Natural Killer-Like T-Cell Lymphomas: Aggressive Lymphomas of T-Large Granular Lymphocytes

By William R. Macon, Michael E. Williams, John P. Greer, Richard D. Hammer, Alan D. Glick, Robert D. Collins, and John B. Cousar

Natural killer (NK)-like T cells are major histocompatibility complex-unrestricted cytotoxic T cells that are surface CD3-positive, express NK-cell antigens, and rearrange their T-cell receptor. Most neoplasms arising from this T-cell subpopulation have been a chronic lymphoproliferative disease referred to as T-large granular lymphocyte (LGL) leukemia. Only 10 NK-like T-cell lymphomas have been described in detail previously; this study presents the clinicopathologic features of six others and distinguishes these lymphomas from T-LGL leukemia. All patients presented with B-symptoms and often had marked hepatosplenomegaly without significant peripheral lymphadenopathy. Four of the six patients were immunosuppressed. All had CD3, CD8, CD56-positive tumors, presumptively of hepatosplenic (n = 3), intestinal (n = 1), pulmonary (n = 1), or nodal (n = 1) origin. Three patients had lymphomatous bone marrow infiltrates, and four had peripheral blood involvement by neoplastic large lymphocytes, some of which had a blastic appearance or resembled virocytes. Azurophilic granules, ultrastructurally corresponding to cytoplasmic dense core and/or double density granules, were seen in all cases. T-cell clonality was shown in five tumors by Southern blot analysis, and three had abnormal karyotypes. Two untreated patients died 20 days after presentation, and three patients who received combination chemotherapy died within 5 months of presentation. One patient remains in complete remission 22 months after treatment. These findings suggest NK-like T-cell lymphomas are aggressive, are clinicopathologically distinct from T-LGL leukemia, and should be in the differential diagnosis of extranodal T-cell lymphoproliferations, including those in immunosuppressed patients. Furthermore, the LGL morphology, phenotype, and tissue distribution of some NK-like T-cell lymphomas suggest they may arise from thymic-independant T cells of the hepatic sinusoids and intestinal mucosa.

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MATERIALS AND METHODS

Patient population. Six patients with NK-like T-cell lymphomas, diagnosed at Vanderbilt University Medical Center (VUMC) since 1989, were included in this study. Four patients received their therapy at VUMC. Two others (patients 1 and 5), whose pathology materials were reviewed as Vanderbilt hematopathology consultation cases, were hospitalized elsewhere; their clinical data were retrieved through chart review and discussion with the referring pathologists. Cytologic, histologic, and ultrastructural studies. Wright’s stained films or touch imprints were evaluated from peripheral blood and aspirated bone marrow (patients 2 through 6), pleural fluid (patient 5) and resected tumors (patients 1 and 6). Neoplastic lymphocytes in patient peripheral blood films were compared with those from four patients with clonal T-LGL leukemia and from four patients known to have infectious mononucleosis. Differential counts of 200 hematopoietic cells were performed on marrow aspirate films for patients 2, 3, and 4. The morphological features on 4 μm thick, hematoxylin and eosin-, periodic acid-Schiff (PAS), and methyl green pyronin-stained sections of formalin- or B5-fixed, paraffin-
Table 1. Clinical Features of Patients With NK-Like T-Cell Lymphomas

