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Clonal Gene Rearrangement Patterns Correlate with Immunophenotype and Clinical Parameters in Patients with Angioimmunoblastic Lymphadenopathy

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T cell receptor β (TcR_β) chain gene rearrangements have been reported in cases of angioimmunoblastic lymphadenopathy (AILD) and provided evidence for the presence of clonal T cell proliferations in this disorder. Twenty-three cases of AILD and two cases of hyperimmune reaction (HR) were investigated. In the two HR cases, essentially the same histologic pattern was present as in AILD but lymph node follicles were hyperplastic. Both HR cases showed germline configuration for the TcR and immunoglobulin heavy chain (Ig_H) genes. All other patients diagnosed with AILD had clonal rearrangements for TcR gamma and β chain genes. In addition, seven out of these cases had clonally rearranged their Ig_H genes. These two different rearrangement patterns (TcR with or without Ig gene rearrangement) correlated to immunohistochemical and clinical data. Cases with TcR but without Ig gene rearrangements (group I) exclusively showed $CD4^+$ proliferating T cells, whereas those cases with TcR and Ig gene rearrangements had significantly elevated numbers of $CD8^+$ proliferating cells (group II). Group II patients significantly more often presented with hemolytic anemia and went into transient remission spontaneously or under steroid treatment. Group I patients, however, had a higher response to chemotherapy and a longer survival time. These data show that, based on different rearrangement patterns, it is possible to divide AILD into two different groups with distinct immunophenotypic properties and differences in clinical parameters. Immunogenotyping in AILD thus will have prognostic and therapeutic implications. (Am J Pathol 1988, 133:549–556)

IN THE EARLY 1970s, several authors recognized a distinct clinicopathologic entity hallmarked by an acute onset of constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, immunologic abnormalities, and a characteristic histologic picture in lymph node biopsy specimens. Terms mainly used for largely identical observations were immunoblastic lymphadenopathy (IBL), angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), and lymphogranulomatosis X (LgX).[1–3] Generally, this disease was believed to be a primary abnormal immune reaction with severe impairment of cell mediated immune surveillance that therefore rendered patients liable both to fatal opportunistic infections and to development of lymphoid neoplasia.[4–6] Frequent evolution into malignant lymphoma soon led to the designation as a prelymphomatous le-

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Table 1—Murine Anti-Human Monoclonal Antibodies Employed for Immunohistologic Analysis

Antibody	CD	Specificity	Source
Lyt3	CD2	Sheep E receptor	NEN
Anti-Leu-4	CD3	Pan T cell	Becton-Dickinson (BD)
Anti-Leu-3a	CD4	Helper/inducer T cells macrophages	BD
Anti-Leu-2a	CD8	Suppressor/cytotoxic T cells	BD
Anti-Leu-1	CD5	Pan T cell, mantle zone B cells	BD
Ki-67		Proliferation associated antigen	Gerdes et al[24]
HD39	CD22	Pan B cell (except plasma cells)	Dörken et al[25]
C3RTo5	CD35	C3b receptor	Gerdes et al[26]
Ki-B1	CD23	Follicle mantle cells, DRC	Radzun, Kiel
Ki-M4b		Dendritic reticulum cells (DRC)	Parwaresch et al[27]
Anti IgA, M, D, G, kappa, lambda		Human immunoglobulin heavy and light chains	DAKO, Copenhagen

sion.[7,8] Shimoyama et al were the first to propose a distinction between IBL and so-called "IBL-like T cell lymphoma" on the grounds of cytomorphologic criteria.[9] Furthermore, chromosome analyses revealed consistent clonal abnormalities in AILD cases.[10–12] In at least part of the cases, the analogy of these chromosomal abnormalities with cytogenetic findings in proven T cell malignancies suggested a true neoplastic nature of the process *ab origine.*

More recently, molecular probes for immunoglobulin (Ig) and T cell receptor (TcR) genes became available and were shown to be useful for the detection of clonality and lineage determination in lymphoproliferative diseases.[13–15] Rearrangement studies of the TcR_{β} chain gene in AILD cases gave additional support for the clonal nature of this disease in a high proportion of patients.[16–19] Still, an explanation for the variable clinical course in AILD is missing.

