CD56+ CD7+ Stem Cell Leukemia/Lymphoma with D2-J51 Rearrangement


Object We describe the characteristics of three patients with CD56+CD7+ stem cell leukemia/lymphoma. Methods These blasts were analyzed for morphologic, karyotypic, immunophenotypic, and immunogenotypic features using Southern blot and polymerase chain reaction analysis. Materials Peripheral blood, bone marrow aspirates, or biopsied mediastinal tumor specimens of three CD56+CD7+ stem cell leukemia/lymphoma patients were investigated. Results The bone marrow of all patients showed myeloperoxidase (MPO) negative blast cells with basophilic cytoplasm and distinct nucleoli with no azurophilic granules. The blasts of two patients were classified as acute lymphoblastic leukemia (L2). The liver, spleen, and lymph nodes were unaffected in all patients. All had an aggressive clinical course. The blasts were strongly positive for both CD7 and CD56 but negative for other T-lineage associated antigens, including CD1, CD2, surface membrane CD3, cytoplasmic CD3c (2/2), CD4, CD5 and CD8. The additional antigens were recognized as follows: CD19 (1/3 cases) as a B lineage, CD33 (1/3) as a myeloid marker, CD34 (2/3) as a stem cell, CD38 (1/1) and HLA-DR (2/3). When the patients relapsed, the phenotypes changed to blasts positive for CD5, CD10 and CD13 in patient 1, CD5 in patient 2, and CD33 in patient 3. MPO, however, remained negative. Cytogenetic analysis showed no common abnormal karyotype. All had a common D2-J51 induced by T-cell specific enhancer. Rearrangement of TCR β and γ genes occurred in patient 2, and IgH and TCR β underwent rearrangement in patient 3. Conclusion Although a more comprehensive case analysis is necessary, these data suggest the possibility that the blasts of the present cases come from a common lymphoid precursor (T, NK, and B cell) or from a NKT precursor as the fourth lymphoid lineage.

Key words: NKT cell, NK-like T cells, prothymocyte, T-specific δ recombination, NK-related stem cell leukemia

Introduction

Natural killer (NK)-like T cells are phenotypically mature T cells that have a large granular lymphocyte (LGL) morphology, express NK-cell antigens, and have properties similar to NK cells, such as cytotoxic activity in the absence of major histocompatibility complex antigen presentation (1–4). These NK-like T cells are surface CD3-positive and rearrange their T-cell receptor, either αβ or γδ, which distinguishes them from true NK cells (1–4). NK-like T cells comprise less than 5% of human peripheral blood lymphocytes (1–4), and are distributed in the intestinal mucosa, particularly within the epithelium (5–7) and in the hepatic sinusoids (8).

NK-like T-cell neoplasms are usually considered a chronic lymphoproliferative disease, carrying the names of Tγ lymphoproliferative disease, T-chronic lymphocytic leukemia, lymphoproliferative disorder of granular lymphocytes, and T-LGL leukemia (9). Recently, some cases have been reported as aggressive CD56+ or CD57+ hepatosplenic or intestinal tumors with variable nodal, cutaneous, and peripheral blood involvement (10, 11). Scott et al proposed a myeloid/NK cell acute leukemia as NK-related stem cell leukemia, which is a distinct disease entity presenting the HLA-DR–, CD33+, CD56+, and CD16– phenotype (12). Their leukemic blasts are
similar to those of acute promyelocytic leukemia (APL). Suzuki et al also described a CD7+ and CD56+ myeloid/natural killer cell precursor acute leukemia as a distinct hematolymphoid disease entity (13).

On the other hand, T-cell receptor (TCR) δ gene rearrangement occurs earlier in T cell differentiation than that of other TCR genes. So far, δ rearrangement with joining region (J) gene is recognized in only T-cell leukemia or lymphoma but not in any other lineage malignancies (14–17). Recently, it was demonstrated that D2-Jδ rearrangements require activation of a T-cell specific enhancer in contrast to V2Dδ3 rearrangements (18). It has been suggested that D2-Jδ occurs at the earliest stage of T-cell differentiation (prothymocyte stage 1) followed later by expression of cytoplasmic CD3ε (CyCD3ε)(14). Analysis of D2-Jδ in the TCRδ locus should further clarify the lineage and clonality of leukemic cells even at the stem cell stage of T-cell differentiation (14, 17, 19, 20).

