ALK-Positive Anaplastic Large Cell Lymphoma With Leukemic Peripheral Blood Involvement Is a Clinicopathologic Entity With an Unfavorable Prognosis

Report of Three Cases and Review of the Literature

Mihaela Onciu, MD,1 Frederick G. Behm, MD,1,3 Susana C. Raimondi, PhD,1,3 Sheila Moore, MD,4 Emma L. Harwood, MD,5 Ching-Hon Pui, MD,2,3 and John T. Sandlund, MD2,3

Key Words: Leukemia; Blood; Non-Hodgkin lymphoma; Anaplastic lymphoma; Anaplastic lymphoma kinase; ALK

Abstract

Leukemic peripheral blood involvement in anaplastic large cell lymphoma (ALCL) is uncommon. We describe 3 children with such manifestations and review the features of 9 pediatric and adult patients previously described in the literature. Leukemic involvement in ALCL may occur at the time of initial diagnosis or develop during the course of disease. It most often is associated with the small cell histologic features and the t(2;5)(p23;q35). Clinical features commonly include significant respiratory distress, diffuse lung infiltrates or pleural effusions, and hepatosplenomegaly. Most cases have an aberrant T-cell immunophenotype with frequent expression of myeloid antigens, most often CD11b or CD13. Ten of the 12 cases reviewed had a poor response to therapy or early relapse.

Thus, while anaplastic lymphoma kinase–positive ALCL and young patient age generally are associated with a favorable prognosis, leukemic involvement seems to identify a high-risk malignant neoplasm that requires more aggressive therapy, including hematopoietic stem cell transplantation.

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphomas (ALCLs) are non-Hodgkin lymphomas (NHLs) of T-cell lineage characterized by a broad spectrum of histologic features and by expression of CD30 (Ki-1) and ALK. Currently recognized as a distinct clinicopathologic entity in the World Health Organization classification of hematopoietic neoplasms,1 these tumors previously were designated as high-grade lymphomas (large cell immunoblastic polymorphous type) in the Working Formulation of the National Cancer Institute.2 Within the category of ALCL as recognized by the World Health Organization, a subset of cases are ALK-negative, and, due to their distinct clinicopathologic manifestations, it still is controversial whether they should be included within this same disease category.1

ALCL represents 20% to 50% of the large cell lymphomas in children and 2% to 8% of NHLs in adults.1,3 Virtually all ALCLs seen in children are ALK-positive. Morphologically, these lymphomas share the presence of “hallmark” large, pleomorphic (anaplastic) tumor cells, small lymphoma cells, and reactive inflammatory cells, admixed in variable proportions. This variability results in a wide array of histologic subtypes, including variants such as common, small cell, lymphohistiocytic, giant cell–rich, sarcomatoid, monomorphic, and neutrophil-rich.1,4-8 Despite this variability, all these tumors share the aberrant expression of ALK, which can be detected by routine immunohistochemical analysis.

In most cases (70%),1 ALK expression is the result of the t(2;5)(p23;q35) chromosomal translocation that juxtaposes the ALK locus at 2p23 to the NPM (nucleophosmin) gene locus at 5q35.9,10 In these cases, the translocation can be demonstrated by fluorescence in situ hybridization (FISH).11
and the *NPM-ALK* fusion transcript can be detected by molecular methods such as reverse transcriptase–polymerase chain reaction (RT-PCR). In a smaller percentage of cases, the 2p23 locus may be involved in variant translocations, in which the *ALK* gene is fused to different gene partners. Clinically, ALCL is characterized by a high incidence of systemic symptoms (most often fever) and extranodal disease, and the most common sites involved include skin, bone, soft tissue, and lung.

Leukemic peripheral blood involvement is a well-known occurrence in NHL of B- or T-cell lineage and is particularly frequent in small lymphocytic lymphoma/chronic lymphocytic leukemia, splenic marginal zone lymphoma, mantle cell lymphoma, adult/human T-lymphotropic virus (HTLV)—related T-cell lymphoma, and mycosis fungoides. However, it has been reported only rarely in ALCL, although the presence of lymphoma cells in peripheral blood has been well documented in this entity. Owing to the rarity of this type of presentation and the wide morphologic spectrum of ALCL, such cases may represent a diagnostic challenge, especially at initial diagnosis.