The present study attempts to show that clonal lymphocyte populations are present in all cases of AILD and addresses the question of whether different genotypic profiles correlate with the immunophenotype of the proliferating cell population and different clinical parameters of the patients. We found that all 23 patients investigated in this study had clonal T cell proliferations except those two patients with the primary diagnosis of a hyperimmune reaction. Based on the pattern of the rearrangements, patients with AILD could be divided into two different groups, each of which has distinct immunophenotypic properties and correlates to different clinical parameters. To our knowledge, this is one of the first reports in which different rearrangement patterns in a lymphoproliferative disorder correlate with immunophenotypic and clinical data.[20]

Materials and Methods

Cases were referred from various hospitals in the Federal Republic of Germany. Lymph node biopsy specimens were obtained during the acute initial phase from 24 patients. In one patient transformation from hyperimmune reaction into AILD occurred 33 months later, and the corresponding specimen was also included in this investigation. Statistical significance was calculated by Mann–Whitney and Fisher's exact test (double sided). All lymph node specimens were divided into three parts. One was used for conventional histology, another for immunohistochemistry, and the third for gene rearrangement analyses. Diagnosis was confirmed by conventional light microscopy of routinely formalin-fixed and paraffin-embedded material. Four-micron sections were cut and stained for hematoxylin and eosin (H & E), Giemsa, periodic acid-Schiff (PAS), and Gomori silver impregnation.

Diagnosis of AILD was established morphologically and relied on the following criteria[3]: 1) Complete obliteration of nodal architecture by a disperse and variegated cellular infiltrate consisting of lymphocytes, plasma cells, immunoblasts, and occasionally epithelioid cells and eosinophils, with varying predominance of one or the other subpopulation; 2) Effacement of follicles except for occasional presence of residual coils of dendritic reticulum cells depleted from lymphoid elements, representing "burnt-out" germinal centers; and 3) Marked proliferation of epitheloid (high endothelial) venules with PAS-positive hyalinized distention of basement membranes. Hyperimmune reaction was diagnosed if criteria 1 and 3 were fullfilled but, contrary to criterion 2, hyperplastic germinal centers were detectable.

Immunohistology

Fresh biopsies were snap-frozen in liquid nitrogen and stored at −80 C until further processing. Immunohistological staining was performed using an extensive panel of murine monoclonal antibodies (MAb) to distinct human cell subsets (Table 1) by an indirect immunoperoxidase method.[21]

Alternatively, staining was achieved by the use of an unconjugated (rabbit anti-mouse) linking antibody and alkaline phosphatase (mouse) anti-alkaline phosphatase (APAAP) complex, with naphthol ASBI phosphate and Fast Red TR (Sigma Chemical Co., St.

Louis, MO) used as substrate and coupler, respectively.[22]

For assessment of proliferative activity of distinct cell subsets, sequential staining of cell surface markers and the monoclonal antibody Ki-67 was performed according to the procedure described by Feller and Parwaresch.[23] Binding of MAb Ki-67 to nuclei of any cell lineage has been found to be strongly associated with cell proliferation.[24] The different monoclonal antibodies used are given in Table 1. Lymphoid subpopulations were quantified by the ratio of cell surface marker positive cells to the total cell number counted in at least 8 randomly chosen high-power fields (not less than 500 cells overall). Furthermore, in double-stained sections the percentage of cells that express both the proliferation associated antigen Ki-67 and cell surface markers CD3, CD4, or CD8 was determined.

