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Research Article

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Clonality of Angioimmunoblastic Lymphadenopathy and Implications for Its Evolution to Malignant Lymphoma

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Abstract

To investigate the relationship of the lymphoid hyperplasia of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) to supervening malignant lymphoma, we subjected DNA from lymph nodes and peripheral blood mononuclear cells from five AILD patients to Southern blot analysis to detect clonal rearrangements of immunoglobulin and T-cell receptor genes.

Lymph nodes and peripheral blood from AILD patients were found to contain clones of lymphoid cells harboring either immunoglobulin or T-cell receptor gene rearrangements that, in some instances, regressed during the course of disease. A lymph node from one patient was involved by immunoblastic lymphoma and manifested an additional gene rearrangement pattern not seen in premalignant specimens from that patient. In contrast, DNA obtained from normal peripheral blood mononuclear cells and 11 examples of other forms of lymphoid hyperplasia showed no gene rearrangements.

As a disorder of cellular immunoregulation in which lymphoid cells may escape normal growth controls, AILD provides a natural model to dissect stages of lymphomagenesis in man.

Introduction

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)¹ is a potentially fatal disorder of uncertain etiology characterized by generalized lymphadenopathy, hepatosplenomegaly, skin rash, polyclonal hypergammaglobulinemia, and hemolytic anemia (1–3). Despite the lymphomalike clinical syndrome, the histological picture is often more consistent with a benign polymorphous immunoproliferative disorder (4). Indeed, in some patients, the disease may remain indolent or even regress in the absence of cytotoxic therapy (2). However, in the majority of patients the disease pursues an aggressive course, leading to death in 75% of the cases and a median survival of 30 mo (5).

The most serious complication of AILD is the development of an aggressive (immunoblastic) non-Hodgkin's lymphoma, which occurs in nearly half of all patients (4). It is not known if

AILD is neoplastic at onset, and the relationship between AILD and subsequent lymphoma has been difficult to define. Tissues involved by AILD contain mixtures of T and B lymphocytes (6), whereas lymphomas arising in AILD have been variously described as poly- or monoclonal B-cell type (7–10) or T-cell type (11). Cells from lymph nodes containing both AILD and lymphoma demonstrate cytogenetic abnormalities (12), but it is not known whether these abnormalities occur in the malignant lymphoma cells or are in cells of B or T lineage.

To help resolve questions concerning the cellular derivation and clonality of AILD and its associated malignant lymphomas, we performed gene rearrangement analysis on patient material. As previously demonstrated, detection of rearranged genes by Southern blot analysis can reveal cellular lineage and clonality in lymphoid neoplasms (13–19). In this study we have subjected tissues from patients with AILD and other forms of lymphoid hyperplasia to Southern blot analysis, using probes that detect gene rearrangements characteristic of either B cells (immunoglobulin genes) (14, 15) or T cells (T-cell receptor β -chain gene) (16–18) to determine both lineage and clonality. With this approach we now provide evidence that AILD is a disease of proliferating lymphoid clones, in which supervening malignant lymphomas may develop by a process of clonal selection.

Methods

Patient samples. All patients were seen at the National Institutes of Health and each presented with the typical clinical and laboratory features of AILD, including generalized lymphadenopathy, skin rash, polyclonal gammopathy, and classic histologic features of AILD (4) in lymph node specimens. A chronology of specimens and their diagnoses obtained from each patient during the course of disease is presented in Table I. Lymph nodes containing other forms of lymphoid hyperplasia were obtained for comparison. Histological diagnoses in these 11 cases included follicular hyperplasia (six cases), mixed follicular and paracortical hyperplasia (two cases), and atypical lymphoid hyperplasia (three cases). Underlying diseases in these patients included hypereosinophilic syndrome, common variable hypogammaglobulinemia, rheumatoid arthritis, AIDS-related complex with persistent lymphadenopathy, and Hodgkin's disease. In addition, peripheral blood mononuclear cell DNA from three normal donors was examined.

DNA analysis. High-molecular-weight genomic DNA was extracted from the lymph nodes and peripheral blood by standard methods. DNA was digested with appropriate restriction endonucleases, size separated by electrophoresis on 0.8% agarose gels, transferred onto nylon membranes (GeneScreen Plus, New England Nuclear, Boston, MA) by the method of Southern (20), and hybridized with ³²P-radiolabeled DNA probes (21), as previously described (14, 21). Probes included a constant region-specific, *Ava*I/*Pst*I fragment of the human T-cell receptor β -chain cDNA clone YT35 (22), and human genomic J_H, C_κ, J_κ, and C_λ immunoglobulin gene probes, as reported (14). Rearrangements were con-

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1. Abbreviations used in this paper: AILD, angioimmunoblastic lymphadenopathy with dysproteinemia.