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Presentation</th>
<th>Hematologic Findings</th>
<th>Known Sites of Tumor</th>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64/M</td>
<td>Fever, abdominal pain, and rectal bleeding</td>
<td>WBC = 17.9 × 10^9/L (75% PMN, 10% lymph), Hct = 29.2%, Plt = 333 × 10^9/L.</td>
<td>Duodenum and mesentery</td>
<td>IV</td>
<td>None</td>
<td>DOD 20 d after presentation</td>
</tr>
<tr>
<td>2†</td>
<td>32/M</td>
<td>Fever, night sweats, and marked hepatosplenomegaly</td>
<td>WBC = 2 × 10^9/L (on presentation), Hct = 32%, Plt = 8 × 10^9/L; WBC = 20.6 × 10^9/L (postsplenectomy) (44% PMN, 26% lymph)</td>
<td>Spleen, marrow, and blood</td>
<td>IV</td>
<td>Mega IVe</td>
<td>DNED 2 mo after presentation</td>
</tr>
<tr>
<td>3</td>
<td>9/F</td>
<td>Fever, lymphadenopathy, and marked hepatosplenomegaly; pneumonia</td>
<td>WBC = 18.2 × 10^9/L (8% PMN, 86% lymph), Hct = 30%, Plt = 285 × 10^9/L.</td>
<td>Marrow and blood</td>
<td>IV</td>
<td>MSK-NY-IIP</td>
<td>CR × 22 mo</td>
</tr>
<tr>
<td>4†</td>
<td>16/M</td>
<td>Fever, night sweats, and marked hepatosplenomegaly</td>
<td>WBC = 6.0 × 10^9/L (5 weeks preadmission) (67% PMN, 17% lymph); WBC = 26 × 10^9/L (on admission) (42% PMN, 44% lymph), Hct = 10%, Plt = 82 × 10^9/L.</td>
<td>Marrow and blood</td>
<td>IV</td>
<td>MSF-NY-II</td>
<td>DNED 3 mo after presentation</td>
</tr>
<tr>
<td>5†</td>
<td>62/M</td>
<td>Fever, shortness of breath, pulmonary infiltrate, pleural effusions, and hepatosplenomegaly</td>
<td>WBC = 3 × 10^9/L (75% PMN, 11% lymph), Hct = 40.3%, Plt = 66 × 10^9/L.</td>
<td>Lung, pulmonary lymph node, pericardium, pleural fluid, and blood</td>
<td>IV</td>
<td>None</td>
<td>DOD 20 d after presentation</td>
</tr>
<tr>
<td>6†</td>
<td>64/M</td>
<td>Fever, night sweats, shortness of breath, mediastinal lymphadenopathy, and moderate splenomegaly</td>
<td>WBC = 2.6 × 10^9/L (86% PMN, 9% lymph), Hct = 31.6%, Plt = 172 × 10^9/L.</td>
<td>Mediastinal lymph nodes</td>
<td>III</td>
<td>CHOP522</td>
<td>DOD 5 mo after presentation</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood cell count; PMN, neutrophils; lymph, lymphocytes; Hct, hematocrit; Plt, platelet count; DOD, died of disease; DNED, died with no evidence of disease; CR, complete remission; PR, partial response.

* Immunosuppressed with cyclosporin A, azathioprine and prednisone for ulcerative colitis; Coombs'-positive hemolytic anemia on presentation.
† Immunosuppressed with cyclosporin A, azathioprine and prednisone 4 years after renal (patient 4) or 7 and 15 months after cardiac (patients 5 and 6) transplantation.

Antibodies directed against T-cell antigens, with vendor and technique indicated, included CD1 (OKT6, Ortho Diagnostics, Raritan, NJ; FACS), CD2 (Leu-5, BD; FACS and IAP), CD3 (Leu-4, BD; FACS and IAP or polyclonal CD3, DAKO, Carpenteria, CA; PIP), CD4 (Leu-3, BD; FACS and IAP), CD5 (Leu-1, BD; FACS and IAP or CD5, Novocastra Laboratories, Newcastle upon Tyne, United Kingdom [obtained from Vector Laboratories, Burlingame, CA]; PIP), CD7 (Leu-9, BD; FACS and IAP), CD8 (Leu-2, BD; FACS and IAP), CD43 (Leu-22, BD or DF-T1, DAKO; PIP), CD45RO (UCHL1, DAKO; PIP), and T-cell receptor beta chain (βF1, T Cell Diagnostics, Cambridge, MA; PIP). Antibodies directed against NK-cell antigens included CD11b (Leu-15, BD; FACS and IAP), CD11c (Leu-M5, BD; FACS and IAP), CD16 (Leu-11, BD; FACS and IAP), CD36 (Leu-19, BD; FACS and IAP), and CD57 (Leu-7, BD; FACS, IAP and PIP). Other antibodies used included those directed at CD45 (HL-1, BD; FACS or LCA, DAKO; PIP), CD10 (CALLA, BD; FACS), CD15 (Leu-M1, BD; PIP), CD30 (Ki-1, DAKO; FACS or Ber-H2, DAKO; PIP), terminal deoxynucleotidyl transferase (TdT, Supertechs, Bethesda, MD; IF), S-100 (DAKO; PIP), and Epstein-Barr virus (EBV) latent membrane protein (LMP) (CS1-4, DAKO; PIP).

