Monocytoid B-Cell Lymphoma

A Novel B-Cell Neoplasm

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Monocytoid B lymphocytes (MBLs), originally described as part of the histologic picture of toxoplasmic lymphadenitis, have been recognized as a reactive component in a variety of lymph node disorders. The authors now report 3 cases of non-Hodgkin's lymphoma in which a multidisciplinary approach allowed them to confirm the existence of a malignant lymphoma composed of the neoplastic counterpart of the MBLs found in nonneoplastic disorders. In all 3 cases, the lymphoma was composed of a relatively monomorphous infiltrate of atypical MBLs that had rather uniform-appearing nuclei and had well-defined, moderately abundant pale cytoplasm. The pattern of lymph node involvement in all 3 cases was predominantly sinusoidal and interfollicular. The neoplastic lymphoid cells were strongly positive for B-cell-restricted antigens; the light- and heavy-chain phenotypes were κ-IgM (2 cases) and κ-IgG (1 case). In all 3 cases, rearrangement of heavy- and/or light-chain genes was clearly identified by Southern blot hybridization. The name "monocytoid B-cell lymphoma" is proposed for this newly described malignant B-cell neoplasm. (Am J Pathol 1986, 124:310–318)

MONOCYTOID B lymphocytes (MBLs) were first described in toxoplasmic lymphadenitis. They have been referred to by various descriptive names, such as "monocytoid cells"[1,2] and "immature sinus histiocytes,"[3] which assumed a histiocytic/monocytic derivation. The immunohistochemical documentation that monocytoid cells are, in fact, polyclonal B lymphocytes was reported by our laboratory[4] and substantiated by others.[5–7] Although MBLs are still most commonly found to be associated with toxoplasmic lymphadenitis, they have been recognized as a reactive component in a variety of nonneoplastic,[1,2,8] preneoplastic,[9] and neoplastic lymph node disorders,[3,10] as well as in acquired immune deficiency syndrome (AIDS) and in AIDS-related lymphadenopathy.[11]

The significance of the presence of MBLs in so many different lymphoproliferative disorders is unknown, but it may indicate that MBLs are more prevalent than was previously thought. Similarly, neoplastic MBLs presumably have existed without being recognized.[12] We recently received in consultation a lymph node containing monoclonal B lymphocytes that we interpreted to be morphologically similar to polyclonal reactive MBL. This prompted us to review the files of the James Irvine Center for the Study of Leukemia and Lymphoma at the City of Hope National Medical Center for similar cases. We now report 3 cases that, on the basis of morphologic and immunologic evidence, represent a new and distinct B-cell neoplasm for which we propose the name "monocytoid B-cell lymphoma" (MBCL).

Patients

The clinical findings for our 3 patients are summarized in Table 1.

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Case 1

The patient, a 74-year-old man, had epigastric discomfort and weight loss, both of recent onset. At laparotomy, he was found to have a retroperitoneal mass with extension to the stomach and involvement of perigastric lymph nodes. A liver biopsy done during laparotomy showed involvement of the liver by malignant lymphoma. A bone marrow biopsy gave negative results. The retroperitoneal mass was removed, and the patient subsequently received radiation therapy (1800 rads) to the stomach and retroperitoneum; he also completed six cycles of chemotherapy with CHOP. The patient has been in complete remission for 17 months.

Case 2

The patient was a 66-year-old man who had generalized lymphadenopathy and gastrointestinal symptoms. An axillary lymph node biopsy was performed and showed involvement by malignant lymphoma. The patient subsequently received chemotherapy with COP, and he achieved a complete remission. The patient remained in complete remission for 29 months until he died after a relapse in the periaortic lymph nodes and spleen.

Case 3

A 64-year-old woman had an asymptomatic submandibular mass. The patient had had a bronchial carcinoid which was resected a year prior to her current hospitalization. Except for the submandibular mass, the physical findings were unremarkable. The submandibular lesion was excised, and the patient received no further treatment. There has been no evidence of malignant lymphoma during the 11 months following excision of the mass.

Materials and Methods

Patients and Samples

Tissues from the 3 patients were submitted for multidisciplinary laboratory analysis[4,13] to the James Irvine Center for the Study of Leukemia and Lymphoma at the City of Hope National Medical Center. For inclusion in this study, we required 1) a diagnosis of non-Hodgkin's lymphoma, with the neoplastic cells morphologically similar to those of polyclonal MBLs, and 2) availability of fresh material for immunophenotypic analysis.

