CD11c (LEU-M5) Expression Characterizes a B-Cell Chronic Lymphoproliferative Disorder With Features of Both Chronic Lymphocytic Leukemia and Hairy Cell Leukemia

By Curtis A. Hanson, Thomas E. Gribbin, Bertram Schnitzer, June A. Schlegelmilch, Beverly S. Mitchell, and Lloyd M. Stoolman

Chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL) are two common chronic lymphoproliferative disorders, each having characteristic clinical, morphologic, and immunologic features. Phenotypically, CD5 reactivity in CLL and CD11c (Leu-M5) reactivity in HCL have characterized these two leukemias among B-cell disorders. In this study, we report 14 cases of a novel chronic lymphoproliferative disorder characterized by lymphocytosis and CD11c expression, but morphologically similar to CLL. The patients’ ages ranged from 46 to 81 years (median 62). Eleven had palpable splenomegaly, five with markedly enlarged spleens; only one patient had generalized lymphadenopathy. The white blood cell count ranged from 5.2 to 131 × 10^9/L (median 20.8). The morphologic diagnosis in all cases was CLL, with the cells usually having abundant cytoplasm. No morphologic features of hairy cells were evident; tartrate-resistant acid phosphatase cytochemistry was negative in all cases. Bone marrow biopsies were available in 8 of 14. Four showed focal nodular infiltrates and two had diffuse infiltrates similar to CLL; two showed only minimal interstitial involvement. All cases expressed multiple B-cell markers, and 12 of 14 had monoclonal surface immunoglobulin. The leukemic cells of all cases strongly expressed CD11c, while CD5 was expressed in 7 of 14; only 1 of the 14 cases expressed the lymph node homing receptor, Leu-8. This unique group of leukemias appears to represent the malignant transformation of lymphocytes arising from a stage of lymphocyte differentiation between that found in typical cases of CLL and that of HCL. CD11c is known to have an important function in cellular adhesion and may be important in determining the pattern of lymphocyte tissue distribution found in this group of patients.

Delineation of sequential stages of B-lymphocyte development provides a framework for classifying B-cell malignancies according to phenotypic maturity. While malignancies frequently show aberrant phenotypic characteristics, one can usually assign an approximate developmental stage by quantifying expression of stage-restricted antigens. In general, chronic lymphocytic leukaemias (CLL) resemble virgin B lymphocytes, expressing the CD5 antigen and low-density surface immunoglobulin (Ig). In contrast, the normal B-cell equivalent of hairy cell leukemia (HCL) appears to be at a later stage of B-cell development, expressing strong surface Igs and lacking expression of CD5. Anderson et al. have contended that HCL represents a stage of B-cell differentiation very close to plasma cells with expression of antigens characteristic of late B-cell differentiation, such as PCA-1. CD25, the interleukin-2 (IL-2) receptor, and CD11c (Leu-M5) have most recently been shown to play a role in B-cell function and may have important diagnostic implications.

The CD11c antigen is a member of the diverse family of heterodimeric intercellular and cell-adhesion receptors termed integrins. Several subfamilies exist, each distinguished by a common β chain. A series of structurally related α chains noncovalently linked to the common β chain constitute the members of each family. The CD11c antigen is one of three α chains comprising the leukocyte-restricted β2 (CD18) subfamily. The complete group of adhesion receptors in this family are designated CD11a/CD18 (LFA-1), CD11b/CD18 (OKM1, Mo-1, MAC-1, Leu-15), and CD11c/CD18 (p150,95 and Leu-M5). The CD11c/CD18 complex is found normally on tissue macrophages, monocytes, and some cytotoxic T cells, and appears to be a necessary molecule for cell-cell and cell-surface adhesion and interaction.

This report describes a group of patients with chronic lymphoproliferative disorders intermediate between CLL and HCL. Cytologic, cytochemical, and surface marker characteristics, with the exception of CD11c and Leu-8 expression, were typical of CLL. In contrast, these patients had prominent splenomegaly without lymphadenopathy and frequently only a mild lymphocytosis, features more consistent with HCL. In addition, these findings suggest that the CD11c/CD18 receptor and Leu-8 antigen may help define the pattern of tissue involvement in chronic lymphoproliferative disorders.

