Leukopenic Chronic T Cell Leukemia Mimicking Hairy Cell Leukemia: Association With Human Retroviruses


We report two cases of a T cell lymphoproliferative disease not previously described, with cytologic and clinical features similar to those associated with Galton’s “prolymphocytic” leukemia (PL). Our patients, like those with Galton’s PL, had massive splenomegaly and minimal or absent hepatomegaly and lymphadenopathy. In contrast, however, our patients had leukopenia, as well as low percentages of leukemic cells in the peripheral blood and in the bone marrow. In splenic imprints, the nuclear chromatin pattern of most of the leukemic cells was intermediate between those of mature lymphocytes and those of lymphoblasts, and the nuclei contained single, centrally located, conspicuous nucleoli. In sections of the spleen, the leukemic cells diffusely infiltrated the red pulp in a pattern strikingly similar to that of hairy cell leukemia; however, when the leukemic cells were studied cytochemically, the cytoplasmic acid phosphatase positivity was punctate and absent.

The leukemic cells were sheep erythrocyte rosette-positive and expressed T cell-associated antigens. Initially, both patients responded well to therapeutic splenectomy. One patient received combination chemotherapy after splenectomy and is alive and well 24 months after diagnosis. The other patient was in complete clinical remission for one year after splenectomy and received chemotherapy at relapse. He died, however, 23 months after splenectomy, with disseminated disease. IgG antibody titers against human T lymphotropic virus type I (HTLV-I) were detected in one patient and against HTLV-II in the other. The leukemia in these patients represents a distinct clinicopathologic entity within the spectrum of peripheral T cell lymphoproliferative diseases that includes Galton’s PL of T cell derivation, T cell chronic lymphocytic leukemia, T cell hairy cell leukemia, and adult T cell leukemia/lymphoma.

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THE CLINICOPATHOLOGIC and immunophenotypic heterogeneity of T cell malignancies is reflected in the growing list of T cell lymphoproliferative diseases that includes chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), adult T cell leukemia/lymphoma (ATL), and peripheral T cell lymphoma.** as well as mycosis fungoides/Sézary syndrome, and acute lymphoblastic leukemia/lymphoma.** Even within T cell CLL (T-CLL), several immunophenotypic and/or morphologic subtypes have been recognized, one of which is the so-called T cell “prolymphocytic” leukemia (PL).**

Galton et al initially described PL as a distinct clinicopathologic variant of CLL characterized by marked lymphocytosis, massive splenomegaly, lesser hepatomegaly, and minimal or absent lymphadenopathy. Although most PLs have been shown to be of B cell derivation, even within T cell CLL (T-CLL), several immunophenotypic and/or morphologic subtypes have been recognized, one of which is the so-called T cell “prolymphocytic” leukemia (PL).**

**"Prolymphocytic" leukemia as described by Galton et al is a rare variant of CLL and differs from the prolymphocytic variant of acute lymphoblastic leukemia that has been described by one of us (G.M.). We agree with Huhn that the term prolymphocytic as applied to Galton’s PL does not reflect our current knowledge about the stage of differentiation of the leukemic cells but, in accordance with the numerous existing reports on Galton’s PL and for the sake of convenience, we will use the designation PL for the disease described by Galton.

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Morphologic Studies

Tissue for light microscopy was fixed in Bouin’s solution in case 1 and in 10% buffered formalin in case 2, embedded in paraffin, and stained with hematoxylin and eosin. Touch imprints were available from the spleen in case 1 and from the spleen and splenic lymph nodes in case 2. The touch imprints as well as the blood and bone marrow smears were stained with May-Grünwald Giemsa.

Cytochemical Studies

Stains for acid phosphatase and for tartrate-resistant acid phosphatase were done on splenic imprints in case 1 and on blood smears in case 2. The a-naphthyl acetate esterase (ANAE) stain was done on blood smears in both cases. The cytochemical studies were carried out according to methods described previously.

