RAPID COMMUNICATION

Clonal T-Cell Populations in Angioimmunoblastic Lymphadenopathy and Angioimmunoblastic Lymphadenopathy-like Lymphoma

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Ten cases of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) and AILD-like lymphoma were studied by immunophenotypic and immunogenotypic analysis. All specimens were found to have a predominance of T cells by immunophenotypic analysis. DNA hybridization analyses showed three of five specimens of AILD and five of six specimens of AILD-like lymphoma to contain clonal rearrangements of the β T-cell receptor gene. No rearrangements of the heavy or light chain immunoglobulin genes were seen in any case. A single case showed a progression of AILD with a germ-line pattern of β T-cell receptor DNA to AILD-like lymphoma with detectable clonal rearrangements for β T-cell receptor DNA. These results suggest that many, but not all, cases diagnosed histologically as AILD or AILD-like lymphoma contain a clonal proliferation of T-lymphocytes. (Am J Pathol 1986, 122:392–397)

ANGIOIMMUNOBLASTIC lymphadenopathy is a systemic disease, of uncertain etiology, in which the major pathologic findings are noted in lymph nodes. Originally described by Frizzera and co-workers in 1974 as angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), this condition was characterized clinically as having a predilection for the elderly and an association with generalized lymphadenopathy, hepatosplenomegaly, fever, anemia, and immunologic abnormalities.[1,2] Pathologically, involved lymph nodes showed an obliteration of the normal architecture by a mixed cellular infiltrate which included plasma cells and immunoblasts, together with overall lymphocyte depletion, a proliferation of small blood vessels, and deposition of an intercellular PAS-staining amorphous substance. The outcome of patients in early reports was variable, with about half dying relatively quickly regardless of any form of therapy and the remainder experiencing a more indolent clinical course. One year later, Lukes and Tindle described the disorder immunoblastic lymphadenopathy, which was probably a similar entity, although the criteria for its diagnosis were perhaps more rigorous than for AILD.[3] These authors emphasized the prominence of activated nonneoplastic B lymphocytes in lesions from patients with this disorder.

Shortly after the original descriptions of AILD and immunoblastic lymphadenopathy first appeared, a number of reports were published that documented the high incidence of malignant lymphoma in patients with AILD.[4-7] For instance, in one study of 84 patients with histologic features of AILD, 36 patients had additional histologic features interpreted as malignant lymphoma

of the immunoblastic type arising in AILD.[4] Paraffin section immunoperoxidase studies for light and heavy chains in 32 cases of AILD with immunoblastic lymphoma could not demonstrate a monoclonal B-cell population in any of the cases. In 1979, Shimoyama et al reported a series of patients with an immunoblastic lymphadenopathy-like T-cell lymphoma.[8] Their patients had a clinical presentation very similar to AILD, with the same preponderance of adult patients, generalized lymphadenopathy, and polyclonal hypergammaglobulinemia. Enlarged lymph nodes showed histologic features similar to those described for AILD, including obliteration of architecture, a proliferation of blood vessels, and a mixed cellular infiltrate that contained immunoblasts and "pale cells." Immunologic studies disclosed that these immunoblasts, including plasmacytoid forms, and pale cells possessed T-cell markers. These investigators therefore regarded this disease as a variant of peripheral T-cell lymphoma.

A number of different causes for AILD have been proposed. These have included neoplasia, infection, and a primary immune disorder.[1,5,9,10] Evidence in support of any one of these etiologies has been inconsistent, but clearly a relationship exists between AILD and lymphoma, as reflected by the number of cases in which the histologic distinction between these two diagnoses is difficult or in which there appears to be a progression from AILD to lymphoma over time. To better understand AILD and its relationship to malignant lymphoma, we undertook a comprehensive study of 10 patients with histologic findings suggestive of either

AILD or AILD-like lymphoma. Clinical, histologic, immunologic, and immunogenotypic parameters were studied and correlated. In the majority of cases, our studies revealed a clonal population of T cells within tissues from patients with these disorders, thereby suggesting that many of these lesions actually represent T-cell lymphomas. However, in a minority of cases our data are consistent with the existence of the separate nonneoplastic entity of AILD.

