Biphenotypic acute leukemia with t(15;17) lacking promyelocytic-retinoid acid receptor α rearrangement

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Abstract

Biphenotypic acute leukemias (BAL) account for less than 4% of all cases of acute leukemia. Philadelphia chromosome and 11q23 rearrangement are the most frequently found cytogenetic abnormalities. Since t(15;17) is almost always associated with acute promyelocytic leukemia, t(15;17) in BAL cases is extremely uncommon. We report here a rare and instructive case of BAL with t(15;17) and the successful treatment approach adopted. A 55-year-old Japanese woman was referred to our hospital for an examination of elevated white blood cell (WBC) counts with blasts. Her laboratory data on admission showed rising WBC counts (13.4×10^9/L; 76% blasts, 1% band, 6% segmented, 16% lymphocytes, 1% monocytes) with anemia and thrombocytopenia (hemoglobin 9.3 g/dL and platelets 110×10^9/L). Coagulation studies were normal. Lactate dehydrogenase was slightly raised to 367 IU/L (normal range 120-245). Bone marrow aspiration revealed replacement of normal marrow by blasts (94%). We detected differences in the size of the blasts, corresponding to an abnormal lymphocyte-like cell population with a high nuclear/cytoplasmic (N/C) ratio, but without granules in the cytoplasm (Figure 1). These blasts were negative for myeloperoxidase (MPO) and esterase. Morphological findings were compatible with acute lymphoblastic leukemia (ALL-L2, FAB classification).

Flow cytometry analysis

ImmunoPhenotype with double-color flow cytometry showed positivity (>30%) for CD19 (90.8%), CD22 (45.4%), CD79a (92.4%), CD13 (40.9%), CD33 (94.6%), CD34 (95.8%) and HLA-DR (93.8%). MPO was negative (2.0%). Double staining for CMDxCD33 was strongly positive (96.6%). The use of the EGIL scoring system revealed 5 points for B-lymphoid lineage and 2 points for myeloid lineage. The immunoPhenotype analysis was conclusive for a diagnosis of BAL.

Cytogenetic analysis

Chromosomal analysis with G-banded karyotype of the bone marrow cells showed 46, XX, t(4;12)(q21;p11), t(15;17)(q22;q12) in all 24 metaphase spreads (Figure 2A). Fluorescence in situ hybridization (FISH) performed on interphase nuclei using an LSI PML/RARA dual color, dual fusion translocation probe (Vysis, USA) showed two separate PML and RARα signals (Figure 2B) in 1000 interphase nuclei and all metaphases analyzed. No PML/RARα fusion signal was identified.

Clinical course

The patient was initially treated with the Japan Adult Leukemia Study Group (JALSG)-ALL202 chemotherapy protocol (Table 1) and induction for ALL treatment was completed. The bone marrow aspirate at the end of the induction phase revealed hematologic complete remission (CR). After the consolidation phase I (with a high dose of cytarabine), the patient experienced the complication of septic shock with acute phlegmonous gastritis. Thereafter, we administered a single dose (9 mg/m²) of gemtuzumab ozogamicin (GO), an anti-CD33 antibody conjugate, independent of the JALSG protocol, and subsequently, completed the course until consolidation phase V. Furthermore, we continued maintenance phase therapy using the JALSG protocol until two years after the onset of disease, during which time we administered GO (6 mg/m²) twice. At present, 1.7 years after the end of chemotherapy, the patient has remained in hematologic first CR during the over 3.7 years follow up.

Discussion and Conclusions

According to the 2001 WHO classification...
and EGIL scores, which are the established
diagnostic criteria for BAL, a diagnosis of BAL
in our patient was confirmed. This is due to
scoring (>2 points) that includes blasts of B-
lymphoid lineage consistent with morphologi-
cal ALL, as well as myeloid lineages such as
CD13 and CD33. However, in the 2008 WHO
classification, the criteria for myeloid lineage
were revised so that MPO or monocytic differ-
entiation was a necessary condition. Acute
leukemia with dual phenotype was classified
in a new category called mixed phenotype
acute leukemia (MPAL). According to these
diagnostic criteria, our case would not fall
under MPAL.

About one-third of cases of BAL have the
Philadelphia chromosome, and some cases are
associated with the t(4;11)(q21;q23) or other
11q23 abnormalities. We observed 4q21
abnormalities (AF4 gene) in our patient, but
could not confirm 11q23 abnormalities.

Although a case of APL by the G-banding
method with the insertion of PML-RARα
fusion gene in 4q21 was previously reported,7
we could find no evidence of a relationship
between 4q21 abnormalities and t(15;17) in
our patient.