DNA-Analysis

DNA was extracted from snap-frozen lymph node material as described elsewhere.[17] Ten micrograms of DNA were digested with restriction enzymes BamHI, EcoRI, and HindIII (Boehringer, Mannheim, FRG) and the resulting fragments were separated by electrophoresis on a 0.7% agarose gel. Separated DNA fragments were transferred to nitrocellulose filters by the Southern blotting procedure.[28] Membranes were hybridized with cDNA probe fragments that had been radiolabeled with ^{32}P by nick-translation procedures. Details of the methods of hybridization and autoradiography have been described. DNA probes specific for the Ig heavy chain (Ig_H) joining region,[29] the constant region of kappa light chain genes (Ig_K),[30] and a cDNA of the gamma[31] and the constant region gene fragment of the β[32] subunit of the T cell receptor were employed. Rearrangement was determined by the appearance of new bands.

Results

Patients

Fifteen men and nine women were investigated (Table 2). Age at onset of clinical symptoms ranged between 42 and 82 years (mean, 71 years). Symptoms were generalized lymph node swelling and constitutional symptoms in all patients but number 17, who had extensive supradiaphragmatic involvement only; hepatosplenomegaly (14 patients); hyper/hypogammaglobulinemia (20 patients) or paraproteinemia (2 patients), anemia (10 patients, with signs of Coomb's positive hemolysis in 6), skin rash or edema of extremities (4 patients each) and pulmonary or pleural infiltrates (2 patients). As no particular therapeutic recommendations in AILD have met with wide acceptance so far, patients were treated variably, based on the severity of symptoms and extension of disease. Spontaneous remission before treatment occurred in six patients. It was judged complete when full involution of lymphoma supervened and all accompanying symptoms subsided. This happened in four patients and lasted from 3 to more than 16 months (mean, 8.3 months). Hydrocortisone treatment was administered to nine patients and resulted in complete remission of disease in three. Seven patients received polychemotherapy on initial presentation. This led to complete remission in two patients that lasted more than 24 months, and one stable partial remission (9 months). Relapses were treated by polychemotherapy.

Overall survival was 17 ± 12 months. Three patients succumbed to progressive disease at initial presentation. Four died during the first relapse after an average of 12.3 months. Six did not survive their second relapse, diagnosed 10–56 months (mean, 22.7 months) after initial presentation. One patient survived 18 months until the fifth relapse. Three died from unrelated disorders in full remission. There were six survivors (26%) within the observation period. Due to the small number of patients, no attempt was made to relate treatment modalities to the clinical outcome.

Histology

Twenty-three patients showed the typical histologic picture of AILD as described above. The lymph node structure was totally effaced and lymph node follicles with germinal centers were absent. Because of the existence of hyperplastic follicles, 2 other patients were diagnosed as hyperimmune reactions.

Immunohistochemistry

Immunohistochemically, the cells diffusely infiltrating the lymph nodes predominantly expressed T cell surface antigens. Seventy to ninety-five percent (mean ± SD, 78 ± 18%) showed a positivity for CD2, CD3, and CD5 antigens. A partial antigen loss was not found. The CD4:CD8 ratio ranged between 0.3 and 9.8 (3.9 ± 2.6, Table 2). Two to fifteen percent (8 ± 5%) of the total cell number were B cells with a polytypic immunoglobulin expression. The B cells appeared diffusely intermingled within the T cell infiltrates. In 16 cases, there was a marked hyperplasia of dendritic reticulum cells (DRC) visualized by monoclonal antibodies Ki-M4, Ki-B1 (CD23), and To5

Table 2—Clinical Data, Immunophenotypic Data and Gene Rearrangement Patterns in AILD Patients