MATERIALS AND METHODS

The 14 cases described in this study were analyzed in the Clinical Hematology and Flow Cytometry Laboratories at the University of Michigan Hospital (Ann Arbor). In all cases, peripheral blood smears were obtained for morphologic evaluation. Eight cases had bone marrow aspirates and bone marrow trephine sections available for review. Nine patients were seen at the University of Michigan Hospital; five cases were referred for morphologic and immunologic

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evaluated. Twelve cases were studied at the time of initial presentation of disease.

Peripheral blood and bone marrow aspirate smears were evaluated after Wright's stain; an exhaustive search for cells having morphologic features of hairy cells was performed in each case. Bone marrow trephine biopsy specimens were fixed in B-5 and processed each case on blood and/or bone marrow smears, according to routine methods. Cytochemical stains for acid phosphatase and tartrate-resistant acid phosphatase (TRAP) were also performed in each case and/or bone marrow smears, according to previously described methods.25

Immunophenotypic analysis was performed by flow cytometry in each case: 10 with peripheral blood only, 1 with bone marrow aspirate only, and 3 with both peripheral blood and bone marrow aspirate material. Mononuclear cells were isolated from heparinized peripheral blood and/or bone marrow specimens by standard Ficoll-Hypaque density gradient centrifugation. An indirect immunofluorescence procedure was used, and the cells were separated into subpopulations based on light scatter characteristics using an Epics V flow cytometer (Coulter Corp, Hialeah, FL); 5,000 to 10,000 cells were analyzed for each monoclonal antibody (MoAb) used.26 The actual percentage of cells positive for each marker was calculated by subtraction of background and nonspecific labeling with an Ig-type specific mouse MoAb (IMMUNO, Coulter).

Surface immunophenotyping used a wide panel of lymphoid MoAbs. B-cell-associated MoAbs included: CD19 (B4); CD20 (B1); CD21 (B2); CD22 (Leu-14); CD24 (BA-1); PCA-1; and anti-surface Ig heavy and light chains.12 T-cell-associated MoAbs included: CD2 (T11); CD3 (T3); CD4 (T4); CD5 (Leu-1); CD7 (Leu-9); and CD8 (T8).12 Other MoAbs used included: CD10 (J5); CD11b (Leu-11); CD11c (Leu-M5); CD14 (My4); CD25 (IL-2R); CD38 (T10); Leu-8; and HLA-DR.2

RESULTS

Clinical and Laboratory Findings

The major clinical and laboratory findings are summarized in Table 1. Nine of the patients were men and five were women, with ages ranging from 46 to 81 years (median 62 years). Ten patients presented with the constitutional symptom of fatigue. Lymphadenopathy was an uncommon feature, with only one case (case 6) exhibiting generalized lymphadenopathy; case 9 had small localized lymph nodes palpable on physical examination, and case 1 had enlarged abdominal nodes identified by computed tomography scan only. Lymph node biopsies obtained from two of the patients (cases 3 and 8) showed reactive hyperplasia with no evidence of malignancy. Lymphadenopathy has not progressed in any of the patients during the course of disease. In contrast, splenomegaly was present in 11 of 14 patients on examination and was massive in 5 (cases 8, 9, 10, 11, and 14). One patient (case 8) underwent splenectomy after failing to respond to chemotherapy; the spleen showed extensive white pulp infiltration in contrast to the red pulp pattern of involvement characteristic of HCL.

Leukocytosis was present in 10 patients, with the white blood cell count (WBC) ranging from 5.2 to 131.0 x 10^9/L. An absolute lymphocytosis was present in 13 of the 14 patients with total lymphocyte counts ranging from 3.8 to 125.0 x 10^9/L. Cytopenias including mild anemia and mild to severe thrombocytopenia were present in 10 of the 14 patients. An IgM monoclonal protein was present in one of five individuals tested. Two of seven patients had a positive direct Coomb's test, without evidence of hemolysis. Serum lactic acid dehydrogenase (LDH) was minimally elevated in 5 of 11 patients (300 to 450 IU/L) and markedly elevated (2,325 IU/L) in only one patient.

Three patients underwent treatment. Patient 3 received chlorambucil/prednisone with no improvement in symptoms. Only a partial response was achieved in patient 6, who received cytoxan, vincristine, and prednisone. Patient 8 had an incomplete response to splenectomy and subsequently received velban, prednisone, and α-interferon without achieving any clinical response. Subsequent therapy with pentostatin in this latter patient did yield a partial response.

