Precursor T-Cell Acute Lymphoblastic Leukemia in Adults

Age-Related Immunophenotypic, Cytogenetic, and Molecular Subsets

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Abstract

We analyzed the clinicopathologic and molecular findings in 26 adults (age 16-72 years) with T-cell acute lymphoblastic leukemia (T-ALL) and observed features that correlated with age. Patients older than 60 years (n = 5) had a low frequency of hepatosplenomegaly (0 [0%]), anterior mediastinal mass (1 [20%]), and lymphadenopathy (2 [40%]), and completely responded to chemotherapy (4 of 4). The T-ALL in this group commonly expressed myeloid antigens (4 [80%]), had lineage-inappropriate gene rearrangements (2/3 [67%]) and chromosome 2 deletion (3/4 [75%]), and exclusively used the V_{III} or V_{IV} families of the T-cell receptor (TCR) gamma gene. In comparison, patients 16 to 60 years old (n = 21) more commonly had an anterior mediastinal mass (8 [38%]), hepatosplenomegaly (10 [48%]), and lymphadenopathy (16 [76%]). The tumors in these patients commonly used the TCR gamma gene V_I or V_{II} families (17/25 total rearrangements [68%]). Myeloid antigen expression (5 [24%]) and lineage inappropriate gene rearrangements (4/15 [27%]) were uncommon. Within this group, CD1a expression correlated with age 28 to 60 years. These results illustrate considerable age-related heterogeneity in adult T-ALL, which may reflect differences in tumor cell maturation.

Malignant lymphoid neoplasms of precursor T-cell origin have been designated as precursor T-cell lymphoblastic leukemia/lymphoma in the recently published World Health Organization classification for hematologic neoplasms.[1] Most of these neoplasms arise in patients in the second and third decades of life, who commonly develop an anterior mediastinal mass, lymphadenopathy, and organomegaly. Although most patients have involvement of the bone marrow or peripheral blood at the time of diagnosis, the true incidence of leukemic involvement is unclear.[2] Arbitrary cutoffs that have been used to separate acute lymphoblastic leukemia (ALL) from lymphoblastic lymphoma include the presence of circulating blasts and more than 25% blasts in the bone marrow.[3]

T-cell ALL (T-ALL) represents approximately 15% to 20% of all cases of ALL in Western countries. Only a small subset of these tumors occur in adults, and this disease is less common with increasing patient age, being truly rare in patients exceeding 60 years of age.[4-7] Owing to its relative rarity, T-ALL arising in adults, particularly in elderly people, has not been studied extensively. While older age has been associated with worse prognosis in ALL, most of these studies have focused predominantly on precursor B-cell ALL, which is far more common than T-ALL in the elderly.[4-9] Furthermore, although it is well documented that precursor B-cell ALL occurring in elderly people (ie, older than 60 years) has a poor prognosis, possibly related to a relatively high prevalence of the Philadelphia chromosome, the prognosis of T-ALL in this age group is unclear.

To address these issues, we collected all cases of T-ALL in adult patients at our institution during a 6-year interval, defined for the purposes of this study as older than 15 years

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of age at time of diagnosis. We identified 26 cases and analyzed their clinicopathologic, immunophenotypic, cytogenetic, and molecular features. Our results demonstrate significant heterogeneity among cases of adult T-ALL that correlate with patient age, with T-ALL in elderly patients (older than 60 years) having distinctive clinical and molecular features.