Tumors were considered slightly positive when 20% to 39% of the neoplastic cells marked with an individual antibody, moderately embedded tissue were also reviewed for each patient. Electron microscopy was performed by standard methods to assess ultrastructural features of tumor cells in patients 1 through 5.

Immunohistologic studies. Several techniques were used in concert for immunophenotypic analysis of tumor cells from each patient. Cell surface antigens were detected by flow cytometry (FACS), Becton-Dickinson (BD), Mountainview, CA) of mononuclear cells isolated from omental tumor (patient 1), bone marrow (patients 2 and 4), peripheral blood (patient 3), pleural fluid (patient 5), and lymph node (patients 5 and 6). Immunoalkaline phosphatase (IAP) studies using a labeled streptavidin-biotin system and indirect immunofluorescence (IF) (patients 1 through 4) were performed on cytocentrifuge preparations of cells suspended from the same tissues as those analyzed by flow cytometry (FACS). Paraffin immunoperoxidase (PIP) studies were performed on 4-μm sections of omental tumor (patient 1), spleen (patient 2), bone marrow (patients 3 and 4), and lymph node (patients 5 and 6) using either a manual three-stage indirect immunoperoxidase technique (27) for monoclonal antibodies and an indirect peroxidase-antiperoxidase procedure (28) for polyclonal antibodies, or an avidin-biotin complex method (29) with appropriate antigen retrieval using an automated immunostainer (Ventana 320 Automated Immunohistochemistry System, Ventana Medical Systems, Tuscon, AZ).
Peripheral blood films from patients with NK-like T-cell lymphomas, T-LGL leukemia, and infectious mononucleosis. (A) Circulating tumor cells from patient 2 were mostly large lymphocytes with round to oval nuclei having dispersed chromatin and prominent nucleoli. Occasional neoplastic cells had a blastic appearance (inset). Azurophilic cytoplasmic granules were seen easily. (B) Lymphocytes from a patient with clonal T-LGL leukemia were smaller, and the nuclei had dense chromatin with less discernible nucleoli. Azurophilic granules were present. (C) Circulating tumor cells from patient 3 were often large lymphocytes with a high nuclear:cytoplasmic ratio and marked nuclear irregularity. Azurophilic granules were scant in these cells. (D) Erythrocytes from a patient with infectious mononucleosis had a much smaller nuclear:cytoplasmic ratio and regular nuclear profiles.

positive when 40% to 59% of the neoplastic cells marked, and strongly positive when 60% or more of the neoplastic cells marked.

Cytogenetic and molecular genetic studies. Karyotypic analysis was performed on harvested cell suspensions from omental tumor (patient 1) or bone marrow (patients 2, 3, and 4). Metaphases from 20 cells in each sample were evaluated by Giemsa staining with

Fig 1. Peripheral blood films from patients with NK-like T-cell lymphomas, T-LGL leukemia, and infectious mononucleosis. (A) Circulating tumor cells from patient 2 were mostly large lymphocytes with round to oval nuclei having dispersed chromatin and prominent nucleoli. Occasional neoplastic cells had a blastic appearance (inset). Azurophilic cytoplasmic granules were seen easily. (B) Lymphocytes from a patient with clonal T-LGL leukemia were smaller, and the nuclei had dense chromatin with less discernible nucleoli. Azurophilic granules were present. (C) Circulating tumor cells from patient 3 were often large lymphocytes with a high nuclear:cytoplasmic ratio and marked nuclear irregularity. Azurophilic granules were scant in these cells. (D) Erythrocytes from a patient with infectious mononucleosis had a much smaller nuclear:cytoplasmic ratio and regular nuclear profiles.

