Clinical and Phenotypic Diversity of T Cell Lymphomas

By Sandra J. Horning, Lawrence M. Weiss, Gertrude S. Crabtree, and Roger A. Warnke

Forty-one cases of T cell lymphoma were identified on the basis of morphology and the expression of two or more T cell antigens with an absence of B cell markers. Mycosis fungoides and lymphoblastic lymphoma were excluded. Marked clinical, morphological, and immunologic diversity was observed. Cutaneous lymphoma was found in ~50% of the patient group, and 27% had a prior history of dermatologic or immunologic disease. No correlations among immunologic and morphologic phenotypes and clinical course were apparent. Survival data was comparable to that of a concurrent group of non-T cell lymphoma patients studied at this institution, suggesting that, contrary to previous reports, T cell lymphoma may not necessarily confer a more unfavorable prognosis. Prospective studies using uniform treatments are necessary to address the clinical significance of the T cell phenotype definitively, independent of established histologic and clinical features.

MAStIGNANT Lymphomas of T cell origin have been broadly classified as those expressing thymic antigens (lymphoblastic lymphoma) or postthymic, “mature” antigens. The latter group includes mycosis fungoides (MF) and Sézary syndrome, which have well-described clinical, pathologic, and immunologic features. The term “peripheral” T cell lymphoma has been applied to the heterogeneous group of diffuse lymphomas other than MF which express postthymic T cell antigens.

Varied descriptions of the morphological appearance of T cell lymphomas have been provided by pathologists in this country, Europe, and Japan. The clinical features described for these T cell lymphomas have been nearly as heterogeneous as their morphology. The criteria for diagnosis of T cell lymphoma have not been uniform but have usually included the identification of neoplastic cells within E rosettes. Expert pathologists are not able to distinguish between B and T cell lymphomas by morphology alone, even in the most distinctive entities.

We have previously reported on the clinical relevance of immunophenotype in diffuse large cell lymphoma, which included a small number with the T cell phenotype. The current study was undertaken to expand these observations and correlate the clinical characteristics with morphological and immunologic features of diffuse lymphomas expressing T cell antigens.

MATERIALS AND METHODS

Sixty-four cases of T cell lymphoma (TCL), excluding MF and lymphoblastic lymphoma, were identified in the Laboratory of Immunopathology at Stanford University Medical Center from 1981 through 1984. Further review excluded 13 cases from this analysis due to inadequate material or reinterpretation of histologic or immunologic features. Clinical data was not available for correlation in nine cases; one case was excluded because malignant lymphoma developed in association with the Wiskott-Aldrich syndrome. Thus, 41 cases of T cell lymphoma, identified on the basis of morphology and the expression of two or more T cell antigens with an absence of B cell markers, are studied in this report. Clinico-pathologic correlations in ten of these cases have been previously reported. In addition, a detailed morphological and immunohistochemical characterization of 39 of the 41 cases has been recently reported. No patient was excluded from this series based on clinical behavior.

Tissue samples were obtained from the following sites: lymph node (19 cases), skin (17 cases), lung (2 cases), nasopharynx (2 cases), and one each in spleen, gastrointestinal tract, mediastinum, and chest wall. These samples included initial diagnostic material in 31 cases, disease recurrent after therapy in 7 cases, and both initial and recurrent material in 3 cases. The hematoxylin-stained and cosinestained paraffin sections of all cases were classified according to a modification of the Working Formulation for the non-Hodgkin’s lymphomas. A new category was also added, that of angioimmunoblastic lymphadenopathy-like (“AILD-like”) T cell lymphoma as morphologically defined by Shimoyama and three patients did not have bone marrow biopsies. Thirty-seven original staging data were extracted and actuarial survival curves were calculated from the time of diagnosis. Tests of statistical significance between survival curves were calculated as described by Gehan.