Tissue Preparation for Histologic and Immunologic Examination

The tissue sections were fixed in buffered formalin and B5 solution, embedded in paraffin, and stained with hematoxylin and eosin (H & E) for routine histologic examination. The paraffin-embedded, fixed, and fresh-frozen tissues were prepared for immunohistochemical studies according to previously described techniques.[4]

Immunohistologic Procedures

Surface immunoglobulin was evaluated by the direct technique. A modification of the avidin–biotin complex (ABC) technique was used for identification of other antigens as previously described.[4] Biotinylated, affinity-purified anti-mouse antibody and avidin–biotin–peroxidase complex were obtained from Vector Laboratories, Burlingame, California. The substrate color reaction product was developed with 3-amino-9-ethylcarbazole (AEC).[14]

Sections of normal tonsil were included as positive controls. Procedures for negative control in each case included the use of irrelevant purified isotopic antibody or the substitution of primary antibody by mouse ascitic fluid or nonimmune serum.

Table 1—Clinical Findings in 3 Cases of Monocytoid B-Cell Lymphoma

Case	Age/sex	Initial site of involvement	Bone marrow involvement	Clinical stage	Treatment		Survival
					Type	Response	
1	74/M	Retroperitoneal mass with extension to stomach	Absent	IV	Rad. (1800) to mass, CHOP (×6)	CR (17 months)	Alive
2	66/M	Generalized lymphadenopathy	Absent	IIe	COP	CR (29 months)	Dead
3	64/F	Submandibular lymph node	Not done	I	Excisional biopsy only	CR (11 months)	Alive

C, cyclophosphamide; H, doxorubicin; O, vincristine; P, prednisone; CR, complete remission; PR, partial remission; NR, no remission; Rad, radiation therapy (rads).

Reagents

The monoclonal antibodies and conventional antisera used in this study, their reactivity, and their sources are listed in Table 2. Biotinylated, affinity-purified anti-mouse antibody and avidin-biotin-peroxidase complex were obtained from Vector Laboratories. The chromogen substrate AEC was obtained from Polyscience Inc., Warrington, Pennsylvania.

Gene Rearrangement Studies

High-molecular-weight DNA was prepared from frozen tissue sections by a method to be described in detail elsewhere.[15] After digestion by appropriate restriction endonucleases, Southern blot hybridizations with nick-translated probes were used for analysis of the arrangements of immunoglobulin genes in the specimens.[16,17] The IgH locus was analyzed after digestion of DNA with endonucleases Bam HI, Eco RI, or Hind III. Arrangements at the kappa locus were analyzed in Bam HI or Bgl II digests, and at the lambda locus in Eco RI digests. Immunoglobulin gene probes were derived from the plasmids pHuJH, pHuKc, and pHuλc_2, a generous gift of Dr. P. Leder, Harvard Medical School.

Table 2—Antibody Panel

Antibodies	Primary immunoreactivity	Source
Anti-κ, λ	Immunoglobulin light chains	Tago Laboratories (Burlingame, CA)
Anti-γ, α, μ, δ	Immunoglobulin heavy chains	Tago
LN1	B cells of germinal center, ductular epithelium, erythroid cells, macrophages	Technicon (Santa Ana, CA)
LN2	B cells of germinal center and mantle zone, dentritic reticulum cells	Technicon
HLA-DR	B cells, macrophages, activated T cells, some epithelial cells	Becton-Dickinson (Sunnyvale, CA)
B1	B cells of peripheral blood and lymphoid organs	Coulter Immunology (Hialeah, FL)
Leu-14	B cells of peripheral blood and lymphoid organs	Becton-Dickinson
B4	B cells	Coulter Immunology
B2	B cells, dendritic reticulum cells	Coulter Immunology
BA-1	B cells, pre-B cells	Boehringer-Mannheim (San Diego, CA)
BA-2	Early B cells, some myeloid cells	Boehringer-Mannheim
J5	Common ALL antigen, early B cells	Coulter-Immunology
T11	E-rosette receptor associated T cells	Coulter Immunology
Leu-1	T lymphocytes, some B-CLL cells, but not normal B cells	Becton-Dickinson
Leu-2a	Suppressor/cytotoxic T cells	Becton-Dickinson
Leu-3a	Helper T cells, some histiocytes	Becton-Dickinson
OKT10	Immature thymocytes, plasma cells	Ortho (Raritan, NJ)
Tac	T cells, hairy cell leukemia cells	Becton-Dickinson
Leu-M1	Myeloid/histiocytic cells, Hodgkin's Disease, some epithelial neoplasms	Becton-Dickinson
Leu-M3	Macrophages, histiocytes	Becton-Dickinson
Lysozyme	Macrophages, histiocytes, granulocytes	DAKO (Santa Barbara, CA)