Fig 2. Peripheral blood and pleural fluid films from patients with NK-like T-cell lymphomas. (A) Some circulating tumor cells from patient 3 had a “cloverleaf” appearance. Azurophilic granules were often absent in these cells. (B) A dysplastic large lymphocyte was occasionally seen in the pleural fluid sample from patient 5. Azurophilic granules could be seen in smaller tumor cells from this sample (not shown).
NATURAL KILLER-LIKE T-CELL LYMPHOMAS

Fig 3. Bone marrow aspirate film and biopsy section from patient with an NK-like T-cell lymphoma. (A) Tumor cells were easily found in aspirate films from patient 2, including some exhibiting erythrophagocytosis. (B) Neoplastic cells were much more difficult to find in tissue sections from this patient because of the accompanying erythroid hyperplasia. Tumor cells that phagocytosed nucleated red blood cells helped identify the interstitial lymphomatous infiltrate (arrows) (PAS stain).

RESULTS

Clinical features. Table 1 summarizes the clinical features of each patient, including the principal hematologic findings and histologically documented sites of tumor. All patients presented with advanced stage disease (Stage III or IV) by the Ann Arbor staging system and B-symptoms (fever, night sweats, weight loss). Most patients also had hepatosplenomegaly without significant peripheral lymphadenopathy and had an aggressive clinical course. Five patients were anemic, including patient 2 who presented with a Coombs'-positive hemolytic anemia. Three patients had an absolute lymphocytosis (range, 5,536 to 15,652/µL) with rapidly rising counts in patients 2 and 4. Patient 3 had an absolute neutropenia that was associated with pneumonia. Four patients were chronically immunosuppressed for long-standing ulcerative colitis (patient 2) or after solid organ transplantation (patients 4, 5, and 6).

Morphologic features. Peripheral blood involvement was extensive in patients 2, 3, and 4 and slight in patient 5. Circulating tumor cells were mostly large lymphocytes with abundant pale cytoplasm; fine to coarse azurophilic granules


DNA for molecular genetic analysis was isolated from omental tumor (patient 1), bone marrow (patients 2 and 4), peripheral blood (patient 3), pleural fluid (patient 5), and lymph node (patient 6) using standard phenol-chloroform extraction. Purified DNA was digested with the restriction endonucleases BamH I, EcoR I, and Hind III and electrophoresed on agarose gels. The DNA was transferred to nylon membranes, and Southern blot analysis was performed as previously reported. Blots were serially hybridized with probes for the T-cell receptor (TCR) beta-chain joining gene (Jβ) (Oncor, Gaithersburg, MD) in six patients, the TCR beta-chain constant gene (Cβ) (Oncor) in one patient, the TCR gamma-chain joining gene (Jγ) (Oncor) in three patients, and the TCR delta-chain constant gene (Cδ) (Dr Tak Mak, University of Toronto, Toronto, Ontario, Canada) in two patients. Probes for the immunoglobulin (Ig) heavy-chain joining gene (JH) (Oncor) and Ig kappa light-chain joining gene (Jκ) (Oncor) were used in four and one patient, respectively. A c-myc exon 1 probe (Dr Takis Papas, National Cancer Institute, Bethesda, MD) was also used for patient 2. Rearrangements indicating clonality were identified by the presence of nongermline bands, as compared with placental control DNA or with previously identified positive and negative control DNA.

