Childhood Ki-1 Lymphoma Presenting With Skin Lesions and Peripheral Lymphadenopathy

By Marshall E. Kadin, Dianne Sako, Nancy Berliner, Wilbur Franklin, Bruce Woda, Michael Borowitz, Karen Ireland, Abe Schweid, Philip Herzog, Beverly Lange, and Ronald Dorfman

We describe a large-cell lymphoma of activated lymphoid cells in six children and adolescents. The presenting clinical features of regressing skin lesions and peripheral lymphadenopathy, sinus infiltration of lymph nodes, and infrequent tumor cell erythrophagocytosis resulted in initial diagnoses of malignant or regressing atypical histiocytosis in five cases. Binucleate and multinucleate tumor cells, sometimes with prominent eosinophilic nucleoli, resembled Reed-Sternberg (RS) cells and occasionally were found in a cytoarchitectural milieu that was consistent with a diagnosis of Hodgkin’s disease (HD). The tumor cells did in fact express the HD–associated antigen Ki-1, but unlike most types of HD, the RS-like cells expressed common leukocyte antigen and were negative for Leu-M1. A T cell origin for the malignant cells was demonstrated with monoclonal antibodies in two cases, by focal staining for nonspecific esterase in one case, and by rearrangement of the β-chain genes for the T cell receptor in a fourth case. These studies provide further evidence that some cases previously interpreted as malignant or regressing atypical histiocytosis and some types of HD are actually T cell disorders.

STEIN ET AL have recently described a large-cell lymphoma of activated lymphoid cells expressing a Hodgkin’s disease–associated antigen, Ki-1. This Ki-1 lymphoma is further distinguished histologically by a sinus pattern of lymph node infiltration simulating metastatic carcinoma or malignant histiocytosis. Among the 45 patients described by Stein et al the diagnostic biopsy site was the skin in three times with prominent eosinophilic nucleoli, resembled Reed-Sternberg (RS) cells and occasionally were found in a cytoarchitectural milieu that was consistent with a diagnosis of Hodgkin’s disease (HD). The tumor cells did in fact express the HD–associated antigen Ki-1, but unlike most types of HD, the RS-like cells expressed common leukocyte antigen and were negative for Leu-M1. A T cell origin for the malignant cells was demonstrated with monoclonal antibodies in two cases, by focal staining for nonspecific esterase in one case, and by rearrangement of the β-chain genes for the T cell receptor in a fourth case. These studies provide further evidence that some cases previously interpreted as malignant or regressing atypical histiocytosis and some types of HD are actually T cell disorders.

In five cases, both lymph node and skin biopsy results were available for study. In a sixth case, only a biopsy of skin was taken. All patients had examination of peripheral blood, bone marrow, aspirate, and trephine biopsy for tumor cells. Lymph nodes were fixed in B5 for routine histology. Skin biopsies were fixed in either B5 or formalin, although B5 gave better morphology of lymphoid cells.

In each case, a corresponding piece of unfixed tissue was snap frozen in isopentane or acetone cooled by dry ice and then used to prepare frozen sections of 5 to 6 μm in thickness. Frozen sections were studied with monoclonal antibodies against cellular activation antigens including antigens expressed preferentially by Reed-Sternberg cells of Hodgkin’s disease—Ki-1, Leu-M1, HLA-DR, Tac, OKT9; T cell-specific antigens (T11, Leu-1, Leu-4, T4, T8, 3A1); B cell–specific antigens (HLB-3, B1, B4, Leu-12, Leu-14) and surface immunoglobulin heavy and light chains (IgM, IgD, κ, λ); macrophage-specific antigens (OKM1, Leu-M3); Ki-M1, Ki-M2, Ki-M3, Ki-M4); and leukocyte common antigen (T200) by use of an indirect immunoperoxidase method or, in case 5, an alkaline phosphatase/anti-alkaline phosphatase technique. A tumor cell suspension from case 1 was studied for rosette formation with sheep erythrocytes, IgG-coated bovine erythrocytes, and complement-IgM–coated erythrocytes as previously described. Direct touch imprints or cytocentrifuge preparations of tumor cells were studied for the cytotoxic enzymes myeloperoxidase, Sudan black B, acid phosphatase, and alphalanphiphyl acetate or butyrate esterase as previously reported.