We report the clinicopathologic features of 3 new pediatric patients with ALCL who had an associated leukemic phase, either at diagnosis or relapse. In addition, we review the characteristics of 9 previously reported pediatric and adult cases with similar presentation. Our findings suggest that ALCL involving peripheral blood has a characteristic morphologic and immunophenotypic spectrum and often is associated with specific patterns of extranodal involvement and a poor prognosis.

**Case Reports**

**Case 1**

A 6-year-old girl received treatment with oral antibiotics because of a brief history of fever and right axillary adenopathy. She subsequently developed mild respiratory distress with bilateral pulmonary infiltrates identified on a chest radiograph. Despite aggressive broad-spectrum antimicrobial coverage, her respiratory distress worsened and required intubation. At that time, a CBC count revealed a WBC count of 60,000/µL (60 × 10⁹/L). She was treated with high-dose methylprednisolone, and her respiratory status improved. However, she had progressive increase in the WBC count to approximately 216,000/µL (216 × 10⁹/L) and was transferred to St Jude Children’s Research Hospital, Memphis, TN, for further workup. Except for moderate respiratory distress, the physical examination findings were unremarkable, and no appreciable lymphadenopathy was noted. An abdominal ultrasound revealed bilateral nephromegaly.

The CBC count included a WBC count of 204,000/µL (204 × 10⁹/L), a hemoglobin concentration of 9.2 g/dL (92 g/L), and a platelet count of 396 × 10⁹/µL (396 × 10⁹/L). The leukocyte differential count included 51% atypical lymphocytes and 38% neutrophils. A bone marrow aspiration showed 20% involvement by ALCL, small cell variant. The cerebrospinal fluid (CSF) was negative for tumor cells.

The girl initially was treated with the APO regimen (doxorubicin, vincristine, and prednisone). She had a poor response to this treatment, and the treatment was switched to MIE (high-dose methotrexate, ifosfamide, etoposide, and dexamethasone). She also had a poor response to this regimen, so alternating courses of lomustine, vinblastine, and bleomycin and lomustine, vinblastine, and cytarabine were given. Although her WBC count decreased throughout these various treatment regimens, she continued to have active disease as reflected by peripheral blood morphologic features and flow cytometric analysis. She underwent haploidentical allogeneic hematopoietic stem cell transplantation 5 months from initial diagnosis, with a preparative regimen consisting of total body irradiation, thiotepa, alemtuzumab, etoposide, and cyclophosphamide. She is free of disease, 17 months from the initial diagnosis.

**Case 2**

A 9-month-old girl was admitted because of a 2-week history of coughing, fever, and lymphadenopathy. On admission, she had a temperature of 103°F (39.5°C) and an oxygen saturation of 84%. Physical examination revealed an erythematous macular rash on her face and upper chest; lymphadenopathy (1-2 cm) in the cervical, supraclavicular, axillary, and inguinal areas; and massive hepatosplenomegaly. A chest radiograph showed diffuse bilateral pulmonary infiltrates. The CBC count results were as follows: WBC count, 35,000/µL (35 × 10⁹/L); hemoglobin concentration, 10.6 g/dL (106 g/L); platelet count, 417 × 10³/µL (417 × 10⁹/L); and a differential count that included 30% lymphocytes.

An initial diagnosis of pneumonitis was made, and the patient was treated with broad-spectrum antibiotics. An extensive infectious disease workup, including blood cultures, was negative. Despite antibiotic therapy, she developed respiratory failure that required intubation, the lymphadenopathy progressed, and the WBC count increased to 104,000/µL (104 × 10⁹/L). A lymph node biopsy showed ALCL, small cell variant. The bone marrow was positive for lymphoma (3%). The CSF examination was negative for tumor. The patient initially was given therapy with corticosteroids, cyclophosphamide, and vinblastine, which resulted in marked improvement during the next 48 hours. She then was treated with dexamethasone, cyclophosphamide, daunorubicin, asparaginase, and intrathecal methotrexate. She initially had a complete clinical response; however, low-level bone marrow...
involvement persisted (1%-2% ALK-positive cells). The disease progressed again before blood count recovery. Therapy with cycarabine and etoposide had similar results. The disease was controlled partially with weekly doses of vinblastine during a period of approximately 10 weeks. Hematopoietic stem cell transplantation was considered, but a matched donor could not be found. The patient developed progressive neurologic symptoms. Magnetic resonance imaging examination of the brain showed multiple lesions. The disease continued to progress, and the patient died 1 month later, 9 months from the initial diagnosis.