Fig 4. Tissue sections from patient with small bowel/omental NK-like T-cell lymphoma (PAS stains). (A) The lamina propria of the duodenum from patient 1 is filled by lymphoma cells. A lymphoepithelial lesion is created by tumor cells that infiltrate a residual mucosal gland (arrow). (B) Medium-size tumor cells with dispersed chromatin efface the omental fat. Numerous mitoses are also evident.
were seen in some neoplastic cells in all cases from films of peripheral blood, marrow, or pleural fluid, or from touch imprints of tumor (Fig 1A). The neoplastic cells in patients 2 and 4 had oval nuclei with dispersed chromatin and prominent nucleoli (Fig 1A); large cell size and a blastic appearance in some lymphocytes distinguished these neoplastic cells from those in patients with T-LGL leukemia (Fig 1B).

Some tumor cells in patients 3 and 5 resembled “atypical” lymphocytes in patients with infectious mononucleosis; however, other neoplastic cells had increased nuclear to cytoplasmic ratios and markedly irregular nuclear profiles, which distinguished them from virocytes (Fig 1C and D). “Cloverleaf” peripheral blood tumor cells in patient 3 (Fig 2A) and markedly enlarged, dysplastic pleural fluid tumor cells in patient 5 (Fig 2B) demonstrated the extreme variability of nuclear shape and cell size.

Marrow involvement was more easily observed on films than in tissue sections. Differential counts on films from patients 2, 3, and 4 showed tumor cells comprised 59%, 28%, and 58% of marrow cells, respectively (Fig 3A). On the other hand, sections showed only subtle interstitial lymphoid infiltrates without focal lesions in hypercellular marrows from each of these patients (Fig 3B). Furthermore, erythrophagocytosis by tumor cells was readily identified in marrow films from patient 2, but was difficult to detect in splenic or marrow sections (Fig 3).

The duodenal surface was ulcerated in patient 1. Neoplastic lymphocytes filled the deeper lamina propria and focally infiltrated residual mucosal glands producing “lymphoepithelial” lesions (Fig 4A). Lymphoma cells in patient 1 and those that effaced the splenic architecture in patient 2 were medium-size in sections (Fig 4B). Dysplastic large lymphocytes effaced pulmonary hilar or mediastinal nodes in patients 5 and 6. They also infiltrated lung parenchyma, pleura, and pericardium in patient 5. Additionally, autopsy on patient 5 showed congestive hepatosplenomegaly (liver 2,240 g and spleen 630 g) with erythrophagocytosis by histiocytes; no lymphoma was identified in the liver or spleen.

Electron microscopy demonstrated cytoplasmic dense core and/or double density granules (Fig 5) in some tumor cells from each patient studied. No parallel tubular arrays were found in obviously neoplastic cells.

**Immunologic features.** Table 2 summarizes the T-cell and NK-cell antigen expression of the tumor cells in each patient. The common phenotype was CD2+, CD3+, CM-, CDS', CD56', and CD57-, and there was variable expression of other T-cell and NK-cell antigens. The tumor cells were phenotypically mature as there was no expression of CD1, CD10 or TdT. Tumors cells were CD45+, and none expressed CD15 or S-100. CD30 staining of tumor cells was seen only in patient 6. LMP staining was seen in most tumor cells from patients 1, 5, and 6, but was negative in patient 2.