In this report, we describe the clinical, morphologic, immunologic, karyotypic, and genotypic features of three CD56+ CD7+ stem cell leukemia/lymphoma as NK-related leukemia. We also discuss the possibility that some of these neoplasms may arise from a common progenitor for T, NK, B cells and/or from a NKT progenitor.

Materials and Methods

Patients and cell preparation

Three patients, whose blast cells are strongly positive for CD56 and CD7, were examined in this study. Mononuclear cells were separated from heparinized peripheral blood, bone marrow (BM) aspirates, or biopsied mediastinal tumor specimens by Ficoll-Hypaque density gradient centrifugation. Chromosomal preparations of BM cells were made after 48 hours of unstimulated culture. After trypsin-Giemsa banding, suitable metaphases were photographed and karyotyped according to the International System for Human Cytogenetic Nomenclature (21).

Morphologic examination and cytochemistry

Biopsy touch smears of BM, peripheral blood, and mediastinal tumor were stained with May-Grunwald-Giemsa and cytochemical staining was performed on a frozen section of lymph nodes by using an avidin-biotin-alkaline phosphatase complex method. The monoclonal antibodies (MoAbs) used were as follows: CD1 (recognized by T6), CD2 (T11), CD3 (Leu 4), CD4 (T4), CD5 (Leu 1), CD7 (3A1), CD8 (T8), CD19 (Leu 12 and/or B4) and CD20 (B1) were used for B-cell markers; CD13 (My 7) and CD33 (My 9) as early myeloid markers; and CD34 (My10) was tested as a stem cell marker. CD10, CD38 and HLA-DR were examined with J5, T10, and OKIa1, respectively. Those MoAbs were prepared with Becton-Dickinson, Coulter Immunology (Hialeah, FL), and Dakopatts (Glostrup, Denmark). Cytoplasmic expression of CD3 (CyCD3) was detected in frozen tissue sections and cytocentrifuge preparations, using Leu4. Rabbit anti-CD3ε antibody (DAKO) was applied to paraffin sections. Acetone-fixed cytocentrifuge preparations were used to examine the immunocytochemistry of MPO (Dakopatts).

DNA probes and southern blot analysis

DNA probes were labeled by use of a DNA random primer kit (Amersham International plc, London, UK), following the manufacturer’s recommendations. The JH probe was a 3 kilobase (Kb) embryonic EcoRI-HindIII fragment provided by Dr. P. Leder (Harvard University, Boston, MA, USA) (23). The Cβ probe was a 720-bp fragment, isolated from the HBVT 96 clone (24). The Cy probe was a 0.7 Kb HindIII-EcoRI fragment provided by Dr. T.H. Rabbitts (Cambridge University, Cambridge, UK) (25). The rearrangements of the TCRγ chain gene were examined by using a 1.0 Kb germline ProT1-EcoRI fragment containing the first Jγ region (Jγ1), a 1.5 Kb Xbal genomic fragment containing the third Jγ region (Jγ3), the Dγ1/2 genomic fragment, a 2.6 Kb EcoRI-EcoRI, and a 1.5 Kb Cβ probe region isolated from a thymic complementary DNA (cDNA) clone including the 5’-untranslated region (26, 27).

High molecular weight DNA was extracted from leukemic cells isolated from each patient. Southern-blot analysis was performed as previously described (28). Briefly, DNA (10µg) digested with EcoRI, HindIII, or BamHI was separated by electrophoresis through 0.8% agarose gels, transferred to a nitrocellulose filter, and hybridized with α-32P dCTP-labeled DNA probes.

Polymerase chain reaction

The TCRδ rearrangement pattern was examined by using a polymerase chain reaction (PCR) system. Second step PCR was performed as previously described (14). PCR products were detected on ethidium bromide-stained agarose gels or by the 32P-blotting methods using specific probes. The primers used were the following: 5’D1 (sense): TAC TCC ATG TTC AAA TAG ATA TAG T, 5’D2 (sense): AAG GAA AGG GAA AAA GGA AGA, 3’D3 (anti): TTG TAG CAC TGT GCG TAT CC, 3’J1 (anti): AAA TGC TAG CTA TTT CAC CCA, J1 (anti): GGG TTC CTT TTC CAA AGA TGA G.