Results

Morphologic Observations

In 2 cases (Cases 1 and 2), the lymph node architecture was distorted by fairly monomorphous populations of atypical MBLs located predominantly within sinuses, but with extension to other interfollicular regions. Because of the monomorphous nature of the MBL infiltration in the interfollicular areas, the low magnification appearance of the MBCL resembled a leukemic process. The proliferation of neoplastic MBLs surrounded scattered islands of nonneoplastic lymphocytes. These lymphoid aggregates generally corresponded to residual B-cell areas, and many contained germinal centers (Figure 1). The germinal centers varied from atrophic and without well-defined mantle zones to hyperplastic, with large follicles having irregular and serpiginous shapes. Focally, where mantle zones were absent, the proliferation of neoplastic MBLs were in contact with the germinal centers. A focal interfollicular reactive process consisting of plasma cells, immunoblasts, and increased vascularity was identified in 1 case.

In Case 3, the lymph node architecture appeared to be basically intact, with scattered germinal centers surrounded by distinct mantles of small lymphocytes. However, the interfollicular areas contained multiple, sharply demarcated sinuses expanded by atypical MBLs (Figure 2). The sharp demarcation resulted from the prominence of the endothelial cells which lined the sinuses, a finding that was absent in the other 2 cases. In some areas, the number of expanded sinuses was so great that they created a focally nodular appearance. As in the other 2 cases, some of the MBLs within the expanded sinuses impinged on adjacent germinal centers. The monomorphous population of atypical lymphocytes was focally interrupted by a few scattered,

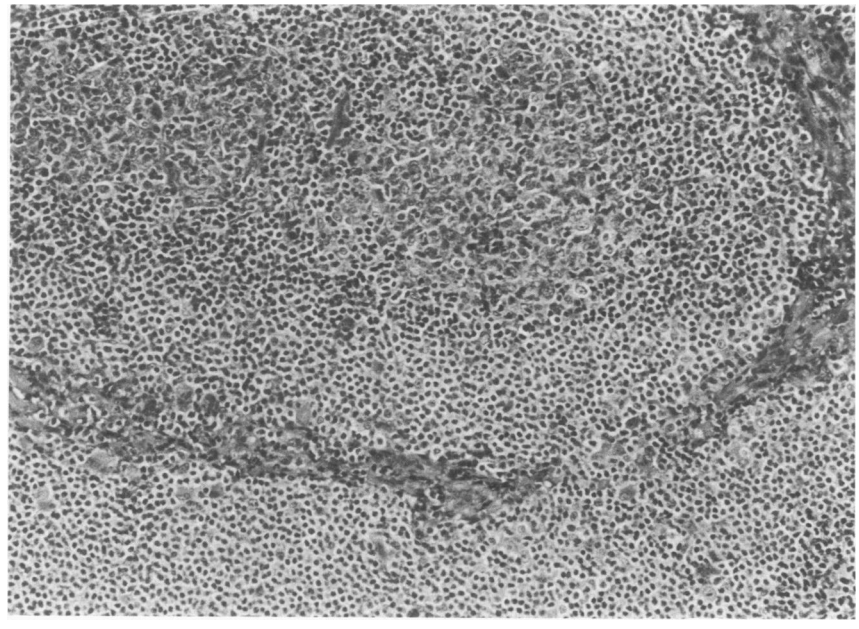

Figure 1—At low magnification, the neoplastic MBLs surround a germinal center; the pattern of involvement is primarily interfollicular (Case 2). (H&E, ×250)

