American Journal of Pathology, Vol. 139, No. 1, July 1991

Rearrangement of the T-cell Receptor Delta Chain Gene in T-cell Lymphomas with a Mature Phenotype

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The configuration of the T-cell receptor (TCR) delta chain gene was assessed using restriction fragment analysis and the Southern blot technique in 39 T-cell lymphomas with a mature immunophenotype. The TCRδ gene was rearranged in four lymphomas although the γ/δTCR was not expressed in two cases studied. The TCRδ gene was the only TCR gene rearranged in two cases. Each lymphoma with TCRδ gene rearrangement had an aberrant T-cell immunophenotype and three cases were of the large cell anaplastic type. The TCRδ gene was deleted in 22 cases and was in the germline configuration in 13 lymphomas. Deletion of the TCRδ gene was characteristic of mycosis fungoides, adult T-cell leukemia/lymphoma (human T cell leukemia-lymphoma virus positive), and Lennert's lymphoma, and was not identified in angiocentric lymphomas. In eight cases with TCRδ deletion, however, a large number of polyclonal (presumably reactive) T cells were present and, in these lymphomas, the authors could not determine if TCRδ gene deletion occurred in the polyclonal T cells, the neoplastic cells, or both cell populations. The authors conclude that the TCRδ gene is usually deleted in mature T-cell lymphomas, as would be expected in α/β TCR T cells. However, TCRδ gene rearrangement is detectable in approximately 10% of cases. Analysis of this locus may be useful diagnostically, as it occasionally may be the only molecular marker of clonality in mature T-cell lymphomas. T-cell receptor delta chain gene rearrangement also is found most often in lymphomas of the large cell anaplastic type. (Am J Pathol 1991, 139:161–168)

Mature T-cell lymphomas form a heterogeneous group of malignant neoplasms that may be difficult to diagnose using morphologic and immunophenotypic criteria.[1,2] Histologically a spectrum of cell sizes and types are typically found in T-cell lymphomas, including many non-neoplastic cells, making differentiation of T-cell lymphomas from reactive lesions problematic. Immunophenotypic analysis also may not be definitive because T cells do not express a clonal marker analogous to immunoglobulin light chain expression by B cells.[1,2]

Gene rearrangement analysis of the T-cell receptor (TCR) genes has been shown to be a useful method for distinguishing reactive from malignant T-cell infiltrates.[2–4] There are two TCRs, α/β and γ/δ, encoded by four genes that each rearrange during T-cell development before expression of the polypeptide chains that constitute the TCR.[2–4] Studies of the α-chain locus have been limited because of the large size of this gene.[2,4] Both the TCR β and γ genes are often rearranged in T-cell leukemias and lymphomas.[5–10] Up to 20% of T-cell lymphomas, however, may be germline for the TCR β gene.[9] In contrast, the genomic configuration of the recently described TCRδ gene, although well described in T-cell lymphoblastic lymphomas and leukemias,[11–15] is less understood in mature T-cell lymphomas.[16,17]

In this study, we analyzed the TCRδ gene in 39 mature T-cell lymphomas, diagnosed by conventional histologic and immunophenotypic criteria, to assess its possible value in the diagnosis of these neoplasms.

Materials and Methods

Thirty-nine malignant lymphomas with a mature T-cell immunophenotype were analyzed. Each neoplasm was accessioned in the Hematopathology Laboratory of the Na-

Dr. van Krieken was a visiting fellow from the Department of Pathology, University of Leiden, the Netherlands, supported by the Giesela Thier fund at the time this work was done.

Accepted for publication February 21, 1991.