Materials and Methods

Study Group

Adult cases of T-ALL were identified by a review of the files of the Department of Hematopathology, University of Texas M.D. Anderson Cancer Center, Houston, diagnosed between January 1, 1994, and December 31, 1999. Criteria for inclusion in this study included the following: (1) older than 15 years at diagnosis and (2) morphologic and immunophenotypic features compatible with T-ALL. The charts of all patients were reviewed for clinical and laboratory findings at time of initial examination, therapy received, and outcome. Each case was classified morphologically according to the criteria of the French-American-British group.[10] The cutoff levels of leukocytosis, anemia, and thrombocytopenia used for statistical comparison were derived from earlier studies that established significant correlations of these values with patient survival.[8]

Immunophenotypic Methods

All cases were evaluated by flow cytometry, using CD45 expression vs side scatter to analyze the blast cell population. A panel of monoclonal antibodies was used specific for terminal deoxynucleotidyl transferase, HLA-DR, CD1a, CD2, CD3 (cytoplasmic and surface), CD4, CD5, CD7, CD8, CD10, CD13, CD14, CD19, CD20, CD22 (cytoplasmic and surface), CD33, CD64, CD117, immunoglobulin light chains (surface), and IgM and IgD heavy chains (cytoplasmic and surface). The cases were assigned immunologic subtypes according to the classification of the European Group for Immunological Classification of Leukemias,[11] with pro-T (designated as T-I) positive for only CD7, pre-T (T-II) positive for CD2 and/or CD5 and/or CD8, cortical T (T-III) positive for CD1a (irrespective of other markers), and mature T (T-IV) positive for surface CD3 and negative for CD1a (irrespective of other markers).

Conventional Cytogenetics

Cytogenetic analysis was performed on all bone marrow samples using 24-hour unstimulated bone marrow cultures followed by routine harvesting and G-banding, as previously described.[12] At least 20 metaphases were analyzed in each case, and the karyotypes were reported according to the ISCN (International System for Human Cytogenetic Nomenclature, 1995).

Molecular Analysis

Southern blot analysis was performed using *Eco*RI, *Bam*HI, and *Hin*dIII restriction enzyme digests of fresh bone marrow aspirate samples. The DNA probes used to assess the T-cell receptor (TCR) genes included a cDNA probe specific for the constant region of the TCR beta-chain gene (C_{beta}) and genomic probes specific for the joining region of the TCR gamma (J_{gamma})- and TCR delta (J_{delta})-chain genes. The DNA probes used to assess the immunoglobulin heavy (J_H) and kappa (J_{kappa}) light-chain genes were genomic probes specific for the joining region of each gene.

Variable segment use by the TCR gamma gene was assessed using a multiplex polymerase chain reaction (PCR) assay and DNA extracted from formalin-fixed, paraffin-embedded bone marrow biopsy tissue. Fluorescently labeled consensus variable (V) region primers specific for each V family (V_I through V_{IV}) and the 310-Genetic Analyzer with GeneScan software (PE/Applied Biosystems, Foster City, CA) were used in this assay, as described previously.[13]

Statistical Analysis

The association between CD1a expression and patient age was examined using the logistic regression method. The results were applied to determine the age cutoff required for a statistically significant association with this parameter, resulting in 3 age groups: older than 60 years, 28 to 60 years, and 16 to 27 years. The frequencies of various characteristics in the 3 age groups were compared using the 2-tailed Fisher exact test or the chi-square test, depending on the numbers included in each statistical analysis. A *P* value of less than .05 was considered statistically significant.

Results

Of 135 cases of ALL in adult patients identified in our files from 1994 to 1999, 26 (19%) cases were of T-cell lineage. These included 18 men and 8 women, with a median age of 32 years (range, 16-72 years). The percentage of blasts in the bone marrow of these patients ranged from 42% to 99% (median, 86%). Peripheral blood blasts were identified in 24 patients, ranging from 2% to 94% (median, 41%) of the total leukocyte count. Twenty-five patients received combination chemotherapy; 1 declined treatment. Nineteen patients underwent induction chemotherapy using the hyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin], dexamethasone) regimen[9]; 6 patients received other chemotherapy regimens.