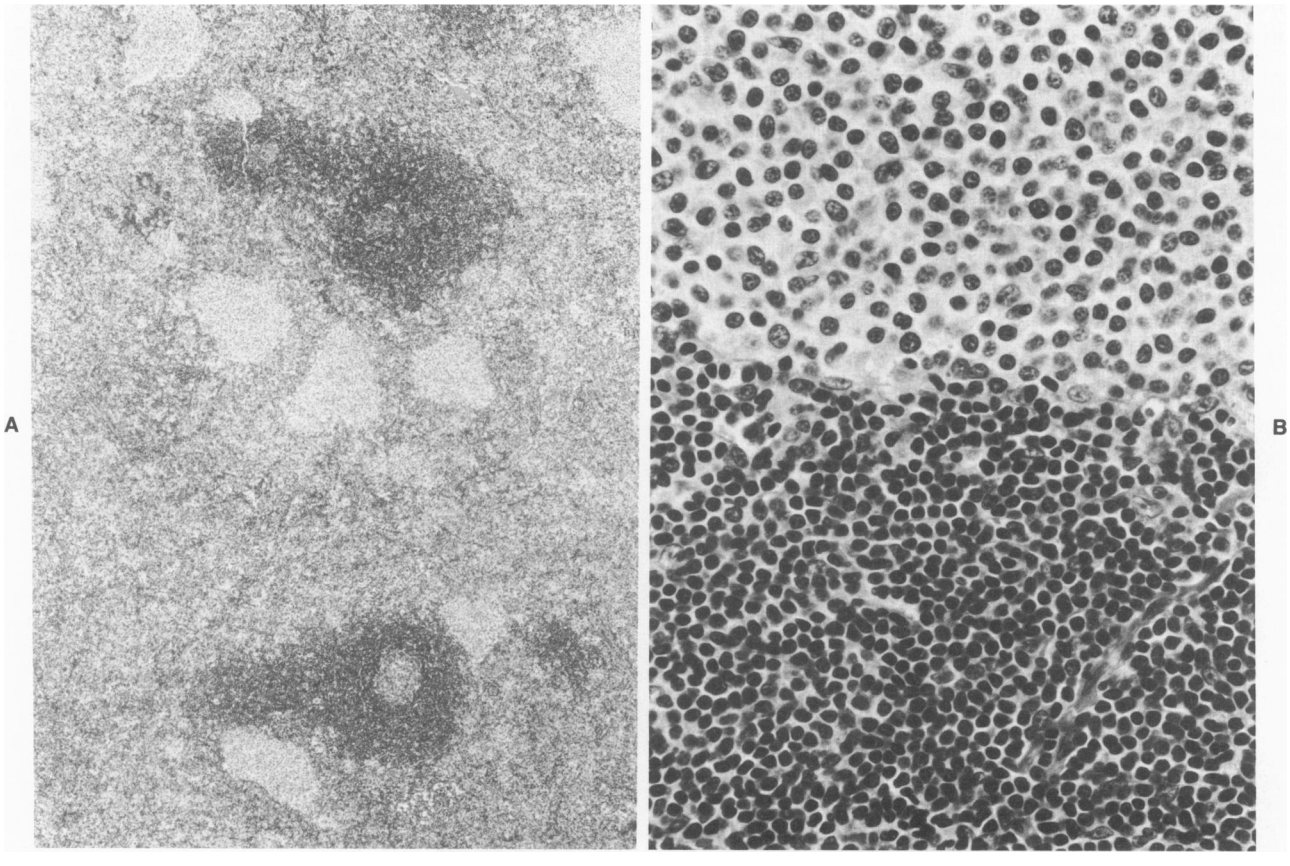

Figure 2—The interfollicular areas contain sharply demarcated sinuses, expanded by neoplastic MBLs in this case (Case 3), which were difficult to distinguish from an atypical reactive process (**A**). Higher magnification of neoplastic MBLs (**B**) (Case 3). (H&E, ×160 and ×400)

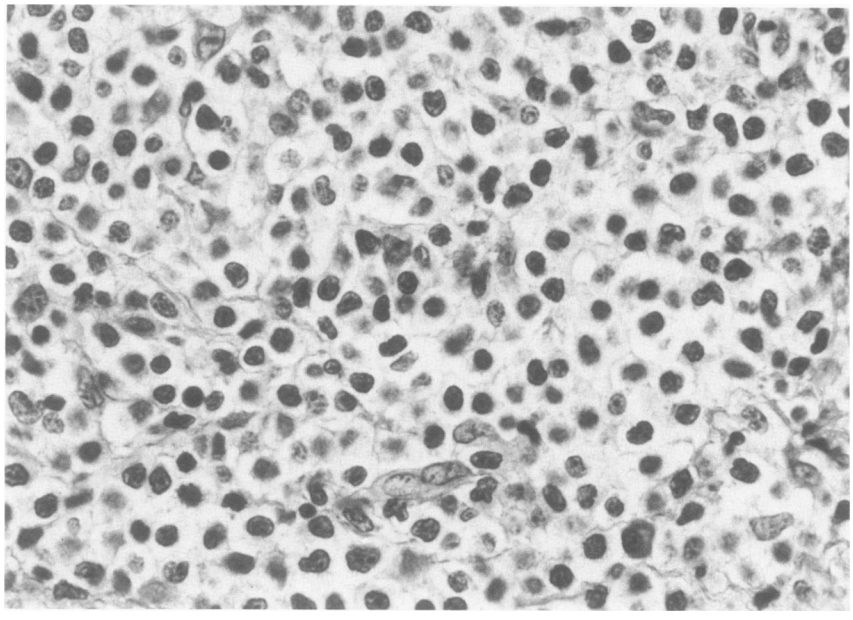

Figure 3—The neoplastic monocytoid cells have abundant pale cytoplasm and well-defined cell borders (Case 1). (H&E, ×640)

small lymphocytes and occasional neutrophils and histiocytes. The interfollicular regions not involved by lymphoma contained a polymorphous mixture of normal-appearing reactive lymphocytes and scattered histiocytes.