Table I. Gene Rearrangements in Angioimmunoblastic Lymphadenopathy

Case	Date	Site	Diagnosis	Gene rearrangements			
				IgH	Ig κ	Ig λ	T β
1a	9/84	LN	AILD	R	G	G	R
1b	10/84	PB	NL	R	G	G	R
1c	11/84	LN	AILD + IBL	2R	G	2R	R
2a	6/81	LN	AILD	G	G	G	G
2b	9/82	LN	AILD	G	G	G	R
2c	12/83	LN	AILD	G	G	R	G
2d	1/84	PB	L	G	G	G	G
3a	11/84	PB	NL	G	R	G	R
3b	1/85	PB	NL	G	G	G	G
4a	10/84	PB	NL	R	G	G	G
4b	11/84	PB	NL	G	G	G	G
4c	1/85	LN	AILD	G	G	G	2R
5a	8/84	PB	NL	G	G	G	R
5b	11/84	PB	NL	G	G	G	G

Abbreviations: AILD, angioimmunoblastic lymphadenopathy with dysproteinemia; G, germline; IBL, immunoblastic lymphoma; L, leukocytosis; LN, lymph node; NL, normal; PB, peripheral blood; R, rearranged (preceding number indicates number of nongermline bands).

firmed by the use of multiple enzymes whenever possible. The restriction endonucleases used were *EcoR*I and *Hind*III for J_H; *Bam*HI for C _{κ} ; *Hind*III for J _{κ} ; *EcoR*I for C _{λ} ; and *Bam*HI, *EcoR*I, and *Hind*III for C _{μ} .

Results

The diagnosis of AILD was established histologically in lymph node biopsies from all patients. In addition, a diffuse malignant lymphoma, large cell immunoblastic type, developed in patient 1 following previous evidence of AILD (Fig. 1).

Southern blot analysis of DNA obtained from the lymph nodes and peripheral blood of all five AILD patients revealed gene rearrangements in at least one tissue site from each individual (Table I). Rearrangements were found in lymph nodes from each patient studied and in the peripheral blood of four of five patients.

In patient 1, a single immunoglobulin heavy-chain gene rearrangement and a single T-cell receptor β -chain gene rearrangement persisted in all three specimens (Fig. 2). Coincident with histological progression to malignant lymphoma (sample 1c) was the appearance of additional immunoglobulin gene rearrangements involving a second heavy-chain allele and two lambda light-chain alleles. The new heavy- and light-chain gene rearrangements in specimen 1c are most consistent with the emergence of a clonal B-cell lymphoma in this lymph node.

Of the four specimens analyzed from patient 2, rearrangements were found in two lymph node biopsies exhibiting AILD (samples 2b and 2c). However, the gene rearrangements were different between these samples since only a T β rearrangement was seen in sample 2b (not shown) but a single Ig λ gene rearrangement was found in 2c (Fig. 3) without evidence of a T β rearrangement. Thus, two separate specimens from patient 2 apparently contained substantial expansions of two separate lymphoid clones.