Survival was calculated from the time of diagnosis. Tests of statistical significance between survival curves were calculated as described by Gehan. Staging followed the convention of the Ann Arbor Conference and was based on results of chest x-ray, lymphography and/or computed tomography of the abdomen, and pelvis and bone marrow biopsy, in addition to physical examination. However, original staging data was not available for review in eight patients and three patients did not have bone marrow biopsies. Thirty-seven patients were primarily managed or seen in consultation by the clinical or academic Stanford faculty. The clinical records were obtained from the responsible physician in the remaining four cases.

RESULTS

Clinical and morphological features. Table 2 shows the clinical and morphological features of the study. The study included 19 females and 22 males. Ages ranged from 4 to 91
years with a median of 56 years. Limited disease was observed in 13 patients (11 with stage I and two with stage II), nine of whom had lymphoma in extranodal sites. The sites of extranodal involvement in these limited-stage patients consisted of skin in seven cases and nasopharynx and lung in one each. Twelve patients had stage III and 16 patients had stage IV disease. Systemic symptoms were present at diagnosis in 11 patients (27%), all of whom had advanced disease. Extranodal sites of lymphoma in the entire group of 41 patients included skin (20 cases), bone marrow (4 cases), liver (4 cases), lung (5 cases), gastrointestinal tract (2 cases), nasopharynx (2 cases), and one case each involving the heart and pleura. In two patients, subsequent bone marrow biopsies, sampled following three and six cycles of chemotherapy, showed no evidence for lymphoma but were markedly hyperplastic with prominent myelodysplastic features. One of these patients had a peripheral eosinophilia of 59% (absolute count 5,900/μL). Peripheral eosinophilia was noted in one additional patient at diagnosis.

Eleven patients (27%) had a prior history of dermatologic or immunologic disease including: psoriasis (2 cases), chronic exfoliative dermatitis (2 cases), celiac sprue (2 cases), and one case each with a history of Sjogren's syndrome, rheumatoid arthritis with iritis, erythema multiforme, Sweet's syndrome, immune thrombocytopenia with auto-antibodies and nonspecific dermatitis. Cutaneous lymphoma was present in six of these 11 patients.

Of the 20 patients with cutaneous lymphoma at diagnosis, disease was restricted to the skin in ten. The skin lesions were highly variable in appearance and included maculopapular lesions, nodules, plaques, and ulcers, which ranged from erythematous to violaceous in color. A history of waxing and waning skin disease and response to topical steroids were not infrequent. In nine patients, skin lesions had been present for several months to three years prior to the diagnosis of lymphoma. Five of these nine patients had previous skin biopsies in the same region that were interpreted as benign or atypical lymphocytic infiltration.

Primary therapy is shown in Table 2. Two patients were never treated. One died of gastrointestinal hemorrhage shortly after diagnostic laparotomy. Another had a spontaneous regression of diffuse adenopathy and arthralgias prior to the planned institution of therapy. Among the 27 patients receiving primary chemotherapy, 21 received Adriamycin in combination with Cytoxan, vincristine, and prednisone with or without methotrexate and bleomycin. The others were treated with Cytoxan, vincristine, and prednisone alone (two patients) or with procarbazine (four patients). Eleven patients were treated with irradiation alone, including two patients with stage IV cutaneous lymphoma; three patients received combined chemotherapy and radiotherapy.

The majority of patients had a morphologic diagnosis of high-grade, diffuse large cell, immunoblastic (14 patients), which could be subcategorized into polymorphic (3 cases), plasmacytoid (3 cases), clear cell (6 cases), and epithelioid (2 cases). Twelve cases were intermediate-grade, diffuse large cell, and eight were diffuse mixed small and large cell. Three patients in the diffuse mixed category were subcategorized as AILD-like. Two of these patients, both males, presented with a clinical syndrome consistent with AILD, including rash, diffuse adenopathy, and systemic symptoms; hepatosplenomegaly was objectively documented in one. Neither had Coomb's-positive anemia or hypergammaglobulinemia. Overall, there was no correlation between morphology and stage, site, or previous history of dermatologic or immunologic disease.