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tional Cancer Institute and was selected on the basis of frozen tissue or cells being available for DNA extraction and Southern blot analysis. All cases were diagnosed using histopathologic and immunophenotypic criteria. According to the Working Formulation,[18] every case was diffuse: 13 cases were mixed small and large cell type, 23 lymphomas were large cell immunoblastic, two lesions were mycosis fungoides (MF) and one neoplasm was diffuse but not further classified. In addition, 25 lymphomas were further specified in the following manner: 4 cases were angiocentric lymphomas (ie, angiocentric immunoproliferative lesions, grade III),[19] 5 lesions had the morphologic features of Lennert's lymphoma,[20] 4 lymphomas occurred in the setting of human T-cell leukemia-lymphoma virus infection,[21] and 12 cases were of the large cell anaplastic type.[22]

Immunophenotypically, all neoplasms had a mature T-cell immunophenotype as defined by the expression of one or more pan–T-cell antigens (CD2, CD3, CD5, or CD7) and the absence of TdT or the CD1 antigen, immunoglobulin heavy and light chains, and pan–B-cell antigens. Twenty-eight tumors (72%) did not express one or more pan–T-cell antigens as described by others.[1] Immunophenotyping was performed using either cell suspensions and flow cytometric analysis or frozen section immunohistochemistry as previously described.[23] The core panel of monoclonal antibodies used included: Leu-I (CD5), Leu-4 (CD3), Leu-3a (CD4), Leu-2a (CD8) (Becton-Dickinson, Sunnyvale, CA), T11 (CD2), T6 (CD1), B1 (CD20), B4 (CD19), (Coulter Monoclonal Antibodies, Hialeah, FL), 3A1 (CD7) (courtesy of B.F. Haynes, MD), and immunoglobulin light and heavy chains (kappa, lambda, mu, gamma, alpha) (Bethesda Research Labs, Bethesda, MD). The CD30 antigen (using either the Ki-1 or BerH2 antibodies; DAKO, Santa Barbara, CA) was assessed in 33 cases and was positive in 13 cases, including all 10 large cell anaplastic lymphomas studied. In addition, in 10 cases (including two with TCRδ gene rearrangement), expression of the γ/δ TCR was assessed using the TCRδ-1 and TCS-1 antibodies (T Cell Sciences, Cambridge, MA) that react with Vδ1 and a TCRδ framework antigen, respectively.[15] These cases were also stained with the BF-1 antibody (T Cell Sciences), which reacts with a framework antigen of the α/β TCR.

Southern Blot Analysis

High–molecular-weight DNA was extracted from frozen tissue blocks or cell suspensions using a standard proteinase K phenol/chloroform technique. After purification, 10 to 15 μg of DNA were completely digested using the *Eco*R1, *Hind*III, and *Bam*H1 restriction enzymes. The digested DNA was electrophoresed in 0.7% agarose gels, depurinated in 0.25 N HCl, and transferred in 0.4 N NaOH[24] to nylon membranes (Gene Screen Plus, New England Nuclear Research Products, Boston, MA) The membranes were sequentially hybridized at high stringency in 50% formamide at 42°C with DNA probes radiolabeled with P32 using the random primer method.[25] The probes used in this study have been described previously. The TCR β gene was assessed with a cDNA probe of the constant region (Cβ).[26] The JH,[26] Jδ1[15] and Jγ1.3[27] probes were genomic. Because Jδ1 is the predominantly used J region of the TCRδ locus,[17,28,29] a probe of this region would be expected to detect most productive rearrangements as well as deletions of this region. Deletion of the TCRδ gene was determined by visual comparison of the intensity of the germline Jδ1 band with the germlines obtained with the other probes on the same blots.

Results

The clinicopathologic and genotypic data are listed in Tables 1 and 2.

TCRδ Gene Rearrangements

The TCRδ gene was rearranged in four lymphomas (10%), and the rearranged restriction fragments were variously sized in each case (Figure 1). In three lymphomas, a single rearranged band and a germline band were identified. In one neoplasm, two rearranged bands and a faint germline band were identified. In two cases, both the TCRβ and TCRγ chain genes were also rearranged, whereas in the other two lymphomas, the TCRβ and TCRγ genes were germline.