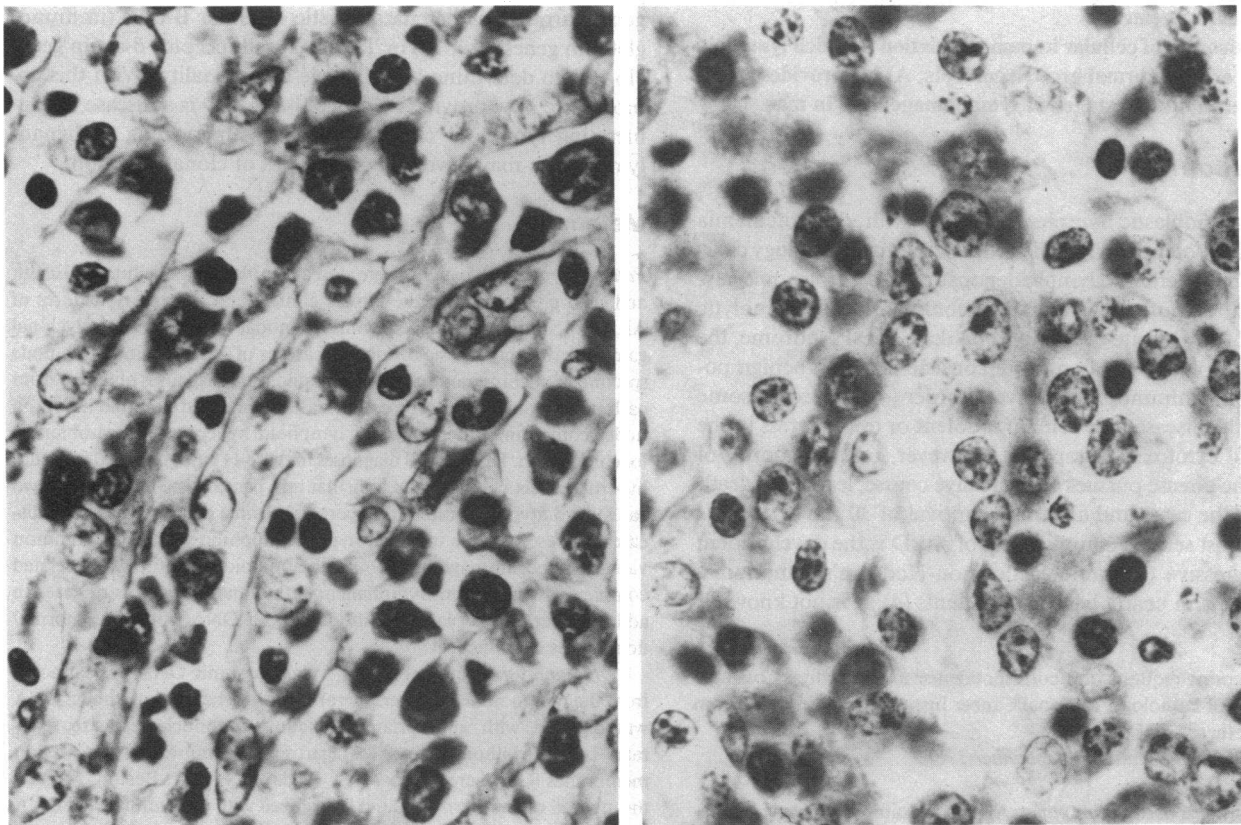


Figure 1. Histology of lymph node specimens from patient 1 reveals in the earlier specimen (*left*) a polymorphous cellular infiltrate of lymphocytes, plasma cells, and immunoblasts typical of AILD. A subsequent biopsy (*right*) shows clustering and aggregates of large lymphoid cells with open chromatin and nucleoli characteristic of immunoblastic lymphoma arising in AILD ($\times 650$).

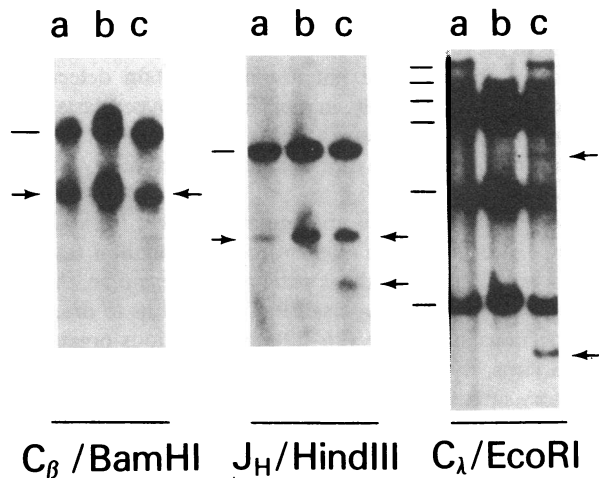


Figure 2. Gene rearrangements in specimens from patient 1. Specimens *a*, *b*, and *c* (see Table I) show consistent T-cell receptor β -chain (C_β) and immunoglobulin heavy-chain gene rearrangements (J_H) (rearrangements are indicated by arrows). In addition, specimen *c* (immunoblastic lymphoma) shows a new immunoglobulin heavy chain (J_H) and two new lambda light-chain gene rearrangements (C_λ). Germline bands are indicated by a dash. Probes and enzymes are indicated beneath each set of lanes.