**Genetic features.** Karyotypic and genotypic data are shown in Table 3. Three of four patients studied had an abnormal karyotype. A t(2;17) was observed in two analyzed cells from patient 3. Isochromosome 7q was present in 17 and 20 analyzed cells from patients 2 and 4, respectively. Patient 2 also had a t(8;14) (q24;q24). T-cell clonality was demonstrated in five of six patients. No c-myc rearrangement was identified for patient 2, suggesting the possibility of a breakpoint 5' to the c-myc locus or of point mutations within c-myc not detected with the exon 1 probe.
We have described six T-cell lymphomas whose LGL morphology, expression of CD3 and NK-cell antigens, and ability to rearrange their T-cell receptor indicate an origin from NK-like T cells. Ten other T-cell lymphomas with the features of NK-like T-cell lymphomas have been reported in detail (Table 4). Data from our series and the other case reports suggest these lymphomas are a separate clinicopathologic entity that can be distinguished from T-LGL leukemia by multiparametric analysis. In this combined series, NK-like T-cell lymphomas were aggressive as 93% presented with advanced stage disease and median survival was less than 6 months. The median age was 48 years (range, 9 to 66 years); five patients (31%) were in the pediatric population. There was a 13:2 male:female ratio. Seventy-nine percent of patients presented with B-symptoms, and marked hepatosplenomegaly was common (60%). These lymphomas were usually extranodal (81%) and tended to be distributed in the liver, spleen, and marrow (50%) or in the gastrointestinal tract (25%). Nodal or cutaneous involvement without hepatosplenitic or intestinal disease was unusual. A leukemic phase was common (63%) and developed after splenectomy in five of 10 patients. Peripheral white blood cell counts in patients with a leukemic phase had a median of 18,000/μL (range, 3,000 to 203,000/μL). Thrombocytopenia was present in seven of 12 (58%) patients. A CD4+ CD8− phenotype was most common (n = 10) as compared with CD4− CD8− (n = 2), CD4+ CD8+ (n = 2) and CD4− CD8+ (n = 2). CD56 was expressed on tumor cells in 11 of 12 (92%) lymphomas studied for this antigen, whereas CD57 positivity was observed in only four of 15 (27%) cases. Aberrant chromosomal analyses were found in five of six lymphomas studied, and four of these had an i(7q).

Clinical implications dictate distinguishing leukemic involvement by NK-like T-cell lymphomas from the more indolent T-LGL leukemia. In comparison with T-LGL leukemia, patients with NK-like T-cell lymphomas are more likely to be within the pediatric population, to present with B-symptoms and marked hepatosplenomegaly, and to have thrombocytopenia and a rapid increase in the number of leukemic cells.11,12 NK-like T-cell lymphomas have less frequent neutropenia and infections. Leukemic cells of NK-like T-cell lymphomas often exhibit marked nuclear pleomorphism or have a blastic appearance, the latter being rare in chronic LGL leukemias.14 There is a greater tendency for NK-like T-cell lymphomas to express CD56 rather than CD57, whereas the opposite has been reported for T-LGL leukemia.11 Parallel tubular arrays, frequently seen in ultrastructural studies of T-LGL leukemia,12 are apparently uncommon among NK-like T-cell lymphomas (seen in two of 11 cases studied). Cytogenetic abnormalities are common in NK-like T-cell lymphomas, but not in T-LGL leukemia.12 These differences between the two groups of neoplasms indicate that the recently reported cases of CD56+ aggressive variant of T-LGL leukemia22 may be NK-like T-cell lymphomas with a leukemic phase.

Several features seen in our series of NK-like T-cell lymphomas may have biologic and clinical significance; in
lymphomas rather than NK-like T-cell lymphoma. There- regarded as NCAM-positive PTCLs may be true NK-cell antigens, served for those lymphomas that express surface CD3 (or cytoplasmic granules by light or electron microscopy. NK-like T-cell lymphomas that lack surface CD3 or TCR framework determinants should exhibit TCR gene rearrangements to distinguish them from true NK-cell lymphomas.

Chromosomal abnormalities in NK-like T-cell lymphomas may be of pathogenetic and prognostic significance. For instance, the erythrophagocytic T-cell lymphoma in patient 2 had a t(8;14)(q24;q24), which may have juxtaposed the c-myc gene on 8q24 and a transcriptionally active (housekeeping) cytoskeletal protein gene such as that for α-actinin located on 14q24. Deregulation of c-myc, seen in some T-cell neoplasms, as well as possible alterations in the quantity and cellular localization of cytoskeletal components may have contributed to malignant transformation. Furthermore, altered cytoskeletal proteins may have permitted the phagocytosis of IgG-coated erythrocytes by the tumor cells in this patient, a function not normally ascribed to T cells in normal cytology. Cytogenetic analysis may pinpoint patients with especially poor prognosis, as well as identify specific chromosomal abnormalities. T-cell receptor gene rearrangement studies are recommended to prove clonality in morphologically difficult lesions and to distinguish some NK-like T-cell lymphomas from true NK-cell lymphomas.