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Table 1
Clinicopathologic Characteristics of 26 Adults With T-Cell Acute Lymphoblastic Leukemia Correlated With Age*

Clinicopathologic Characteristics	Group 1 (n = 5)	Group 2A (n = 12)	Group 2B (n = 9)
Clinical features			
Age (y)	>60	28-60	16-27
M/F	4:1	8:4	6:3
Lymphadenopathy	2 (40)	9 (75)	7 (78)
Mediastinal mass	1 (20)	6 (50)	3 (33)
Hepatosplenomegaly	0 (0)	6 (50)	4 (44)
Extrahematopoietic sites†	2 (40)	4 (33)	1 (11)
Central nervous system	0 (0)	4 (33)	1 (11)
Laboratory data			
WBC count >30,000/µL (>30 × 10^9/L)	0 (0)	4 (33)	4 (44)
Hemoglobin <10 g/dL (<100 g/L)	3 (60)	4 (33)	1 (11)
Platelet count <100 × 10^3/µL (<100 × 10^9/L)	3 (60)	6 (50)	3 (33)
Morphologic features (French-American-British)			
L1	2 (40)	4 (33)	2 (22)
L2	3 (60)	8 (67)	7 (78)
Immunophenotype			
T-II (pre-T stage)	3 (60)	2 (17)	6 (67)
T-III (cortical T stage)	2 (40)	10 (83)	2 (22)
T-IV (mature T stage)	0 (0)	0 (0)	1 (11)
Myeloid antigens	4 (80)	2 (17)	3 (33)
Cytogenetics			
Diploid karyotype	0 (0)	5/9 (56)	3 (33)
del 2q31 or –2	3/4 (75)	0 (0)	0 (0)
Clinical outcome			
Complete remission	4‡ (100)	12 (100)	8 (89)
Continuous complete remission	3‡ (75)	4 (33)	5 (56)
Follow-up duration (mo)	4.5-63 (median, 16)	8-67 (median, 17)	5-53.5 (median, 18)

* Data are provided as number (percentage) of group unless otherwise specified as number of cases affected/number of cases studied (percentage).
† Denotes extrahematopoietic tissues other than central nervous system (ie, skin, pleura, pericardium, testis, and orbital soft tissue).
‡ One patient in group 1 declined chemotherapy; therefore, response to therapy was calculated for the 4 patients treated.

Follow-up was available for all 26 patients and ranged from 4.5 to 67 months (median, 17 months).

For the purpose of further analysis, we initially segregated our patients into 2 groups, based on available data in the literature regarding clinical outcomes: group 1, age older than 60 years (n = 5); group 2, age 16 to 60 years (n = 21). However, when immunophenotypic data were examined, we noted a striking clustering of CD1a (cortical thymocyte stage) positivity in patients 28 to 60 years of age. By using the logistic regression method, age older than 27 years was identified as a statistically significant cutoff for an association between patient age and CD1a positivity (P = .03). By the same method, cutoffs of 25 or 30 years of age were not significant (P > .05). Therefore we further subdivided group 2 into groups 2A, age 28 to 60 years (n = 12), and 2B, age 16 to 27 years (n = 9), to determine whether other differences could be found between these groups. The clinicopathologic, immunophenotypic, and molecular features of these groups are summarized in **Table 1**.

Clinical, Peripheral Blood, and Bone Marrow Findings at Diagnosis

No statistically significant differences were identified between the 3 age groups. However, elderly patients (group 1) had a lower incidence of lymphadenopathy, mediastinal mass, hepatosplenomegaly, and central nervous system involvement compared with younger patients (groups 2A and 2B). Elderly patients also had lower levels of peripheral blood involvement and more severe anemia and thrombocytopenia than did younger patients. These findings correlated with bone marrow morphologic findings. Elderly patients generally had lower bone marrow cellularity (20%-40%) than younger patients (80%-90%), although the blast percentage was similar in each group **Image 1**. There was no significant difference in the morphologic features of the blasts (French-American-British type L1 or L2) between the groups.