Results

Clinical and hematological features

We studied three patients (all men, age range from 35 to 50 years) with CD56+ CD7+ stem cell leukemia/lymphoma, as a NK-related leukemia. Their clinical characteristics are outlined in Table 1. In patient 2, the histologic examination of mediastinal tumor verified the diagnosis of T-cell diffuse large cell type with sclerosis. The BM of all patients contained MPO
negative blast cells with basophilic cytoplasm and distinct nucleoli without azulgranule. The blast cells of two patients (patients 1 and 3) were classified as type L2 by the FAB classification (Fig. 1). The liver, spleen, and lymph nodes were unaffected in all patients. Leukocytosis (26.8 x 10^9/μl, 70% blast cells) was found in patient 3 but circulating blast cells were absent in the other two cases. All patients had an aggressive clinical course. Although patient 1 achieved a complete remission after intensive combination chemotherapy, he relapsed within one year and died. Two patients failed to respond to treatment for the disease.

**Phenotypic characteristics**

At the time of diagnosis, the blast cells of the three patients were MPO-negative. The blast cells of all patients were strongly positive for both CD7 and CD56 but negative for other T-lineage associated antigens, including CD1, CD2, surface membrane CD3, CyCD3ε (2/2), CD4, CD5 and CD8 (Table 2). The presence of additional antigens were recognized which included CD19 in one of 3 cases (1/3) as a B lineage marker, CD33 (1/3) as a myeloid marker, CD34 (2/3) as a stem cell marker, CD38 (1/1) and HLA-DR (2/3).

When patients relapsed, the phenotypes of all leukemic cells changed, i.e. blast cells became positive for CD5 and CD13 in

![Figure 1](image-url)

**Table 1. Clinical Features of Three Patients with CD56+CD7+ Stem Cell Leukemia/Lymphoma**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diag/FAB</th>
<th>Lym</th>
<th>Hp</th>
<th>Sp</th>
<th>Med</th>
<th>CNS</th>
<th>Pl</th>
<th>BM</th>
<th>NCC* (Blast%)</th>
<th>WBC* (Blast%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>ALL/L2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>4.6 (81%)</td>
<td>1.1 (0%)</td>
<td>CR → Died 13M</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>D. Large</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>dry tap</td>
<td>4.5 (0%)</td>
<td>Died 5M</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>M</td>
<td>ALL/L2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>23.5 (71%)</td>
<td>26.8 (70%)</td>
<td>Died 7M</td>
</tr>
</tbody>
</table>


*; x10^9/μl, †; x10^3/μl.

Figure 1. Morphologic and cytochemical features of CD56+CD7+ stem cell leukemia/lymphoma. May-Giemsa-stained bone marrow smears of patients 2 (A) and 3 (C). (A) The leukemic cells are large in size indicating 4N (tetraploidy). (C) The leukemic cells show FAB L2 in morphology with irregular nuclei, prominent nucleoli, and pale cytoplasm. Azurophilic granules are not apparent in the cytoplasm. (B) and (D) MPO-stained bone marrow smear of patients 2 and 3. Less than 3% of leukemic cells are positive for MPO staining (x400).
Table 2. Immunophenotypes of Blast Cells at Diagnosis and at Relapse

<table>
<thead>
<tr>
<th>Case No.</th>
<th>CD7</th>
<th>CD19</th>
<th>T6</th>
<th>T11</th>
<th>SmCD3</th>
<th>CyCD3</th>
<th>T4</th>
<th>Leu1</th>
<th>T8</th>
<th>J5</th>
<th>My7</th>
<th>Leu11</th>
<th>B4</th>
<th>B1</th>
<th>My9</th>
<th>My10</th>
<th>T10</th>
<th>Leu7</th>
<th>HLADR</th>
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<tbody>
<tr>
<td>1-D</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>1-R</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
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<td>+</td>
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<tr>
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</table>


Table 3. Cytogenetic and Immunomolecular Analysis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cytogenetics</th>
<th>Southern Blot of TCR</th>
<th>PCR of δ gene</th>
<th>δ Rearr.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>IgH</td>
<td>β</td>
<td>γ</td>
</tr>
<tr>
<td>1-D</td>
<td>46, XY, 7q+, 18q−</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>1-R</td>
<td>47, XY, 4q+, +i (7q), del (9) (p13) (21/25)</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>2-I</td>
<td>91, XXYY, del (5) (q?) ×2, −8</td>
<td>G</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>3-D</td>
<td>46, XY,</td>
<td>r/t</td>
<td>r/g</td>
<td>G</td>
</tr>
</tbody>
</table>

D: at initial diagnosis, R: at relapse, I: increase of abnormal cells, G: germ line, r or R: rearranged band. H4.8: 4.8 kb HindIII rearranged band, B10.4: 10.4 kb BamHI rearranged band.
CD56+CD7+ Stem Cell Leukemia/Lymphoma

3.9% 94.3 2.0 96.5 3.7 61.0 41.4 56.9 1.7 2.3 43.5 1.2 0.1

CD6 CD5 CD19 CD7 CD6 CD5 CD19 CD7 CD6 CD5 CD19 CD7

Figure 2. Two-color flow cytometry on patient 2 (peripheral blood at time of relapse).