Three lymphomas with TCRδ gene rearrangements were classified histologically as large cell immunoblastic in the Working Formulation and were also of the large cell anaplastic type. Immunophenotypically all cases with TCRδ rearrangement had an abnormal T-cell phenotype. Each neoplasm was CD5 antigen negative. In addition, one lymphoma also lacked the CD3 antigen, in one lymphoma the CD2 and CD7 antigens were also negative, and in one lymphoma the CD3 and CD7 antigens as well CD5 antigen were absent. Each case was strongly CD30 antigen positive.

TCRδ Gene Deletion

In 22 lymphomas, the TCRδ gene (more precisely, the Jδ1 region) was deleted. In 19 of these cases, the TCRβ gene was rearranged and 16 of these lymphomas also had rearrangement of the TCRγ gene. In three T-cell lymphomas, deletion of the TCRδ gene was the only geno-

Table 1. Summary of Clinicopathologic, Immunophenotypic, and Genotypic Data

Case	Biopsy site	Histologic diagnosis*	Additional features	Immunophenotype			
				CD2	CD3	CD5	CD7
1742	Paraspinal mass	LCIB	LCAL	–	+	–	–
1807	LN	LCIB	LCAL	+	+	–	+
2005	Skin	LCIB	LCAL	+	–	–	–
2014	Nasopharynx	DM	AL	+	–	–	+
2073	Skin	MF		+	+	+	–
2094	LN	MF		+	+	+	–
856	Skin	DM	LL	+	+	ND	ND
933	LN	LCIB	LL	+	+	+	+
1315	LN	DM	LL	+	–	+	+
2239	Skin	DM	LL	+	+	–	+
862	LN	LCIB	ATL	+	+	+	ND
1148	LN	DM	ATL	+	+	+	–
1372	LN	DM	ATL	+	+	+	–
1894	LN	LCIB	ATL	+	+	+	–
757	LN	LCIB		+	–	ND	ND
1436	LN	DM		+	+	–	–
1485	LN	DM		+	–	+	–
1666	LN	LCIB		ND	+	–	–
2063	LN	LCIB		+	+	–	+
2119	LN	LCIB		+	+	+	+
1092	Skin	LCIB	LCAL	+	+	+	–
1254	LN	LCIB	LCAL	+	+	+	+
1685	Skin	LCIB	LCAL	+	+	–	–
1891	LN	LCIB	LCAL	+	+	–	–
1893	Flank mass	LCIB	LCAL	+	+	–	+
2139	LN	LCIB	LCAL	ND	+	–	+
1595	Nasopharynx	DU	AL	+	–	–	+
1887	Liver	DM	AL	+	+	+	+
2400	Lung	LCIB	AL	+	+	+	+
1378	LN	DM	LL	+	+	+	ND
1000	LN	LCIB	LCAL	+	+	+	+
1222	LN	LCIB	LCAL	+	–	+	–
1658	LN	LCIB	LCAL	–	–	–	+
291	LN	DM		+	+	ND	ND
739	LN	LCIB		+	–	–	–
834	LN	DM		+	–	ND	ND
1565	Skin	LCIB		+	–	–	+
2194	Skin	DM		+	+	+	+
2345	Skin	LCIB		+	+	–	–

* Working formulation. + TCRδ expression.

NC, neoplastic cells; BTC, benign T cells (% positive); LN, lymph node; MF, mycosis fungoides; DM, diffuse mixed small- and large-cell lymphoma; AL, angiocentric lymphoma (angiocentric immunoproliferative lesion, grade III); LL, Lennert's lymphoma; ATL, adult T-cell leukemia/lymphoma (HTLV-I+); LCIB, large-cell immunoblastic lymphoma; LCAL, large-cell anaplastic lymphoma; DU, diffuse unclassified lymphoma; D, deletion; R, rearrangement; P, TCRγ gene polyclonal T cell pattern; R**, TCRγ gene rearrangement and polyclonal T-cell pattern; G, germline; ND, not done.

mic change detected with these probes. In addition to the presence or absence of TCRγ gene rearrangement, analysis with the Jγ probe demonstrated up to eight bands in eight of these lymphomas, indicating the presence of a substantial number of polyclonal (non-neoplastic) T cells, constituting at least 10% of the cell population in these cases.[27] Because it is difficult to determine the percentage of admixed non-neoplastic T cells, either by morphologic or immunophenotyping methods, it is uncertain whether the TCRδ gene deletion occurred in the neoplastic cells, the polyclonal cells, or both cell populations.

