A Syndrome of Lymphoblastic Lymphoma, Eosinophilia, and Myeloid Hyperplasia/Malignancy Associated With t(8;13)(p11;q11): Description of a Distinctive Clinicopathologic Entity

By Roger C. Inhorn, Jon C. Aster, Sheila A. Roach, Christopher A. Slapak, Robert Soiffer, Ramana Tantravahi, and Richard M. Stone

We report two patients with a distinctive biphenotypic hematologic disorder characterized by lymphoblastic lymphoma (LBL), eosinophilia, and myeloid malignancy and/or hyperplasia associated with a t(8;13)(p11;q11) chromosomal translocation in both bone marrow and lymph node specimens. Both patients presented with lymphadenopathy pathologically classified as LBL with a T-cell immunophenotype, myeloid hyperplasia of the bone marrow, and peripheral blood eosinophilia. The first patient achieved clinical complete remission after receiving several regimens of chemotherapy and remains disease-free 16 months after undergoing allogeneic bone marrow transplantation. The second patient developed progressive lymphadenopathy despite several courses of chemotherapy directed against non-Hodgkin's lymphoma. Eight months after his initial presentation, he developed acute myelogenous leukemia that was refractory to therapy. Comparison of these patients with four similar cases recently reported in the literature suggests that this constellation of findings constitutes a distinctive clinicopathologic syndrome. Molecular analysis of the t(8;13) translocation breakpoint may identify genes located in this region and provide insight into the pathogenesis of this interesting biphenotypic hematologic malignancy.

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LYMPHoblastic lymphoma (LBL) is a high-grade non-Hodgkin's lymphoma first described as a distinctive pathologic entity in 1975.1-4 Patients are most commonly children or young adults who typically present with an anterior mediastinal mass. The malignant progenitor cells in LBL usually display a T-cell immunophenotype, although B-cell and biphenotypic variants have been reported.4,5

Since the original description of LBL, considerable clinical heterogeneity has been reported. Patients with LBL whose malignant cells manifest a T-cell immunophenotype have a variable degree of bone marrow involvement. The distinction between LBL and T-cell acute lymphoblastic leukemia (ALL) is arbitrarily based on the percentage of bone marrow blasts. LBL with a B-cell immunophenotype, in contrast, tends to present without a mediastinal mass, and bone marrow involvement is more common. Eosinophilia has occasionally been described in association with LBL,6,7 although eosinophilia is more commonly associated with ALL.8-10 Finally, acute myelogenous leukemia (AML) has rarely been described in conjunction with LBL.7,11,12

Abruzzo et al12 first reported three cases of a syndrome consisting of LBL associated with eosinophilia and myeloid hyperplasia. Two of these patients subsequently developed AML, while the third developed granulocytic sarcoma and a myeloproliferative disorder. Cytogenetic analysis of the bone marrow from one of these patients showed t(8;13)(p23;q14) at initial presentation. Three subsequent case reports have described similar clinical presentations in patients with (8;13) translocations.13-15 We report two additional patients with LBL, eosinophilia, and myeloid hyperplasia/malignancy associated with t(8;13)(p11;q11) chromosome translocation. The present report, together with the previously reported cases, suggest the existence of a distinctive cytogenetic-clinopathologic syndrome that manifests as a biphenotypic hematologic malignancy.

MATERIALS AND METHODS

Data collection. Patient 1 was diagnosed and treated at the Dana-Farber Cancer Institute (Boston, MA). Patient 2 was originally diagnosed and treated at New York Hospital, (New York, NY) then his care was transferred to the Dana-Farber Cancer Institute. Case histories were based on medical record review.

RESULTS

Patient 1. Patient 1, an 18-year-old woman, presented in March 1992 for prepartum care. Routine complete blood

Pathology. Bone marrow and lymph node biopsy specimens were prepared using standard hematoxylin-eosin staining. Immunophenotyping was performed on snap-frozen lymph node specimens using a panel of commercially available monoclonal antibodies. CD7 and CD20 antibodies were from Becton Dickinson (Mountain View, CA), CD22 antibody, TdT and myeloperoxidase were from Dakopatts (Glostrup, Denmark); and all other monoclonal antibodies were from Coulter Immunology (Hialeah, FL). All pathology specimens were reviewed by J.C.A.

