T-Cell Lymphoma and the Chediak-Higashi Syndrome

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The majority of patients with Chediak-Higashi syndrome (CHS) develop a lymphoproliferative disorder during the accelerated phase of the disease. Controversy exists regarding the benign versus malignant nature of this cellular proliferation. For the first time, we have characterized the immunologic cell markers on the cellular infiltrate in a lymph node from a patient with CHS. The infiltrate was composed almost entirely of T cells, with histopathologic features consistent with a non-Hodgkin's T-cell lymphoma.

The Chediak-Higashi Syndrome (CHS) is a rare, autosomal recessive disorder characterized by ocularcutaneous hypopigmentation, photophobia, and increased susceptibility to infections.1 The pathognomonic feature of this disorder is the presence of abnormally large granules in cells throughout the body, including renal tubular epithelial cells, neurons of the central nervous system, melanocytes, and leukocytes.2 Eighty-five percent of patients with the syndrome develop an accelerated lymphoma-like phase characterized by pancytopenia and a diffuse mononuclear cell infiltrate. This rapidly progressive phase usually leads to death from infection or hemorrhage.3 The nature of the cell infiltrate is controversial; to our knowledge, immunologic phenotyping of the involved cells has not been reported previously. We wish to describe a patient who developed the accelerated phase of the disease in association with a possible T-cell lymphoma.

CASE REPORT

A 3.5-year-old white male was admitted to the University of Utah Medical Center with a 2-wk history of sore throat, marked cervical lymphadenopathy, and fever. The child had a history of recurrent upper respiratory tract infections and occasional minor skin abscesses, but was considered to be otherwise in good health. The nonconsanguineous parents, one brother, and seven half-siblings are in good health.

On admission the febrile child was found to have hypopigmented skin, hair, and irises. Firm, nontender, anterior and posterior bilateral cervical lymph node measured approximately 3-4 cm each. The liver and spleen were both palpable 6 cm below the costal margins. The total peripheral leukocyte count was 9.0 × 10^9/liter with 0.27 × 10^9/liter segmented neutrophils, 8.5 × 10^9/liter lymphocytes, and 0.18 × 10^9/liter monocytes. Large, abnormal granules were present in most granulocytes, and in many lymphocytes and monocytes. The hemoglobin was 10.1 g/dl, and platelet count was 0.083 × 10^9/liter. The peripheral blood smear revealed mild anisocytosis and some target erythrocytes. Abnormal serum chemistry values expressed in international (SI) units included: sodium 130 mmol/liter, potassium 3.9 mmol/liter, calcium 2.1 mmol/liter, phosphorous 1.03 mmol/liter, albumin 31 g/liter, alkaline phosphatase 470 U/liter, lactate dehydrogenase (LDH) 328 U/liter, aspartate aminotransferase (SGOT) 71 U/liter, alanine aminotransferase (SGPT) 46 U/liter, and cholesterol 2.24 mmol/liter. Cytomegalovirus was cultured on the ninth hospital day from urine obtained at admission, but the serologic titer was not elevated. Concentrations of serum immunoglobulins were normal. There were too few granulocytes in the peripheral blood to perform functional assays or tests for cellular cyclic nucleotide levels.

The boy was treated with antibiotics and ascorbic acid (1 g daily). Over the next several days, his condition deteriorated with decreased activity and increased respiratory effort. When a cervical lymph node biopsy obtained on the sixth hospital day revealed a possible T-cell lymphoma, he was started on methotrexate (12 mg intrathecally), prednisone (27 mg orally/day), vincristine (1 mg intravenously/wk), and loparinoz (10 mg/kg/day). The patient became disoriented and somewhat delirious, and on the ninth day of hospitalization he suffered a respiratory arrest and a secondary cardiac arrest. He was quickly resuscitated but remained comatose with seizure activity and decerebrate posturing. A CAT scan of the brain was normal.

Beginning on the tenth hospital day, there was marked diminution and softening of the cervical lymph nodes and a decrease in the size of the liver and spleen. On the thirteenth hospital day the patient appeared septic and died when his blood pressure dropped acutely. Klebsiella, Pseudomonas, and Citrobacter organisms were isolated from blood cultures. A postmortem transcuateous liver biopsy was obtained, but permission for a complete autopsy was refused.