Case 3
A 10-year-old boy presented with complaints related to a left alveolar ridge mass extending into the pterygopalatine fossa. A staging workup revealed occipital, supraclavicular, paratracheal, and retroperitoneal adenopathy. Biopsies of the oral mass and an occipital lymph node showed ALK-positive ALCL, monomorphous type. Bone marrow examination showed no morphologic evidence of lymphoma but was positive for the NPM-ALK transcript by RT-PCR. The CSF examination was negative for tumor cells.

He was treated on an institutional protocol that includes MIED: cyclophosphamide, vincristine, doxorubicin, prednisone, and high-dose methotrexate; dexamethasone, cytar- bine, and carboplatin; an intensification phase comprising cyclophosphamide; and etoposide followed by weekly vinblastine for 1 year. Several weeks after completing therapy, the patient developed recurrent disease along the maxillary ridge that was responsive initially to prednisone and vinblas- tine. He subsequently developed left optic nerve disease with proptosis, and a right parenchymal brain lesion, which was transiently sensitive to dexamethasone. He then was treated with APO and MIED, and hematopoietic stem cell transplant-ation was scheduled. However, he had a progressively increasing WBC count despite further therapy with dexamethasone and cladribine. A CBC count performed at that time showed the following: WBC count, 150,000/µL (150 × 10⁹/L); hemoglobin concentration, 9.0 g/dL (90 g/L); platelet count, 30 × 10⁹/µL (30 × 10⁹/L); with 70% lymphoma cells. The family declined further therapy, and the patient died of progressive disease, 2 years from the initial diagnosis.

Materials and Methods

Hematologic and Histopathologic Examination
Peripheral blood and bone marrow smears were air dried and stained with Wright-Giemsa, followed by routine microscopic examination and 100-cell differential counts. For histopathologic examination, lymph node, tissue, bone marrow biopsy specimens, and cell block preparations were fixed in formalin or B-5, paraffin embedded, and stained with H&E.

Immunohistochemical Staining
Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections. The avidin-biotin peroxidase technique was used, using an autostainer (Ventana, Tucson, AZ) with antibodies for CD3, ALK1, CD30/Ber-H2, and lysozyme (DAKO, Glostrup, Denmark); CD20/L-26, CD45, CD45RO/UCHL-1 (Ventana); and CD15 (Becton Dickinson, San Jose, CA).

Flow Cytometric Analysis
Immunophenotypic analysis of peripheral blood and bone marrow lymphoid cells in case 1 was performed using the whole blood lysis method, followed by 4-color flow cytometric analysis on a FACSscan analyzer (Becton Dickinson) using the CD45 vs side-scatter gating strategy. Monoclonal antibodies conjugated to fluorescein isothiocyanate, phycoerythrin, allophycocyanin, or peridinin chlorophyll protein were used, specific for the following antigens: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD21, CD22, CD25, CD33, CD34, CD45, CD45RO, CD56, CD65, CD117, terminal deoxynucleotidyl transferase, and HLA-DR. Flow cyto- metric analysis also was performed in case 2, and the anti-gens tested for this patient included CD2, CD3, CD4, CD5, CD7, CD8, CD13, CD14, CD25, CD33, CD34, CD45, CD56, terminal deoxynucleotidyl transferase, and HLA-DR. Flow cytometric analysis was not performed in case 3.

Cytogenetic Analysis
Cytogenetic analysis was performed on bone marrow samples in cases 1 and 3 and on a lymph node from case 2, using direct preparations and overnight unstimulated cultures, followed by banding with trypsin-Wright stain. A total of 20 metaphases were analyzed in each case. The karyotypes were written according to the 1995 International System for Human Cytogenetic Nomenclature. FISH was performed using the dual-color-labeled LSI ALK probe (Vysis, Downers Grove, IL) according to the manufacturer’s recommendations and counterstained with DAPI (4’,6-diamino-2-phenylindole) (Vysis).