The lymphomas with TCRδ gene deletion were classified in the working formulation as follows: seven diffuse mixed small and large cell, 13 large cell immunoblastic, and two MF. T-cell receptor delta chain gene deletion was identified in all cases of MF and adult T-cell leukemia/lymphoma and in four of five Lennert's lymphomas. Six of twelve large cell anaplastic lymphomas and 6 of 13 cases of T-cell lymphomas not further characterized as a clinicopathologic entity also had deletion of the TCRδ gene. There was no correlation between immunophenotype and TCRδ gene deletion. The incidence of pan–T-cell antigen absence was similar in cases with and without deletion of the TCRδ gene.

TCRδ Gene Germline

In 13 T-cell lymphomas, the TCRδ gene was in the germline configuration. In five of these tumors, the TCRβ

Table 2. Summary of Clinicopathologic, Immunophenotypic, and Genotypic Data

	Immunophenotype			TCRδ+		Genotype			
Case	CD4	CD8	Ig/pan-B	NC	BTC	Jδ	Cβ	Jγ	J_H
1742	+	−	−			R	R/R	R	G
1807	−	−	−	−	<5%	R	R/G	R	G
2005	+	−	−			R	G/G	G	G
2014	−	−	−	−	<5%	R	G/G	G	G
2073	+	−	−			D	R/G	R	G
2094	+	−	−			D	R/G	R	G
856	+	−	−			D	R/G	R	G
933	+	−	−	−	<5%	D	R/R	P	G
1315	+	−	−	−	<5%	D	G/G	P	G
2239	+	−	−			D	R/G	R	G
862	+	−	−			D	R/G	R	G
1148	−	−	−			D	R/R	R	G
1372	+	−	−			D	R/R	R	G
1894	+	−	−			D	R/R	R**	G
757	−	+	−			D	R/R	R	G
1436	+	−	−			D	R/R	R**	G
1485	+	−	−	−	<5%	D	R/R	R**	G
1666	+	−	−			D	R/G	R	G
2063	−	−	−	−	<5%	D	R/R	R	G
2119	−	+	−			D	R/R	G	G
1092	+	−	−			D	R/R	R	G
1254	+	−	−	−	<5%	D	G/G	P	G
1685	+	−	−			D	G/G	P	G
1891	+	−	−	−	<5%	D	R/R	P	G
1893	+	−	−			D	R/R	R	G
2139	+	−	−			D	R/G	R	G
1595	−	−	−			G	G/G	G	G
1887	+	−	−			G	G/G	P	G
2400	+	−	−			G	G/G	P	G
1378	ND	ND	−			G	R/R	P	G
1000	+	−	−			G	R/G	P	G
1222	+	−	−			G	G/G	P	G
1658	+	−	−			G	G/G	G	G
291	ND	ND	−			G	R/G	R	G
739	+	ND	−	−	<5%	G	R/G	R	G
834	+	−	−			G	R/R	P	G
1565	+	ND	−	−	<5%	G	G/G	G	G
2194	+	−	−			G	G/G	P	G
2345	−	+	−			G	G/G	P	G

Abbreviations can be found in Table 1.

gene was rearranged (two that also had TCRγ gene rearrangements). Analysis with the Jγ probe also demonstrated numerous bands indicating the presence of numerous polyclonal T cells in eight cases.

In eight T-cell lymphomas, all TCR genes were in the germline configuration. These cases included three angiocentric lymphomas and two large cell anaplastic lymphomas.