Cytogenetic analysis. Bone marrow aspirates were cultured for 24 hours at 37°C in 5% CO2 in RPMI 1640 medium supplemented with 16% (vol/vol) fetal bovine serum, 2 mmoL/L-glutamine, and antibiotics. Standard air-dried slides were stained with quinacrine mustard, and well-banded metaphases were photographed. Analysis was performed on photographic prints.16 Fluorescence in situ hybridization was performed using a commercially available probe to the chromosome 8 centromere (catalog no. P5013; Oncor Inc. Gaithersburg, MD). Briefly, slides were incubated in 2X SSC for 30 minutes. After dehydration steps in alcohol series, slides were denatured in 70% formamide in 2X SSC for 2 minutes. On each slide, 2 ng of probe was placed, coverslips were added, and hybridization was performed overnight at 37°C. Posthybridization washes were performed at 43°C in 65% formamide in 2X SSC. The probe was detected with fluorescein-conjugated avidin. Photography was performed with Kodak 400 Gold film (Eastman-Kodak, Rochester, NY) and a Leitz fluorescence microscope.

RESULTS

Patient 1. Patient 1, an 18-year-old woman, presented in March 1992 for prepartum care. Routine complete blood

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count (CBC) was notable for a white blood cell (WBC) count of 19.3 × 10^9/L with a left shift and 6% eosinophils. She was otherwise in excellent health. During the ensuing 2 months, she developed progressive leukocytosis as high as 36.0 × 10^9/L with persistent left shift and eosinophilia. In May, she underwent bone marrow biopsy, which showed myeloid hyperplasia and eosinophilia, but no evidence of excess blasts or myelodysplastic changes. Leukocyte alkaline phosphatase score was 98, and polymerase chain reaction (PCR) probe for the BCR-ABL translocation did not show the BCR rearrangement. Cytogenetic analysis showed a 46,XX,t(8;13)(p11;q11) karyotype in 25 of 27 metaphases, whereas two cells were 46,XX.

The patient remained asymptomatic until July 1992, when she first noted right inguinal adenopathy. During the ensuing month she developed rapidly progressive bilateral, bulky inguinal adenopathy as well as submandibular and cervical adenopathy. In August 1992 she underwent biopsy of a femoral lymph node, and histology showed immature granulated cells believed to be consistent with myeloblasts. A significant eosinophilic infiltrate was noted. Histochemistry showed staining for chloroacetate esterase. Immunohistochemistry showed the tumor cells to be positive for leukocyte common antigen (CD45) and negative for pan-B-cell and pan-T-cell markers. Pathology was believed to be most consistent with granulocytic sarcoma or myeloblastoma.

In September 1992 at 35 weeks gestation, the patient presented to our institution for further evaluation. Physical examination showed diffuse adenopathy as noted above, with a matted right inguinal lymph node chain measuring 12 × 8 cm. Details of the hematologic data are presented in Table 1. Bone marrow biopsy again showed myeloid hyperplasia and eosinophilia, with less than 5% blasts and no myelodysplastic changes. Cytogenetic analysis of bone marrow cells showed the same aneuploid clone seen in the original sample in 21 of 23 metaphases (Fig 1). An identical translocation was also observed in 13 of 14 metaphases prepared from a lymph node biopsy specimen. The location of the breakpoint on chromosome 8 was confirmed with fluorescence in situ hybridization using a chromosome 8 centromeric probe (Fig 2).

