Cutaneous Lymphoblastic Lymphoma With Pre-B Markers

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Two children with cutaneous convoluted lymphoblastic lymphoma are reported. Malignant cells from both patients contained cytoplasmic Mu heavy chains characteristic of pre-B-cells and expressed CALLA and Ia antigens as well. Most cases of convoluted lymphoblastic lymphoma are T-cell-derived neoplasms. The non-T, non-B phenotype found in these two children demonstrates that histology does not necessarily predict immunophenotype. The association of the pre-B phenotype with cutaneous lymphoma has not been previously reported, but may represent a unique clinical-histopathologic-immunologic entity that occurs in young children.

STUDIES OF IMMUNOLOGIC markers of blast cells from children with acute lymphoblastic leukemia and non-Hodgkin’s lymphoma (NHL) have provided considerable insight into the heterogeneity of these diseases. Approximately 20% of children with acute lymphoblastic leukemia (ALL) have lymphoblasts of T-cell lineage that bear T-cell surface antigens and/or receptors for sheep erythrocytes. Less than 2% of children with ALL have blast cells of B-cell type that bear surface membrane immunoglobulin. The remaining 75%—80% of children with ALL have blast cells that lack T- and B-cell characteristics (so-called “non-T, non-B ALL”). The majority of these cases have lymphoblasts that react with antiserum directed against Ia antigens and the common acute lymphoblastic leukemia antigen (CALLA). In nearly 20% of cases of non-T, non-B ALL, the lymphoblasts demonstrate immunoglobulin heavy chains in the cytoplasm, even though surface immunoglobulin is absent. This phenotype of ALL is felt to represent a malignant proliferation of pre-B-cells.

By contrast, studies of childhood NHL have revealed a conspicuously different distribution of the various immunophenotypes when compared with ALL. Approximately 50% of children with NHL have malignancies of T-cell origin, while almost all of the remaining patients have B-cell-derived neoplasms. The rarity of non-T, non-B lymphoma in children has been stressed in a number of series. Moreover, a striking correlation has been found between the immunophenotype and histopathology in individual cases.

The lymphoblastic lymphomas have been found to be T-cell lymphoproliferations, while the undifferentiated lymphomas (Burkitt and non-Burkitt types) are almost all B-cell-derived. These studies have led many investigators to presume the immunophenotype based on histopathology when tissue is unavailable for immunologic studies.

We report two children with convoluted lymphoblastic lymphoma presenting with cutaneous masses in the scalp. The malignant cells from both of these patients contained cytoplasmic Mu heavy chains, characteristic of pre-B-cells, and expressed CALLA antigens as well.

MATERIALS AND METHODS

Malignant cells for marker studies were obtained from the bone marrow at the time of relapse in patient no. 1 and from a lymph node at the time of presentation in patient no. 2. Specimens were greater than 90% replaced by malignant cells at the time of analysis. Mononuclear cells were separated by Ficoll-Hypaque density sedimentation, washed in balanced salt solution with 10% fetal calf serum, and incubated at 37°C for 45 min to remove cytophilic antibody. Spontaneous rosette formation with sheep erythrocytes was used as a marker for T lymphoblasts.

Cell surface light and heavy chains were detected by staining viable cells with fluorescein-isothiocyanate-conjugated purified goat anti-human antibody to specific light or heavy chains, as previously described. Surface-stained cells were adhered to glass slides by cytorefugitation and fixation in cold 95% ethanol-5% glacial acetic acid and washed in phosphate-buffered saline. Cytoplasmic staining for immunoglobulin light or heavy chains was detected by applying 100 μl of rhodamine-conjugated antibody to the pellet of surface-stained cells. The slides were incubated at room temperature for 20 min in a moist chamber, washed, mounted, and examined with a Leitz Orthoplan microscope. Mature B cells are positive for surface but lack cytoplasmic immunoglobulin (slg⁺, clg⁻). Pre-B-cells contain cytoplasmic but lack surface immunoglobulin (slg⁻, clg⁺). Surface antigens were detected by indirect immunofluorescence using fluorescein-isothiocyanate-conjugated goat antibodies to mouse and rabbit immunoglobulin where appropriate. Analyses were performed by flow cytometry using the fluorescence-activated cell sorter (FACS-III, Becton-Dickinson, Mountain View, CA) in patient no. 1, or by fluorescence microscopy in patient no. 2. Ia (HLA-DR) antigens were detected with the use of the murine monoclonal anti-human HLA-DR (Becton-Dickinson) in patient no. 1 or with rabbit anti-human p23,30 in patient no. 2 (kindly supplied...
**CASE REPORTS**