TCRδ Expression

Expression of the TCRδ protein (and presumably the γ/δ TCR) was assessed in 10 lymphomas in which frozen tissue was available for additional immunohistochemical staining (Figure 2). Each case had been previously stained with an anti-CD3 antibody. The cases studied included two lymphomas with TCRδ gene rearrangement (cases 1807 and 2014; both CD30+, 1 CD3+), six lymphomas with TCRδ gene deletion, five of which had >10% polyclonal T cells (cases 933, 1254, 1315, 1485, 1891, and 2063; five of six CD3+), and two lymphomas with the TCRδ gene in the germline configuration (cases 739, 1565; both CD3−). In all cases (including the two lymphomas with TCRδ gene rearrangement), the neoplastic cells did not react with either the TCRδ-1 or TCS-1 antibodies. The neoplastic cells in three lymphomas with TCRδ gene deletion were stained by BF-1 (cases 933, 1315, and 2063; all CD3+) indicating α/β TCR lineage. The tumor cells were BF-1 negative in seven cases (739, 1254, 1485, 1565, 1807, 1891, and 2014; three of seven CD3+), including both neoplasms with TCRδ gene rearrangement (cases 1807 and 2014). The majority of the non-neoplastic T cells in each biopsy were stained by the BF-1 antibody, whereas less than 5% (visual estimate) of these cells reacted with the TCRδ-1 and TCS-1 antibodies.