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**Table 1. Clinical and Pathologic Characteristics of Patients Presenting With Translocation t(8;13)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Leslie et al 1</th>
<th>MacDonald et al 1</th>
<th>Fagan et al 2</th>
<th>Case 2</th>
<th>Present Report</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>68</td>
<td>43</td>
<td>47</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Splanomegaly</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B symptoms</td>
<td>Weight loss, night sweats</td>
<td>Weight loss</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>14.0</td>
<td>16.1</td>
<td>13.2</td>
<td>15.5</td>
<td>13.6</td>
</tr>
<tr>
<td>Plt (×10^3)μL</td>
<td>NR</td>
<td>336</td>
<td>199</td>
<td>263</td>
<td>194</td>
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<tr>
<td>WBC count (×10^3μL)</td>
<td>85</td>
<td>31.3</td>
<td>44.8</td>
<td>38.0</td>
<td>43.0</td>
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<tr>
<td>% Neutrophils</td>
<td>45.1</td>
<td>70.2</td>
<td>49.0</td>
<td>30.0</td>
<td>71.0</td>
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<tr>
<td>% Monocytes</td>
<td>15.1</td>
<td>1.9</td>
<td>8.0</td>
<td>9.0</td>
<td>2.0</td>
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<tr>
<td>% Eosinophils</td>
<td>18.0</td>
<td>8.0</td>
<td>29.0</td>
<td>11.0</td>
<td>7.0</td>
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<tr>
<td>% Blasts</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
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<tr>
<td>BM aspirate</td>
<td>% Blasts</td>
<td>5</td>
<td>WNL</td>
<td>WNL</td>
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<tr>
<td>Myeloid hyperplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Eosinophilia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cyto genetic</td>
<td>46,XY, t(8;13)(p11;q12)</td>
<td>46,XY, t(8;13)(p11;q12)</td>
<td>47,XY,+21, t(8;13)(p11.2;q12)</td>
<td>46,XY, t(8;13)(p23;q14)</td>
<td>46,XX, t(8;13)(p11;q11)</td>
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<td>LN biopsy Dx</td>
<td>T-cell lymphoma</td>
<td>Immature hematopoietic cells</td>
<td>LBL</td>
<td>LBL</td>
<td>LBL</td>
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<tr>
<td>Eosinophilia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>L-cell markers</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B-cell markers</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Death 7 mo after presentation of myeloproliferative disorder</td>
<td>CR, 14 wks S/P BMT</td>
<td>Death 12 mos after presentation of stem cell leukemia</td>
<td>Death 13 mos after presentation of MO AML</td>
<td>CR, 16 mos S/P BMT</td>
</tr>
</tbody>
</table>

Abbreviations: Hgb, hemoglobin level; Plt, platelet count; BM, bone marrow; LN, lymph node; Dx, at diagnosis: NR, not reported; WNL, within normal limits; CR, complete remission; S/P BMT, after allogeneic bone marrow transplant.
To expedite initiation of chemotherapy, labor was induced, and the patient underwent uncomplicated vaginal delivery. Computed tomography (CT) scan performed after delivery showed splenomegaly and extensive retroperitoneal, iliac, and femoral adenopathy. No mediastinal mass was shown. Three days after delivery, chemotherapy consisting of daunorubicin and cytarabine was started. Immediately before initiating chemotherapy, the patient underwent cervical lymph node biopsy for further characterization (Fig 3). Immunoperoxidase studies performed on fixed lymph node tissue showed reactivity for TdT, CD1a, CD2, CD3, CD4, CD5, CD7, and CD23. The cells were negative for CD13, CD20, CD33, and CD34. Marked eosinophilic infiltration was noted. Chloroacetate esterase activity and myeloperoxidase reactivity appeared to be confined to the mature eosinophils. Because the histologic and immunophenotypic analyses supported a diagnosis of LBL, vincristine and prednisone were added to the therapeutic regimen.

She had a marked initial response to the first cycle of chemotherapy and continued treatment with a standard LBL regimen. Despite chemotherapy, however, the patient again developed worsening inguinal adenopathy. High-dose cytarabine demonstrated persistent myeloid hyperplasia and eosinophilia. Cytogenetic analysis demonstrated a normal 46,XX karyotype in 29 of 30 metaphases, with the persistence of (8;13)(p11;q11) translocation in 1 of 30 metaphases. A second course of high-dose cytarabine was administered, but the patient subsequently developed recurrent bulky adenopathy. Repeat bone marrow biopsy showed 46,XX,t(8;13)(p11;q11) karyotype in 32 of 34 metaphases.

Chemotherapy consisting of ifosfamide, carboplatin, and etoposide was initiated in March 1993, and complete clinical remission was achieved after two cycles of therapy. Three months later the patient underwent a CD6-depleted allogeneic bone marrow transplantation from her HLA-compatible brother with a conditioning regimen of cytoxan and total body irradiation. The transplant course was uneventful, and the patient remains in continuous complete remission 16 months after bone marrow transplantation. Three subsequent bone marrow biopsies have shown a normal male karyotype.