Immunologic Studies

The preparation of cell suspensions from solid tissues, the separation of mononuclear cells by Ficoll-Hypaque density gradient centrifugation, and the immunologic study of the cell suspension samples were carried out as previously described. Neuraminidase-treated fresh sheep erythrocytes were used for the quantitation of spontaneous sheep erythrocyte rosette (sER) formation.

Cell suspensions were prepared from the spleen in case 1 and from the peripheral blood in case 2. In case 1, Leu-4 (Becton Dickinson, Sunnyvale, Calif) and T4 and T8 (Coulter Immunology, Hialeah, Fla) were used as T cell markers, and rhodamine-conjugated F(ab’)2 fragments to human γ, α, μ, κ, and Λ chains (Kallestad Laboratories, Austin, Tex) were used for the study of surface immunoglobulins. In case 2, T11 (Coulter Immunology) was the pan-T cell marker, and γ, α, μ, δ, κ, and Λ immunosorbed F(ab’)2 goat anti-human immunoglobulins labeled with fluorescein isothiocyanate (FITC) (Tago, Burlingame, Calif) were used for detection of surface immunoglobulins. In case 2, the peripheral blood lymphoid cells were also studied by a reference laboratory (Speciality Laboratories, Inc, Los Angeles) which used OKT4 and OKT8 (Ortho Diagnostics, Raritan, NJ) as T cell markers according to standard procedures. Terminal deoxynucleotidyl transferase (TdT) activity was determined with an indirect immunofluorescence method as previously described.

Serologic study for human T cell lymphotropic virus (HTLV)

Serum samples were collected, frozen, and later tested for antibodies to the HTLV by an enzyme-linked immunosorbent assay (ELISA) developed at Cytotech, Inc, San Diego, Calif. HTLV-I was harvested from the supernatant of a cell line producing this variant (C10/MJ2, provided by Dr R. C. Gallo), HTLV-II was harvested from the 344 cell line (provided by Drs R. C. Gallo and M. Popovic), and HTLV-III was harvested from a HUT 78 cell line transfected with this virus (HUT 78/013LK). Virus-producing cells were pelleted by centrifugation, and extracellular virus was concentrated. After fractionation, the purified virus was suspended in phosphate-buffered saline (PBS) and pelleted. Donor serum was diluted to 1:100 for assay. Goat anti-human IgG conjugated to glucose oxidase was used as a labeling antibody and was counterstained. The development of a green hue was determined as 0.405 nm in a Multiscan (Flow Laboratories, McLean, Va) automated spectrophotometer after exactly 30 minutes of incubation. Specimens were scored as positive if absorbance was 1.8 times that of a standard negative control sample for HTLV-II and 3.0 for HTLV-I and HTLV-III. Western blot analysis for HTLV-I and HTLV-III was performed as previously described.

Case reports

Case 1. A 42-year-old white woman from Sicily was referred to the Hôpital Universitaire Paul-Brousse, Villejuif, France, with asthenia, low-grade fever, and a two-month history of a rapidly growing abdominal mass in the left upper quadrant. The spleen was palpable 10 cm below the left costal margin, and the liver was palpable 5 cm below the right costal margin. The patient had minimal cervical and inguinal lymphadenopathy. Peripheral blood studies revealed a WBC count of 1.9 x 109/L with a differential count of 32% lymphocytes, 10% lymphoid cells with single conspicuous nuclei (Fig 1a), 44% bands and neutrophils, 3% metamyelocytes, 2% eosinophils, and 9% monocytes. The Hb level was 7.2 g/dL, and the platelet count was 112 x 109/L. The bone marrow biopsy specimen was hypercellular and partially infiltrated by lymphoid cells. The bone marrow aspirate smear had originally been reported to contain 30% lymphoblasts. On review, most of these cells were interpreted as having the appearance of Galton’s prolymphocytes. At splenectomy, the spleen was found to be grossly enlarged and involved by a leukemic process (Fig 2a) characterized, on touch imprints, by atypical lymphoid cells, the nuclei of which had single conspicuous nuclei (Fig 2b). The liver biopsy specimen showed involvement by leukemia (Fig 3).