			Gene rearrangements				Clinical data			Immunophenotyping			
No.	Age	Sex	TcR_β	TcR_γ	Ig_H	Ig_K	Hemol. anemia	Spont. rem.	Cortison rem.	CD8/Ki67 (%)	CD4/CD8 ratio	No. of relapses	Survival (months)
1H	63	f	G	G	G	G		−	+	na	3.8		30
2H	63	m	G	G	G	nd		+	−	3	2.0		33*
3	80	m	R	R	G	G	−	−	+	3	3.0		2
4	66	m	R	R	G	nd	−	−	−	3	6.0		9*
5	74	f	R	R	G	nd	−	−	−	3	5.0		5
6	76	m	R	R	G	G	−	−	−	3	6.0		6
7	42	m	R	R	G	G	−	+	−	3	7.0	2	56
8	51	m	R	R	G	nd	−	−	+	3	7.5		13†
9	71	m	R	R	G	G	−	−	−	3	9.0		16
10	70	m	R	nd	G	nd	−	+	−	5	3.0		20†
11	48	f	R	R	G	nd	−	−	+	5	3.0	2	14
12	76	m	R	R	G	nd	−	−	−	5	4.0	2	24*
13	56	f	R	R	G	nd	−	+	−	6	1.9		16*
14	71	m	R	R	G	nd	+	−	+	6	3.0	2	10
15	58	m	R	nd	G	nd	−	−	−	8	1.9		1
16	77	m	R	R	G	nd	−	−	+	10	6.5		18
17	58	f	R	R	G	nd	−	−	−	12	1.4		23*
18	59	m	R	R	G	G	+	−	−	15	0.3		10
19	74	m	R	R	R	nd	+	−	+	3	1.0	2	30
20	63	m	R	R	R	G	+	−	+	15	4.0	2	11
21	81	f	R	R	R	G	+	−	+	15	4.0		37*
22	61	f	R	R	R	R	−	+	−	20	1.5	5	18
23	67	m	R	R	R	G	+	+	−	20	2.0	2	21†
24	69	f	R	R	R	G	−	+	−	24	4.0	2	23
25	78	f	R	R	R	G	−	−	−	40	1.0		24*

TcR_β, T cell receptor β-chain; $Ig_{H/K}$, immunoglobulin heavy/kappa light chain; G, germline; R, rearranged; nd, not done.
* Patients are alive.
† Patients died because of non-AILD related reason.

(CD35). This highly characteristic feature appeared as a coarse network of dendritic processes extending far beyond residual B cell foci and covering 50–90% of the section area. Between 5 and 70% (37 ± 20%) of the total cell count expressed the proliferation-associated antigen Ki-67. From 45–95% (76 ± 16%) Ki-67 positive cells simultaneously expressed the CD3 antigen. Proliferating B cells made up only less than 5% of the total B cell number. Among the T cell subsets, 20–80% (55 ± 18%) of Ki-67 positive cells simultaneously reacted with an antibody to CD4, whereas 3–40% (10 ± 9%) expressed the CD8 antigen (Tables 2 and 3).

DNA Restriction Analysis

DNA hybridization analysis showed clonal rearrangement for the TcR_β chain gene in 23 patients (Table 2). Only one or two rearranged bands were detected in each case regardless of which restriction enzyme was used. All 21 patients probed for the gamma chain gene also had detectable rearrangements (data not shown). Seven patients also had clonal rearrangements when probed for the J region of the heavy chain gene (Figure 1). In the majority of cases, the intensity of the bands indicating a rearrangement of the Ig_H gene was comparable to or lower than the intensity of the new bands detected with the TcR_β chain gene probe. Only one of these seven patients showed a faint rearranged band when probed for the kappa light chain gene (Figure 2). The two remaining patients diagnosed primarily as hyperimmune reaction retained germline configuration with all cDNA probes after di-

Table 3—Major Differential Criteria in the Two Groups of AILD Cases with Different Rearrangement Pattern

Rearrangement pattern	N	CD8/Ki-67 ratio (%)	Hemolytic anemia	Spontaneous/ steroid-induced remission	Survival (months)	Relapse†
TcR_γ + TcR_β (group I)	16	6 ± 4*	2*	8	15 ± 13	4*
TcR_γ + TcR_β + Ig_H (group II)	7	20 ± 10*	4*	6	23 ± 8	4*

* Indicates statistically significant differences with $P < 0.025$.
† Number of patients with two or more relapses.