The roles of immunosuppression and EBV infection in NK-like T-cell lymphomas are unclear. Four patients in our series were chronically immunosuppressed, including three who had received solid organ transplants. Therefore, NK-like T-cell lymphomas should be included in the differential diagnosis of T-cell proliferations developing in immunosuppressed patients. It is also interesting that two of our posttransplant patients and another with an intestinal NK-like T-cell lymphoma had strong LMP immunopositivity in nearly all tumor cells, suggesting they were EBV-associated. However, it remains to be determined whether EBV is a pathogenetic factor in the development of NK-like T-cell lymphomas, or if infection of the tumor cells occurs after clonal expansion.

Of further biologic interest is the observation that hepatosplenic and intestinal NK-like T-cell lymphomas not only have cytological (LGL morphology) and immunological (CD56 or CD57) features in common with thymic-independent T cells, but also have similar tissue distributions. NK-like T-cell lymphomas also may be of αβ or γδ types, as are extrathymically derived T-cells. Furthermore, thymic-independent T cells may be CD4-CD8-, CD4+CD8+, CD4+CD8+, or CD4-CD8+. As noted above, all four of these phenotypes have been observed among NK-like T-cell lymphomas. Therefore, it is possible that these lymphomas are derived from T-cell subpopulations with extrathymic pathways of differentiation. Finally, NK-like T-cell lymphomas should be considered for all lymphomas of presumed hepatosplenic and intestinal origin if patients present with B-symptoms and advanced stage disease, including a leukemic phase. We recommend, in agreement with Warzynski et al., multiparametric analysis, as described below, to facilitate recognition of these aggressive lymphomas. Cytoplasmic granules may be demonstrated in tumor cells using Romanovsky’s-type stains on peripheral blood, marrow, or other body fluid films or on touch imprints of tumors. Electron microscopy may be used to detect granules not seen by light microscopy. Immunephenotypic analysis should include a broad panel of T-cell and NK-cell antigens (see Table 2). Cytogenetic analysis may pinpoint patients with especially poor prognosis, as well as identify specific chromosomal abnormalities. T-cell receptor gene rearrangement studies are recommended to prove clonality in morphologically difficult lesions and to distinguish some NK-like T-cell lymphomas from true NK-cell lymphomas.

NOTE ADDED IN PROOF

Dr Mohamed Elkhalifa, Director of Hematopathology, University of South Alabama, Mobile, Alabama, has kindly provided us data and patient materials on another NK-like T-cell lymphoma since this manuscript was prepared. The patient was a 62-year-old female who presented with B-symptoms, hepatosplenomegaly, abdominal pain, and slight lymphadenopathy. Peripheral blood (WBC = 55 × 10^9/L) with 80% lymphocytes, hematocrit = 31.6%, and platelets...
Table 4. Clinical Features of Previously Reported Patients With NK-like T-Cell Lymphomas