After splenectomy, the patient’s WBC count slowly increased to 12 x 109/L, accompanied by an increase in the percentage of leukemic cells. There was also a transient increase in the percentage of normal-appearing monocytes. The post-splenectomy bone marrow specimen showed diffuse lymphoid leukemic infiltrations (Fig 4). The patient was treated with prednisone, vincristine, t-asparaginase, and doxorubicin, followed by maintenance therapy with 6-mercaptopurine, methotrexate, and vindesine, and by intensification therapy every three months. The agents used for intensification therapy were doxorubicin and vincristine, with either cyclophosphamide or cytosine arabinoside given alternately in successive intensification.
HUMAN RETROVIRUS ASSOCIATED LEUKOPENIC T CELL

Fig 2. (A) Spleen, case 1. Red pulp showing diffuse invasion of cords and sinuses by the abnormal lymphoid cells. The abundant clear cytoplasm of many of the cells mimics the appearance of hairy cells. Hematoxylin and eosin stain. (Magnification x 340.) (B) Splenic imprints exhibiting the characteristic features of the leukemic cells. The atypical lymphoid cells are characterized by a relatively abundant cytoplasm, irregular nuclear contours, distinct nucleoli, and, in most cells, a chromatin pattern intermediate between that of lymphoblasts and that of mature lymphocytes. May-Grünewald Giemsa stain. (Original magnification x 1360; current magnification x 884.)

Fig 3. Liver biopsy, case 1. showing diffuse infiltration and distention of the liver sinusoids by abnormal lymphoid cells. This leukemic pattern closely resembles that observed in hairy cell leukemia. Hematoxylin and eosin. (Magnification x 340.)

splenic hilar lymph node, and liver biopsy specimens showed leukemic involvement. After splenectomy, the WBC count, Hb level, and platelet count returned to normal, although leukemic cells persisted in the peripheral blood. The patient was followed at monthly intervals and remained clinically well for one year.

Twelve months after splenectomy, the patient had a sudden, steady increase in the number of circulating leukemic cells. Biopsy specimens of bone marrow and axillary lymph nodes contained extensive leukemic infiltrates (Fig 5). Monthly five-day courses of

courses. The patient has remained clinically well for 24 months, although a few leukemic cells have persisted in the peripheral blood.

Case 2. A 48-year-old black American man from Los Angeles had pancytopenia and splenomegaly at diagnosis. The spleen was palpable 10 cm below the left costal margin; there was no appreciable hepatomegaly or peripheral lymphadenopathy. The patient’s peripheral blood showed a WBC count of 1.2 × 10^9/L, an Hb level of 9.2 g/dL, and a platelet count of 78 × 10^9/L. The WBC differential count showed 60% lymphocytes, including “abnormal lymphocytes” (Fig 1b), 16% neutrophils, 5% bands, 1% eosinophils, and 18% monocytes. The slightly hypercellular bone marrow biopsy specimen showed no detectable leukemic infiltration, but 8% of the cells in the bone marrow aspirate smear were lymphoid cells of intermediate size with single conspicuous nucleoli. At splenectomy, the spleen was found to be massively enlarged. Microscopic evaluation of spleen,
chlorambucil and dexamethasone were begun when the WBC count reached 52.5 x 10^9/L, with almost exclusively leukemic cells; this therapy controlled but did not eradicate the leukemic cells in the peripheral blood. Five months later, the patient was again found to have an increase in the number of peripheral blood leukemic cells as well as hepatomegaly. The chemotherapy was changed to monthly cycles of cyclophosphamide, vincristine, procarbazine, and prednisone. Over the next three months, the patient’s WBC count varied from 2.8 to 9.1 x 10^9/L, with 2% to 34% leukemic cells. The patient died of disseminated leukemia 23 months after clinical presentation. A postmortem examination was authorized and performed.

The clinical and antemortem pathologic findings in both cases are summarized in Table 1.