DNA extractions were performed as described previously. Briefly, high–molecular weight DNA was prepared from a tumor cell suspension from patient 1. Cells were incubated overnight at 37 °C in 0.5% sodium dodecyl sulfate (SDS) and 0.2 mg/mL proteinase K. This was followed by phenol-chloroform extraction and ethanol precipitation. DNA was digested with appropriate restriction enzymes, size-fractionated by agarose gel electrophoresis, and transferred onto nitrocellulose paper by the method of Southern. Filters were hybridized to nick-translated, 32p-labeled probes of the immunoglobulin heavy- and light-chain loci and of the β-chain of the T cell receptor. The filters were then washed at 55 °C in 0.1% SDS and 0.15 mol/L NaCl–0.0015 mol/L Na citrate prior to autoradiography.

RESULTS

Clinical findings. The clinical features at presentation as well as therapy, and follow-up data are summarized in...
Table 1. Presenting Clinical Features, Initial Pathologic Diagnosis, and Results of Treatment

<table>
<thead>
<tr>
<th>Age/Sex/Race</th>
<th>Presenting chief complaint</th>
<th>Initial pathologic diagnosis</th>
<th>Constitutional symptoms</th>
<th>Peripheral lymphadenopathy</th>
<th>Skin lesions</th>
<th>Therapy (duration)</th>
<th>Response to therapy</th>
<th>Survival (months from onset)</th>
<th>Survival (months from diagnosis)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>13/M/Asian tender lymph nodes and subcutaneous nodules of abdominal wall</td>
<td>malignant or regressing atypical histiocytosis</td>
<td>0 fever</td>
<td>I, C, A</td>
<td>+ + local radiation (1,400 rad), CHOP (6 mo), COMP (12 mo)</td>
<td>complete remission</td>
<td>relapse of cutaneous nodules on left arm 4 mo after therapy. Added chemotherapy, whole-body radiation, and bone marrow transplant</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>8/M/white skin nodule, right part of neck, &quot;? insect bite or ringworm infection&quot;</td>
<td>large-cell lymphoma or malignant histiocytosis</td>
<td>0 fever</td>
<td>C</td>
<td>+ + COMP (6 mo) and local radiation (2,400 rad)</td>
<td>complete remission</td>
<td>relapse of cutaneous nodules with hilar and retroperitoneal adenopathy, systemic symptoms 3 mo after therapy</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>12/M/white nodules on right part of neck and chest wall, &quot;? insect bites&quot;</td>
<td>reactive or inflammatory v large-cell lymphoma</td>
<td>0 fever</td>
<td>C, A</td>
<td>+ + COMP, daunomycin IV + IT methotrexate (8 mo)</td>
<td>relapse of cutaneous nodules</td>
<td>relapse in skin of right breast</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>12/F/black enlarged lymph node &quot;cat scratch&quot;</td>
<td>Hodgkin’s disease v malignant histiocytosis</td>
<td>0 fever</td>
<td>E</td>
<td>+ + radiation to involved field, mantle, para-aortic lymph nodes, and splenic pedicle</td>
<td>immediate relapse in abdomen treated with PROMACE-MOPP</td>
<td>complete remission</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>19/F/white antecubital mass ? abcess</td>
<td>granulomatous inflammation, squamous carcinoma, regressing atypical histiocytosis</td>
<td>0 fever</td>
<td>A</td>
<td>+ + local radiation (4,200–5,000 rad)</td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 6</td>
<td>11/M/black ulcerating skin lesions on buttock, thigh, and arm</td>
<td>large-cell lymphoma v malignant histiocytosis</td>
<td>0</td>
<td>0</td>
<td>+ + COMP + IT MTX, Ara-C, then modified LSA2 (6 mo)</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: I, inguinal; C, cervical; A, axillary; E, epitracheal; BMT, bone marrow transplant; IV, intravenous; IT, intrathecal; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; COMP, cyclophosphamide, vincristine, methotrexate, prednisone; LSA2, cyclophosphamide, vincristine, prednisone, methotrexate, daunomycin, cytosine arabinoside, 6-thioguanine, l-asparaginase, BCNU, hydroxyurea; PROMACE-MOPP, prednisone, methotrexate, adriamycin, cyclophosphamide, VP-16–nitrogen mustard, vincristine, procarbazine, prednisone.
Table 1. Four patients were male, and two were female. Their ages ranged from 8 to 19 years. Three were white, two black, and one of Asian ancestry. Four patients presented with painful nodular skin lesions around the neck, chest, and upper or lower extremities, suggesting clinical diagnoses of insect bite or abscess. Cutaneous nodules developed in the remaining patients soon after their initial presentation of localized, tender lymphadenopathy. In three cases the skin lesions underwent temporary spontaneous regression a few weeks after their initial appearance but reappeared at the same sites shortly thereafter. Three patients received a trial of antibiotics with no response. Three patients had fever, and a fourth patient had night sweats at presentation. In patient 3, who had no systemic symptoms at presentation, high fevers and weight loss developed upon relapse of his disease.