Materials and Methods

Frozen biopsy specimens adequate for immunophenotype and immunogenotype studies were available from 10 cases that had been submitted to the Laboratory of Surgical Pathology at Stanford University Medical Center between 1982 and 1985 and were interpreted as showing AILD or AILD-like T-cell lymphoma. Histologic sections of all cases were seen at the time of original diagnosis by one of us (R.F.D.); criteria for the diagnosis of AILD were those of Frizzera et al.[1,2]

Immunophenotype Studies

The methods for the frozen section immunologic studies have been presented before.[11] Briefly, the staining consisted of a first-stage incubation with monoclonal antibodies directed against the following antigens: B1 or TO15 (B lineage antigens), kappa and lambda light chains, mu heavy chain, Leu 1-5, 8, and 9 (T-cell antigens). After washing, biotin-conjugated goat anti-

Table 1—Clinical Data

Case	Age	Sex	Clinical presentation	Therapy	Status
1	73	M	Generalized lymphadenopathy, hepatosplenomegaly, fever, anemia	Steroids, cyclophosphamide, vincristine, Adriamycin	Dead of disease, 7 months
2	58	M	Generalized lymphadenopathy, fever, polyclonal gammopathy	Steroids, cyclophosphamide, vincristine	Dead of disease 5 months
3	74	F	Generalized lymphadenopathy, hepatosplenomegaly, skin rash, anemia, thrombocytopenia	Steroids, cyclophosphamide	Alive with disease, 13 months
4	62	F	Generalized lymphadenopathy, skin rash, fever, pulmonary infiltrates	Steroids, cyclophosphamide	Alive with disease, 7 months
5	64	F	Generalized lymphadenopathy, skin rash, fever, thrombocytopenia, pulmonary infiltrates	Steroids, cyclophosphamide, CHOP*	Alive with disease, 23 months
6	56	F	Generalized lymphadenopathy, ascites, skin rash, fever, anemia, thrombocytopenia	Steroids	Dead of disease, 3 months
7	52	M	Generalized lymphadenopathy, hepatosplenomegaly, fever, anemia, thrombocytopenia	Steroids, cyclophosphamide	Dead of disease, 8 months
8	67	F	Bilateral inguinal lymphadenopathy	No initial therapy, then M-BACOD,* procarbazine, VP-16, cytosine, arabinoside, nitrosurea	Dead of disease, 37 months
9	48	M	Generalized lymphadenopathy, edema, skin rash, fever	Steroids, methotrexate, CHOP*	Alive with disease, 23 months
10	67	M	Generalized lymphadenopathy, hepatosplenomegaly, skin rash, pulmonary infiltrates	Steroids, cyclophosphamide	Alive with disease, 13 months

* CHOP, cyclophosphamide, Adriamycin, vincristine, prednisone; M-BACOD, methotrexate, bleomycin, Adriamycin, vincristine, dexamethasone.