Table 1. Clinical and Laboratory Findings

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<th>ALC‡ (10^9/L)</th>
<th>Hgb‡ (g/dL)</th>
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Median (m) = 62/1 M:F = 8:5 11/14 m = 20.8 m = 17.9 (2/14 < 11) (8/14 < 180)

†Age of onset/duration of disease in years.
‡Symptoms at presentation (A, asymptomatic; F, fatigue; S, symptomatic splenomegaly).
§ND, no bone marrow studies performed; D, diffuse; F, focal; I, interstitial.

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Morphologic Features

Peripheral blood. Examination of the peripheral blood in each case showed varying degrees of lymphocytosis. The lymphocytes were quite homogeneous in appearance within each individual case and had cytologic features of CLL. The cells were intermediate in size, although some small lymphoid cells could be identified in each case. The nuclei were round to oval, having coarsely clumped chromatin; nucleoli were faint and inconspicuous in all cases. In all but three cases the cytoplasm was quite abundant (Fig 1). The cytoplasm appeared slightly basophilic in seven of the cases, but no plasmacytoid differentiation was cytologically evident. Exhaustive morphologic analysis showed no cytoplasmic projections or scalloped borders characteristic of HCL (Fig 1). No cytoplasmic granules or vacuoles were seen.

Bone marrow aspirate. Bone marrow aspirates showed a lymphocytosis in five of eight cases studied, ranging from 20% to 95%; only a minimal increase in lymphocytes was seen in two cases, accounting for 5% and 7% of the nucleated bone marrow cells. The lymphoid cells in the bone marrow were identical in appearance to those described in the peripheral blood, being round to oval in appearance and intermediate in size. The lymphocytes had coarse chromatin and typically abundant cytoplasm. No cytoplasmic or nuclear features of HCL were seen in any of the eight bone marrow aspirates. The bone marrows were easily aspirated in all patients.

Bone marrow trephine sections. The cellularity of the bone marrow trephine sections ranged from hypercellular in five cases to normocellular in three cases. The leukemic cell infiltrate diffusely involved the bone marrow with almost complete replacement of the normal myeloid elements in two cases (Fig 2). The four remaining hypercellular bone marrows and one of the normocellular bone marrows showed a mixed interstitial and a focal, nodular, non-paratrabecular pattern of infiltration (Fig 3). The leukemic cells were closely packed with poorly discernible cytoplasmic borders, features typical of CLL. Widely spaced cells, characteristic of HCL, were not a feature in any of these cases. The remaining two cases had a sparse interstitial infiltrate that was difficult to appreciate morphologically. The nuclear features of the leukemic cells were quite uniform, with most having nuclei that were round to only slightly angulated in appearance; rare irregular, clefted, or convoluted cells were seen. The nuclear chromatin was coarse; nucleoli were small and inconspicuous, with only rare cells having prominent central nucleoli. Mitotic figures were extremely rare and were identified in only two cases. Plasmacytoid differentiation was not seen, with only rare scattered perivascular plasma cells evident. Vascularity was not a prominent feature. Reticulin stain showed no reticulum fibrosis in any of the eight cases.

Cytochemical Staining

Acid phosphatase cytochemical staining was performed on peripheral blood and/or bone marrow aspirate material in each case with and without tartrate inhibition. No staining of the lymphoid cells was present in any of the 14 cases, either with acid phosphatase alone or with the addition of tartrate.

Flow Cytometric Immunophenotyping

Results from flow cytometric immunophenotyping are summarized in Tables 2 and 3. Immunophenotyping from 12 of 14 cases showed a monoclonal B-cell proliferation with κ Ig
light chain expression in seven cases and λ Ig light chain expression in five cases; the remaining two cases failed to demonstrate any surface Ig. Studies for Ig heavy chain expression showed surface IgM in three, IgD in two, both IgM and IgD in two, IgG in four, and both IgG and IgD in one case. Intensity of the surface Ig staining was faint in all but two cases, comparable with the intensity of surface Ig staining seen in more typical cases of CLL and less than that seen in other B-cell malignancies. In addition, one or more B-cell-associated markers, such as CD19, CD20, CD22, or CD24, were expressed in all cases; the plasma cell-associated markers, PCA-1 and CD38, were negative in all cases.

Fig 2. (A and B) Bone marrow trephine biopsy section. The bone marrow has been diffusely replaced by a small lymphocytic infiltrate (H&E).