At presentation no patient had a mediastinal mass, hepatosplenomegaly, or symptoms of gastrointestinal obstruction. The bone marrow was not involved, and no abnormal cells were found in the blood. Hemoglobin, WBC count, and \( \gamma \)-globulin levels were within normal limits in all but the sixth patient who had a hemoglobin concentration of 10.2 g and a hematocrit value of 32%. Initial differential diagnoses of pathologists included malignant histiocytosis (four cases), regressing atypical histiocytosis (two cases), Hodgkin’s disease (one case), large-cell (immunoblastic) lymphoma (three cases), squamous carcinoma (one case), or nonmalignant inflammatory disease (two cases). In four of the six cases, treatment was delayed for weeks to months while uncertainty about the initial pathologic diagnosis was resolved. Four patients experienced relapse of their disease shortly after completing therapy. Relapses were noted first in the skin in new and original sites and later in the chest and/or abdomen. Temporary regression of skin lesions in patient 3 and confusion of a large ulcerated skin lesion with radiation necrosis in patient 4 caused delay in recognizing recurrent disease.

Pathology. Lymph nodes showed similar architectural alterations in all cases. Sheets of basophilic or pale-staining tumor cells infiltrated the thymic-dependent paracortical regions and surrounded residual follicles of B lymphocytes (Fig 1). Moderate numbers of plasma cells and some small lymphocytes but no eosinophils or neutrophils were found among the sheets of tumor cells. Occasional diffuse fibrosis but no broad sclerotic bands of collagen were present. Most distinctive was the focal, often massive infiltration of subcapsular sinuses imparting an appearance of metastatic tumor or malignant histiocytosis (Fig 2). A diagnosis of histiocytosis was supported by tumor cell erythrophagocytosis in touch imprints of a lymph node from case 1. Multinucleate Reed-Sternberg or Reed-Sternberg-like cells were sometimes found in a cytoarchitectural milieu that was consistent with Hodgkin’s disease (Fig 3).

In skin, there was no primary infiltration of the epidermis (epidermotropism) and no cells with cerebriform nuclei, making a distinction from mycosis fungoides possible in all cases. The tumor cell infiltrate was confined to the lower reticular dermis in four cases, but in two cases (nos. 4 and 6), the infiltrate was more extensive and involved the entire dermis, destroying skin appendages and focally ulcerating the epidermis (Fig 4). As shown in this Figure, the tumor cells in case 6 consisted of highly atypical mononuclear and multinucleated cells. Bone marrow biopsy specimens were normocellular in all but case 4 in which the marrow was slightly hypercellular. None of the specimens contained fibrosis or evidence of tumor cell infiltration.

Cytochemistry. Four cases were studied cytochemically. In no case was there staining of tumor cells for myeloperoxidase.
Fig 3. Reed-Sternberg or Reed-Sternberg–like cell in cellular environment consistent with Hodgkin’s disease from lymph node of patient 5 (HE; original magnification x 400; current magnification x 300).

dase-, Sudan black B-, or periodic acid–Schiff–positive material. In case 1, most tumor cells contained a slight to moderate number of acid phosphatase–positive granules. In no case did tumor cells show diffuse staining for nonspecific esterases (macrophage pattern), but in case 3, 10% of cells stained focally in a pattern similar to that of mature T lymphocytes.

Immunochemistry. Interpretation of immunoperoxidase stains was facilitated by the focal or compartmental tumor cell infiltration of lymph nodes and dense tumor cell infiltration of skin. Tumor cells from cases 1 through 5 were nonreactive with a panel of monoclonal antibodies directed against surface determinants of macrophage/histiocytes (Table 2). No surface or cytoplasmic immunoglobulin or surface B cell antigens were found. In cases 5 and 6 some or all of the large tumor cells expressed the T cell antigen T11. Moreover, in case 5, there was staining of some tumor cells for the helper T cell antigen T4 although the exact percentage of cells stained was difficult to determine because of some background staining of tissue macrophage/histiocytes. In all cases the large majority of tumor cells expressed the cellular activation antigens HLA-DR (Ia-like), TAC and T9, and the Hodgkin’s disease–associated antigen Ki-1 (Fig 5). However, in contrast to most types of Hodgkin’s disease other than the lymphocyte predominance type, staining of tumor cells for Leu-M1 antigen was negative (weak or equivocal Leu-M1 staining was found in cytocentrifuge preparations of case 1). Also, unlike most forms of Hodgkin’s disease other than the lymphocyte predominance type, staining of tumor cells for common leukocyte antigen T200 was found in all cases.