Molecular Analysis
RT-PCR for the chimeric NPM-ALK transcript was performed as previously described at the time of initial diagnosis in cases 1 and 3, using bone marrow and material from the tissue biopsy, respectively. In case 3, testing also was performed on a bone marrow sample and on the palate biopsy material at the time of relapse.
Results

Clinical Findings

The initial clinical features of the 2 girls and 1 boy, aged between 9 months and 10 years, included fever, leukocytosis, and diffuse lung infiltrates associated with significant respiratory distress that required intubation in 2 cases. Two patients had liver, spleen (case 2), and kidney (case 1) involvement, with no significant lymphadenopathy in case 1 and widespread lymphadenopathy in case 2. The patient in case 3 initially had an alveolar ridge–maxillary sinus mass, and minimal bone marrow involvement was identified by RT-PCR only. At relapse, in addition to involvement of the optic nerve and brain parenchyma, he also had large numbers of circulating lymphoma cells.

The clinicopathologic findings for our patients, as well as those of the additional 9 cases identified by the literature review, are summarized in Table II.

Table II
Clinicopathologic Features of 12 Patients With ALK-Positive ALCL in Leukemic Phase

<table>
<thead>
<tr>
<th>Reference/Case No.</th>
<th>WBC (/µL)/Lymphocytes (%)</th>
<th>Bone Marrow Disease</th>
<th>ALCL Histologic Variant</th>
<th>Karyotype/Molecular Abnormality</th>
<th>Nodal Disease</th>
<th>Extranodal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bilateral kidney, lung (diffuse)</td>
</tr>
<tr>
<td>1/F/6 y 1/F/9 mo</td>
<td>112,000/55/55 62,600/35/35</td>
<td>20% 3%</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M/10 y</td>
<td>151,000/73/60</td>
<td>RT-PCR</td>
<td>Large cell, monomorphic</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td>Cervical, mediastinal, retroperitoneal</td>
<td>CNS (optic nerve), maxillary sinus</td>
</tr>
<tr>
<td>Bayle et al21 4/F/10 y</td>
<td>54,800/38/28</td>
<td>Rare cells</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM rearranged</td>
<td>Mediastinal</td>
<td></td>
</tr>
<tr>
<td>5/F/18 y</td>
<td>15,000/61/90</td>
<td>Rare cells</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM rearranged</td>
<td>Cervical, mediastinal</td>
<td>Mediastinal mass, skin, liver, spleen, lung (diffuse)</td>
</tr>
<tr>
<td>6/F/20 mo</td>
<td>120,000/NA/90</td>
<td>Rare cells</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM rearranged</td>
<td>Axillary</td>
<td>Liver, spleen</td>
</tr>
<tr>
<td>7/M/7 y</td>
<td>23,100/22/8</td>
<td>Rare cells</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td>Generalized</td>
<td>Skin, spleen, lung (diffuse)</td>
</tr>
<tr>
<td>Villamor et al20 8/M/36 y</td>
<td>21,000/NA/51</td>
<td>57%</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td>Inguinal, iliac, retroperitoneal</td>
<td>Liver, spleen, lung (diffuse)</td>
</tr>
<tr>
<td>Anderson et al19 9/M/36 y</td>
<td>106,000/62/5</td>
<td>4%</td>
<td>Common type</td>
<td>t(2;5)(p23;q35)/NPM rearranged</td>
<td>Cervical, thoracic, abdominal, pelvic</td>
<td>Spleen, pleural effusion, CNS</td>
</tr>
<tr>
<td>Meech et al22 10/M/18 mo</td>
<td>94,000/NA/66</td>
<td>Cyto genetics only</td>
<td>Large cell lymphoma</td>
<td>t(2;19)(p23:p13.1)/TPM4-ALK</td>
<td>—</td>
<td>Liver, spleen, pleural effusion</td>
</tr>
<tr>
<td>Kinney et al7 11/M/17 y</td>
<td>45,000/58/NA</td>
<td>“Numerous lymphoma cells”</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td>Inguinal</td>
<td>Skin, liver, pleural effusion</td>
</tr>
<tr>
<td>Awaya et al23 12/M/63 y</td>
<td>118,000/71/92</td>
<td>Rare cells</td>
<td>Small cell</td>
<td>t(2;5)(p23;q35)/NPM-ALK</td>
<td>Cervical</td>
<td>Liver, lung (diffuse), pleural effusion</td>
</tr>
</tbody>
</table>