Fig 3. Bone marrow trephine biopsy section. The bone marrow is only focally involved with a small lymphocytic infiltrate (H&E).
A limited number of non–pan-B-cell antigens, such as CD5, CD11c, and CD25, have been used as characteristic markers of particular subtypes of B-cell malignancies: CD5 in CLL and other low-grade lymphoproliferative malignancies, and CD11c and CD25 in HCL.\textsuperscript{1,2,8,11} In this study, CD5 expression was found in 7 of the 14 cases. CD25 (anti–IL-2R) staining was found in greater than 20% of the cells in only 1 of the 14 cases (Table 2); in contrast, 29 of 39 (74%) staining in these cases was comparable with that found in CLL. All 14 of the cases showed staining with CD11c, with the fluorescent intensity of CD5 staining in these cases was comparable with that found in CLL. All 14 of the cases showed staining with CD11c, with the fluorescent intensity being quite bright and clearly beyond background staining. The CD11c positivity was not due to reactivity with mononuclear or granulocytic cells, as indicated by the low percentage of staining with CD11b, CD14, and CD10 antibodies. Expression of Leu-8 was found in only 1 of the 14 cases (Table 2); in contrast, 29 of 39 (74%) cases of CLL and one of three HCL analyzed in our laboratory strongly expressed Leu-8 (data not shown). Most T-cell–associated markers were negative in these 14 cases. However, case 1 did express CD7 in the majority of cells in contrast to the lack of staining with other pan-T-cell markers.

**DISCUSSION**

B-cell chronic lymphoproliferative disorders include a variety of entities such as chronic lymphocytic leukemia, B-cell non-Hodgkin’s lymphoma, Galton’s prolymphocytic leukemia, HCL, plasmacytoid lymphoma (Waldenstrom’s), and multiple myeloma.\textsuperscript{28,29} Their relatively distinct clinical, morphologic, and immunologic features suggest that these disorders arise from the malignant transformation of lymphocytes at various stages of B-cell maturation.\textsuperscript{1,2} Within this spectrum, CLL represents an early stage and HCL a later stage in mature B-cell development. CLL cells classically express CD5, pan-B-cell antigens, and faint surface Ig (IgM and/or IgD), but not CD11c or CD25.\textsuperscript{1,2} Hairy cells, on the other hand, express strong surface Ig, CD11c, and CD25, but lack the CD5 antigen. CD11c (Leu-M5) and CD25, in particular, have been used to discriminate HCL from other B-cell disorders.\textsuperscript{1,3} Clinically, it is usually not difficult to distinguish HCL from CLL. Patients with HCL classically present with pancytopenias, prominent splenomegaly, and usually the absence of lymphadenopathy. In contrast, CLL patients frequently have adenopathy at diagnosis and only

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Abbreviation: ND, not done.

*Reactivity in background T cells.
with progressive disease do they develop organomegaly and cytopenias. HCL also has a unique morphologic appearance on smears and in bone marrow tissue sections that is quite distinct from CLL; HCL is also characterized by TRAP cytochemical staining.

However, there is evidence that the two diseases are not as distinct as these features might suggest. Several studies have shown that with phorbol ester stimulation, CLL cells acquire many of the morphologic features of hairy cells, have detectable TRAP cytochemical positivity, and express the CD11c and CD25 antigens. In addition, CD11c may be capable of being induced after lymphocyte activation, suggesting the possibility that HCL and the CD11c-positive cases from this study represent particular subsets of activated B cells. Further studies of these subgroups for B-cell activation antigens would be of interest in confirming the activation status of these lymphoproliferative disorders. Other chronic lymphoproliferative syndromes have been described with features common to both CLL and HCL, or to CLL and prolymphocytic leukemia. Most pertinent to this report are the data of Vardiman et al, who in a report of CD11c positivity in HCL presented three cases of CD11c-positive, chronic lymphoproliferative disease having morphologic features common to both CLL and HCL. The leukemic cells were described as having slightly villous borders, suggestive of hairy cells, and one of the three had positive TRAP staining. As with our patients, however, the bone marrow had a pattern of infiltration more typical of CLL, and prominent splenomegaly was present without lymphadenopathy. Further supporting this association is a recent abstract describing 16 patients with chronic B-cell leukemia characterized by splenomegaly, thrombocytopenia, and TRAP-negative malignant cells with abundant lymphocyte cytoplasm. The malignant cells in these patients also expressed CD11c but not the CD25 antigen. Thus, CLL and HCL may represent malignant transformation and maturational arrest at discrete, but overlapping stages of B-cell development.