Cytologically, the atypical MBL in all cases were of intermediate size and had a relatively uniform appearance. The neoplastic cells had moderately abundant pale, lucent cytoplasm and bland nuclei (Figure 3). Because of the lucent cytoplasm and the well-defined interlocking cell borders, the nuclei appeared evenly spaced and, at low magnification, made areas of infiltration by these atypical MBLs readily recognizable. Although the nuclei were generally oval, most had slight indentations suggesting a reniform configuration. The nuclear chromatin was generally coarse, and nucleoli were either absent or inconspicuous. In general, mitotic activity was low.

In touch imprint preparations of the lymph nodes, most of the neoplastic cells had moderately clumped chromatin with variable numbers (one to three) of small nucleoli per nucleus. Nuclear membrane indentations were a prominent feature in the touch imprints. The cytoplasm was moderately abundant and pale; clear

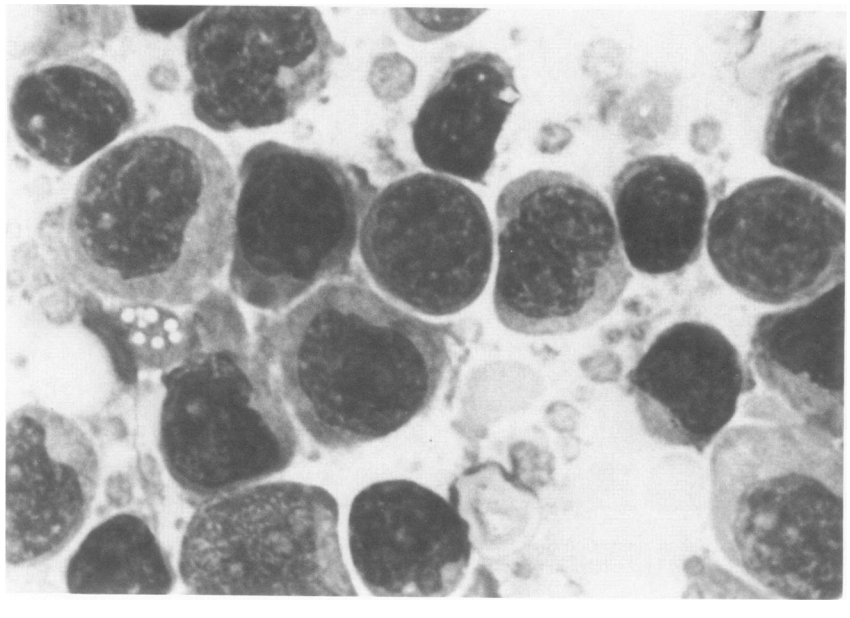

Figure 4—Imprint preparation of lymph node. Indentations in the nuclear membrane of the neoplastic monocytoid cells were a prominent feature in the touch imprints (Case 3). (×1500)

Table 3—Antigenic Phenotype of the 3 Cases of Monocytoid B-Cell Lymphoma

Antibody	Case 1	Case 2	Case 3
κ, λ	κ	κ	κ
γ, α, μ, δ	γ	μ	μ
LN1	+	+	+
LN2	+	+	+
HLA-DR	+	+	+
B1	+	+	+
Leu-14	+	+	+
B4	–	–	–
B2	–	–	–
BA-1	–	–	–
BA-2	–	–	–
J5	–	–	–
T11	–	–	–
Leu-1	–	–	–
Leu-2a	–	–	–
Leu-3a	–	–	–
OKT10	–	–	–
Tac	–	–	–
Leu-M1	–	–	–
Leu-M3	–	–	–
Lysozyme	–	–	–

+, reactive; –, nonreactive.

areas were apparent within the cytoplasm adjacent to the nuclear indentations (Figure 4).

In 1 case (Case 1), wedge and needle biopsy specimens from the liver and a biopsy specimen from the stomach were available for histologic examination. In the liver, multiple aggregates of atypical MBLs were scattered throughout the parenchyma and portal areas and were present diffusely in the hepatic sinuses. The mucosa in the gastric specimen was almost totally replaced by a dense, obviously malignant infiltrate of identical, atypical MBLs. A few gastric glands were observed, and these were surrounded by the lymphomatous cells.

