 33,40-49 This patient also had an older sister with ataxia telangiec-tasia, who died of an atypical T-cell lymphoproliferation that was not sufficient for the diagnosis of T-CLL. 40 Cyto- genetics on this older sister showed a t(14;14)(q11;q34) abnormality as well as other karyotypic abnormalities.

The basic classification scheme for B-CLPDs is well established. 51 The separation of B-CLL, B-PLL with pro- lymphocytoid features, and B-PLL is based on identifying an increasing percentage of prolymphocytes: less than 15%, 15% to 55%, and greater than 55%, respectively. Other com- ponents of the B-cell chronic lymphocytic proliferation scheme are based on unique morphologic as well as immuno- phenotypic characteristics. In contrast, there has been a different approach regarding the classification of BM-based T- cell proliferations. T-prolymphocytic leukemia has remained the core of the T-cell classification system with other disor- ders such as ATL, LGL leukemia, and Sézary syndrome being separated based on morphologic features and viral studies.

Morphologic and laboratory studies would seem to indicate that the T-CLPDs are probably more complex than the current classification system implies. 51 Although rare, mature T-cell malignancies expressing a y/6 T-cell receptor have a unique immunophenotype and appear to have a different tissue predilection than those cases with the more common α/β receptor. 52 Another example is the chronic T-cell leukemic proliferations expressing the S100 antigen, which are aggressive disorders that have characteristic clinical and morphologic features. 53 The non-LGL cases displaying a CD8 immunophenotype may represent a distinct entity as well. 54 Cyto genetic studies also suggest that there may be karyotypic subgroups within the T-cell malignancies worth further study. Future classification schemes of the T-CLPDs may need to incorporate a variety of morphologic, immuno- logic, cytogenetic, and molecular features in subclassifying this heterogeneous group of malignancies.

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