ALK, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; alloBMT, allogeneic BMT; APO, doxorubicin, prednisone, vincristine; BMT, bone marrow transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CNS, central nervous system; COPAD-M, cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate; CR, complete remission; ESHAP, etoposide, cisplatin, prednisone, cytarabine; HSCT, hematopoietic stem cell transplantation; MEGA, dose-intensive chemotherapy regimen used at Vanderbilt University7; MIEED, high-dose methotrexate, ifosfamide, etoposide, dexamethasone; NA, not available; ND, not done; NPM, nucleophosmin; PR, partial response; RT-PCR, reverse transcriptase-polymerase chain reaction; TPM4, tropomyosin 4.

* The WBC and lymphocyte counts are given in conventional units; the conversions to Système International units are as follows: WBC (× 10⁹/L), multiply by 0.001; lymphocytes (proportion of 1.00), multiply by 0.01. The percentage of lymphoma cells was reported as a fraction of the lymphocytes in cases 4-7 (Bayle et al21) and 12 (Awaya et al23) and of the WBC count in the remaining cases.

† In tissue biopsy specimen.

‡ Receiving therapy.
Morphologic Findings

Examination of peripheral blood smears from all 3 patients showed similar features. There was marked leukocytosis, consisting of neutrophilia and lymphocytosis. In all cases, the neutrophils showed variable left shift and toxic granulation. The lymphoid population (absolute lymphocyte counts, 21,000-105,000/µL [21-105 × 10⁹/L]) consisted of a mixture of small markedly atypical lymphoid cells and medium-sized and large lymphoma cells. The small cells represented the predominant cell type in all cases and showed scant cytoplasm, containing occasionally few azurophilic granules, and markedly irregular, cerebriform, and cloverleaf-shaped nuclei, with condensed chromatin and inconspicuous nucleoli. The large cells, representing 4%, 8%, and 25% of all cells in cases 1, 2, and 3, respectively, showed a range of morphologic features. Most of these cells showed moderate amounts of deeply basophilic, vacuolated cytoplasm; moderately condensed nuclear chromatin; and occasional single prominent nucleoli. Some of these cells were very large and binucleated, with a Reed-Sternberg–like appearance (more numerous in case 3).

Bone marrow aspirates at the time of leukemic presentation were available for cases 1 and 3. In both cases, lymphoma cells morphologically similar to those seen in the peripheral blood were present and represented 20% and 3% of all nucleated cells, respectively.

Of note, the morphologic features noted in these samples were concordant with those reported by others in patients with leukemic ALCL, or ALCL with peripheral blood involvement, but without leukemia.

Tissue biopsy specimens were available for cases 2 and 3. The lymph node biopsy revealed partial involvement by lymphoma, with sinusoidal and paracortical growth patterns. In case 2, the tumor had the features of the small cell subtype of ALCL. In case 3, tumor cells were predominantly immunoblastic in appearance with moderate amounts of amphisophilic cytoplasm, eccentric nuclei, and single prominent nucleoli. Rare hallmark cells, characterized by very large size; eccentric, horseshoe-shaped nuclei; and abundant amphisophilic cytoplasm, also were present. Tumor cells were accompanied by reactive histiocytes, some of which showed hemophagocytic activity. In the maxillary sinus and soft palate biopsy specimens, similar tumor cells formed sheets, with associated surface ulceration and inflammatory changes. In these extranodal locations, tumor cells had monocytoid morphologic features, with irregular, creased nuclei and fine chromatin.