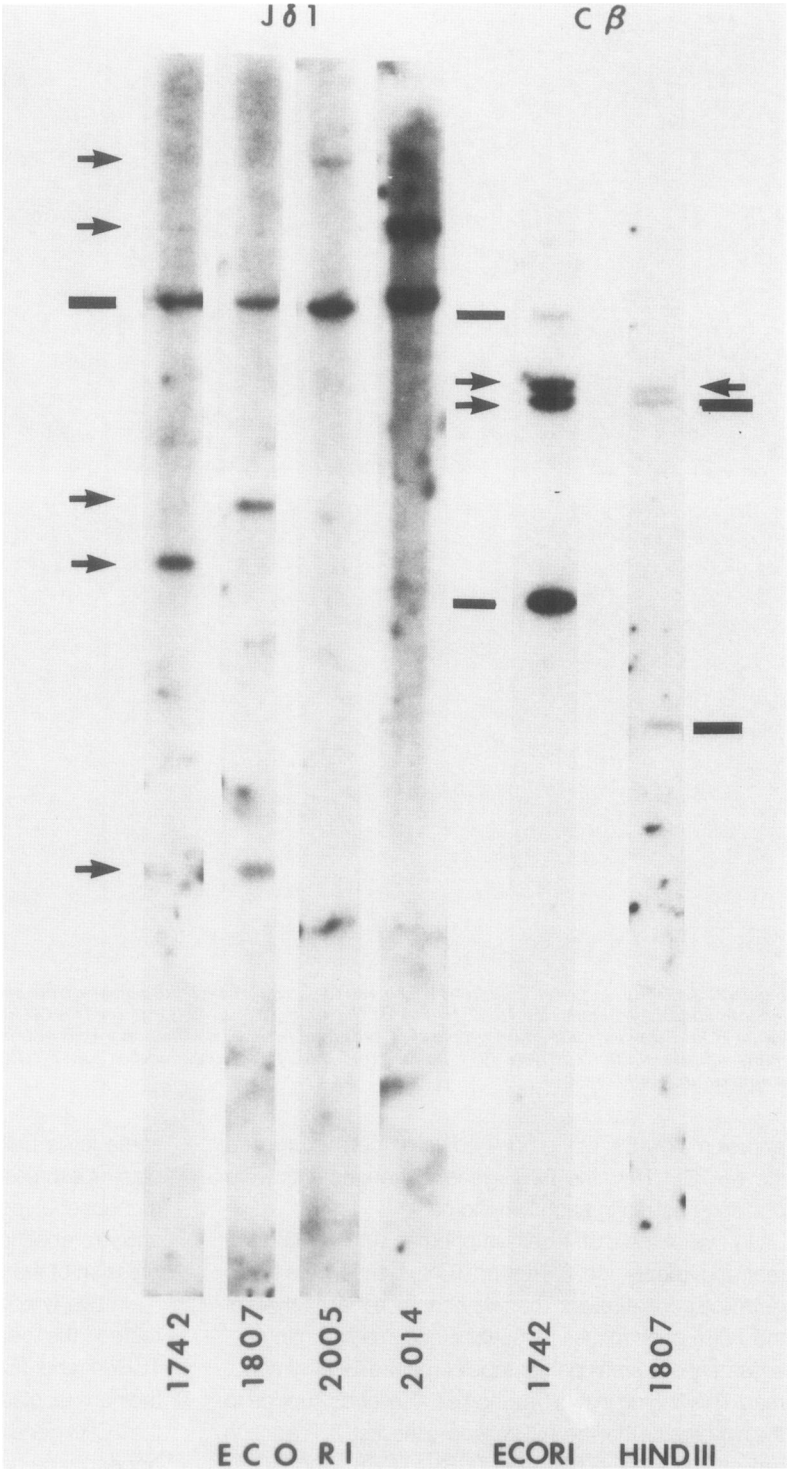

Figure 1. *Four of thirty-nine (10%) mature T-cell lymphomas (cases 1742, 1807, 2005, and 2014) had rearrangements of the TCRδ gene. The rearrangements were of different sizes in each case. Case 1807 had two rearrangements. Cases 1742 and 1807 also had rearrangements of the TCRβ gene.*

Discussion

In this study, we have identified rearrangements of the TCRδ gene in 4 of 39 (10%) T-cell lymphomas with a mature immunophenotype. Although we have not shown directly that the TCRδ gene rearrangements occurred in the neoplastic and not the non-neoplastic (presumably reactive) T cells, we believe that the rearrangements are likely to have occurred in the neoplastic cell population for the following reasons: First in each case with TCRδ gene rearrangement the neoplastic cells were the predominant cell population (more than 50% of all cells were neoplastic by visual estimate). Second in two cases stained with the TCRδ-1 and TCS-1 antibodies, less than