Immunophenotype

The distribution of the various immunophenotypic subtypes in the 3 groups is outlined in Table 1. The T-ALL in group 2A had a higher frequency of the T-III subtype and a lower frequency of the T-II subtype than the T-ALL in group 2B (P = .009 and .03, respectively; Fisher exact test). There was no statistically significant difference in the distribution of immunophenotypic subtypes of T-ALL between group 1 and either group 2A or 2B. However, T-ALL in group 1 had a significantly higher frequency of myeloid antigen expression (P = .02; Fisher exact test) and CD34 expression (P = .05; Fisher exact test) compared with T-ALL in group 2A. The myeloid antigens expressed in T-ALL of group 1 included the following: CD13 in 2 cases, CD33 in 1

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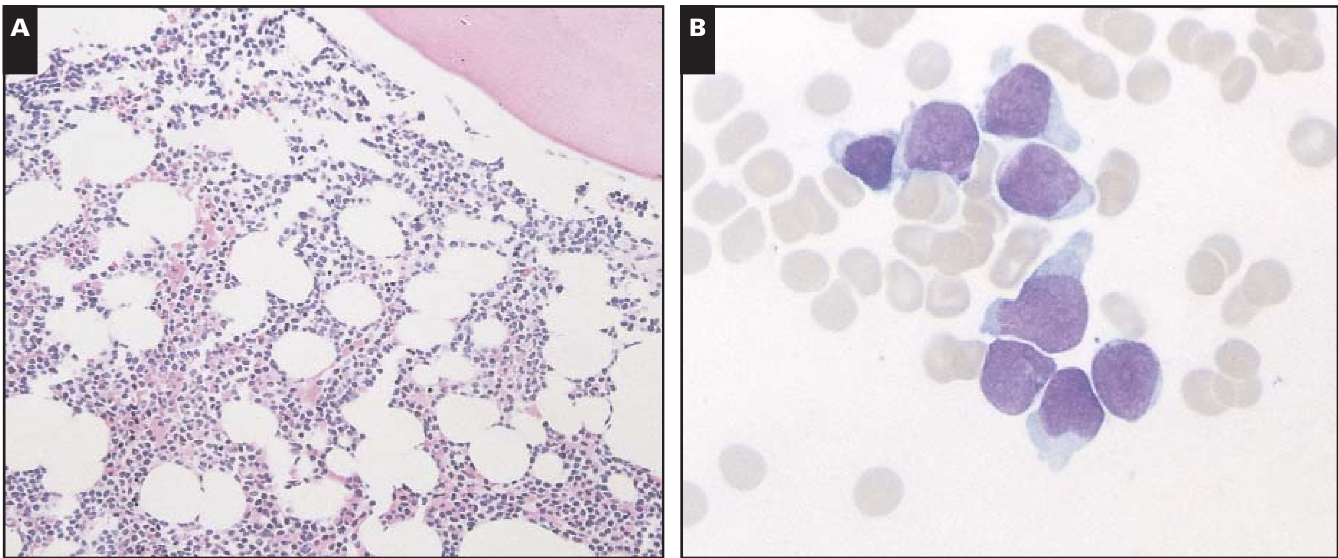
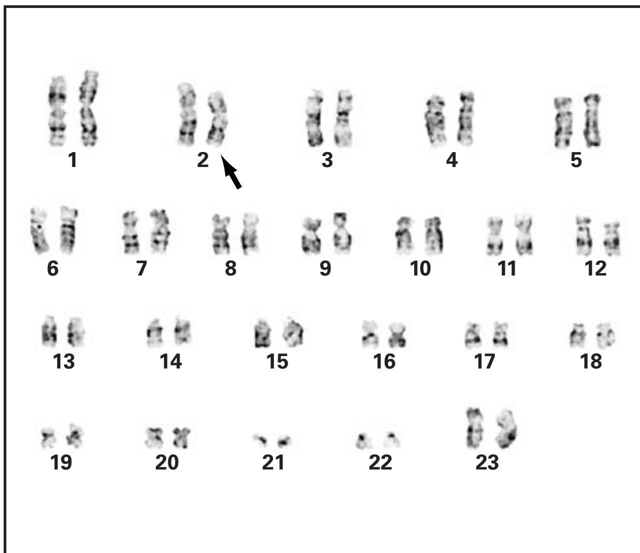


▮Image 1▮ A, Bone marrow biopsy specimen in a group 1 patient. As in all elderly patients in the study group, the bone marrow cellularity ranged from 20% to 40%, consisting predominantly of blasts (H&E, ×200). **B**, Bone marrow aspirate smear. The differential count showed 90% blasts, variable in size and amount of cytoplasm, with occasional prominent nucleoli (Wright-Giemsa, ×400).