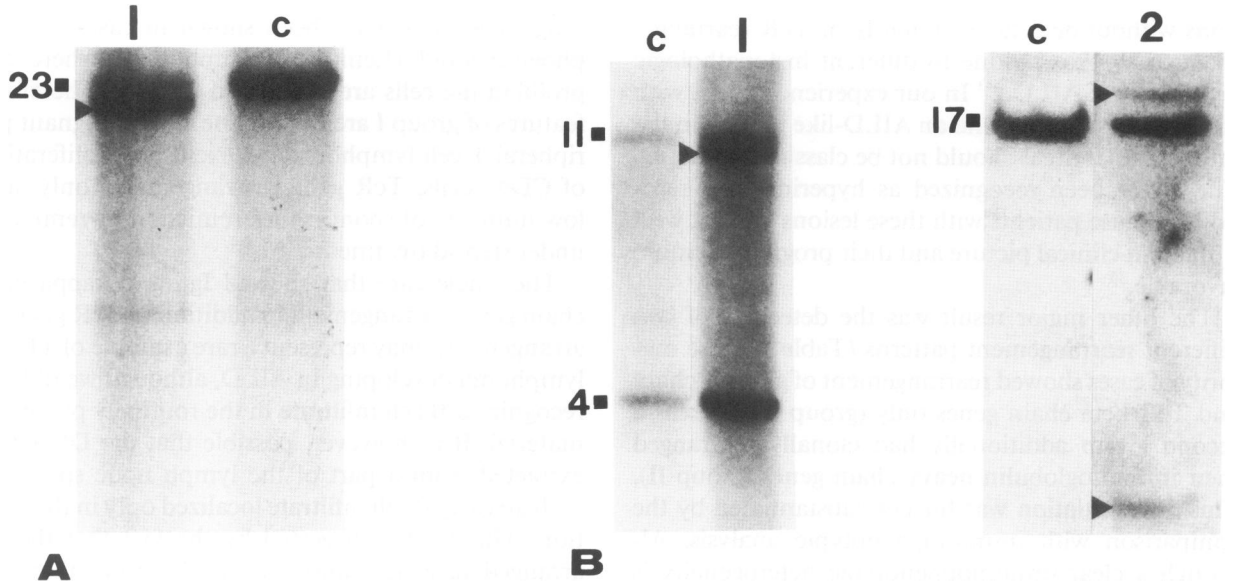

Figure 1—Southern blot analysis of genomic DNA from lymph nodes of patients with angioimmunoblastic lymphadenopathy (AILD). Control DNA (c) was obtained from human placental tissue. **A**—DNA of an AILD sample from a group I patient cut with BamHI and hybridized with a TcR_β constant region gene probe (lane 1). **B**—DNA from a group II patient cut with EcoRI and hybridized with the TcR_β probe (lane 1) and the Ig heavy chain joining region gene probe (lane 2). Germline bands are marked with ■ and their size is given in kilobases. Arrowheads mark rearranged bands.

gestion with each of the three restriction enzymes (Table 2, No. 1 and 2). One of these two patients (number 2) had a second biopsy after 33 months that showed histologic changes of AILD. Gene rearrangement of the gamma and β chain gene could be detected in this biopsy specimen (Table 2, No. 4).