RESULTS

Morphologic Findings

Peripheral blood. The leukemic cells from both patients were atypical lymphocytes with relatively abundant cytoplasm. The nuclei had round to oval contours, often with one and sometimes two deep indentations. The chromatin pattern was of intermediate coarseness; usually, there was a single conspicuous nucleolus (Fig 1a and b). In case 1, the cytoplasm of many of the leukemic cells contained several azure granules (Fig 1a). No cytoplasmic granules were identified in the leukemic cells of case 2 (Fig 1b). After splenectomy, the presence of leukemic cells in the peripheral blood was more obvious because the number of circulating leukemic cells increased as the disease progressed.

Bone marrow. In case 1, the core biopsy specimen obtained prior to splenectomy showed hypercellular marrow, with persistent erythroid and megakaryocytic foci, partially infiltrated by mononuclear cells in a pattern resembling that of HCL. The aspirate smear contained 30% atypical lymphoid cells with the same appearance as that of the leukemic cells in the peripheral blood. In case 2, there was no detectable leukemic infiltration in the initial core biopsy. The aspirate smear in this case showed only 8% leukemic cells.

In the postsplenectomy bone marrow biopsy specimens from both patients, more prominent, diffuse leukemic infiltration was evident. The lymphoid cells showed variations in nuclear size and shape and had irregular nuclear outlines (Fig 4).

Spleen. The spleens in cases 1 and 2 weighed 2,460 and 2,394 g, respectively. The cut surfaces were homogeneous and free of tumor nodules; Malpighian corpuscles were not grossly visible.

In microscopic sections, the leukemic cells filled the red-pulp cords and sinuses and encroached on or obliterated the white pulp; the pattern of involvement was strikingly similar to that in HCL (Fig 2a). The leukemic cells were of medium size and had round to oval nuclei. In routine histologic sections, the chromatin appeared less heavily clumped than in the lymphocytes of CLL. The nucleolus was often difficult to identify except when cells were examined under oil immersion. Irregularities in the nuclear contours, including deep indentations, were noted in a few of the cells. In touch imprints prepared from the spleens, the moderately coarse chromatin pattern, the single centrally located nucleolus, and the moderate to abundant pale-blue cytoplasm were clearly evident (Fig 2b).

Liver. Liver biopsy specimens from both patients contained mononuclear cell infiltrates in the sinusoids and portal areas. The pattern of infiltration, although nonspecific, resembled that of HCL (Fig 3). In the histologic sections, the cytologic features of the leukemic cells were not clearly apparent. The leukemia could not have been classified by the sections of the liver biopsies alone.

Lymph nodes. In case 2, splenic hilar lymph nodes obtained at the time of splenectomy contained leukemic infiltrates in the paracortical and medullary areas. Scattered atypical cells were identified in distended sinuses. The lymph nodes were initially interpreted as being reactive but, with the aid of the lymph node touch imprints which showed clusters of cells having single conspicuous nucleoli, they were reinterpreted as containing focal leukemic infiltrates. Focal plasma cell infiltration was also present. In the axillary lymph nodes in case 2, biopsied one year after splenectomy, sheets of leukemic cells expanded the paracortical areas and filled the sinuses (Fig 5).

Table 1. Clinical Findings

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age/Sex</th>
<th>Splen (g)</th>
<th>Liver</th>
<th>Lymph Nodes</th>
<th>Leukemic Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42 F</td>
<td>2,460</td>
<td>5 cm*</td>
<td>Minimal cervical and inguinal adenopathy</td>
<td>Partially infiltrated</td>
</tr>
<tr>
<td>2</td>
<td>48 M</td>
<td>2,394</td>
<td>Not enlarged</td>
<td>Not detected</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Below right costal margin.
Postmortem examination. In Case 2, an autopsy was performed, revealing marked hepatomegaly (3,600 g) as well as moderate lymphadenopathy involving the mediastinum and the porta hepatitis. Histologically, the liver contained extensive mononuclear cell infiltrates in the sinusoids and portal tracts. The lymph nodes and bone marrow were massively and diffusely involved by leukemia, whereas scattered leukemic cells were found within the interstitial tissues of the kidneys.