Rosette studies. In contrast to small normal T cells, the tumor cells in case 1 did not form E rosettes with sheep erythrocytes. Also, in contrast to normal macrophage-histiocytes, the tumor cells in this case did not demonstrate surface receptors for IgG-coated erythrocytes or IgM- and complement-coated erythrocytes and showed no in vitro phagocytosis of these reagents.

Detection of T cell receptor β-chain rearrangement. We detected a unique rearrangement of the constant region Cβ2 in DNA from patient 1. As demonstrated in Fig 6, digestion with EcoRI and hybridization to the T cell receptor β-chain probe revealed only germine fragments. Hybridization of the probe to XbaI digests of the same DNA, however, revealed a third band in addition to the two predicted germline bands. This is consistent with the presence of a monoclonal proliferation of T cells with a unique rearrangement of Cβ2. Similar studies using probes of the immunoglobulin gene loci showed only germline configuration of the DNA, consistent with a non-B cell origin of the tumor cells.

DISCUSSION

The six cases of childhood lymphoma reported here are remarkable for their similar clinical features, histopathology, and immunophenotype of tumor cells. Each patient had rapidly growing skin lesions. Signs of inflammation and temporary regression of skin lesions in three cases suggested a nonneoplastic process, and in two cases a reaction to an insect bite was suspected. Lymphadenopathy was confined initially to peripheral, usually regional, lymph nodes. The usual sites of disease in other childhood lymphomas were not initially affected. At presentation, there was no mediastinal or intra-abdominal mass and no bone marrow or CNS involvement. However, mediastinal and intra-abdominal disease eventually developed in two of our patients and was found at presentation in some other children with Ki-1 lymphoma who had no skin lesions and are not included in this report.

The pathologic diagnosis was difficult in these cases. Because of the unusual histology and the unfamiliarity of most pathologists with this clinicopathologic syndrome, a variety of other diagnoses was reasonably made, including malignant or regressing histiocytosis, squamous carcinoma, Hodgkin’s disease, or inflammation. A similar experience has been recorded for adult lymphomas of this histology and immunophenotype. The distinctive pattern of lymph node sinus and paracortical infiltration by large pleomorphic cells was consistent with malignant histiocytosis or metastatic carcinoma. The presence of Reed-Sternberg or Reed-Stern-
Table 2. Immunologic Results

<table>
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<tr>
<th>Markers</th>
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<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<td></td>
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<td>Activation antigens</td>
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</table>

Abbreviation: NA, not assessed.

berg-like cells was suggestive of Hodgkin's disease. However, the large sheets of tumor cells, lack of reactive cells, and extensive sinus involvement would be unusual for Hodgkin's disease. Ulceration of skin lesions with associated inflammation and temporary regression of skin lesions caused some hesitation about a diagnosis of malignancy.

Immunophenotyping of tumor cells helped to clarify the diagnosis and establish the distinctive character of this disorder. In each case the majority of tumor cells expressed the Hodgkin's disease-associated antigen Ki-1, but unlike most types of Hodgkin's disease, the Reed-Sternberg-like cells in these cases were not reactive with antibody Leu-M1.

A further distinction from Hodgkin's disease was the finding that the tumor cells were positive for common leukocyte antigen T200, an antigen usually not expressed on Reed-Sternberg cells. This also helped to distinguish these cases from metastatic carcinoma or sarcoma, which are negative for common leukocyte antigen. An absence of macrophage-histiocyte antigens, lack of tumor cell rosette formation or phagocytosis of IgG-coated erythrocytes, and lack of diffuse cytoplasmic staining for nonspecific esterase distinguished these cases from malignant or regressing atypical histiocytosis.

The T cell nature of the malignant cells was established by DNA analysis and studies with T cell–specific monoclonal antibodies in three cases. The pattern of cytochemical staining for nonspecific esterase and tumor cell infiltration of thymic-dependent regions of lymph nodes was consistent with a T cell origin for the tumor cells in a fourth case. Similar cytochemical staining can sometimes be observed in certain B cell tumors and interdigitating reticulum cells. However, the tumor cells lacked several B cell antigens, surface and cytoplasmic immunoglobulin, and KiM1, KiM2 antigens, which mark interdigitating reticulum cells. Thus the balance of evidence seems to favor a T cell origin for the majority of our cases as it does in the majority of Ki-1 lymphomas of adults.