MATERIALS AND METHODS

Peripheral blood smears, a bone marrow aspirate, a right cervical lymph node, and a postmortem transcuateous liver biopsy were available for study. Smears of peripheral blood and marrow obtained on the second day of hospitalization were stained with Wright's periodic acid Shift (PAS), peroxidase, Sudan black B, and nonspecific esterase using α-naphthyl butyrate as substrate (NSE).2

Histopathologic studies were performed on a cervical lymph node biopsy. Imprints were made of the unfixed tissue. Portions of the node were fixed in B5 fixative, buffered formaldehyde, and Karpsak's fixative and processed for light and electron microscopic examination. An additional portion of the unstained tissue was infiltrated through 40-gauge stainless steel wire mesh into RPMI-1640 (M.A. Bioproducts, Walkersville, Md.) culture media. The cell suspension obtained was washed 3 times with RPMI-1640 and incubated for 45 min at 37°C for removal of surface-labile immunglobulins. The cells were again washed, checked for viability by trypan blue exclusion, and adjusted to 3.0 × 10^6 cells/ml.

Commercial nonspecific, aggregate-free, fluorescine-conjugated F(ab')2 fragments of antiserum to human total gamma globulins, αδγμκ, and ο chains (Kallestad Inc., Chaska, Minn.) were

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Fig. 1. Bone marrow aspirate demonstrating abnormal large cytoplasmic granules within granulocytes at various stages of maturation (Wright's stain, x800).

used for detection of surface immunoglobulins (Slg). An indirect immunofluorescent technique with hybridoma monoclonal antibodies was used for the detection of T-cell antigens. Monoclonal antibodies used were: anti-human T cell (HTA, Hybritech Inc., La Jolla, Calif.), OKT1, OKT4, OKT9, and OKT11A (Ortho, Raritan, N.J.). Common ALL antiserum (J5-CALLA) was kindly provided by Dr. J. Ritz, Sidney Farber Cancer Institute. Cells were incubated with sheep red blood cells (SRBC) and examined for spontaneous E-rosette formation. Cytocentrifuge preparations of the E-rosettes were Wright's stained.

Special stains performed on lymph node imprints and cytocentrifuge preparations of the original cell suspension were terminal deoxynucleotidyl transferase (TdT) activity by the fluorescent antibody technique, peroxidase, Sudan black B, acid phosphatase, and nonspecific esterase with α-naphthyl butyrate as substrate (NSE).

Ultrastructural studies were performed on leukocyte suspensions from peripheral blood and portions of the lymph node biopsy.

RESULTS

Light Microscopic Examination

Light microscopy, cytochemical, and electron microscopy studies of leukocytes from peripheral blood and marrow showed the characteristic lysosomal granules as previously described in CHS (Fig. 1). The peripheral blood also revealed a few large (possibly malignant) mononuclear cells with the cytologic features of transformed lymphocytes or immunoblasts (Fig. 2). The bone marrow aspirate showed mild eosinophilia, but no evidence of a lymphoproliferative disorder.

Histologic examination of the lymph node biopsy revealed the normal architecture to be effaced by a diffuse, pleomorphic mononuclear cell infiltrate, with occasional small atrophic follicles remaining in the cortex. The subcapsular sinusoids were compressed. The infiltrate was composed of predominantly medium-sized and large transformed lymphocytes (Figs. 3 and 4). The nuclei were round to ovoid with irregular contours, and prominent nucleoli were seen in the large transformed lymphocytes. Scattered histiocytes and small lymphocytes were also noted. Erythrocytes and nuclear debris were seen in macrophages. The imprints of the lymph node showed intracytoplasmic lysosomes within lymphoid cells identical to those

Fig. 2. Transformed (possibly malignant) lymphocyte in the peripheral blood (Wright's stain ×800).

Fig. 3. Cervical lymph node showing atrophic follicles surrounded by a mononuclear cell infiltrate (hematoxylin and eosin, ×100).

Fig. 4. Lymph node infiltrate, showing medium-sized and large transformed lymphocytes that phenotype as T cells (hematoxylin and eosin, ×400).
observed in lymphocytes in the peripheral blood (Fig. 5).

The postmortem liver biopsy showed fatty metamorphosis and a slight mononuclear cell infiltrate confined to the portal areas.

**Electron Microscopic Examination**

The ultrastructural features observed in blood leukocytes were similar to those that have been previously described in CHS. Large dense lysosomes were observed in the lymphocytes.

The lymph node revealed a mixture of medium and large lymphoid cells that frequently contained irregular nuclear indentations and sparse cytoplasmic organelles. Large dense lysosomes were seen in several lymphoid cells (Fig. 6).