▮Image 2▮ Karyotype in the case shown in Image 1, 46,XX,del(2)(q31q33)[6]/46,XX[14] (G-banding technique). Arrow points to del(2q).

case, and both CD13 and CD33 in 1 case. Group 1 T-ALL also had a higher frequency of myeloid antigen expression than their counterparts in group 2B, but this difference was not statistically significant.

Cytogenetics

The most striking feature in group 1 was the presence of chromosome 2 deletions in 3 of 4 cases that had analyzable metaphases. Monosomy 2 was observed in 1 case and del(2)(q31) was detected in 2 cases **▮Image 2▮**. These abnormalities were not seen in any other age groups (P = .01; Fisher exact test). We did not observe any other statistically significant differences in the frequency of other karyotypic abnormalities, although group 2A cases seemed to more often have diploid or pseudodiploid karyotypes (5 of 9 patients with analyzable metaphases). Of note, hyperdiploid (ie, >50) chromosome numbers were not identified in any case analyzed.

Molecular Analysis

The molecular findings, including Southern blot and PCR results, are summarized in **▮Table 2▮**.

Southern Blot Results

Four of 5 group 1 cases were analyzed by Southern blot analysis. In 1 case, all of the TCR genes were in the germline configuration; these results are attributed to sampling error. In the remaining 3 cases, 2 had TCR delta rearrangements, 1 TCR gamma rearrangements, and 1 TCR beta gene rearrangements. Two cases had molecular evidence of lineage infidelity, with both carrying immunoglobulin heavy-chain gene rearrangements and 1 also carrying immunoglobulin kappa gene rearrangements.

In group 2A, Southern blot analysis was performed on 10 of 12 cases. All cases assessed had at least 1 TCR gene rearrangement: TCR delta (n = 6) and TCR gamma (n = 7) in all cases assessed and TCR beta in 7 of 10 cases. Three of 9 cases had immunoglobulin heavy-chain gene

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Table 2
Molecular Findings in 21 Adult Patients With T-Cell Acute Lymphoblastic Leukemia*

Method	Group 1 (>60 y)	Group 2A (28-60 y)	Group 2B (16-27 y)
Southern blot analysis			
TCR gamma	1/4 (25)	7/7 (100)	4/7 (57)
TCR beta	1/4 (25)	7/10 (70)	4/7 (57)
TCR delta	1/4 (25)	6/6 (100)	6/6 (100)
Immunoglobulin heavy-chain gene	2/3 (67)	3/9 (33)	1/6 (17)
Ig kappa light-chain gene	1/3 (33)	0/1	0/4
PCR for V gamma			
Clonal rearrangements	4/5 (80)	10/10 (100)	4/6 (67)
Oligoclonal	1/5 (20)	0 (0)	2/6 (33)
Type of V gamma†			
V_I	0 (0)	12/19 (63)	5/7 (71)
V_{II}	0 (0)	2/19 (11)	0 (0)
V_{III}	3/5 (60)	3/19 (16)	2/7 (29)
V_{IV}	2/5 (40)	2/19 (11)	0 (0)

TCR, T-cell receptor gene.
* Data are provided as number (percentage) of group unless otherwise specified as number of cases affected/number of cases studied (percentage). V_I, V_{II}, V_{III}, and V_{IV} indicate the TCR gamma variable gene family.
† Total number of TCR gamma rearrangements (n = 31).

rearrangements. The immunoglobulin kappa chain gene was germline in 1 case analyzed.