The 14 cases that we have described presented clinical diagnostic dilemmas because they have characteristics common to both CLL and HCL. The fatigue, degree of splenomegaly, absence of peripheral adenopathy, and frequent cytopenias were more typical of HCL. While the malignant population of lymphocytes was detectable in peripheral blood, that population was small compared with most CLL patients, especially in consideration of the degree of cytopenias and splenomegaly in our patients. In fact, only 4 of 14 patients would have met minimum criteria for CLL by the Rai classification criterion of having greater than a 15.0 x 10^9/L absolute lymphocyte count. However, morphologically these cases were best classified as CLL, typified by a homogeneous population of intermediate-sized lymphocytes, having coarse, condensed chromatin, and lacking the cytologic and nuclear features of HCL. In addition, the negative TRAP cytochemistry in all cases was consistent with the designation of CLL. Interestingly, almost all of the cases had abundant cytoplasm. Previous morphologic studies of CLL have shown that cases with relatively abundant cytoplasm are not uncommon and may account for 15% to 20% of all CLL. Thus, from a morphologic standpoint, these cases were typical of CLL and would not have been confused with HCL.

The expression of CD11c in all cases, however, distinguished this group of chronic lymphoproliferative disorders from CLL. This antigen is part of a larger family of adhesion molecules, termed integrins, which have important roles in cell-cell and cell-matrix interactions. The uniform expression of an adhesion receptor linked to leukocyte accumulation in tissue raises the possibility that the CD11c/CD18 molecule contributes to the distinctive pattern of organ involvement in both the current group and true HCL. Other molecules important in the recirculation pattern of lymphocytes may also be involved. Expression of the Leu-8 antigen is of particular interest in light of its structural homology to the murine peripheral lymph node homing receptor termed gp90^{mel}, a member of the LEC-CAM family of lectin-like adhesion molecules. In the human system, expression of gp90^{mel} initiates the migration of circulating lymphocytes into lymph nodes and may facilitate the hematogenous spread of murine lymphomas into lymph nodes. In humans, Stoolman et al confirmed that the Leu-8 antigen mediates the attachment of both normal and malignant lymphoid cells to the high endothelial venules (HEV) of peripheral lymph nodes. Previous human studies have shown expression of Leu-8 and LAM-1 in the majority of CLL cases (and Tedder et al, submitted for publication). Thus, a receptor capable of mediating attachment to lymph node HEV is frequently expressed in chronic leukemias associated with lymph node involvement. The current study strengthens this association by demonstrating Leu-8 expression in only one (case 5) of 14 CD11c-positive cases and, in contrast, 29 of 39 CD11c-negative CLL cases. Palpable lymphadenopathy was a frequent occurrence in the latter group, but uncommon in the former. Thus, various adhesion molecules involved in the homing and sequestration of normal leukocytes in tissues may help define the pattern of hematogenous dissemination in lymphoid malignancies, based on the different biologic potentials of these antigens. Moreover, strong expression of CD11c coupled with weak or absent expression of the lymph node homing receptor, Leu-8, may identify chronic B-cell lymphoproliferative diseases with a reduced capacity to involve lymph nodes.

We propose that CD11c-positive, Leu-8, CD25, and TRAP-negative B-cell malignancies constitute a spectrum of disorders having clinical, morphologic, and immunologic features intermediate between CLL and HCL and may possibly represent a distinct clinico-pathologic process. Due to the limited follow-up of this newly recognized group of patients, it is not clear whether CD11c expression is of prognostic significance or therapeutic importance. Given the remarkable responsiveness of HCL to both a-interferon and 2-deoxycoformycin, it will be of great interest to determine whether the leukemic cells from this group of CD11c-positive chronic lymphoproliferative disorders have similar sensitivity to either of these agents. Clearly, the use of CD11c immunophenotyping to screen these disorders that have features of both HCL and CLL will facilitate the further delineation of these patients and allow a greater understanding of the pathobiology of the B-cell chronic lymphoproliferative disorders.
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CD11c (LEU-M5) expression characterizes a B-cell chronic lymphoproliferative disorder with features of both chronic lymphocytic leukemia and hairy cell leukemia [see comments]

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