Immunophenotype

Immunophenotypic findings in our cases and the 9 cases identified in the literature are summarized in Table 2.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response to Therapy</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>APO, MIED, cytarabine, lomustine, vinblastine, bleomycin; HSCT</td>
<td>Poor response to chemotherapy; CR following HSCT</td>
<td>Alive*</td>
</tr>
<tr>
<td>Methotrexate, cytarabine, CHOP vinblastine, etoposide</td>
<td>PR, then relapse with brain lesions</td>
<td>Died</td>
</tr>
<tr>
<td>APO, MIED, cladribine</td>
<td>Poor, brief response, then relapse with paraspinal mass</td>
<td>Died</td>
</tr>
<tr>
<td>COPAD-M</td>
<td>CR; relapse</td>
<td>Alive*</td>
</tr>
<tr>
<td>CHOP, then alloBMT</td>
<td>“Good response,” then progressive disease (CNS, skin); CR after BMT</td>
<td>Alive*</td>
</tr>
<tr>
<td>COPAD-M, then vinblastine, alloBMT</td>
<td>CR, then relapse (CNS, skin, bone marrow)</td>
<td>Died</td>
</tr>
<tr>
<td>Vinblastine, doxorubicin, dexamethasone, methotrexate</td>
<td>CR</td>
<td>Alive*</td>
</tr>
<tr>
<td>CHOP, ESHAP, intrathecal methotrexate</td>
<td>CR, then relapse (CNS, lymph node)</td>
<td>NA</td>
</tr>
<tr>
<td>Not specified</td>
<td>Transient, minimal</td>
<td>Died</td>
</tr>
<tr>
<td>Cyclosporine, methyl-prednisolone, then cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate</td>
<td>CR</td>
<td>Alive</td>
</tr>
<tr>
<td>MEGA</td>
<td>Died of systemic candidiasis at the beginning of therapy</td>
<td>Died</td>
</tr>
<tr>
<td>CHOP (2 courses)</td>
<td>PR; died of pneumonia and pancreatitis 1 mo later</td>
<td>Died</td>
</tr>
</tbody>
</table>

Therapy Response to Therapy Status

APO, MIED, cytarabine, lomustine, vinblastine, bleomycin; HSCT Poor response to chemotherapy; CR following HSCT Alive*
Methotrexate, cytarabine, CHOP vinblastine, etoposide PR, then relapse with brain lesions Died
APO, MIED, cladribine Poor, brief response, then relapse with paraspinal mass Died
COPAD-M CR; relapse Alive*
CHOP, then alloBMT “Good response,” then progressive disease (CNS, skin); CR after BMT Alive*
COPAD-M, then vinblastine, alloBMT CR, then relapse (CNS, skin, bone marrow) Died
Vinblastine, doxorubicin, dexamethasone, methotrexate CR Alive*
CHOP, ESHAP, intrathecal methotrexate CR, then relapse (CNS, lymph node) NA
Not specified Transient, minimal Died
Cyclosporine, methyl-prednisolone, then cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate CR Alive
MEGA Died of systemic candidiasis at the beginning of therapy Died
CHOP (2 courses) PR; died of pneumonia and pancreatitis 1 mo later Died

© American Society for Clinical Pathology
Onciu et al / ANAPLASTIC LARGE CELL LYMPHOMA WITH LEUKEMIC MANIFESTATION

and CD25 (dim) and HLA-DR. They were negative for all remaining markers tested.

Flow cytometric analysis of a peripheral blood sample performed in case 2 showed the lymphoma cells to be positive for CD2, CD3, CD4, CD7, CD8, and CD25 and negative for CD5 and the remaining markers tested.

Cytogenetics

Cytogenetic analysis of a bone marrow sample from case 1 showed the following karyotype: 46,XX,t(2;5)(p23;q35), del(10)(q24)[17]/46,idem,—del(10)(q26),+add(10)(q26)[3]. FISH performed in this case was positive for a t(2;5) involving the ALK gene. Cytogenetic analysis of a bone marrow sample from case 2 showed clonal abnormalities that included derivative chromosomes 2, 5, and 20. In case 3, analysis of the bone marrow at the time of relapse showed a single metaphase containing the t(2;5)(p23;q35).

Molecular Analysis

RT-PCR for the NPM-ALK transcript was positive in the bone marrow sample from case 1. In case 3, it was positive in the maxillary sinus and soft palate tissue at initial diagnosis and at relapse, respectively, and in the bilateral bone marrow aspirates obtained at initial diagnosis and following relapse. Of note, in this case, the bone marrow samples were negative for tumor by morphologic examination and immunohistochemical staining for ALK.