**Patient 2.** Patient 2, a 27-year-old white man, presented in April 1990 with cervical, axillary, and inguinal adenopathy and splenomegaly. The initial hematologic profile is summarized in Table 1. Cervical lymph node biopsy was originally interpreted as diffuse mixed cell lymphoma. During the ensuing months, the patient developed progressive adenopathy and leukocytosis (Table 2). A femoral lymph node biopsy was performed, and immunophenotyping showed positivity for CD1, CD2, CD3, CD4, CD5, and TdT, with occasional cells reactive with CD8, CD14, and CD33 and negative staining with CD7 and CD22. The histology was believed to be most consistent with LBL with eosinophilic infiltration, similar to the histology seen in the first patient's cervical lymph node sample. Cytogenetic analysis of bone marrow and lymph node specimens showed t(8;13) (Table 2), whereas phytohemagglutinin-stimulated peripheral lymphocytes showed a normal male karyotype, which ruled out a constitutional abnormality. The patient was treated with hydroxyurea resulting in a decrease in his adenopathy and WBC count. Beginning in June 1990, he received four cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE) with resolution of his adenopathy, splenomegaly, and leukocytosis.

In October 1990, the patient developed recurrent adenopathy and leukocytosis (Table 2). He was again treated with CHOPE without significant improvement. In February 1991,
a peripheral blood sample showed a left shift including 4% blasts, and a bone marrow biopsy specimen was interpreted as AML evolving in the setting of a myeloproliferative disorder (Table 2). Daunorubicin and cytarabine induction therapy was initiated, with resultant marrow hypoplasia and improvement in the patient’s adenopathy.

However, by April 1991, patient 2 again developed diffuse bulky adenopathy and a WBC count of \(61 \times 10^9/L\). Cytogenetic analysis of a bone marrow sample showed three related abnormal clones all carrying the t(8;13) (Table 2). Biopsy of an epitrochlear lymph node was performed, and immunoperoxidase studies demonstrated reactivity for CD13, CD14, and myeloperoxidase, while no cells were reactive for CD2, CD5, CD20, CD22, CD33, or kappa or lambda immunoglobulin light chains. A histochemical stain for chloroacetate esterase showed frequent positive blast forms. These results were believed to be consistent with myeloblastoma (Fig 4).

Despite sequential treatment with high-dose cytarabine, carboplatin, high-dose cytoxan, and mitoxantrone/etoposide, the patient developed progressive adenopathy, splenomegaly, bilateral pleural effusions, and a pericardial effusion leading to tamponade. In August 1994, he died secondary to respiratory failure, pneumonia, and neutropenic sepsis. No autopsy was performed.

**DISCUSSION**

In this report we described two patients who presented with T-cell LBL, eosinophilia, and myeloid hyperplasia associated with t(8;13)(p11;q11) translocation. This unusual clinicopathologic syndrome is similar to that described in four recent case reports.\(^7,13-15\) The clinical and pathologic features of these six cases are summarized in Table 1. Unifying clinical features include presentation with peripheral adenopathy in the absence of mediastinal mass, leukocytosis, and peripheral eosinophilia. The presence of hepatosplenomegaly and B symptoms is variable. There is a male preponderance (five of six patients) in the reported cases. Pathology typically demonstrates T-cell LBL, again with significant eosinophilia.

Association of LBL with AML is extremely uncommon. Kjeldsberg et al\(^11\) reported three patients who presented with mediastinal LBL. One patient had AML on presentation, whereas the other two developed AML within 8 months of their initial diagnoses. All three diagnoses of LBL were made on histology alone, without the benefit of immunophenotypic analysis. Posner et al\(^12\) first described an association between T-cell LBL and AML. In this case, AML arose 25 months after multiagent chemotherapy, suggesting that the development of leukemia may have been treatment-related. A review of cases in which both non-Hodgkin’s lymphoma and AML were reported established a mean interval of 5.2 years between the diagnosis of lymphoma and AML, consistent with treatment-induced leukemogenesis.\(^18\) Of the six cases summarized in Table 1, four died of complications related to AML, all of which arose within 1 year of diagnosis, suggesting a biphenotypic neoplasm. Of note, the two patients who remain alive both underwent allogeneic bone marrow transplantation, which underscores the importance of treatment directed at malignant pluripotent stem cells.