Discussion

One of the main results of our study is the detection of clonal T cell proliferations in all cases diagnosed histologically as AILD. Two other cases that were primarily diagnosed as hyperimmune reaction showed germline configuration with the TcR and Ig gene probes (Table 2, No. 1 and 2). A subsequent biopsy from one of these patients exhibited a typical picture of AILD and revealed rearrangement of the TcR gamma and β chain genes (Table 2, No. 4). Similar observations of transformation of a reactive lesion into AILD with detectable clonal cell proliferations have previously been reported.[19] The fact that some cases in the literature had polyclonal T cell prolifera-

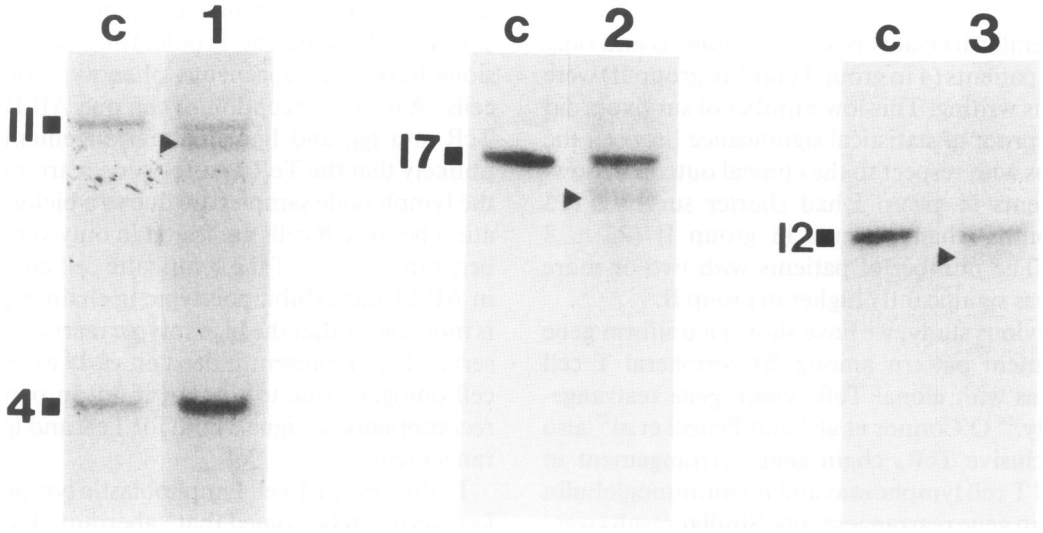

Figure 2—Analysis of DNA from a patient with AILD. Rearrangement of the TcR_β gene (lane 1, EcoRI digest), Ig heavy chain gene (lane 2, EcoRI digest), and Ig kappa light chain gene (lane 3, BamHI digest) occur in the same lymph node specimen.

tions without detectable clonal Ig or TcR rearrangements may thus be due to different histopathologic definitions of AILD.[1-3] In our experience, cases with follicular hyperplasia and an AILD-like pattern in the interfollicular areas should not be classified as AILD. They have been recognized as hyperimmune reactions because patients with these lesions present with a different clinical picture and their prognosis is more favorable.[33]

The other major result was the detection of two different rearrangement patterns (Table 3). The majority of cases showed rearrangement of gamma chain and TcR beta chain genes only (group I), whereas a second group additionally had clonally rearranged their immunoglobulin heavy chain genes (group II). This differentiation was further substantiated by the comparison with immunophenotypic analysis. Although a clear immunophenotypic heterogeneity is evident by the wide range of the CD4:CD8 ratio (0.3–9.8), the double staining procedure with the MAb Ki-67 showed that the major proliferating cell population in group I was $CD4^+$ and only 6 ± 3% of the proliferating cells were $CD8^+$. In group II, however, elevated numbers of proliferating $CD8^+$ cells were found (22 ± 9%). Clinical data were also compared between the two groups. Some factors were found to correlate with presence or absence of additional clonal J_H rearrangement. Within group I, only 2 out of 16 patients had hemolytic anemia, whereas this phenomenon was seen in 4 out of 7 patients in group II. Six out of 7 patients in group II had spontaneous remission or remission under steroid treatment, whereas this phenomenon was found in only 50% (8 out of 16) of patients in group I. These differences between patients in group I and II were statistically significant with $P < 0.025$.