CD7 CD19 CD33 CD34 and CD5, while MPO remained negative throughout the clinical course.

Cytogenetic characteristics

The results of cytogenetic analysis are shown in Table 3. At diagnosis, patient 3 had a normal karyotype, whereas patient 1 had abnormal karyotypes of 46, XY, 7q+, 18q-. Patient 2 had 91, XYYY, del (5)(q?)x2, -8 at the time of relapse showing 4N (tetraploidy) with a large size of blasts (Fig. 1). There was no common abnormal karyotype or 11q23 translocation (29, 30) in these patients when the leukemic cells were examined both at diagnosis and at relapse.

Immunogenotypic Characteristics

DNA samples from bone marrow were studied for immunogenotypic analysis at the time of initial diagnosis for patients 1 and 3 and at relapse for patient 2 (Table 3 and Fig. 3). The rearrangements of the TCRβ and γ genes occurred in patient 2. In patient 3, the rearrangements of IgH and TCRβ genes were noticed, while all exhibited a common 4.8 kb Hind III rearranged band upon Jβ1 probe analysis. This indicated an incomplete D2-Jβ1 recombination (14–19) (Figs. 3 and 4). One allele of both patients 1 and 3 had a rearranged 10 kb BamHI or 3.7 Kb EcoRI band indicating a D2D83 junction.

To identify the D2-Jβ1 and D2D83 rearrangements, two-step PCR experiments were performed (Fig. 4). The 110 bp amplified DNA product for the D2-Jβ1 fragment was detected in all three patients. In patients 1 and 3 (not shown), the D2D83 pattern was identified as a 95 bp fragment from the 2nd round of PCR.

Discussion

In the present study, we have described three cases of CD56+CD7+DDJβ+ acute stem cell leukemia characterized by distinct morphologic, immunophenotypic, genotypic, and clinical features. The BM of all patients showed blast cells with no azurophilic granules, but the liver, spleen, and lymph nodes were not enlarged. Leukemic cells showed immature morphologic appearance (L2) without both MPO reactivity and CyCD3e expression, but with expression of CD34 and HLA-DR. All patients had an aggressive clinical course.

NK cells differentiate from immature thymocytes under appropriate conditions in vitro and in vivo, and share cytotoxic activity and some surface antigens with T cells, indicating a close relationship with T-lineage (31). They express the NK-related antigen CD56 and T-cell markers such as CD2 and CD7, but do not express CD5 or TCR proteins, and their TCR locus is not rearranged. Recently, NK cells were found to develop from a population of CD34+, CD33+, CD56– cells in vitro (31). Although CD56 does not have lineage or disease specificity, its presence may be common to a family of NK-related leukemias and lymphomas (11, 32, 33).

Concerning NK-related precursor leukemia, Scott et al proposed a myeloid/NK cell acute leukemia as a distinct disease entity presenting the HLA-DR–, CD33+, CD56+, and CD16– phenotype (12). The leukemia is considered to develop through transformation of a precursor cell which is common to both the myeloid and NK cell lineage. Those leukemic blasts are morphologically similar to those of APL. The morphological characteristics of mature myeloid cells present with deeply in-
Figure 3. Southern blot analyses of immunoassociated genes. C: control (placental DNA), G: germ line band, R: rearranged band. On Southern blots of bone marrow DNA hybridized with the Jδ1 probe, G indicates a 6 kb EcoRI germ line band, a 6 kb Hind III band, and a 16.8 kb BamHI band. D2Dδ3 and D2-Jδ1 correspond to a 3.7 Kb EcoRI band, a 10.4 kb BamHI band, and a 2.8 kb EcoRI band, a 4.8 kb HindIII band, a 9.4 kb BamHI band, respectively.
vaginated nuclear membrane, scant cytoplasm with fine azurophilic granules, and fine granules of Sudan black B and/or MPO cytochemical reactivity. None of the patients in Scott’s series had clonal rearrangement of genes encoding TCR β, γ, δ chain (12). Recently, Suzuki et al documented seven cases of CD7+ and CD56+ myeloid/natural killer cell precursor acute leukemia as a distinct hematolymphoid disease entity (13). In those patients, extramedullary involvement was striking at initial presentation in association with peripheral lymphadenopathy and/or mediastinal masses. Their leukemic cells were usually FAB L2 in morphology. CyCD3 was positive in 50% of the cases.