Two recent reports show that LBL can manifest lineage infidelity. Childs et al\(^4\) described a patient who presented...
A BIPHENOTYPIC MALIGNANCY ASSOCIATED WITH t(8;13)

Fig 2. Fluorescence in situ hybridization on a metaphase from a bone marrow sample from patient 1 using a chromosome 8 centromeric probe. The top arrow points to normal chromosome 8, and the bottom arrow points to the longer derived chromosome, confirming that the derived chromosome contains the chromosome 8 centromere and the breakpoint is in the short arm.

Fig 3. Cervical lymph node biopsy from patient 1 (original magnification, 500×). The malignant cells are intermediate in size and have condensed chromatin and inconspicuous nucleoli, consistent with a diagnosis of LBL.

Fig 4. Epitrochlear lymph node biopsy from patient 2 showing myeloblastoma (original magnification, 500×). The open chromatin pattern contrasts with that seen in Fig 3. Scattered eosinophilic myeloid forms are present.
with an oropharyngeal tumor. Although the histology was consistent with LBL, immunophenotyping and cytochemistry revealed a biphenotypic tumor, with both T-lymphocytic (CD4, CD5, CD8, OKT-6, and TdT) and granulocytic (CD11b, chlo-roacetate esterase, lysozyme, α-1 antitrypsin) markers. Nosaka et al. reported a case in which a patient presenting with T-cell LBL rapidly developed a bilineal leukemia. The investigators established a myeloid cell line from the patient’s peripheral blood during his leukemic phase. T-cell receptor γ-chain molecular analysis showed that the same clonal rearrangement was present in both the lymph node and the myeloid cell line, suggesting that a primordial hematopoietic stem cell gave rise to both malignancies.

Eosinophilia was first described in association with ALL by Spitzer and Garson. This clinical association has since been confirmed. Although an association between LBL and eosinophilia has also been reported, this correlation appears to be less common. Specific karyotypic abnormalities have been associated with eosinophilia arising in the setting of hematologic malignancies, including t(5;14) (q31;q32) seen in ALL, and 16p13 and 16q22 abnormalities seen in the myelomonocytic (M4EO) subtype of AML. The t(8;13) represents a novel translocation associated with eosinophilia.

Several chromosomal abnormalities have been associated with LBL. Kaneko et al. performed karyotype analysis on a series of 33 patients with T-cell ALL and 17 patients with T-cell LBL. Of 17 patients with LBL, 16 had karyotypic abnormalities, most commonly involving 14q11, 7q35, and 7p15. In addition, three LBL patients possessed a unique t(9;17)(q34;q23) translocation not seen in patients with ALL. Rearrangements involving chromosome 8p11 have previously been associated with myeloproliferative disorders, while interstitial deletions del(7)(q22) and t(1;7)(q21;q11) are involved in some myeloproliferative and myelodysplastic syndromes.

Putative oncogenes or tumor suppressor genes present at the t(8;13) translocation breakpoint may play a role both in normal hematopoiesis and leukemogenesis. Candidate genes located near the breakpoint include fibroblast growth factor receptor 1 (also known as fms-related tyrosine kinase 2), located at 8p12 to p11.2, DNA-directed polymerase beta (8p12 to p11), and the human FLT3/FLK2 gene product (13q12). Interestingly, FLT3/FLK2 encodes a receptor-type tyrosine kinase that is expressed on hematopoietic progenitor cells. Moreover, high-level expression of FLT3 has been demonstrated in both AML and ALL by Northern blot analysis. Further insight into the importance of genes residing at the t(8;13)(p11;q11) translocation awaits the results of ongoing molecular analysis.

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REFERENCES


A syndrome of lymphoblastic lymphoma, eosinophilia, and myeloid hyperplasia/malignancy associated with t(8;13)(p11;q11): description of a distinctive clinicopathologic entity [see comments]

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