Case Report:

**Acute T-lymphoblastic leukemia relapsed with the character of myeloid/NK cell precursor phenotype: A case report.**

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**Key words:** T-ALL, myeloid/NK cell precursor acute leukemia, Pro-T lymphoblast, acute leukemia, CD3 epsilon, CD56.

**Abstract** The leukemic lymphoblasts of a patient expressed CD7, CD13, CD33, CD34, HLA-DR and cytoplasmic CD3ε. He was diagnosed with ALL, and successfully treated with a conventional chemotherapy for ALL. The disease relapsed 3 times, and the character of the cells gradually altered, i.e. CD56 expression increased and CD13, CD7 and cCD3ε decreased. The phenotype of the relapsed ALL was, therefore, compatible with M/NK-AL. Some of M/NK-AL may be closely related with T/myeloid-biphenotypic pro-T blasts, and both types of AL may develop a tendency to express myeloid antigens, and they may belong to the category of immature T lymphoid precursors.

List of abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myelogeneous leukemia; M/NK-AL, myeloid/NK cell precursor acute leukemia; LBL, lymphoblastic lymphoma; CR, complete remission; BMT, bone marrow transplantation; NK, natural killer; DC, dendritic cell; MPO, myeloperoxidase.

**Introduction**

The differential diagnosis of AL is of critical importance to clinical hematologists. Most cases with AML or ALL have been successfully treated with daily intensive combined chemotherapy for 5 to 7 days, and sometimes 10 to 14 days for resistant cases, or weekly moderate combination chemotherapy, respectively. CR of AML is achieved after bone marrow aplasia, and the CR of ALL is mostly achieved without bone marrow aplasia. In contrast, the differential diagnosis of AL is complex and difficult in blasts with similar character to hematopoietic stem cells. Efficient diagnosis depends on the knowledge of hierarchy of the stem cells and lymphoid and myeloid precursors, and on the technology to discriminate between these immature cells.

The FAB classification of AL has added an entity of peroxidase-negative immature AML (M0) [1]. ALs with simultaneous expression of the definite myeloid and lymphoid phenotypes are classified as biphenotypic ALL [2, 3]. A peroxidase-negative AL with myeloid phenotype on the surface and cytoplasmic expression of CD3 may be misdiagnosed as AML (MO) when the cytoplasmic expression of CD3, CD5 and CD22 is not analyzed. Moreover, there remain at least two lymphoid cell lineages left to be further studied, other than the T and B lymphocytes, i.e. NK cells and lymphoid DCs. Information about native NK, NK precursors and their transformed cells is steadily being reported, while there is almost no information about AL and LBL transformed from lymphoid DC precursors. The M/NK-AL was proposed by Suzuki et al. [4, 5]. Is the obscure entity of AL myeloid or lymphoid, or really a transformation of the NK precursors?

The blasts cells from a patient with T/myeloid biphenotypic ALL showed only myeloid markers on the surface despite the expression of cytoplasmic CD3ε. The phenotype of the cells gradually altered each time the disease relapsed; the final phenotype being compatible to the so-called M/NK-AL. Some of the entity of the M/NK-AL is therefore closely related to the pro-T-ALL with myeloid phenotype, and both types of ALL may belong to a spectrum of immature T lymphoid precursor ALs.

**Case report**
A 22-year-old Japanese man was admitted to our hospital for marked leukocytosis in September, 1995. His white cell count was 66,420 /μl, and 97% of the cells were morphologically peroxidase-negative lymphoblasts. The surface phenotype of the blasts was HLA-DR, CD7, CD13, CD15, CD33, CD34, CD38, CD45-positive, and glycophorin A, CD1a, CD2, CD3, CD4, CD8, CD10, CD14, CD19, CD20, CD21, CD22, CD25, CD35, CD41, CD56, CD122-negative. The cytoplasmic antigen expression was analyzed [6], and the cells were MPO, cytoplasmic CD22 (cCD22)-negative, and cCD3ε-positive (Fig 1). The cell cycle analysis of the blasts was also analyzed using 7AAD/PY [7, 8]. The percentages of G1a, G1b, S, G2M, and the levels of the nucleic acid index (NI) and the coefficient of variations of the RNA in the S-phase (SCV) were 75.1%, 13.8%, 7.9%, 3.3%, 1.83 and 11.5, respectively. The NI value was intermediate between Type I (lymphoid precursors, NI < 1.7) and Type 0 (lineage-negative precursors, 2.0 < NI < 2.3) [9]. Chromosomal analysis was performed on the bone marrow which showed normal karyotype in all the metaphases studied. The rearrangements of the TCR and immunoglobulin genes were evaluated in the bone marrow sample by Southern blotting analysis. The sample showed rearranged band for TCR/Cβ gene. The rearranged band was weaker than that of germline of the TCR/Cβ gene, and the reason was unclear. The patient was treated with a DVP regimen as conventional chemotherapy for ALL; weekly intravenous injections of daunorubicine and vincristine, and daily oral administrations of predonisolone. CR was achieved soon after in November, 1999. The blasts at that time showed a low degree of expression of CD7, CD13 and cCD3ε, and almost all of the cells were CD56-positive. He died of a massive gastrointestinal hemorrhage in January, 2000.