Immunologic and Cytochemical Findings

In case 1, immunologic studies of the cell suspensions prepared from the spleen indicated that the predominant lymphoid cell population expressed an immunophenotype consistent with that of suppressor T cells (Table 2). The majority of the cells were sER+, Leu-4+, T4+, T8+. Three percent of the cells were surface immunoglobulin (sIg) positive and had a polyclonal distribution. In case 2, the peripheral blood lymphoid cells studied at the time of lymphocytosis (one year after splenectomy) were sER+, T11+. They were TdT- Six percent were sIg-; these cells also had a polyclonal distribution. The lymphoid cells in a presplenectomy peripheral blood specimen studied by a reference laboratory were reported as OKT4+, OKT8-.

In both cases, the acid phosphatase stain resulted in paranuclear granular cytoplasmic positivity which was trarerate-sensitive and often punctate in appearance. The ANAE stain also resulted in punctate, paranuclear cytoplasmic positivity, which was not diminished by sodium fluoride treatment.

Serologic Study for HTLV

Frozen serum from case 1 contained IgG antibodies to HTLV-I. The ratio of absorbance of patient serum to that of standard negative control serum was 8.4. Western blot analysis of this patient’s serum was positive against HTLV-I target. Furthermore, the ratio of the HTLV-III target was 11.8, but no HTLV-III proteins were detected in the western blot system. The ELISA assay for HTLV-II was negative. Serum from case 2, obtained shortly before the patient’s death, was positive for HTLV-II, with an absorbance ratio of 1.9. This specimen was negative in the ELISA assays for HTLV-I (ratio 0.9) and HTLV-III (ratio 0.96). The specimen from case 2 was also negative for HTLV-I and HTLV-III on western blot analysis.

Table 2. Hematologic, Cytochemical, and Immunologic Findings at Diagnosis

<table>
<thead>
<tr>
<th>Case</th>
<th>WBC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Hemoglobin (g/dL)</th>
<th>Peripheral Blood (%)</th>
<th>Cytochemistry</th>
<th>Immunologic Markers (%)</th>
<th>Western Blot</th>
<th>ELISA HTLV</th>
<th>HTLV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphocytes</td>
<td>AcP/TRAP</td>
<td>sER</td>
<td>HLA</td>
<td>HTLV</td>
<td>HTLV</td>
</tr>
<tr>
<td>1</td>
<td>1.9</td>
<td>112</td>
<td>7.2</td>
<td>32</td>
<td>+/-</td>
<td>65</td>
<td>92 (Leu4)</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td>4 (T4)</td>
<td>80 (T8)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>78</td>
<td>9.2</td>
<td>60</td>
<td>weak +/-</td>
<td>67</td>
<td>93 (T11)</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

An unspecified percentage of abnormal lymphocytes was noted in the initial peripheral blood smear, which was not available for review.

AcP, acid phosphatase; TRAP, tartrate-resistant AcP; +, positive; -, negative; sER, spontaneous rosettes with sheep erythrocytes; sIg, surface immunoglobulin; ELISA, enzyme-linked immunoabsorbent assay.

DISCUSSION

Recent advances in immunologic techniques and the use of multidisciplinary approaches have greatly facilitated not only the identification of T cell lymphoproliferative disorders, but also the study of the state of differentiation of the neoplastic cells. Such studies have supported the assumption that chronic T cell leukemias, including Galton’s PL, T cell type, are in fact derived from postthymic T cells.
tients with this type of HCL generally did not have massive splenomegaly, but they tended to have marked bone marrow and lymph node involvement when first examined. The patients reported as having T-HCL or T- and B-HCL tended to have relatively slow clinical progressions.7,8,10

Only after splenectomy did our patients develop increases in the number of circulating leukemic cells and more extensive bone marrow involvement. At this stage of the disease, the morphologic and clinical findings were indistinguishable from those in Galton’s PL. The patient who was treated with splenectomy and combination chemotherapy is clinically well 24 months after diagnosis, despite the persistence of a few circulating leukemic cells. The patient who was initially treated with splenectomy alone had a clinical remission for one year, but died nine months later with progressive disease. Treatment after relapse with chlorambucil and dexamethasone and then with cyclophosphamide, vincristine, procarbazine, and prednisone was not successful in controlling the disease.