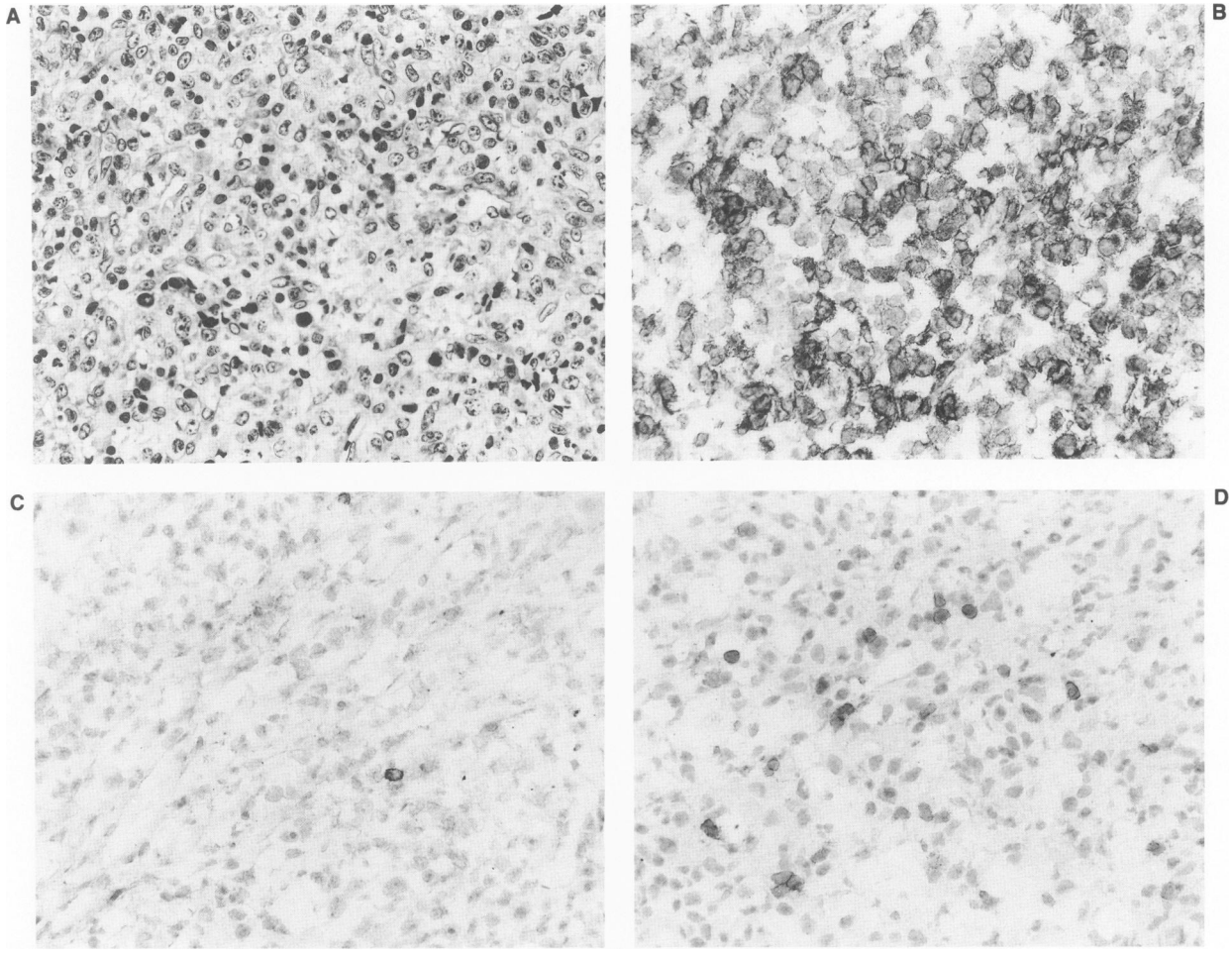

Figure 2. *A CD30+ large-cell anaplastic lymphoma (case 1807) with TCRδ gene rearrangement.* **A**: *The neoplastic cells have bizarre nuclear features and a high mitotic rate. (H&E, ×400).* **B**: *The tumor cells strongly expressed the CD30 antigen.* **C**: *The neoplastic cells were unstained by the TCRδ-1 antibody. Rare non-neoplastic T cells were positive.* **D**: *The tumor cells also were not stained by the BF-1 antibody, although many non-neoplastic cells were BF-1 positive and thus, presumably reactive α/β T cells.* (**B–D**, *immunoperoxidase with hematoxylin counterstain, ×400).*

approximately 5% of the non-neoplastic cells expressed the γ/δ TCR. Third the TCRδ gene rearrangements were of different sizes in each lymphoma.

In two of the four T-cell lymphomas with TCRδ gene rearrangements, the TCRβ and TCRγ genes were in the germline configuration. Thus we conclude that analysis of the TCRδ gene locus is a useful clonal marker in the assessment of a small percentage of mature T-cell lymphomas. This finding in two lymphomas also lends support to the hypothesis that the TCRδ gene is the first TCR gene to rearrange, followed by the TCRγ, TCRβ, and TCRα genes.[13–15,17]

The cases with TCRδ gene rearrangements in this study had certain features in common. All four lymphomas were characterized by bizarre histologic features; three cases were classified as large cell immunoblastic in the Working Formulation and had histologic features typical of the entity large cell anaplastic lymphoma.[22] TCRδ gene rearrangements have been shown previously in some large cell anaplastic lymphomas.[16] All four neoplasms expressed CD30 and had an aberrant T-cell immunophenotype characterized by preservation of CD2 antigen, absence of the CD5 antigen, and variable expression of the CD3 and CD7 antigens.