In group 2B, Southern blot analysis was performed in 7 of 9 cases. Six of 7 had TCR gene rearrangements: 6 of 6 TCR delta (5 rearrangements and 1 rearrangement with deletion), 4 of 7 TCR gamma, and 4 of 7 TCR beta. One of 6 cases had immunoglobulin heavy-chain gene rearrangements. Four cases assessed for immunoglobulin kappa gene rearrangements were germline.

TCR gamma PCR Results

Biopsy material from 21 patients was available for 4-color PCR analysis to assess for TCR gamma gene rearrangements, including 5 group 1 cases, 10 group 2A cases, and 6 group 2B cases (Table 2). This assay uses 4 sets of consensus V and J primers, with each V primer labeled with a different color, thereby allowing determination of which V family is used. Clonal TCR gamma rearrangements were detected in 18 T-ALL cases, including 3 cases that had been shown to be germline by Southern blot methods. In these 18 neoplasms, 31 individual TCR gamma gene rearrangements were detected. The other 3 neoplasms showed an oligoclonal pattern. In group 1, 4 neoplasms had monoclonal TCR gamma rearrangements (5 total rearrangements) and 1 neoplasm was oligoclonal. In group 2A, all 10 neoplasms assessed had monoclonal TCR gamma rearrangements (19 total rearrangements). In group 2B, 4 neoplasms had monoclonal TCR gamma rearrangements (7 total rearrangements) and 2 neoplasms were oligoclonal.

In group 1, all 5 TCR gamma rearrangements used the V_{III} and V_{IV} families. In contrast, in groups 2A and 2B combined, only 7 of 26 TCR gamma rearrangements used the V_{III} and V_{IV} families (P = .009; Fisher exact test). Similarly, V_I family use was significantly higher in groups 2A and 2B T-ALL than in group 1 T-ALL (17/26 vs 0/5 rearrangements, P = .009; Fisher exact test). There were no significant differences in V gamma gene family use between groups 2A and 2B.

Clinical Outcome

In group 1, 4 patients received combination chemotherapy and all achieved complete remission. All 3 patients with abnormalities of chromosome 2 were alive at last follow-up, at 16, 39, and 63 months.

In group 2A, complete remission was obtained in all 12 (100%) patients after combination chemotherapy, but only 4 (33%) remained in complete remission after a follow-up interval of 8 to 67 months (median, 17 months).

In group 2B, 8 patients (89%) were in complete remission after the combination chemotherapy; 5 patients (56%) remained in complete remission after a follow-up interval of 5 to 53 months (median, 18 months).

Statistical comparison of survival in the 3 groups could not be carried out by means of survival curves (Kaplan-Meier method), owing to the small numbers of patients in group 1. By using the Fisher exact test, we did not find significant differences between groups in complete remission rate or number of patients in continuous complete remission at last follow-up.

Discussion

The clinicopathologic, immunophenotypic, and molecular features of T-ALL in adults have not been examined extensively. In this study of 26 cases, we have shown that T-ALL in

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adults is biologically heterogeneous. Importantly, these variations correlate with patient age at the time of diagnosis, allowing the tumors in this study to be grouped as follows: group 1, patients older than 60 years; group 2A, patients 28 to 59 years old; and group 2B, patients 16 to 27 years old. The age parameters for each group were determined statistically using a logistic regression method.

Group 1 cases of T-ALL are most distinctive. Clinically these patients had unusual features in addition to their older age, with a relatively low frequency of hepatomegaly (0%), anterior mediastinal mass (20%), and lymphadenopathy (40%) and absence of high leukocyte counts. The difference in the frequency of these clinical features in patients in groups 1 and 2 was not statistically significant, although this might be due to the small number of patients available for comparison. Abnormalities of chromosome 2 were common in this group (75%), and 2q31 seems to be the important locus. This abnormality has not been reported previously. The genes that are involved are unknown. Two of 3 cases assessed had molecular evidence of lineage infidelity. Clonal TCR gamma gene rearrangements, identified in 4 of 5 neoplasms evaluated, used the V_{III} and V_{IV} gene families exclusively.