Of the two peripheral blood samples available from patient 3, the earlier one, 3*a*, contained both an immunoglobulin gene rearrangement (IgK) and a T cell receptor gene rearrangement ($T\beta$) in the same specimen (Fig. 3). By contrast, when examined

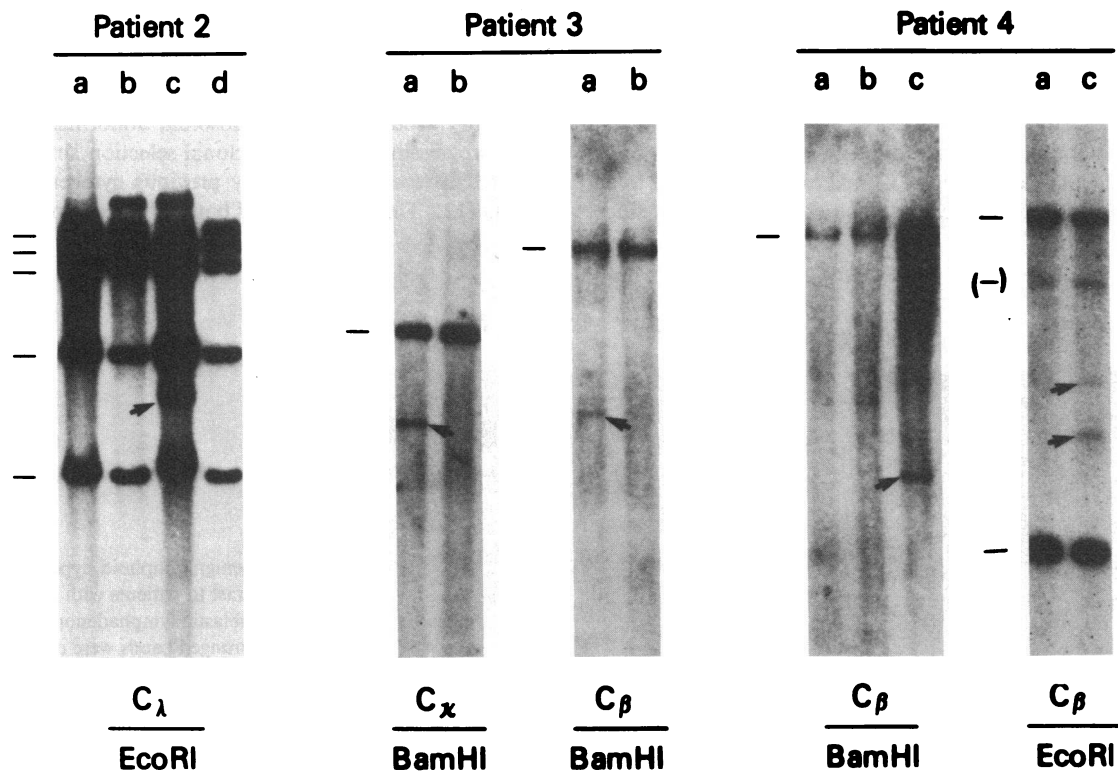


Figure 3. Gene rearrangements in AILD. Rearrangements (arrows) of immunoglobulin (C_λ probe and C_κ probe) and T-cell receptor β -chain (C_β probe) genes appeared during the course of disease. A single lambda light-chain gene rearrangement was detected in sample *c* from patient 2. In patient 3, clonal rearrangements of one kappa light-chain

two months later the peripheral blood (3*b*) contained no detectable rearrangements (Fig. 3).

Sequential sampling of patient 4 revealed a single rearranged IgH allele in the first peripheral blood specimen (4*a*) and no evidence of rearrangements in the second peripheral blood sample (4*b*). A lymph node with the morphological features of AILD (4*c*) contained two rearranged $T\beta$ alleles (Fig. 3) but rearrangement of IgH was no longer apparent. Therefore, in patient 4 a detectable clone in the peripheral blood regressed over a 1-mo period and a new clone, or clones, harboring $T\beta$ rearrangements emerged in a lymph node containing AILD.

Two peripheral blood samples obtained 3 mo apart from patient 5 were analyzed and a single $T\beta$ gene rearrangement was detected in the earlier sample (5*a*) but was not apparent in the later specimen (5*b*).

It is notable that in addition to the emergence and disappearance of detectable clones during the course of disease, rearrangements of immunoglobulin genes as well as T-cell receptor genes were detected in tissues from several patients and even coexisted in the same specimens. The simultaneous presence of immunoglobulin and T-cell receptor gene rearrangements in a single tissue site is attributable to either separate B- and T-clones or to one clone that might harbor rearrangements of both genes, as occasionally occurs in some lymphoid neoplasms (16, 18, 23).