**Phenotypic features.** Twenty-five cases (61%) expressed a helper cell phenotype (Leu 2+3+), and four expressed a cytotoxic-suppressor phenotype (Leu 2+3-). Twelve lymphomas were of undefined phenotype, with eight Leu 2+Leu 3- and four Leu 2-Leu 3+. The cases lacking either helper or cytotoxic/suppressor phenotype expressed two or more T cell antigens, including Leu 1 (2 cases), Leu 4 (6 cases), Leu 5 (5 cases), Leu 9 (6 cases), and did not express B lineage markers. Of the 25 helper cell phenotypes, there was a loss of

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**Table 1. Monoclonal Antibodies Reactive With TCL**

<table>
<thead>
<tr>
<th>Antigen/Clone/Similar Antigens</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu 1/L17F12+/T1,T65</td>
<td>T cells, thymocytes, B-CLL, B lymphoma</td>
</tr>
<tr>
<td>Leu 2a/SK1+/T5,T8</td>
<td>Cytotoxic/suppressor T cells, thymocytes, splenic sinusoids</td>
</tr>
<tr>
<td>Leu 3a/SK3+/T4</td>
<td>Helper T cells, thymocytes, monocytic macrophages, Langerhan's cells</td>
</tr>
<tr>
<td>Leu 4/SK7+/T3</td>
<td>T cells, thymocytes, Purkinje cells</td>
</tr>
<tr>
<td>Leu 5/ATM1.1+/T11,Lyt 3</td>
<td>T cells, thymocytes</td>
</tr>
<tr>
<td>Leu 6/SK9/T6</td>
<td>Cortical thymocytes, Langerhan's cells</td>
</tr>
<tr>
<td>Leu 9/4H9+/3A1</td>
<td>Cytotoxic/suppressor T cells, helper T cells, thymocytes, monocytic macrophages, Langerhan's cells</td>
</tr>
<tr>
<td>IA/L203L227†</td>
<td>Activated T cells, B cells, myeloids, monocytic macrophages, Langerhan's cells, epithelium</td>
</tr>
</tbody>
</table>

*Obtained from Becton Dickinson, Mountain View, Calif.
†Obtained from Ronald Levy Laboratory, Stanford, Calif.

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**Table 2. Summary of Clinical and Morphological Features in 41 Patients With TCL**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and IIE†</td>
<td>14(9)</td>
<td>34(22)</td>
</tr>
<tr>
<td>Stage III and IV</td>
<td>27</td>
<td>66</td>
</tr>
<tr>
<td>Cutaneous lymphoma (only†)</td>
<td>20(10)</td>
<td>49(24)</td>
</tr>
<tr>
<td>Prior history of dermatologic or immunologic disease</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Morphologic diagnosis‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse mixed (AILD-like)</td>
<td>8(3)</td>
<td>20</td>
</tr>
<tr>
<td>Diffuse large cell</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Diffuse large cell, immunoblastic</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>Monomorphic</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Primary Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Combined modality</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Extraneal site.
†Extraneal site.
‡Described in text.
one or more pan-T cell differentiation antigens in 19. Overall, the Ia antigens were expressed in 30 cases. Immunologic phenotype did not correlate with stage, the presence or absence of cutaneous or other sites of involvement, previous history of an immunologic or dermatologic disorder, or other clinical features. Neither was there any correlation between histologic category and immunophenotype. The spleen, the site of another group of described T cell-related malignancy, T \( y \) lymphoma, was not available for study in the Leu 2+3- cases.29