In one case (no. 5), the phenotype of tumor cells was
Fig 6. Organization of the human T cell receptor β chain genes is shown in (A). The two constant region genes (Cβ1 and Cβ2) are diagrammed. Southern blot analysis was performed using a BglII-BglII probe from Cβ2 that hybridizes equally to both constant regions. DNA was digested with EcoRI or XbaI. The restriction sites for those enzymes are shown. As illustrated in (B), digestion with EcoRI revealed two hybridizing fragments consistent with a germline configuration of the Cβ1 genes. Digestion with XbaI and hybridization to the probe revealed a third band that was not seen on digests of control DNA, consistent with a monoclonal population of cells with a unique rearrangement of the Cβ2 genes. The germline fragments are marked by dashes.

Further defined as that of an activated helper T cell expressing Ia, Tac, T9, T11, and T4 antigens. The phenotype of activated helper T cells expressing Hodgkin's disease-associated antigens has been reported previously by one of us (M.E.K.) in lymphomatoid papulosis, a chronic, usually self-healing skin eruption seen mainly in adults. However, in contrast to the patients described here who were clinically ill and had rapid development of lymphadenopathy in five of six cases, extracutaneous disease develops slowly in only a small proportion (4% to 20%) of patients with lymphomatoid papulosis. A helper T cell lymphoma involving lymph nodes and skin in five adults was recently reported by van den Oord et al. However, they did not describe the peculiar pattern of lymph node involvement or the unique Ia+, Ki-1+ phenotype of tumor cells observed in our cases. Nevertheless, the skin lesions of their patients were also nodular and non-epidermotropic. Grogan et al also reported nodular skin lesions in six of 11 elderly patients with aggressive peripheral T cell lymphomas. Therefore, our patients may be part of a spectrum of patients of all ages who have a similar disorder.

Stein et al have recently proposed a lymphoid origin for the tumor cells of Hodgkin's disease and certain large-cell lymphomas that resemble malignant histiocytosis. Several of our Ki-1-positive large-cell lymphomas were initially interpreted as malignant histiocytosis or Hodgkin's disease, in part because no T or B cell antigens were detected. However, in one of these cases it was possible to demonstrate an underlying rearrangement of the genes for the β-chain of the T cell receptor. This is evidence supporting the concept that some types of Hodgkin's disease and other large-cell lymphomas that express Ki-1 antigen but lack lymphoid surface antigens may in fact be of T cell origin.

It is therefore possible that some cases previously reported as cutaneous malignant or regressing atypical histiocytosis (RAH) are actually T cell disorders. Our case 1 in which there was temporary regression of skin lesions and tumor cell erythrophagocytosis, both characteristics of RAH, had no lymphoid surface antigens but was proven to be a T cell disorder by gene rearrangement studies (Fig 6). In our case 6 there were other features of RAH such as epitheliomatous epidermal hyperplasia, frequent mitoses, and highly atypical mononuclear and multinucleated cells (Fig 4). The tumor cells of our case 5 had a similar phenotype (expressing OKT11, but negative for Leu-4 (T3), Leu-1, and T4) to that of tumor cells in a case recently reported as cutaneous malignant histiocytosis by Dodd et al.

Thus it seems that these T cell lymphomas of the skin may be related to other extranodal T cell malignancies such as those involving the intestine in patients with celiac sprue that originally were thought to be malignant histiocytosis.
Erythrophagocytic T γ-lymphoma, which initially involves the spleen, is another T cell malignancy resembling malignant histiocytosis. Similar to the present cases, this T cell lymphoma showed a distinctive infiltration of sinuses and paracortical thymic-dependent regions of lymph nodes. Further immunologic and gene rearrangement studies can be expected to better define the broad spectrum of pathology of T cell malignancies. Although the natural history and optimal therapy for this type of lymphoma (Ki-1 lymphoma) have not been defined, several points may be learned from this group of patients. The disease may present with spontaneously regressing skin lesions, causing confusion about a diagnosis of malignancy.

Two patients who received prompt administration of systemic combined drug chemotherapy have had complete remissions sustained for more than 1 year, whereas four patients who received radiation without chemotherapy or had delayed administration of chemotherapy had relapses in less than 6 months. Improved results are anticipated as clinicians and pathologists become more familiar with this disorder, leading to earlier diagnosis and therapy.

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