**Patient 1**

A 3.75-yr-old white female developed scalp nodules over the parietal and postauricular region over a 1-mo period. Excisional biopsy of both nodules was performed and a diagnosis of convoluted lymphoblastic lymphoma was made (Fig. 1A). The white blood count was 9100/cu mm with 60% polys, 9% bands, 27% lymphocytes, 2% monocytes, and 2% eosinophils. The hemoglobin was 12.9 g/dl, the PCV 38.7%, and the platelet count 355,000/cu mm. A chest x-ray revealed no evidence of mediastinal widening. A bone marrow aspirate and biopsy revealed no evidence of involvement by lymphoma, and the spinal fluid contained no malignant cells. The patient was treated with the Stanford Regimen for Pediatric Non-Hodgkin’s Lymphoma. She remained in continuous complete remission for 11 mo, at which time she sustained an isolated bone marrow relapse. Although she attained a second complete remission, she ultimately relapsed and died with progressive marrow infiltration 2 yr after her initial diagnosis.

**Patient 2**

A 6-yr-old white female developed a scalp mass following head trauma. Despite several courses of topical antibiotic and antifungal treatment and systemic antibiotic therapy, the mass continued to enlarge over the ensuing months. She developed cervical adenopathy, but repeated complete blood counts remained normal. Biopsy of the scalp mass (Fig. 1B) and lymph node showed infiltrates morphologically characteristic of convoluted lymphoblastic lymphoma. By the time of definitive diagnosis, physical examination revealed adenopathy and splenomegaly. Skeletal survey, chest x-ray, and liver scan were normal. The hemoglobin was 9.1 g/dl, hematocrit 25% with normal white blood cell count and differential count. Bone marrow examination showed involvement by lymphoblasts. The patient was treated on the LSA2L2 regimen for childhood non-Hodgkin’s lymphoma. She attained a complete remission, which was maintained for 28 mo, at which time she developed congestive heart failure presumed to be secondary to anthracycline toxicity. Her cardiac function steadily deteriorated despite supportive care, and she died 6 mo later. She had no evidence of recurrent disease at the time of her death 34 mo from diagnosis.

**RESULTS**

**Pathology**

Sections of biopsy material from the scalp lesions of both patients were reviewed by one of us (R.F.D.). Both showed extensive infiltration of the dermis and subcutaneous tissues by atypical lymphoid cells with convoluted nuclear membranes, a fine nuclear chromatin pattern, and inconspicuous nucleoli. Mitoses were frequent. No evidence of epidermotropism was noted. The morphological features were considered to be characteristic of a malignant lymphoma, convoluted lymphoblastic type (Figs. 1A and B).

**Cytochemical Studies**

Neither patients’ cells stained with acid phosphatase, myeloperoxidase, or Sudan Black B. The cells from patient no. 2 demonstrated coarse blocking when stained with periodic acid-Schiff, while the cells from patient no. 1 were negative with this stain.

**Immunologic Studies**

Results of immunophenotyping studies are shown in Table 1. Malignant cells from both patients demonstrated Ia and CALLA antigens on the cell surface. Neither patients’ cells formed rosettes with sheep erythrocytes and cells from patient no. 1 failed to react with anti-Leu-1, Leu-2a, Leu-3a, and Leu-4—all anti-T-cell-specific monoclonal antibodies. The results of surface immunophenotyping of cells from patient no. 1 are shown in Fig. 2.