The blast cells of the present patients appear to be different from those of positive MPO, and mature morphology presented by Scott et al (12), but similar to the patients of Suzuki et al (13) with the L2 morphology, phenotypic characteristics and clinical course. The latter cases, however, did not show the close relation with T-cell lineage. In addition, there was also some difference in superficial lymphadenopathy and lack of bone marrow involvement in 2 cases.

It is suggested that the most immature (prothymoblastic) T-ALL in T-cell precursor leukemias can be defined as CD34+ CD7+ HLA-DR+ TdT+ (CyCD3+/−and/or CD2+/−) (34). Three additional immature pro-T-cell stages have been defined; Stage I cell is CD7+ (CD34+ or CD34−) CyCD3−, Stage II CD7+CyCD3+ (CD5 or CD2+/−), and Stage III pro-T cells represent the CD7+CyCD3+CD5+CD2+ phenotype (34–36). Functionally, a subset of pro-T cells is thought to be multipotent (35). In fact, we experienced that T-stem cell leukemia/lymphoma of pro-T I or II cells were transformed to AML with positive MPO in relapse. The difference in the presence of MPO was observed in the blast cells between BM- and lymph nodes (3/3) (19).

Recently, a common T/NK cell progenitor was found in human fetal thymus (31). Sanchez et al (31) identified a bipotent common T/NK progenitor which is characterized by CyCD3+e+, CD34+CD7+CD13+CD33+, although it is generally believed that co-expression of CD13 and CD33 in the progenitor popu-
lations is an indication of both myeloid and monocytic lineage commitment (37, 38). The T/NK progenitor appears to correspond to a part in stage II pro-T cells. In the absence of MPO or CyCD3e, the expression of CD13 and/or CD33 in our patients suggest that those blasts are less mature lymphoid progenitor (s) than a common T/NK progenitor.

The CD10+CD34+Lin− c-Kit− Thy-1− population in human bone marrow gives rise to T, B, NK, and lymphoid dendric (LD) cells, but very few myeloeiroid cells; they appear to include clonal progenitors for T, B, NK, and LD cells (39). Kondo et al more recently reported the direct evidence for the existence of common lymphoid progenitors (CLPs) that could differentiate into only T cells, B cells, and NK cells, in the sites where early hematopoiesis was seen in mice (40).

In the current study, patients’ blasts apparently correspond to prothymocyte stage I (pro-T I) in T-cell development proposed by Haynes et al (35). The Pro-T population probably includes a small fraction of CLPs (41, 42). All patients’ blasts had incomplete D2-J81 rearrangement at least on one allele even in the absence of CyCD3e (2/2). This D2-J81 recombination, which is promoted by T-cell specific enhancer (18), appears to be T-lineage specific (14–19). Blasts in patient 3 showed IgH rearrangement as B lineage marker. MPO was never detected throughout the clinical course. Therefore, our data suggest a possibility that some of the blasts might arise from a common lymphoid progenitor (CLP).

NKT cells have been determined as a fourth lymphoid lineage (43, 44). It is known that a mature NKT cell is a CD4−CD8− αβ-T cell with Vα24JαQ, and plays an important regulatory role in immune responses. In addition, there is a speculation of the presence of a precursor which is common to αβ- and γδ-NKT cell. It is still possible that the blasts in the present cases were malignant cells of NKT precursor. However, a larger case analysis is necessary to determine those possibilities.

Finally, prothymocytes appear to include T/NK precursors and CLPs which were recently identified. More detailed studies could clarify the different clinical features clear in leukemia/lymphomas which arise from those precursors. TCRδ gene analysis should be an integral part of critical studies that differentiate precursor acute leukemias by delineating the stages of T-lineage (45).

Acknowledgements: This work was supported in part by Grants-in-Aid for General Scientific Research from the Ministry of Education, Science and Culture.

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