No significant superficial lymph node enlargement was clinically evident at the outset. Minimal involvement of the splenic lymph nodes was noted in case 2 at the time of splenectomy. Enlarged axillary lymph nodes removed one year after splenectomy revealed incomplete involvement of the nodes, with a paracortical pattern of infiltration. This pattern was consistent with the T cell derivation of the neoplastic cells, but it may also be observed in HCL.

Our two cases expand the spectrum of lymphoproliferative diseases associated with various HTLV, which constitute a family of human RNA tumor viruses with T cell tropism.57 HTLV-I, antibodies to which were found in our case 1, is associated with ATL,58 usually involves phenotypic helper T cells, and is characterized clinically by skin lesions, lymphadenopathy, hepatosplenomegaly, hypercalcemia, and an aggressive clinical course.11,59 In our case 1, however, the malignant cells expressed a T suppressor phenotype and clinically resembled an “aleukemic” form of lymphocytic leukemia rather than the ATL syndrome. The serologic cross-reactivity with HTLV-III seen in case 1 (i.e., ELISA positive, but negative in the western blot) is a recognized phenomenon.60

HTLV-II, antibodies to which were found in our case 2, is distinct from HTLV-I, based on serologic and molecular parameters, and has previously been reported in only one unusual case of T-HCL.7,61 In contrast, our case 2, although resembling HCL with respect to its clinical presentation and to the patterns of distribution of the leukemic cells in the spleen, liver, and lymph nodes, was, in fact, a variant of chronic T cell lymphocytic leukemia in which the proliferating cells differed both morphologically and cytochemically from hairy cells.

That two clinically and pathologically similar cases were associated with antibodies against different variants of HTLV is of interest, although the significance is not clear, since the presence of these antibodies does not necessarily mean that HTLV is causally related to the evolution of the leukemia reported in our two patients. The presence of these antibodies may merely indicate coincidental infection or immunologic cross-reactivity with a previously unrecognized member of the HTLV group of viruses. Tissues involved by the leukemia were not available from our two patients for molecular or virologic studies (one patient died after the association was recognized and the other patient remains in remission). New cases of leukopenic T-PL that are identified clinically or histopathologically should be studied for evidence of HTLV-I and HTLV-II, so that the spectrum of virus-associated lymphoproliferative diseases may be defined further.

In summary, we have identified two cases of leukopenic chronic T cell leukemia with massive splenomegaly in which the leukemic cells resembled Galton’s proymphocytes. This leukemia can be differentiated from T-PLL and T-HCL on the basis of its distinctive cellular morphology. It also differs from classical T-PLL by virtue of the leukopenia that is present before splenectomy. One patient (case 2) who was treated with splenectomy, died 23 months after clinical onset despite the subsequent addition of increasingly more aggressive chemotherapy. The other patient (case 1), treated with splenectomy and combination chemotherapy, is alive and clinically well after 24 months. These observations suggest the possible importance of early recognition of this distinctive leukopenic form of T cell leukemia, which, in contrast to HCL, appears to have an aggressive course similar to that in Galton’s PL.

ADDENDUM

Since submission of our manuscript, three additional cases of HTLV-I-associated chronic lymphocytic leukemia have been reported,62 although they were not leukopenic. Like our case 1, the patients were from Italy and, along with our case 1, confirm the widespread nature of HTLV-I-associated disease. These cases also suggest that Italy, particularly southern Italy, may be an endemic area for HTLV-I. Furthermore, our case 2, a black man from Los Angeles who had HTLV-II antibodies, was born and lived in the same general area as the first reported case of HCL from which HTLV-II was isolated.63 A second such case was more recently reported by the same group of observers,63 raising the possibility that HTLV-II-associated T cell lymphoproliferative disease may be endemic in the Los Angeles area.

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