Table 2—Pathologic Data

Case	Preceding histologic diagnoses	Site of biopsy	Histologic diagnosis	Interpretation of immunophenotype findings	βT receptor gene	Heavy chain gene	κlight chain gene	λlight chain gene
					Gene rearrangement studies			
1	None	Inguinal lymph node	AILD	Predominant T-cell population with normal H:C/S* ratio and normal T-cell antigens	R(R)†	G(G)	G	(G)
2	Lymph node biopsy 2 months prior interpreted as reactive hyperplasia	Axillary lymph node	Favor AILD	Predominant T-cell population with normal H:C/S ratio and normal T-cell antigens	R(R)	G(G)	G	(G)
3	None	Axillary lymph node	AILD	Predominant T-cell population with low H:C/S ratio (<0.5) and normal T-cell antigens	G(R)	G(G)	G	(G)
4	Lymph node biopsy 4 months prior interpreted as favoring lymphoma	Inguinal lymph node	AILD	Predominant T-cell population with normal H:C/S ratio and normal T-cell antigens	G(G)	G(G)	G	(G)
5	Lymph node biopsy 3 months prior interpreted as AILD	a. Axillary lymph node	AILD	Predominant T-cell population with normal H:C/S ratio and normal T-cell antigens	G(G)	G(G)	G	(G)
		b. Spleen (12 months later than axillary lymph node biopsy)	Favor AILD-like lymphoma	Predominant T-cell population with abnormal absence of Leu 1, 2, and 3	R(R)	G(G)	G	(G)
6	None	Cervical lymph node	AILD-like lymphoma	Predominant T-cell population with low H:C/S ratio (<0.2) and normal T-cell antigens	G(G)	G(G)	G	(G)
7	Lymph node biopsy 3 months prior interpreted as AILD	Cervical lymph node	Favor AILD-like lymphoma	Predominant T-cell population with low H:C/S ratio (<1.0) and normal T-cell antigens	R(R)	G(G)	G	(G)
8	Lymph node biopsy 19 months prior interpreted as AILD	Axillary lymph node	Favor AILD-like lymphoma	Predominant T-cell population with abnormally high H:C/S ratio (>20:1) and abnormal loss of Leu 1 and 9	R(G)	G(G)	G	(G)
9	None	Axillary lymph node	AILD-like lymphoma	Predominant T-cell population with normal H:C/S ratio, but abnormal loss of Leu 9	R(R)	G(G)	G	(G)
10	Lymph node biopsy 4 months prior interpreted as atypical	Axillary lymph node	AILD-like lymphoma	Predominant T-cell population with abnormal absence of both Leu 2 and 3	R(R)	G(G)	G	(G)

* H, helper; C/S, cytotoxic/suppressor.
† Immunogenotypes performed with Eco RI restriction enzyme are shown in parenthesis; all other immunogenotypes performed with Bam HI; G, germ-line, R, rearranged band.

mouse F(ab')₂ antibody (Tago, Burlingame, Calif) or horse anti-mouse antibody (Vector Laboratories, Inc., Burlingame, Calif) was applied prior to a third stage of horseradish peroxidase-conjugated avidin (Vector). The sections were then incubated in diaminobenzidine, followed by copper sulfate, and counterstained with methylene blue.

Immunogenotype Studies

DNA was extracted from tissue specimens and purified according to standard procedures.[12,13] Ten micrograms of DNA were digested with one or the other restriction enzyme, and the resulting fragments were separated by electrophoresis in 0.8% agarose gel. Separated DNA fragments were transferred from the gels onto activated nylon membranes (Genatran-45; Plasco, Woburn, Mass), as described by Southern.[14] Membranes were hybridized with DNA probe fragments, radiolabeled with ^{32}P by the random hexamer priming method.[15] Details of the methods of hybridization and autoradiography have been described.[12,16] DNA probe fragments specific for the heavy chain joining region, the constant regions of the kappa and lambda light chain genes, and the gene for the β subunit of the T-cell receptor were employed. The structure of the im-

munoglobulin and β T-cell receptor DNA probes has been described in detail elsewhere.[12,17] Analyses for rearrangements of heavy chain immunoglobulin genes and of the T-cell receptor gene were carried out on DNA digested with Bam HI and also on DNA digested with Eco RI restriction enzyme. Analyses for rearrangements of kappa and lambda light chain genes were carried out on DNA digested with Bam HI and Eco RI restriction enzymes, respectively. Restriction enzymes were purchased from New England BioLabs, Beverly, Massachusetts.

Results

The results are summarized in Tables 1 and 2. The clinical characteristics of the 10 patients were similar. All patients were adults, with a median age of 63. There were 5 men and 5 women. Lymphadenopathy was apparent at initial presentation in all patients; it was generalized in all but Case 8. Fever was noted in 8 patients, and a skin rash was noted in 5. Anemia, usually Coombs' positive, thrombocytopenia, pulmonary infiltrates, hepatosplenomegaly, and weight loss were also noted in some patients. All patients were treated, usually with both steroids and alkylating agents, most often cyclophosphamide. The patients had a uniformly poor outcome — 5 patients dead of disease from 5 to 37 months, and 5 patients alive with disease from 7 to 23 months after initial presentation.