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Presentation</th>
<th>Hematologic Findings</th>
<th>Known Sites of Tumor</th>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/F</td>
<td>Fever, asthenia, and splenomegaly</td>
<td>WBC = 18.7 \times 10^3/µL (80% lymph), red blood cells and platelets &quot;in normal range&quot;; developed leukemic phase postspenectomy</td>
<td>Spleen, liver, marrow, and blood</td>
<td>IV</td>
<td>&quot;Aggressive chemotherapy&quot;</td>
<td>DOD 23 mo after presentation</td>
<td>14</td>
</tr>
<tr>
<td>52/M</td>
<td>Gastric mass and splenomegaly</td>
<td>Peripheral lymphocytes = 10.8 \times 10^3/µL; developed leukemic phase postspenectomy</td>
<td>Spleen, stomach, marrow, and blood</td>
<td>IV</td>
<td>Prednisone and undefined chemotherapy</td>
<td>CR × 31 mo</td>
<td>14</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>Lymph node</td>
<td>NA</td>
<td>NE</td>
<td>NA</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>48/M</td>
<td>Intestinal obstruction; anorexia, weight loss, asthenia, and night sweats</td>
<td>NA</td>
<td>Jejunum, ileum, mesentery, and lungs</td>
<td>IV</td>
<td>MACOP-B^B^</td>
<td>NA</td>
<td>DOD 5 mo after presentation</td>
</tr>
<tr>
<td>66/M</td>
<td>Abdominal pain, anorexia, and weight loss</td>
<td>WBC = 9.5 \times 10^3/µL (&quot;Intact differential&quot;), Hgb = 13.5 g/dL, Plt = 350 \times 10^3/µL</td>
<td>Jejunum, lungs, and CSF</td>
<td>IV</td>
<td>CHOP^C^</td>
<td>DOD 4 mo after presentation</td>
<td>17</td>
</tr>
<tr>
<td>39/M</td>
<td>Fever, asthenia, hepatosplenomegaly, and lymphadenopathy</td>
<td>WBC = 11.0 \times 10^3/µL (80% lymph)</td>
<td>Spleen, liver, lymph nodes, and blood</td>
<td>IV</td>
<td>None</td>
<td>NA</td>
<td>18</td>
</tr>
<tr>
<td>50/M</td>
<td>Generalized maculopapular rash</td>
<td>NA</td>
<td>Skin</td>
<td>Ie</td>
<td>Chlorambucil then whole body irradiation</td>
<td>DOD 1 yr after presentation</td>
<td>19</td>
</tr>
<tr>
<td>12/M</td>
<td>Fever, petechiae, and hepatosplenomegaly</td>
<td>WBC = 7.3 \times 10^3/µL (on presentation), Hgb = 13.8 g/dL, Plt = 7 \times 10^3/µL; WBC = 203 \times 10^3/µL (80% lymph) (postspenectomy)</td>
<td>Spleen, lymph nodes, marrow, and blood</td>
<td>IV</td>
<td>Prednisone</td>
<td>DOD 2.5 mo after presentation</td>
<td>19</td>
</tr>
<tr>
<td>18/M</td>
<td>Hepatosplenomegaly</td>
<td>WBC = 17.7 \times 10^3/µL (postspenectomy), Hgb = 8.5 g/dL, Plt = 10 \times 10^3/µL</td>
<td>Liver, kidneys, lymph nodes, marrow, and blood</td>
<td>IV</td>
<td>Cyclophosphamide, prednisone, and vincristine; doxorubicin and etoposide</td>
<td>DOD 1.5 mo after presentation</td>
<td>20</td>
</tr>
<tr>
<td>20/M</td>
<td>Fever, anorexia, weight loss, massive hepatosplenomegaly, and mild lymphadenopathy</td>
<td>WBC = 2 \times 10^3/µL, Hgb = 7 g/dL, Plt = 70 \times 10^3/µL</td>
<td>Spleen, liver, lymph nodes, marrow, and blood</td>
<td>IV</td>
<td>Multiple combination chemotherapy</td>
<td>DOD 9 mo after presentation</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood cell count; lymph, lymphocytes; Hgb, hemoglobin content; Plt, platelet count; NA, not available; NE, not evaluable; CSF, cerebral spinal fluid; DOD, died of disease; CR, complete remission.

Acknowledgment

The authors thank Drs Thomas Hanes, Ritchie Clark, Daniel Tench, and James Elrod for providing patient materials and clinical data. We are grateful for diagnostic molecular genetic interpretations by Dr Cindy Vennenc-Jones (VUMC), on patients 2 through 6, and for her commentary and that from Dr Brigitte Schlegelberger (Department of Human Genetics, University of Kiel, Kiel, Germany). We also thank Margaret Whitefield and Patricia Ennis for technical assistance on Southern blots; Sandy Olson for technical support in performing immunohistochemistry; Brent Weedman and Fred Morris for photographic assistance; and Alva Wolfe for manuscript preparation.

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