Although t(15;17) and PML/RARα fusion are
regarded as highly specific for APL, they have
only been reported in rare cases of AML that
were neither morphologically nor immunophe-
notypically consistent with APL. Moreover,
BAL with t(15;17) is extremely rare. Scolnik et
al. reported a case of a 7-year old girl who
received a combined therapy; she was first
treated with ALL protocols, changing to AML
protocols in combination with ATRA in a sec-
ond instance. She showed a good response and
achieved hematologic CR.10

The localization of breakpoints at
PML/RARα had not been clearly defined, being
variously identified as 15q22-q24 and 17q11-
q21. More exactly, the precise location of the
RARα breakpoint had been the subject of vari-
able reports in the literature. The PML/RARα
breakpoint was unified to 15q22 and 17q12
according to the 2001 WHO classification.1
Before 2001, 3 other cases of t(15;17) translo-
cations similar to our case had been described,
where the PML/RARα rearrangement was
absent by FISH, although the chromosomal
breakpoints were 15q22-q24 and 17q11-q21.11-13

In these cases (including ours), the break-
points are considered to be subtly different
from PML/RARα. The previously reported 3
cases were non-APL (M2, M2, M5a), with low
sensitivity to chemotherapy (ATRA was admin-
istered in 2 cases without effect), and all the
patients had died within 1.5 years.

Recently, chemotherapy for ALL has been
shown to be effective for MPAL.14 The progno-
sis appears to be unfavorable, particularly in
adults; the occurrence of the t(4;11) or the

Figure 1. Bone marrow aspiration revealed morphological findings compatible with ALL-L2 (May-Giemsa staining, 1000×).

Figure 2. A) G-banded karyotype of the bone marrow cells showing t(4;12)(q21;p11) and t(15;17)(q22;q21). Arrows indicate the derivative chromosomes. B) FISH analysis with PML/RARα-specific probes showing two orange (PML) and two green (RARα) signals. No PML/RARα fusion signal (which should appear yellow) was detected.
Table 1. JALSG-ALL202 chemotherapy protocol.

| Phase                      | Drug             | Dosage       | Days |
|----------------------------|------------------|--------------|------|
| **Induction**              |                  |              |      |
| Cyclophosphamide           | 1200 mg/m²       | 1            |      |
| Daunorubicine              | 60 mg/m²         | 1-3          |      |
| Vincristine                | 1.3 mg/m²        | 1, 8, 15, 22 |      |
| L-Asparaginase             | 3000 U/m²        | 9, 11, 13, 16, 18, 20 |      |
| Prednisolone               | 60 mg/m²         | 1-21**       |      |
| **Consolidation Phase I & IV** |              |              |      |
| Cytarabine                 | 2000 mg/m²       | 1-3 (twice a day) |      |
| Etoposide                  | 100 mg/m²        | 1-3          |      |
| Dexamethasone              | 40 mg/bodies     | 1-3          |      |
| **Consolidation Phase II & V** |              |              |      |
| Methotrexate               | 1500 mg/m²       | 1, 15        |      |
| Vincristine                | 1.3 mg/m²        | 1, 15        |      |
| Mercaptopurine (6-MP)      | 25 mg/m²         | 1-21         |      |
| **Consolidation Phase III** |                  |              |      |
| Vincristine                | 1.3 mg/m²        | 1, 8, 15     |      |
| Doxorubicin                | 30 mg/m²         | 1, 8, 15     |      |
| Dexamethasone              | 10 mg/m²         | 1-8, 15-22   |      |
| Cyclophosphamide           | 1000 mg/m²       | 29           |      |
| Mercaptopurine (6-MP)      | 60 mg/m²         | 29-42        |      |
| Cytarabine                 | 75 mg/m²         | 29-33, 36-40 |      |
| **Maintenance**            |                  |              |      |
| (repeat until 2 years from onset) |              |              |      |
| Vincristine                | 1.3 mg/m²        | 1            |      |
| Prednisolone               | 60 mg/m²         | 1-5          |      |
| Methotrexate               | 20 mg/m²         | 1, 8, 15, 22 |      |
| Mercaptopurine (6-MP)      | 60 mg/m²         | 1-28         |      |

*Max 2 mg. **tapered in 1 week, days 22-28.

Philadelphia chromosome are particularly unfavorable prognostic findings. On the other hand, Arabi et al. noted CR rates of 78% and an overall survival probability at two years of 60% in 31 adult BAL patients, excluding t(9;22)(q34;q11)-positive cases, undergoing mainly Hyper-CVAD therapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone combined with high-dose cytarabine and methotrexate). On the basis of the morphology and immunophenotype of the blasts at onset, we determined our case to be BAL, also consistent with CD33 strongly positive ALL. As such, we initially managed the patient with induction chemotherapy for ALL and achieved CR. We considered CD33-positive minimal residual disease and added GO to the standard JALSG-ALL protocol as consolidation and maintenance treatment. There was no evidence of recurrence, and this management approach achieved and maintained a first CR of over 3.7 years. We believe that not only chemotherapy for ALL, but also a low, divided dose of GO, was effective in treatment.

In conclusion, we report an extremely rare case of BAL with t(15;17) lacking PML/RARα rearrangement. The clinical course of this patient is proceeding satisfactorily with chemotherapy as for ALL and GO.

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