Lymph node biopsies from Cases 1–4 and the axillary lymph node from Case 5 showed features favoring or diagnostic of AILD. The normal architecture was generally obliterated, with only a rare "burnt-out" ger-

minal center. The nodes were generally depleted of small lymphocytes but contained immunoblasts and plasma cells. Arborizing vessels were conspicuous, and PAS-positive amorphous debris was present. Cases 6–10 and the spleen from Case 5 showed histologic features suggestive or diagnostic of AILD-like lymphoma. In addition to the histologic features noted in the AILD cases, the latter cases generally showed a higher cellularity, with a greater number of immunoblasts in addition to abnormal small lymphocytes. Immunoblasts also showed nuclear atypia, and some possessed abundant clear cytoplasm. Clusters of these cells were noted in several lymph nodes.

By frozen section immunoperoxidase studies, a predominant T-cell population was identified in all cases, demonstrated by large numbers of cells bearing Leu 4 and Leu 5 antigens. In 4 (Cases 8, 9, and 10 and the spleen from Case 5), there was abnormal expression of T-cell antigens, indicated by the absence of Leu 1, 2, and 3 in 1 case, absence of Leu 2 and 3 in 1, absence of Leu 1 and Leu 9 in 1, and absence of Leu 9 in another (see Figure 1). In two additional cases (3 and 6), there were abnormal ratios of helper to suppressor cells. B cells were present as a minority population in all instances. Neither light chain immunoglobulin class was present in marked excess, and there was no abnormal loss of B lineage markers.

By DNA hybridization analysis, clonal rearrangements of the β T-cell receptor gene were present in 8 of the 11 specimens (see Figure 2). Three of five biopsy specimens with histologic features suggestive or diagnostic of AILD on initial examination, with the criteria of Frizzera et al, showed clonal rearrangements. Five