Immunohistologic Observations

The results of the immunohistologic studies are summarized in Table 3. In all 3 cases, the neoplastic cells in paraffin-embedded tissues were reactive with the anti-B-cell-associated antibodies LN1 and LN2.[18] In frozen sections, the neoplastic cells showed strong membrane staining for B-cell-restricted antigens detected by B1 and Leu-14. The cells also exhibited surface membrane-associated immunoglobulin heavy and light chains with a monoclonal staining pattern (Figure 5), and they expressed the HLA-DR (Ia-like) antigen. The neoplastic MBLs were negative, however, for other B-cell-associated antigens, including B4, BA-1, BA-2, and J5. There also was no expression of T-cell-restricted and T-cell-associated antigens, including Leu-1. Similarly, the neoplastic cells showed no positive reactivity with antibodies considered to identify monocyte-histiocyte-associated antigens such as Leu-M1, Leu-M3, lysozyme, and α_1-antitrypsin.

Immunogenotypic Characterization

On analysis of DNA at the immunoglobulin heavy chain locus by Southern blot hybridization, we found unique rearranged bands in all 3 cases (Figure 6 and Table 4). In addition, in 2 of the 3 cases we were able to show rearrangement of κ light-chain genes. In contrast, analysis of the λ light-chain genes demonstrated that the λ locus remained in the germline configura-

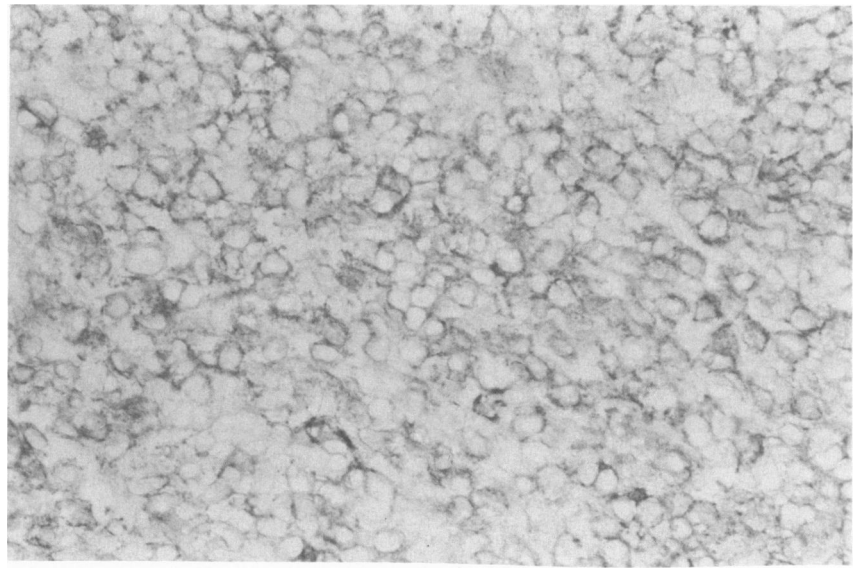

Figure 5—The neoplastic MBLs expressed monoclonal κ light chain (Case 2). (Direct technique, ×400)

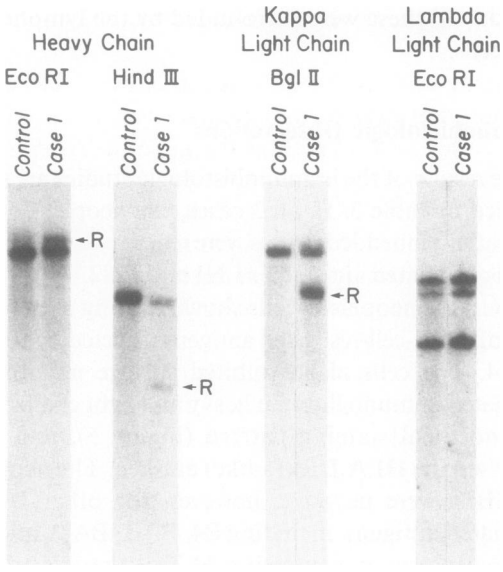

Figure 6—Gene rearrangement analysis. DNA from Case 1 and from control nonlymphoid tissue was digested with restriction endonucleases and subjected to Southern blot hybridization with immunoglobulin gene probes as indicated. Novel rearranged bands are indicated by the letter *R*.

tion in each of these cases (Table 4). The detection of unique rearranged heavy-chain and κ light-chain genes is consistent with the presence of a population of monoclonal B cells in each specimen.