**Survival data.** With a median follow-up of 16 months (range 1 month to 8 years), 18 patients have died; 14 are alive without disease, and 9 are living with disease. The projected actuarial survival for the entire group is 58% at two years (Fig 1). Table 3 describes the 2-year actuarial survival for selected patient groups. Patients with limited-stage disease have an 83% two-year survival, significantly better \((P < 0.01)\) than those with stage III or IV disease. Three limited-stage patients were salvaged with chemotherapy after failing irradiation and/or surgery. The presence or absence of cutaneous disease did not affect survival at two years. A previous history of a dermatologic or immunologic disorder conferred a poor prognosis; however, all of these patients had advanced disease at diagnosis, 64% with stage IV. Neither age nor sex was prognostically significant. Survival comparisons among patients treated with primary irradiation only vs chemotherapy (with or without Adriamycin) yielded no significant differences. Two-year survival was similar for patients with helper cell phenotype and those with an undefined phenotype. However, due to an increased number of early deaths among patients with lymphomas of undefined phenotype, the Gehan test achieved statistical significance \((P = 0.03)\). Three of four patients with cytotoxic/suppressor phenotypes were dead at 2 years. Loss or maintenance of pan-T cell antigen expression or expression of Ia did not influence survival. Evaluation of the morphological subtypes revealed no significant survival differences, although at the time of this writing, only one of seven patients with monomorphic T cell lymphoma was alive without disease as compared with 13 of the remaining 34 patients.

**DISCUSSION**

In this study, we have defined a group of T cell lymphomas on the basis of morphological and immunologic criteria. MF and lymphoblastic lymphoma were excluded on morphologic grounds. Immunologically, all cases expressed at least two T cell antigens with an absence of B cell markers. In contrast to cell-suspension techniques, our method has the advantage of allowing direct comparison of several antibodies as well as identification of cytologic and architectural detail.

As a group, our 41 TCL patients demonstrate marked clinical, immunologic, and morphologic diversity. Several authors have described clinicopathologic features of usually small numbers of patients with TCL as defined by morphologic or erythrocyte rosetting techniques. The recent reports of Brisbane and co-workers and Greer and colleagues included multiple histologic subtypes, as in our series.17,18 Median survivals in these series were 11 months with 70% to 79% of patients in advanced stage. Half or more of the patients in each series had systemic symptoms. In the series of Levine and co-workers, which was restricted to the immunoblastic sarcoma (T-IBS) histologic subtype as defined in the Lukes-Collins system, the median survival of 19 patients was 20 months; 89% of those patients had advanced disease.13 Grogan and colleagues have recently described nine cases of TCL who were assessed for E rosettes and expression of T cell antigens defined by monoclonal antibodies.19 Median survival was only 9 months in this elderly group of patients (median age 69 years). These authors have concluded that TCLs are an aggressive subset of the non-Hodgkin's lymphomas, perhaps requiring alternative therapeutic strategies. A broad range of histologic subtypes, often indistinguishable from diffuse non-Hodgkin's lymphomas with B cell or null phenotypes, has been described among the TCLs.22 It is reasonable then to question whether the T-immunologic features of the intermediate-grade and high-grade lymphomas represent a clinically distinct and significant subset.

Half of our cases had cutaneous lymphoma at diagnosis, in contrast to the series of Greer and colleagues, in which skin involvement was infrequent. However, 6 of 9 patients in Grogan's series had cutaneous involvement. This may be related in part to patient selection as the incidence of dermal involvement could be inflated by the accessibility of cutaneous lymphoma for biopsy. Cutaneous involvement is, of course, a prominent component of other T cell malignancies.
Although the subset of patients with cutaneous lymphoma did not demonstrate unique histologic features or survival data in our series, skin involvement was a prominent aspect of the disease and the exclusive site of lymphoma in 50% of patients. Dermal involvement is usually considered a relatively favorable site of extranodal large cell lymphoma.

A previous history of dermatologic or immunologic disease was noted in 27% of our patients. A history of autoimmune or lymphoproliferative disease has previously been reported in 16% to 36% of patients with TCL, but a history of autoimmune disease is also well described in other non-Hodgkin's lymphomas, particularly the B immunoblastic sarcoma group. Thus, it can be postulated that chronic antigenic stimulation may be related to malignant lymphoma of either B or T cell phenotype.