The overall survival was 17 ± 12 months and only 26% of all patients (4 in group I and 2 in group II) were alive at this writing. This low number of survivors did not allow proof of statistical significance between the two groups with respect to the clinical outcome; however, patients in group I had shorter survivals (15 ± 13 months) than patients in group II (23 ± 8 months). The number of patients with two or more relapses was significantly higher in group II.

In a previous study, we have shown a uniform gene rearrangement pattern among 20 peripheral T cell lymphomas with clonal TcR_β chain gene rearrangements only.[14] O'Connor et al[34] and Pelicci et al[35] also found exclusive TcR_β chain gene rearrangement in peripheral T cell lymphomas and no immunoglobulin heavy chain gene rearrangements. Similar results were reported in the majority of T lymphoblastic lymphomas/leukemias.[36] Clonal TcR gamma and β rearrangements also have been shown in cases of lymphoepithelioid (Lennert's) lymphomas, where the proliferating cells are $CD3^+$ and $CD4^+$.[37] Therefore, features of group I are well in line with malignant peripheral T cell lymphoma, i.e. exclusive proliferation of $CD4^+$ cells, TcR gene rearrangements only, and low numbers of spontaneous remission or remission under steroid treatment.

The single case that showed Ig_H and kappa light chain gene rearrangement in addition to TcR gene rearrangements may represent a rare example of a B cell lymphoma developing in AILD, although we did not recognize a B cell infiltrate in the routinely processed material. It is, however, possible that the DNA was extracted from a part of the lymph node specimen with an early B cell infiltrate localized only in this portion. This is also suggested by the fact that the rearranged Ig gene bands are much fainter than the germline bands. A case of a multiclonal non-Hodgkin's lymphoma with different rearrangement patterns of the malignant cells in different parts of the same biopsy specimen has recently been published.[38]

A genotypic rearrangement pattern with immunoglobulin heavy chain in addition to TcR gene rearrangement is a rare event in T cell neoplasms and has mostly been described in cases of T cell lymphoblastic lymphomas/leukemias.[39-41] These rearrangements are most likely due to incomplete rearrangements joining the diversity with one of the joining regions (DJ rearrangements) and are not the result of complete rearrangement involving a variable region gene, as well (VDJ rearrangement). Furthermore, no Ig light chain gene rearrangement and no full-length RNA transcripts of Ig_H genes have been reported in these cases. The bigenotypic pattern in the clonal cell population does not reflect lineage infidelity on the expression level because the proliferating cells in these lesions have a homogeneous phenotype of mature T cells. With the exception of the one AILD case with TcR and Ig_H and Ig_K gene rearrangement, it is also unlikely that the TcR and Ig_H gene rearrangements in the lymph node samples are due to a biclonal proliferation because B cells are found in only very low numbers (around 8% of the lymphatic cell compartment) in AILD and exhibit polytypic Ig chain expression. It is more likely that the bigenotypic rearrangements observed here represent indeed an early event during T cell ontogeny due to similar, if not in part identical, recombinatorial signals both for TcR and Ig gene rearrangements.[42]

In the case of T cell lymphoblastic lymphomas/leukemias it can be argued that "aberrant" Ig_H gene rearrangement mostly occurs in immature lymphoid cells. However, in AILD the proliferating T lympho-

cytes morphologically and immunophenotypically appear to be mature. This leaves the question of whether the dual genotype in a lymphocyte with a monotypic phenotype reflects a malignant transformation that happened after lineage commitment or if a genotypically unstable cell potentially transforms into a malignant cell at any developmental stage open.

Even though the cellular mechanism of different gene rearrangement patterns in neoplastic T lymphocytic proliferation is not yet understood, there is evidence that these differences detected in AILD cases influence the biologic properties of the malignant process and do correlate with clinical features. We have shown that gene rearrangement studies can indeed assist diagnosis because it can differentiate between two distinct subtypes of AILD with different clinical and immunophenotypic parameters.

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