Discussion

Monocytoid cells, as reactive components in a variety of nonneoplastic and neoplastic lymph node disorders, have recently been recognized as polyclonal B cells.[4-7] Previously, we reported the detailed antigenic phenotype of monocytoid cells in a series of reactive lymphoid disorders[4] and in AIDS-related lymphadenopathy,[11] and we proposed the term monocytoid B lymphocytes (MBLs) for these cells. We believe that the cells described in these 3 cases of unusual non-Hodgkin's lymphomas are the neoplastic counterparts of MBLs. The 3 patients had originally been given a diagnosis of malignant lymphoproliferative disorder, mantle zone lymphoma, or atypical lymphoproliferative disorder. Like reactive MBLs, the neoplastic cells in our cases had a moderately abundant, clear cytoplasm, frequently with well-delineated, interlocking cell borders. The nuclei were cytologically bland-appearing, and the nuclear chromatin was generally coarse. Unlike reactive MBLs, however, the lymphomatous cells in 2 of our cases caused disruption of the lymph node architecture. The general pattern of involvement was diffuse and interfollicular, with MBLs filling nodal sinuses and entrapping residual lymphoid islands and germinal centers. In 1 case (Case 3), the cellular proliferation was confined to interfollicular trabecular sinuses lined by endothelial cells. We strongly considered the possibility that this case represented atypical florid, reactive hyperplasia of MBLs; however, in contrast to the finding in a reactive process, the distended sinuses impinged upon germinal centers, were dramatically discrete and multiple, and focally imparted a nodular appearance.

The results of immunologic and molecular hybridization studies clearly indicate that the monocytoid cell proliferations in these 3 cases were neoplastic and of the B-cell type. Immunologically, positivity for some B-cell-restricted antigens was exhibited in all 3 cases. According to accepted criteria of monoclonality, each of the 3 cases was characterized by surface immunoglobulin light-chain restriction (κ). Moreover, in all 3 cases, rearrangements of heavy- and/or light-chain genes were clearly demonstrable with the Southern blot technique.

The antigenic phenotype of the MBCL in all 3 cases was SIg^+, $LN1^+$, $LN2^+$, $HLA\text{-}DR^+$, $B1^+$, $Leu\text{-}14^+$, $B4^-$, $B2^-$, $BA\text{-}1^-$, $BA\text{-}2^-$, $J5^-$, $T11^-$, $Leu\text{-}1^-$, $Leu\text{-}2a^-$, $Leu\text{-}3a^-$, $T10^-$, Tac^-, $Leu\text{-}M1^-$, $Leu\text{-}M3^-$, $lysozyme^-$. The absence of positivity for B4 and BA-1 suggests that MBCL is not related to small lymphocytic lymphomas, and the J5 negativity suggests that there may not be a relationship to follicular lymphomas or to "pre-B" cells.[19-21] These findings, in conjunction with the absence of T10 and of detectable cytoplasmic immunoglobulin, favor the possibility that the neoplastic cells of MBCL are arrested at a presecretory stage in the B-cell differentiation process.[21,22] According to the B-cell differentiation scheme proposed by Nadler et al.,[21] MBCL may conform to the interfollicular zone of the B-cell differenti-

Table 4—Immunogenetic Phenotype of 3 Cases of Monocytoid B-Cell Lymphoma

	Heavy-chain locus			κ-chain locus		λ-chain locus
Case	Bam HI	Hind III	Eco RI	Bam HI	Bg1 II	Eco RI
1	1R	1R	1R	G	1R	G
2	1R	1R	1R	G	G	G
3	1R	2R	2R	1R	1R	G

R, rearranged gene; G, germline configuration gene.

ation pathway. The MBL may, therefore, represent a small, but unique, compartment of the interfollicular lymphoid cell population. A definitive immunophenotypic characterization of MBL and more precise determination of its stage of differentiation in the scheme of B-cell ontogeny will require additional studies.[23]

The histopathologic differential diagnosis in our cases included, in addition to florid atypical MBL proliferations, a variety of hematopoietic neoplasms such as mantle zone lymphoma, sinusoidal large cell lymphoma, peripheral T-cell lymphoma, hairy cell leukemia and other leukemias, and systemic mast cell disease.