Figure 1— Immunophenotypic analysis of spleen tissues (second specimen) from Case 5. In **A**, a frozen section immunoperoxidase stained for Leu 4 shows the vast majority of the lymphoid cells in the white pulp to express the T-cell antigen Leu 4. The majority of the lymphoid cells also expressed Leu 5 and Leu 9, identifying these cells as T cells. In contrast, **B** shows a similar immunoperoxidase stain for Leu 1, demonstrating that most of the T cells showed an abnormal lack of expression for this pan-T-cell marker. (Immunoperoxidase, ×200)
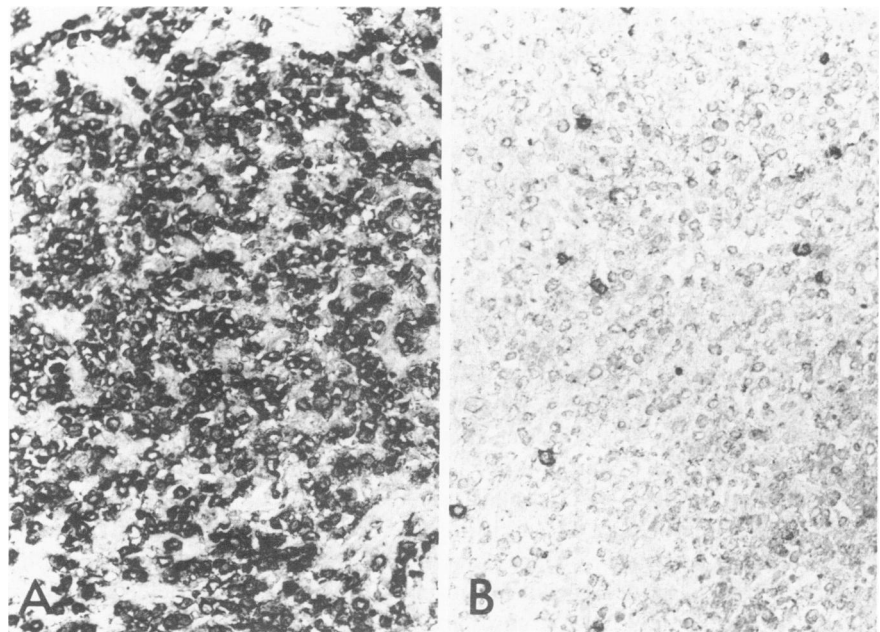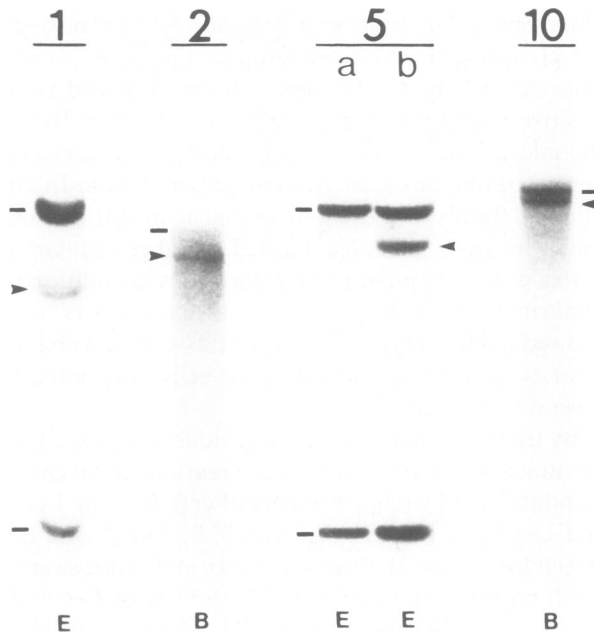
Figure 2—Examples of autoradiographic analyses of β T-cell receptor gene rearrangements in AILD and AILD-like lymphoma. Numbers correspond to cases listed in Tables 1 and 2. The letters above the autoradiograms for Case 5 refer to biopsy sites described in Table 2. The letters below each autoradiogram indicate the restriction enzyme used in preparing each autoradiogram: *B*, Bam HI; *E*, Eco RI. Dashes appear alongside germ-line bands, as determined from positions of bands in control DNA analyzed in parallel, but not shown in the figure; the *arrowheads* indicate clonal, rearranged bands. The germ-line bands correspond to DNA fragments of the following sizes: Cases 1 and 5, 12 kb and 4 kb; Cases 2 and 10, 23 kb.

of six biopsy specimens with histologic features suggestive or diagnostic of AILD-like lymphoma also showed clonal rearrangements. In addition, several cases showed a set of multiple non-germ-line bands significantly lighter in intensity than major rearranged bands when analyses were performed with the Eco RI restriction enzyme. Although this result may be evidence for an oligoclonal T-cell proliferation, we have occasionally seen similar bands in the same Eco RI digested DNA of specimens from patients without T-cell malignancies.[17] No case showed clonal rearrangements of either the heavy or light chain immunoglobulin genes.

Discussion

This study has resulted in several major observations. First, it has demonstrated that the majority of malignant lymphomas arising in a setting of AILD are peripheral T-cell lymphomas. These cases would therefore appear to represent examples of immunoblastic lymphadenopathy-like T-cell lymphoma. This disorder was first described in Japan,[8] and it has been unclear how commonly this entity occurs elsewhere and what its relationship is to AILD. Nathwani et al noted a similarity between the Japanese cases and those which they described as AILD-associated with malignant lym-

phoma.[18] Nathwani et al were unable to demonstrate a B-cell derivation for the malignant lymphomas in AILD, employing immunoperoxidase stains for kappa and lambda light chains on paraffin-embedded tissue.[4] Our studies confirm the absence of a monoclonal B-cell population and also provide strong evidence for a monoclonal T-cell population. A single case of malignant lymphoma arising in a patient with AILD was recently reported by Bertness et al,[19] who also identified β T-cell receptor rearrangements; however, they did not analyze this case for heavy and light chain immunoglobulin gene rearrangements. A B-lineage lymphoma was therefore not excluded conclusively, because some B-lineage lymphomas have been shown to have rearrangements of the β T-cell receptor in addition to immunoglobulin gene rearrangements.[20]