Discussion

ALCL, named after its morphologic variant first recognized by Stein et al.,28 includes a variety of histologic appearances that have in common the presence of a variable proportion of hallmark anaplastic large tumor cells and the
expression of CD30 (Ki-1) and ALK. Despite their histologic variability, these tumors seem to have similar clinical behavior, leading to the suggestion that ALK lymphoma\(^5\) or ALKoma\(^4\) may be more accurate terms for this distinct clinicopathologic entity. Among NHLs, ALK expression is unique to ALCL, with the exception of rare tumors of B-cell lineage that have a distinctive morphologic appearance and lack CD30 expression.\(^29\) Thus, ALK expression aids in the differential diagnosis with other types of lymphoma and inflammatory lesions and permits recognition of tumors with an unusual phenotype\(^22\) as a part of this same category of disorders. ALK expression also permitted us to recognize the cases described herein as part of the spectrum of ALCL.

Leukemic peripheral blood involvement by ALCL is unusual, although lymphoma cells have been described in peripheral blood in several studies in which they were detected by morphologic examination\(^13,14,24,25\) or molecular analysis (RT-PCR for NPM-ALK).\(^24\) We have identified only 2 cases (1 with leukemic manifestations at the time of initial diagnosis and 1 at the time of relapse) among more than 400 children with NHL treated at St Jude Children’s Research Hospital. We identified only 9 additional well-characterized cases from the literature. Gordon et al,\(^14\) in their study of 22 patients aged 21 years or younger with peripheral T-cell lymphoma, described 2 patients with circulating lymphoma cells and a leukocyte count of more than 20,000/µL (>20 × 10⁹/L). Since most of their patients had CD30+ tumors and 5 of them showed the t(2;5), it is likely that their cases also represented ALCL with leukemic involvement. However, further information regarding the 2 patients was not provided in that study.

Of the 12 patients identified in this study, 9 had leukemic disease at initial diagnosis (Table 1, cases 1, 2, 4-7, 10-12) and 2 developed it 1 to 3 weeks thereafter (Table 1, cases 8 and 9). Only 1 patient (case 3) developed leukemic involvement as a sign of disease progression after relapse in the maxillary sinus. Clinically, these patients showed a somewhat unusual spectrum of features. Most of them had fever and leukocytosis that included, in addition to lymphoma cells, variable degrees of neutrophilia with left shift and toxic changes. In addition, 6 of the 12 patients had respiratory distress and diffuse interstitial lung infiltrates, 4 had pleural effusion, and 2 had no significant peripheral lymphadenopathy. This combination of features, which is somewhat unusual for malignant lymphoma, led initially to a diagnosis of infection in several cases (such as pneumonitis, appendicitis, and infectious mononucleosis). A diagnosis of malignant neoplasm was considered only when there was no response to antibiotic therapy.

Morphologically, the peripheral blood lymphoma cells mirrored the spectrum described for tumors involving tissue, but with a striking predominance of the small cell subtype (in 10 of 12 patients). These small cerebriform lymphoma cells overlap morphologically with cells described in other types of peripheral T-cell lymphoma, including, most notably, mycosis fungoides/Sézary cell leukemia and the cerebriform or Sézary cell–like variant of T-cell prolymphocytic leukemia.\(^30\) The immunophenotypic findings and the distinct clinical manifestations of these disorders should help

### Table 2
Immunophenotypic Findings in 12 Cases of ALK-Positive Anaplastic Large Cell Lymphoma in Leukemic Phase

<table>
<thead>
<tr>
<th>Case No.</th>
<th>CD30†</th>
<th>ALK†</th>
<th>EMA†</th>
<th>CD2</th>
<th>CD3</th>
<th>CD4</th>
<th>CD5</th>
<th>CD7</th>
<th>CD11b</th>
<th>CD13</th>
<th>CD34</th>
<th>CD38</th>
<th>CD45RO (UCHL-1)</th>
<th>Other Antigens Expressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>−</td>
<td>c+, s−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>s+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>ND</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>c−, s−</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>s−, c+</td>
<td>−</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>s−, c−</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>+</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>CD11c</td>
</tr>
<tr>
<td>(subset)</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>−</td>
<td>CD57, HLA-DR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>s−, c+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>CD57, HLA-DR</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; c, cytoplasmic; EMA, epithelial membrane antigen; ND, not done or not reported; s, surface.