Mantle zone lymphoma is considered a follicular variant of intermediate lymphocytic lymphoma[24] in which the neoplastic lymphoid cells characteristically surround germinal centers; this results in expanded mantle zones. At low magnification, the process is noted to create a nodular configuration which is related to follicular structures. Although the mantle zone pattern may be simulated by other lymphomas,[25] the cytologic features of the typical case are between those of small (well-differentiated) lymphocytic lymphoma and those of small cleaved (poorly differentiated lymphocytic) lymphoma of follicular center cell origin.[24] In 2 of our cases, the lymphomatous cells also encircled germinal centers, but there was no suggestion of an outward expansion of the cells from the germinal centers which would have conveyed a nodular pattern. Moreover, the MBLs were generally separated from the germinal centers by rims of mantle zone lymphocytes which were morphologically nonneoplastic and distinct from the MBLs. Both nonneoplastic mantle zone cells and the cells of mantle zone lymphoma have indistinct cytoplasm, with resulting close approximation of nuclei. By comparison, the cytoplasm of the MBL is characteristically abundant and clear, so that when these cells are seen in aggregate, their nuclei are discrete and widely separated. In our third case in which the neoplastic MBL formed nodular aggregates, the "nodules" occurred within sinuses and interfollicular areas; they were not related to follicular structures.

Sinusoidal large cell lymphoma[26] (SLCL) may also resemble MBCL. As in MBCL, SLCL distends sinuses throughout the lymph node, forming isolated islands of nonneoplastic lymphocytes with or without germinal centers. The most common variants are immunoblastic plasmacytoid and large noncleaved cell lymphomas. In most cases, the neoplastic cells of SLCL are predominantly immunoblasts with amphophilic cytoplasm.[26] This is in contrast to the lucent, nonamphophilic cytoplasm of the neoplastic MBLs encountered in our cases. The neoplastic cells in MBCL also differ from large noncleaved cells in that the latter lack distinct, clear cytoplasm and consistent nuclear indentations.

Peripheral T-cell lymphomas, specifically the variant composed of cells of intermediate size,[27] should also be included with MBCL in the histologic differential diagnosis, because the interfollicular distribution of the neoplastic MBLs could easily be interpreted as a T-zone pattern. The identification, by immunologic studies, of immunoglobulin light-chain restriction in MBCL will effectively exclude the diagnosis of peripheral T-cell lymphoma.

Hairy cell leukemia (HCL) is perhaps the hematopoietic neoplasm that is most difficult to distinguish morphologically from MBCL. Only rare patients with HCL have lymphadenopathy.[28] In both HCL and MBCL, there is an infiltrative, sinusoidal pattern of nodal involvement, with at least partial preservation of germinal centers and islands of residual small lymphocytes. The cytologic appearance of the neoplastic cells in HCL with clear cytoplasm and relatively bland, reniform nuclei, is virtually identical to that in MBCL. Moreover, the findings in the liver in one of our cases of MBCL were also indistinguishable from those described in HCL. In fact, we can think of no absolute or pathognomonic morphologic criteria which will reliably allow distinction of MBCL from HCL. Immunologic distinction between the two is also difficult. Like MBCL, HCL is a neoplasm of B lymphocytes. However, the neoplastic cells of HCL almost universally express the interleukin-2 receptor or the Tac antigen.[29] Whereas expression of the Tac antigen is not unique to HCL, the finding that all 3 of our cases of MBCL were Tac-negative suggests that the presence or absence of the Tac antigen may be useful in the differential diagnosis of these two disorders. The reliability of this marker remains to be determined. The distinction between HCL and MBCL may also be made on a clinical basis. In contrast to patients with HCL, our patients with MBCL did not have bone marrow involvment, significant splenomegaly, pancytopenia, or evidence of hairy cells in the peripheral blood.

Other leukemias in addition to HCL, such as myelomonocytic and monocytic leukemias, can be distinguished from MBCL on the basis of clinical criteria, cytochemical findings, and immunologic analysis.

Systemic mast cell disease, like HCL, has cytologic similarities to MBCL. In lymph nodes, however, the mast cells form irregular nodules or tumor masses, are associated with reactive fibrosis, and react positively with naphthol AS-D-chloracetate esterase.[30]

In conclusion, MBCL may represent the neoplastic proliferation of a unique population of interfollicular lymphocytes which exhibit distinct morphologic fea-

tures. Clinically, there are too few patients for our results to be conclusive regarding clinical aggressiveness. The bland cytology suggests the these lymphomas should be of low grade; however, two of our three patients have had an aggressive clinical course. Obviously, additional investigations of the immunologic and functional characterization of MBCL, more precise determination of the stage of differentiation of the MBCL in the B-cell differentiation pathway, and clinical follow-up studies are required. Such studies should lead to further clarification of the position of this rare B-cell lymphoma in the scheme of lymphoproliferative disorders.

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