In two lymphomas with TCRδ gene rearrangements tested, the neoplastic cells were negative with the TCRδ-1 and TCS-1 antibodies whereas less than 5% of the non-neoplastic cells in the biopsy were positive. Thus the TCRδ gene rearrangements in these two lymphomas appear to be nonproductive. In view of the propensity of the TCRδ locus to translocate,[3] it is interesting to speculate that some TCRδ gene rearrangements in mature T-cell lymphomas may be a consequence of chromosomal translocation.

The TCRδ chain gene was deleted in 22 of 39 (56%) mature T-cell lymphomas. In three cases, the TCRβ and TCRγ genes were in the germline configuration. In these cases, we can not exclude the possibility that only the Jδ1

region was deleted and that rearrangement into the Jδ2 or Jδ3 regions may have occurred as has been rarely reported.[17,28,29] The Jδ1 probe we used would not address this possibility. In the remaining 19 cases with TCRδ deletion, the TCRβ chain gene was also rearranged, implying that the entire TCRδ gene was deleted, as would be expected on the basis of what is known about the δ/α locus in normal T cells.[15–17,30] The TCRδ gene is located within the TCRα gene locus and is deleted as a prelude to TCRα gene rearrangement in cells that differentiate into α/β T cells. In eight of these lymphomas, however, a substantial number (more than 10%) of polyclonal T cells was also detected with the Jγ probe.[27] Six of these lymphomas with TCRδ gene deletion, five of which had many polyclonal T cells, were stained with the TCRδ-1 and TCS-1 antibodies. The neoplastic cells did not express TCRδ. In each case, the majority of the non-neoplastic T cells also did not express the γ/δ TCR and were α/β (BF-1+) cells. Thus we cannot determine whether the TCRδ gene deletion seen in these cases occurred in the neoplastic cells, the non-neoplastic α/β T cells, or in both cell populations. Interestingly TCRδ gene deletion may correlate with specific clinicopathologic entities within the spectrum of mature T-cell lymphoma. For example, all cases of adult T-cell leukemia/lymphoma showed deletion of the TCRδ gene, as has been reported by others.[17] Similarly all cases of MF and four of five Lennert's lymphomas had TCRδ gene deletion. Presumably these are neoplasms of α/β T cells.

In 8 of the 39 (20%) cases in this study, all TCR genes were in the germline configuration. Four of these lymphomas did not express CD3. Our results as well as those of others would suggest that some of these cases arise from lymphoid precursor cells, before the stage of gene rearrangement, that subsequently acquire surface markers suggestive of a more mature phenotype.[31] Alternatively these cases may be oligoclonal or polyclonal T-cell lymphoproliferations.

Four of the lymphomas without gene rearrangements were CD3+. Perhaps CD3 and TCR expression were discordant, as is seen in lymphoblastic neoplasms.[32] A second possibility may be that the lesions were not truly malignant lymphoma. These cases were clearly malignant using histologic criteria, however, and one lymphoma had an abnormal T-cell immunophenotype, as is typically associated with malignant lymphoma.[1] Another possible explanation is that the tissue analyzed for rearrangements was not representative of the neoplasm. All four biopsies were taken from extranodal sites (skin, liver, lung). Historically in our laboratory DNA extracted from biopsies from extranodal sites is less often representative of the lesion than DNA extracted from lymph node biopsies.

In summary, in this study the TCRδ gene was deleted in the majority of mature T-cell lymphomas and rearranged in a small number of cases, approximately 10%. T-cell receptor delta chain gene rearrangement was the only molecular marker of clonality in two cases and thus analysis of this gene may be useful in the assessment of clonality. In addition, TCRδ gene rearrangement was found most often in large cell anaplastic lymphomas.

Acknowledgment

The authors thank Ms. Kim Condron for her help with the immunohistochemical staining.

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