**Immunologic Cell Markers**

Table 1 summarizes the results of the immunologic studies. The diffuse lymph node infiltrate was composed largely of T lymphocytes. Eighty percent of the cells in the suspension made from the lymph node biopsy were viable by trypan blue exclusion. Eighty percent of these medium-sized and large lymphocytes formed E-rosettes with sheep red blood cells. The presence of T cells was confirmed by a variety of T-cell antisera (Table 1). Many of the cells contained characteristic inclusions, as observed in the cytocentrifuge smear preparations (Fig. 7). Tests for surface (SIg) and intracytoplasmic (CIg) immunoglobulin revealed less than 5% positive cells.

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<th>Table 1. Immunologic Marker Data—Cell Suspension From Lymph Node</th>
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Slg, surface immunoglobulin; Clg, intracytoplasmic immunoglobulin; E, sheep erythrocyte rosette; HTA, human T-cell antiserum; OKT1, monoclonal T antiserum (all T cells); OKT4, monoclonal T antiserum (inducer/helper T cells); OKT9, monoclonal antiserum (transferrin receptor); OKT11, monoclonal T antiserum (sheep red cell receptor); CALLA, common ALL antiserum; TdT, terminal deoxynucleotidyl transferase.

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Fig. 5. An imprint from the cervical lymph node showing intracytoplasmic lysosomes, identical to those observed in peripheral blood lymphocytes, present in many of the lymphoid cells (Wright's stain, x800).

Fig. 6. Electron micrograph of cervical lymph node, showing a large dense lysosome present in a lymphoid cell (uranyl acetate, x9075).
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Fig. 7. E-rosettes formed by T cells that also contain large abnormal granules. Cytocentrifuge preparation (Wright's stain, x800).

DISCUSSION

The majority of patients with CHS develop an "accelerated phase of the disease" characterized by a so-called "lymphohistiocytic infiltrate." The nature of this infiltrate is controversial. The infiltrate is reported to be neoplastic when the architecture of the lymphoreticular tissue is obliterated and benign when the architecture is generally preserved. A benign, reactive process has been favored by those who have observed that the infiltrate is composed of a mixed population of lymphoid cells and not a homogeneous population of highly atypical cells. The observation that some patients experience repeated accelerated phases interrupted by periods of remission has been cited as evidence for the nonmalignant nature of the disease. Since it is now appreciated that some lymphomas can be characterized by a mixed cellular infiltrate that may wax and wane in intensity, the nature of the infiltrate in CHS cannot be judged by these criteria alone.

The histopathologic descriptions have often been vague or lacking in many of the previously reported cases, and there have been no recent descriptions using current classification terminology or techniques. We have been able to determine immunologic surface markers on the infiltrating cells in the accelerated phase of the syndrome. Utilizing the standard E-rosette technique and a variety of T-cell antisera, we have demonstrated that the cellular infiltrate in our patient's lymph node was composed almost entirely of T cells. The cells were reactive with the OKT1 monoclonal antibody which reacts with all peripheral T cells, and with OKT11, which detects the sheep red blood cell receptor. The cells failed to react with OKT9, which identifies the transferrin receptor found on early thymocytes. Thirty-eight percent of the cells were phenotyped as probable helper/inducer cells by the OKT4 monoclonal antibody. The OKT5 and OKT8 antisera, which identify the cytotoxic suppressor subset, were not available to more completely phenotype the infiltrate. Thus, we have partially phenotyped the lymph node infiltrate in a patient with CHS and can describe the infiltrate as consisting primarily of T cells in which a percentage belong to the helper subset.

Patients with CHS have a selective defect in antibody-dependent cell-mediated cytotoxicity (ADCC) and a profound defect in their lymphocyte-mediated ability to spontaneously lyse various tumor cells. Normal lymphocyte cytotoxicity is dependent on two T-cell subpopulations. One population demonstrates the cytotoxic effector activity while the other population provides an inducer (helper) function. The OKT4 monoclonal antibody is thought to identify the helper subset of T cells that is responsible for the proliferation of all major lymphocytic subclasses, including T cells involved in lymphocyte-mediated cytotoxicity. The OKT5 and OKT8 monoclonal antibodies identify the cells with killer activity. Thus, phenotyping the cellular infiltrates in CHS patients may be useful in determining whether the defect in cytotoxicity resides in a numerically abnormal or a functionally deficient subpopulation of T cells.

T-cell proliferations are more difficult to characterize as being benign or malignant than B-cell proliferations. This is particularly the case in mixed or large T-cell proliferations. On the basis of the histopathologic examination, we believe that the patient developed a non-Hodgkin's lymphoma. When compared to previously described T-cell lymphomas, the infiltrate in our patient histologically resembled a recently described node-based T-cell lymphoma or immunoblastic sarcoma of T cells. We cannot be certain, however, that the infiltrate does not represent an abnormal immune reaction of the T-cell type.

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