A second major finding of this study is our observation that many lymph node biopsy specimens histologically interpreted as AILD by classical criteria contain clonal T-cell populations and probably represent peripheral T-cell lymphomas. On the other hand, this study also provides evidence that a "prelymphomatous" lesion may exist. In Case 5, an initial lymph node biopsy specimen interpreted as AILD showed no evidence of immunoglobulin or β T-cell receptor gene rearrangements. One year later, a splenectomy specimen showed histologic and immunologic features supportive of lymphoma and immunogenotypic evidence for a monoclonal T-cell lymphoma. Despite these results, it is still conceivable that a monoclonal T-cell process was present in the original lymph node biopsy. However, if a monoclonal T-cell population was present, it represented less than 1% of the total cells in the biopsy specimen, because this is the threshold of detection for monoclonal populations by DNA hybridization analysis.[12] If such a small monoclonal component actually exists within this tissue, it seems unlikely that it could by itself be responsible for the dramatic pathologic changes seen in the specimen. Therefore, the designation of AILD seems reasonable for those cases that lack detectable T-cell receptor rearrangements. It also seems reasonable to propose that lymphomas may arise in a preexisting condition of AILD, rather than that all cases diagnosed as AILD are actually *ab initio* T-cell lymphomas. In support of this contention, two recently reported cases of AILD have also shown no evidence of rearrangement of the T-cell receptor.[19]

One case histologically identified as an AILD-like lymphoma in the current study showed no detectable clonal rearrangements. This case may represent AILD simulating lymphoma. It is also possible that this case is actually a peripheral T-cell lymphoma, but one without detectable β T-cell receptor gene rearrangements. Occasional cases of T-cell lymphoma fail to show gene rearrangements even after analysis of DNA with mul-

tiple restriction enzymes, presumably due to the superimposition of germ-line and rearranged bands in autoradiograms.[20] However, in our experience (Weiss et al[17] and Weiss LM, Hu E, Sklar J, unpublished observations) and that of some other investigators,[21] this occurrence is rare.

In the present study, tissues were analyzed for morphologic features, antigen expression, and gene rearrangements. One advantage of a multiparameter study of this type is the ability to compare the sensitivity of various diagnostic methods against one another. In the present study, DNA hybridization analyses proved much more sensitive than histologic assessment or immunophenotyping. Nevertheless, we think that, rather than replacing these two techniques, gene rearrangement analyses are best used in conjunction with histology and immunologic data and to help refine conventional diagnostic criteria. Just as immunologic studies have aided in redefining histopathologic criteria in the past ten years, we believe correlative histopathologic, immunologic, and gene rearrangement studies will allow further refinement of the surgical pathologist's ability to diagnose malignant lymphoma. For example, retrospective histologic review of these cases by two of us (J.G.S. and R.F.D.), taking into account more recently defined criteria for T-cell lymphoma that have been shaped in large part by the results of immunologic studies, revealed histologic features suggestive of malignancy in several cases originally interpreted as AILD. Also, when correlating results of immunophenotyping with immunogenotyping in the present study, we noted that all 4 cases with abnormal T-cell antigen loss showed β T-cell gene rearrangements, providing support for the hypothesis that abnormal T-cell antigen loss in peripheral lymph node T-cell populations constitutes evidence for the diagnosis of peripheral T-cell lymphoma.[22] However, 4 cases without abnormal T-cell antigen loss also showed β T-cell receptor gene rearrangements. Therefore, abnormal patterns of T-cell antigens may be a useful indicator of neoplasia, but based on results of our gene rearrangement analysis, the contrapositive conclusion—that normal patterns of T antigen expression indicates nonneoplastic changes—cannot be regarded as reliable, at least in this clinical and histologic setting.

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