Discussion

The European Group for the Immunological Characterization of Leukemia (EGIL) has proposed that T-lineage ALL is defined as blasts with the expression of cytoplasmic or membrane CD3, and that AML expresses two or more antigens of MPO, CD13, CD33, CD65 and/or CD117 [2]. A scoring system for the diagnosis of biphenotypic leukemia has also been proposed, and this type of leukemia tends to express CD7, CD34, CD38 and HLA-DR. The system has regarded cytoplasmic CD3 and MPO as important markers for lineage definition, and the expression of CD13, CD33 and/or CD15 less so as myeloid markers, even though the expression of CD15 helps the diagnosis of CD13/CD33-negative AML [10]. The phenotype of the blasts at onset was therefore compatible with biphenotypic T-ALL, and the patient was successfully treated with a conventional chemotherapy for ALL.

M/NK-AL, argued to be the abnormal counterpart of common precursor for myeloid and NK cell lineages [4, 11], expressed CD7, CD33, CD34 and CD56 on the surface, and showed dim expression of CD3 in the cytoplasm by flow cytometry and/or Northern blotting. The immunophenotype of the blasts at the relapses
was compatible to M/NK-AL. Although the blastic cells showed normal karyotype, and therefore there was no evidence that the blastic cells at onset and the cells at the relapses arose from the same clone, both sets of cells supposed to have arisen from the same clone because the expression of cCD3ε in the blasts gradually decreased, and phenotype of the pathological cells were basically very similar except CD56, they were therefore likely to be subclones of the original leukemia, but not one or more clones arisen from second leukemia at each relapse after BMT.

It is not clear whether NK cells arise from the supposed common myeloid/NK cell precursor or from the lymphoid precursor. CD3-/CD56+ NK cells were induced from CD34+/CD33+/CD56-progenitors in vitro [12], and CD34+/CD33+ progenitors do not mean strictly myeloid-committed progenitors, but they may include B- and T-lymphocyte progenitors. Although it is not known at which stage of maturation of the NK cell lineage the CD56 molecules express, CD56 is negative at the immature stage of NK progenitors. In contrast, T-lymphocytes, B-lymphocytes, NK-cells and lymphoid DC arise from CD34+/CD10+, lineage marker-negative common lymphoid precursors [13, 14]. NK cells, therefore, may arise not from the supposed CD56-positive common myeloid/NK cell precursor, but from CD56-negative common lymphoid precursor. If so, the alteration of the immunophenotype in this case may explain the close relationship between the progenitor-T cells and a part of the so called M/NK-AL that expresses cytoplasmic CD3ε, and may mean that supposed M/NK-AL is not the abnormal counterpart of common precursor for myeloid and NK cell lineages, and moreover, the expression of CD56 in this part of so-called M/NK-AL does not mean it is an NK-marker.

CD3-positive or CD56-positive mature lymphocytes include heterogeneous subsets, and therefore the clarification and definition of the subsets are confusing. CD3-positive cells include thymic- and extrathymic-T cells, or CD56-negative and positive-T (NK-like T) cells. The majority of CD56-positive T cells, that are of extrathymic origin, show granular lymphocyte morphology and NK-activity to a low degree [15, 16]. In other words, the wide spectrum of killer lymphocytes includes cells supposed to be primitive to sophisticated killers, HLA-non restricted and restricted cells, i.e., CD3+/CD8+/CD56- activated killer T cells, CD3+/CD56+ NK-like T cells, and CD3-/CD56+ natural killers. Most of the cells express CD3ε, perforin and granzyme B in the cytoplasm, and therefore, whatever the precursors of the cells are, the precursors may show similar phenotype. NK cells in fetal liver, cord blood and decidua express cCD3ε [17, 18]. It is also unclear whether the immature cells named progenitor-T and precursor-T are strictly the progenitors for thymic-T or the common progenitors of this vast spectrum of non-B lymphocytes. To understand the hematopoesis of the cells, it is important to study the in vivo and in vitro maturation of the precursors, as well as to analyze the malignant counterparts of the cells in detail, such as in AL and LBL.

References


Fig. 1  The phenotype alteration of the blastic cells. Surface expressions of CD7, CD13, CD56, and cytoplasmic expression of CD3ε are shown. A, onset, peripheral blood (PB) in September, 1995; B, 1st bone marrow relapse, bone marrow (BM) in March, 1997; C, 2nd bone marrow relapse, PB in November, 1999; and D, meningeal relapse, liquor in December, 1998.

Fig. 2  Possible scheme of cCD3ε-positive progenitor. SC, hematopoietic stem cell; cCD3, intracytoplasmic CD3. Note that this scheme is simplified by disregarding minorities as TCRα/β extrathymic T, CD56-negative extrathymic T, CD2+/CD3-/CD56-/CD57+ strange granular lymphocytes, etc.