In view of the frequent occurrence of substantial clonal populations in the lymph nodes and peripheral blood of AILD patients, we next questioned whether clones could also be detected in other types of lymphoid hyperplasia. Lymph nodes exhibiting various lymphoid hyperplasia morphologies were analyzed from

gene and one T-cell receptor β -chain gene were present in the same specimen (3*a*). In specimen 4*c*, a second T-cell receptor β -chain gene rearrangement was revealed by digestion with *Eco*RI. In this blot, (dash) indicates an inconsistent germline band found in some samples and is not considered a rearrangement.

11 patients (see Methods). When examined for the presence of immunoglobulin and T-cell receptor gene rearrangements, none of the 11 lymphoid hyperplasias exhibited detectable rearrangements (Fig. 4). The polyclonal nature of the hyperplasia was further confirmed by a relatively diminished intensity of the 12-kb *EcoRI* T β fragment. This fragment contains the germline D β_1 -J β_1 -C β_1 complex, which is rearranged or deleted in mature T cells and thereby results in a decrease in the dosage of the germline 12-kb fragment in a T cell population (24).

Discussion

The cellular derivation, clonality, and neoplastic nature of the AILD have remained in question since its initial description in 1974 (1-3, 11, 25). The elusiveness of its characterization may be attributable to the fact that some lesions spontaneously regress, whereas other clinically and morphologically similar lesions progress to high-grade lymphoma (7, 25). Immunological phenotyping studies have demonstrated mixed populations of T cells and B cells without consistent evidence of monoclonality of the B-cell population, since both κ and λ immunoglobulin light chains are often present (7, 10). Direct analysis of the clonality of the T-cell population could not be readily performed until recently, following the discovery and application of probes for the rearranging T-cell receptor β -chain gene (22). The advent of gene rearrangement analysis, using a combination of immunoglobulin and T-cell receptor gene probes, offers the opportunity to address questions regarding clonality and lineage of enigmatic lymphoid hyperplasias such as AILD.

In the present study, we have discovered clonal lymphoid populations in the peripheral blood and lymph nodes of five patients with typical clinical and laboratory findings of AILD. This result indicates that AILD is a lymphoproliferative process in which clones of B cells, T cells, or both, expand during the course of disease and infiltrate lymph nodes as well as the peripheral circulation. One may detect rearrangements of either immunoglobulin or T-cell receptor genes. Clonal expansion of both B and T cells suggests that AILD may be a disorder of

immunoregulation, in which lymphoid cells are permitted to proliferate in great excess. In contrast to AILD, other forms of lymphoid hyperplasia were not found to contain detectable lymphoid clones. Presumably, in most forms of hyperplasia, immunoregulatory controls remain intact and no individual lymphoid clone can expand to a threshold level detectable by Southern blot analysis.

The etiology of the immunoregulatory defect in AILD is unknown, but it is possible that antigenic stimulation triggers lymphoid proliferation in these patients. For example, AILD has been associated with hypersensitivity reactions to drugs to other exogenous substances (26-28). An infectious organism, such as a virus, might selectively stimulate or destroy immunoregulatory subsets, leading to deregulation of the immune response. Consistent with this hypothesis, T cells from some patients produce factors which induce immunoblastic transformation of B cells (29).

Because of their propensity to disappear or not progress to overt malignant lymphoma, the proliferating lymphoid clones in AILD might not be malignant neoplasms at onset. However, expanding clones would be susceptible to genetic errors during the repeating cell division process. For example, a chromosomal translocation could result in constitutive activation of a growth-promoting substance, perhaps encoded by an oncogene, as has been suggested for a number of hematopoietic malignancies (30). Such an activation of the cellular oncogene *c-myc* has been previously reported in patient 2 from this series (31). It is hypothesized by analogy that Burkitt's lymphoma arises in a setting of chronic Epstein-Barr virus stimulation, in which B cells undergoing repeated rounds of cell division are at risk of a chromosomal translocation involving the *c-myc* oncogene and one of the immunoglobulin genes (32, 33). Likewise, it appears that in AILD a secondary event or events must occur to produce malignant transformation and selective proliferation of the malignant clone. Although we did not perform cytogenetic studies that might identify accumulated chromosomal abnormalities during disease progression, patterns of clonal selection similar to those reported here are suggested by previous cytogenetic studies in AILD (12). The availability of both the precursor le-