The relatively good clinical outcome for group 1 patients is unexpected, as ALL in elderly people has been reported to have a poor outcome, even with the advent of the newer chemotherapy regimens and the availability of hematopoietic growth factor therapy.[14,15] In most studies,[4-7,9] the median survival of patients has ranged from 1 to 9 months with a 5-year overall survival of 4% to 17%. The rates of complete remission reported in the literature range from 35% to 79%, with the higher complete remission rates reported with the hyperCVAD regimen.[9] Most likely, the unique features of T-ALL in the elderly (>60 years of age) have gone unnoticed owing to its rarity, with a reported incidence in this age group ranging from 0% to 8%.[4,5,7] A likely explanation for the relatively good clinical outcome in these elderly patients may be related to biologic factors intrinsic to the disease process. Our finding of deletions of chromosome 2 in 3 (75%) of 4 cases with analyzable metaphases supports this view.

The immunophenotypic and molecular findings in group 1 cases of T-ALL suggest that these tumors arise from a progenitor arrested at an early stage of maturation. This evidence includes the high frequency of myeloid antigen (80%) and CD34 (60%) expression, high frequency of immunoglobulin gene rearrangements (67%), and the presence of TCR gamma-chain gene rearrangements that exclusively use the V_{III} and V_{IV} gene families. Others have shown previously that immunophenotypic and gene rearrangement evidence of lineage infidelity is more common in immature lymphoid neoplasms. In addition, V segment use by the TCR gamma gene has been linked to maturational stage. Boehm et al[16] and Hara and colleagues[17] have suggested that the pattern of V family use within TCR gamma rearrangements is nonrandom and correlates with the stage of T-cell maturation. In their studies, T-ALL with an immature immunophenotype had TCR gamma rearrangements that used downstream V gamma genes (ie, $V_{III\text{-}IV}$ gene families). In contrast, peripheral blood T cells and more mature T-ALL cases had TCR gamma rearrangements that exclusively used the V_I gene family. Other studies,[18,19] however, have not confirmed these findings.

By contrast, group 2 cases of T-ALL (patients 16-60 years old) had a higher frequency of lymphadenopathy, mediastinal mass, hepatosplenomegaly, and a leukocyte count of more than 30,000/µL ($>30 \times 10^9$/L). Myeloid antigen expression in these tumors was significantly less frequent compared with group 1 (5/21 vs 4/5; $P = .03$), and chromosome 2 abnormalities were not identified. Compared with group 1, lineage infidelity was less common in group 2 (26%), and most TCR gamma gene rearrangements used the V_I and V_{II} families. Group 2 could be further segregated into 2 subgroups based on the predominant (83%) cortical (T-III) immunophenotype of the leukemic blasts in patients 28 to 60 years old. This feature did not seem to correlate with any distinctive clinicopathologic or molecular findings in the 2 subgroups, and, therefore, its significance remains unclear. However, in previous studies of T-ALL in children, others have suggested that patients with CD1a+ T-ALL tend to have a better early response to corticosteroid therapy.[20,21]

Our results are not entirely unexpected. Others have suggested previously that immunophenotypic subtypes of T-ALL and lymphoblastic lymphoma tend to correlate with clinical manifestations and prognosis.[22-28] However, none of these studies have correlated immunophenotype and molecular findings with age and clinical behavior specifically in adults with T-ALL.

Although some of our findings lack statistical strength, mainly owing to the relatively small number of patients included in the study, T-ALL in adults is a rare entity. Multicenter studies might be necessary to further correlate these findings with the clinical behavior of these tumors. Nevertheless, our results add to the existing knowledge base, particularly for cases of T-ALL arising in patients older than 60 years. The good prognosis of the patients in this age group and the correlation with chromosome 2 deletions are unique findings, further suggesting that this group is biologically distinct. The data also suggest that clinical treatment protocols may be tailored to subsets of T-ALL patients that correlate with their age.

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