† For information about the cases, see Table 1.

† Studies performed by immunohistochemical analysis; all other results are from flow cytometric analysis.
in the diagnostic differentiation. Only 1 patient in this series had a predominance of large lymphoma cells in the peripheral blood associated with the t(2;5)-positive ALCL. The second patient with a predominance of large lymphoma cells had a more unusual disease subtype, with a novel variant chromosomal translocation, t(2;19)(p23;p13.1), that juxtaposed the ALK gene to the TPM4 (tropomyosin 4) gene, resulting in an ALK-TPM4 fusion transcript. In this latter case, lymphoma cells also displayed an unusual combination of myeloid and natural killer (NK) cell markers, as well as in vitro NK activity, and lacked T-cell receptor gene rearrangements. These features led the authors to postulate that this tumor might represent a myeloid/NK precursor-cell malignant neoplasm, rather than a T-cell lymphoma.

Histologically, the most common ALCL variant associated with a leukemic presentation at diagnosis was the small cell variant (present in 9 of 12 cases). While the number of cases is too small to permit definitive conclusions, this finding is consistent with the initial observation by Kinney et al that the small cell ALCL variant may be associated with more frequent bone marrow involvement and a worse prognosis. Interestingly, the degree of bone marrow involvement was considerably less than that seen in peripheral blood in most of the patients. This finding suggests that the primary proliferation site is outside the bone marrow, and the finding also has been described in other types of peripheral/mature T-cell lymphomas, most notably mycosis fungoides/Sézary syndrome and adult T-cell leukemia/lymphoma, HTLV-associated. Interestingly, similar to mycosis fungoides, small cell ALCL, including cases with leukemic manifestations, has a propensity for skin involvement, albeit with only minimal epidermotropism seen on histologic examination.

Immunophenotypically, the data for circulating lymphoma cells do not seem significantly different from data reported for lymph node–based disease. In all cases, tumor cells were positive for CD30 and ALK. Also, all cases tested for epithelial membrane antigen were positive for this antigen. With the exception of the case described by Meech et al, all remaining 11 tumors showed immunophenotypic evidence of T-cell differentiation (Table 2). Of the 10 tumors evaluated for CD4 and CD8 expression, 3 were only CD4+, 3 were only CD8+, 1 was CD4+ and CD8+, and 3 were CD4– and CD8–. The most frequently lost antigens, as part of the aberrant T-cell phenotype, were CD5 (6/7 cases tested) and CD7 (4/11 cases tested). Notably, many of these tumors expressed at least 1 myeloid-associated antigen, most frequently CD13 (5/6 cases tested); other positive myelomonocytic markers included CD11b and lysozyme. These features are concordant with the findings of Juco et al who reported that more than a third of the nodal ALCL tumors assessed in their study were CD13+. The tumor described by Meech et al also showed immunohistochemical but not cytochemical positivity for myeloperoxidase. Such findings may raise the differential diagnoses of acute myeloid leukemia and acute biphenotypic leukemia, if ALCL is not considered. Another interesting feature is the lack of CD30 and sometimes ALK by the circulating lymphoma cells in at least a subset of ALCLs with leukemic manifestations (cases 4, 6, and 12).

Follow-up data are limited and incomplete for many of the cases included in this review. Many patients were still receiving therapy or had recently discontinued it at the time of the last follow-up. However, leukemic manifestations seem to correlate with a poor prognosis. In our series, of the 2 patients with leukemic ALCL at initial examination, one is alive and disease-free 17 months after hematopoietic stem cell transplantation, after induction therapy failed, while the other had a relapse after a brief response to intensive multiagent chemotherapy. The third patient, who developed the leukemic phase at relapse, did not respond to salvage therapy, and died of progressive disease.

The leukemic phase of ALCL is unusual and may raise the differential diagnosis with other T cell–lineage leukemias, although its unique immunophenotypic features, including expression of CD30 and ALK, permit an accurate diagnosis. It can occur in cases associated with the classic t(2;5) chromosomal translocation or with other variant translocations. It often is associated with small cell morphologic features, a low level of bone marrow involvement, marked diffuse pulmonary infiltrates, and a poor prognosis.

References