The results of surface and cytoplasmic immunoglobulin staining of malignant cells from the two
Table 1. Results of Immunophenotyping Studies

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>SIgM</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>SIgD</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>SIgG</td>
<td>0.1</td>
<td>1.4</td>
</tr>
<tr>
<td>SIgA</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>S Kappa</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>S Lambda</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>SIgM⁺, clgM⁺</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>SIgM⁺, clgM⁺</td>
<td>73.0</td>
<td>&gt;90.0</td>
</tr>
<tr>
<td>clgG</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>clgA</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>cKappa</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>cLambda</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>75</td>
<td>99.5</td>
</tr>
<tr>
<td>CALLA</td>
<td>60</td>
<td>65.1</td>
</tr>
<tr>
<td>E rosette</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Leu-1</td>
<td>3.4</td>
<td></td>
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<tr>
<td>Leu-2a</td>
<td>1.2</td>
<td></td>
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<tr>
<td>Leu-3a</td>
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<tr>
<td>Leu-4</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
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patients are also shown in Table 1. Malignant cells from both patients demonstrated only cytoplasmic heavy chains, without light chain expression.

DISCUSSION

The two cases reported here demonstrate that histology does not necessarily predict immunophenotype. These two children clearly had lymphomas morphologically characteristic of the convoluted lymphoblastic type—an entity that is associated with T-cell markers in the Lukes-Collins classification schema for non-Hodgkin’s lymphoma. The presence of Ia and CALLA antigens on the blast cells of the two patients reported here supports the concept that these patients had non-T lymphoproliferations, since reactivity with both anti-Ia and anti-CALLA is unusual in pediatric patients with T-cell malignancies.3,26,27 Furthermore, the demonstration of immunoglobulin heavy chains in the cytoplasm of the blast cells from both patients confirms the pre-B phenotype. While the majority of lymphoblastic lymphomas (especially those presenting with anterior mediastinal mass) are T-cell-derived neoplasms, marker studies must be performed to determine immunophenotype, particularly in lymphoblastic lymphoma arising outside the mediastinum.

The remarkable association of cutaneous lymphoma in childhood with pre-B markers has not been described previously. Bernard et al.14 performed immunophenotyping on tissue specimens from 116 pediatric patients with non-Hodgkin's lymphoma and noted that only eight patients demonstrated non-T, non-B markers. Of the non-T, non-B lymphomas, four presented as primary cutaneous lymphoblastic lymphoma (one convoluted, three nonconvoluted), and all were CALLA positive. Tests for cytoplasmic immunoglobulin were not performed in these patients, but the clinical and pathologic features are reminiscent of the cases in our report. It is noteworthy that the four cases of cutaneous NHL in Bernard’s series were younger than the usual mean age (7-9 yr) for children with NHL, as were our patients. Although relatively rare, cutaneous lymphoblastic lymphoma with pre-B markers and reactivity with anti-CALLA may represent a unique clinical-histopathologic-immunologic entity that occurs in young children.

Previous studies have demonstrated the rarity of non-T, non-B lymphomas in childhood. In some of these studies, T-cell disease was defined by E-rosetting, although it is now known that blast cells from certain patients with lymphoid malignancies react with anti-T-cell heteroantisera and monoclonal antibodies but fail to rosette with sheep erythrocytes.1,3,17,24,25 Some of the putative non-T, non-B lymphomas from past studies may represent E-rosette-negative T-cell disease. Certain of the large cell lymphomas, especially those of "true histiocyte" origin, are also non-T, non-B derived malignancies, but these are very rare in children.13

A problem in defining the true incidence of non-T, non-B lymphoma in childhood is that a significant percentage of patients present with localized disease,
which is completely excised, and no tissue is submitted for immunophenotyping. Most immunophenotyping studies, and subsequent immunophenotype-histopathologic correlations, have thus been performed in patients presenting with advanced disease where fresh tumor cells are easily accessible for investigation. The majority of these patients have either mediastinal primaries with lymphoblastic morphology and T-cell markers, or massive abdominal primaries with undifferentiated histology and B-cell markers. Further studies of patients with localized disease should be performed to determine if the same immunologic-histopathologic correlations are valid for this group of patients as well.

ACKNOWLEDGMENT

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REFERENCES

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