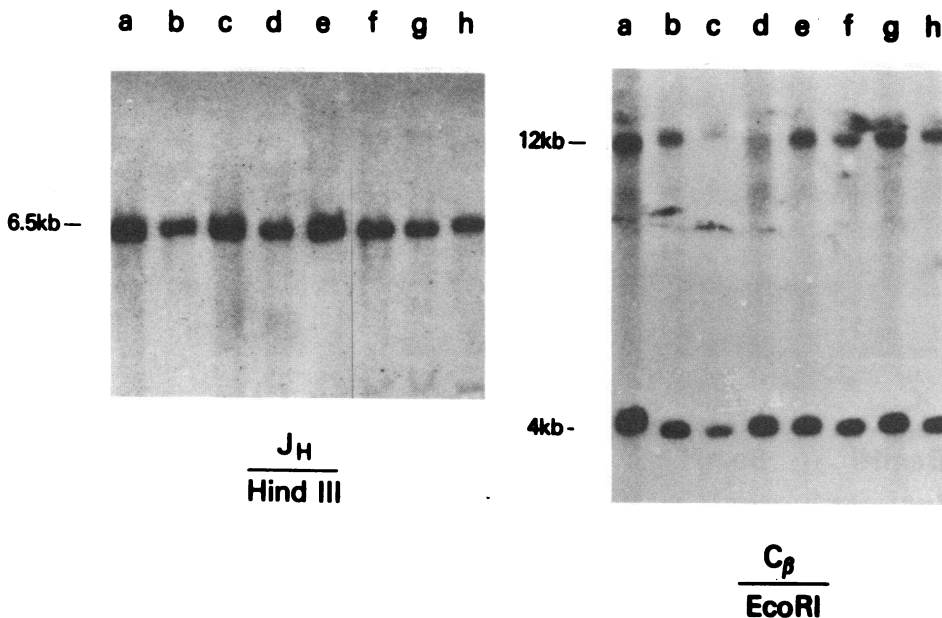


Figure 4. Benign lymphoid hyperplasia. In contrast to patients with angioimmunoblastic lymphadenopathy, no rearranged bands were detected in other types of lymphoid hyperplasia (lanes a-f, see Methods for diagnosis) or in normal peripheral blood mononuclear cells (lanes g and h). In several samples, the presence of polyclonal T cells, which harbor a variety of β -chain gene rearrangements, has led to a diminution of the 12-kb *EcoRI* germline band.

sions and the malignant lymphoma in patients with AILD provides an opportunity to investigate molecular changes associated with lymphomagenesis, such as chromosomal translocation, amplification, or deregulated transcription of cellular oncogenes or other growth promoting factors.

The consistent presence of one or more nongermline bands in the Southern blots of the tissues of AILD patients implies that clonality does not always indicate a diagnosis of malignancy. The interpretation of a gene rearrangement must be made in the context of the clinical and histological picture, as would any other laboratory technique. Increasing evidence has accumulated to show that in patients with either inherited (14, 34) or acquired (35) immunosuppression, lymphoid clones can be detected by gene rearrangement analysis. Iatrogenically immunosuppressed organ transplant patients may harbor multiple lymphoid clones, with each clone having its own distinct rearrangement pattern at different sites throughout the body (35). Many of these are probably B-cell clones infected by Epstein-Barr virus, a B-cell mitogen, and they frequently regress upon reduction or cessation of immunosuppressive therapy (36); therefore, they are best regarded as poorly regulated B-cell clones.

Molecular genetic analysis of human lymphoproliferative disease has provided evidence for the clonality and cellular origin of a number of disorders such as common acute lymphoblastic leukemia and hairy cell leukemia (13, 37). This demonstrates their monoclonality and cellular lineage simultaneously without the necessity of gene expression. For example, immunophenotypic analysis of the present cases revealed no evidence of clonality despite the detection of lymphoid clones by genetic hybridization. Furthermore, as no readily available phenotypic marker of T-cell clonality exists, clonality as determined by T-cell gene rearrangement analysis has effectively assumed a preeminent role in the diagnosis and classification of T-cell disorders (16-19, 23). With this technology, we have explored questions regarding the origin of AILD and its associated malignant lymphoma. This methodology should be generally helpful in the diagnosis of AILD and in investigations to determine its etiology.

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