Three patients in this series had clinical syndromes consistent with AILD. One who later developed clear cell T-IBS had Coomb's-positive anemia and polyclonal gammapathy in addition to adenopathy. Another patient presenting with systemic symptoms, diffuse adenopathy (which was diagnostic of non-Hodgkin's lymphoma and expressed T cell markers) and prominent arthralgias had a spontaneous regression of all disease with a follow-up of 6 months, as has been occasionally described in AILD.

Although the clinical features of TCL patients are indeed heterogeneous, manifestations unique to T cell lymphoma may exist. Myeloid hyperplasia and/or peripheral eosinophilia were seen in three of our patients. Peripheral eosinophilia was noted in 29% of TCL patients reported by Greer and co-workers and is well described in Japanese adult T cell leukemia. Griffin and colleagues have described myeloid colony-stimulating activity in a group of T cell lines, some with preferred stimulation of eosinophilic colonies.

A distinct subset of TCLs associated with the human T cell leukemia/lymphoma virus (HTLV) has been recognized. Typical features of this clincopathologic entity include diffuse adenopathy, hypercalcemia, leukemia at diagnosis or during the clinical course, skin and bone marrow involvement, lytic bone lesions, and eventual involvement of the central nervous system (CNS). In this country, HTLV-associated TCLs have been described predominantly among young blacks born in the southeastern United States. Ninety-three percent of patients in our series are white. Sera from two of our patients were tested for HTLV-specific antibody by Dr Robert Gallo's laboratory at the National Institutes of Health. Both were negative. Only one of our patients (who was HTLV-antibody negative) was diagnosed with hypercalcemia, and none fit this clinical picture.

Descriptions of the clinical features of TCL must be interpreted cautiously with respect to the criteria for diagnosis, selection factors, and the number of cases studied. In the literature, cases have been described as primarily nodal, primarily extranodal, with prominent lung or pleural involvement, with systemic symptoms, without systemic symptoms, with or without cutaneous involvement, and of favorable, unfavorable and indistinctive prognosis. In a previous study of the clinical relevance of immunologic phenotype in diffuse large cell lymphoma, we found that stage, age >65 years, systemic symptoms, and marrow involvement had the greatest impact on survival. To address the influence of T cell phenotype better, we compared survival data in the current series of 41 TCL patients with the previous group of 59 cases studied with the same methodology from 1977 to 1982. The latter cases had diffuse large cell morphology, non-T cell phenotypes, and no history of histologic transformation from a low-grade lymphoma. The survival curves of these two groups shown in Fig 2 do not differ significantly. Among these 41 T cell cases and 59 non-T cell cases, the incidence of the following clinical features was: systemic symptoms (27% vs 37%), age >65 years (29% vs 25%), stage IV (37% vs 39%), and marrow involvement (7% vs 12%), respectively. Although treatment varied greatly in both groups of patients, these data suggest that the T cell phenotype may not necessarily confer a worse prognosis in a group of patients studied at a single institution.

Neither morphological subtype or antigenic profile correlated with clinical features at presentation or predicted outcome in our study. It is interesting that morphological and immunophenotypic diversity has also been described in HTLV-associated lymphomas, despite similar clinical features. With the exception of the HTLV-related lymphoma/leukemia, TCLs are clinically heterogeneous. Contrary to B cell lymphomas, in our experience, TCLs do not show phenotypes that recapitulate stages of T cell differentiation. In this regard, perhaps the term “peripheral” T cell lymphoma should not be used, because it may be confusing to clinicians treating other T cell malignancies with peripheral blood or nodal involvement. Prospective studies using uniform treatments are necessary to address the clinical significance of the T cell phenotype definitively, independent of established histologic and clinical features.

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