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# Acute Lymphoblastic Leukemia with Mature B-Cell Phenotype and t(9;11;11)(p22;q23;p11.2): A Case Study and Literature Review

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Patients with infantile ALL are fundamentally different from adult patients in that infants have a worse prognosis, which is attributed to the increased relative incidence of *MLL* gene rearrangements [1, 2]. *MLL* is located on chromosome 11q23 and is a frequent target of chromosome translocations in hematopoietic malignancies. Patients with ALL and *MLL* rearrangements usually have distinct characteristics, such as organomegaly, marked leukocytosis, and a high incidence of central nervous system leukemia [3, 4]. Most importantly, regardless of the age at presentation, *MLL* rearrangement in ALL is associated with a poor response to therapy and a poor prognosis [5].

In contrast to lymphoblastic leukemias with *MLL* rearrangements, B-lineage acute leukemias with surface immunoglobulin expression are generally associated with leukemic manifestation of Burkitt lymphoma. Leukemic cells typically have a deeply basophilic and vacuolated cytoplasm and a t(8;14) translocation or its variants, which can be generally identified by using conventional cytogenetic or FISH analysis [6]. However, a series of cases of B-cell lymphoblastic leukemia with surface immunoglobulin expression and without features of Burkitt lymphoma have been reported [7-16]. Among these cases, a small number of patients presented with *MLL* gene rearrangements, especially the t(9;11) [10-16]. We describe an infant with ALL with surface immunoglobulin expression and *MLL* gene rearrangements including the t(9;11).

The patient was a 4-month-old boy who presented with fever for 5 days. At admission, the patient had leukocytosis (white blood cells, $117.2\times10^9$/L), anemia (Hb, 9.4 g/dL), and thrombocytopenia (platelets, $54\times10^9$/L). The results of physical examination were unremarkable. There was no lymphadenopathy or organomegaly. The serum uric acid (10.7 mg/dL) and lactate dehydrogenase (1,186 μmol/L) levels were elevated. Radiographic evaluation revealed no thoracic or abdominal masses. In the sample collected at admission, approximately 90% of the white blood cells were blasts having small to medium size, high nuclear-cytoplasmic ratio, round nuclei with fine chromatin and inconspicuous nucleoli, and pale blue cytoplasm without granules or vacuoles (Fig. 1A). The cellular elements of bone marrow aspirates and biopsies consisted almost entirely of blasts with a similar morphology. Immunophenotypic analysis by flow cytometry performed on bone marrow aspirate showed blasts expressing CD19, cytoplasmic CD79a, CD10, cytoplasmic CD22, and surface immunoglobulin λ light chain. CD34 and terminal deoxynucleotidyl transferase (TdT) were not expressed

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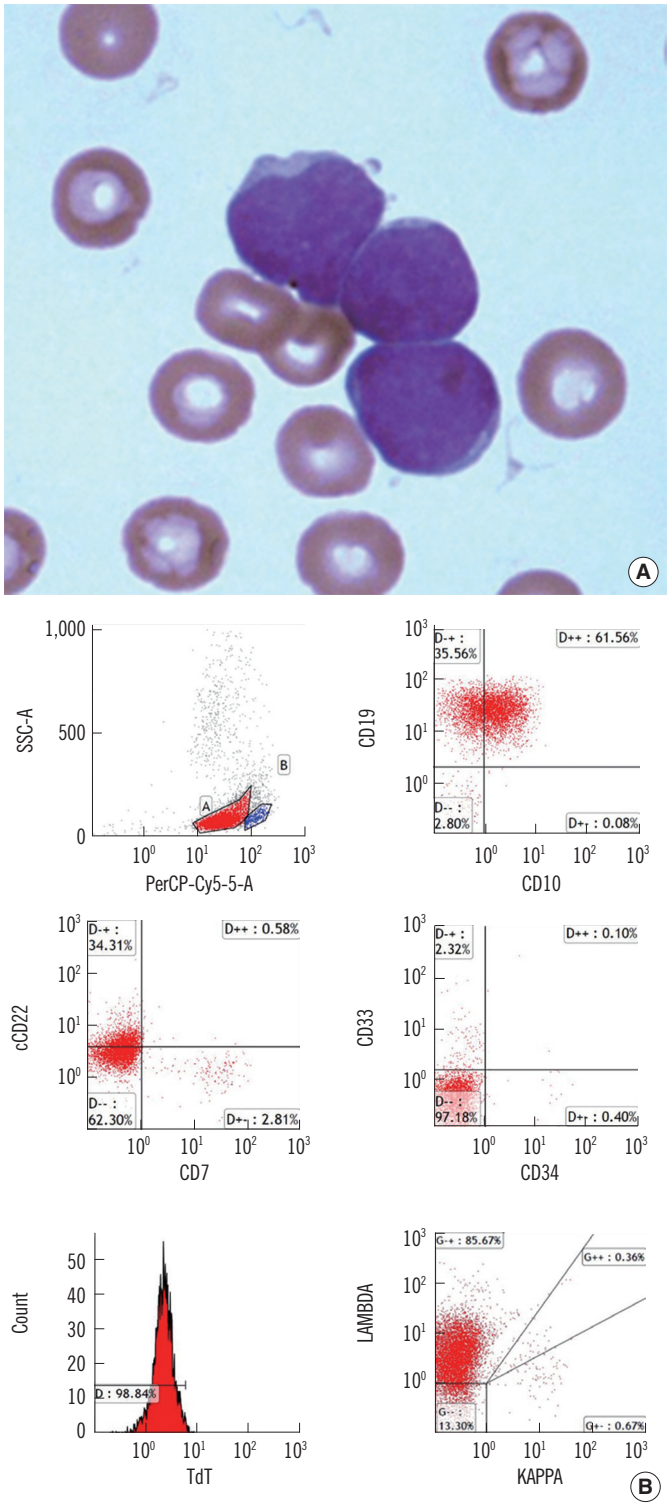


**Fig. 1.** (A) Blasts of the patient exhibit non-FAB-L3 morphology. (B) Scatter plots of flow cytometric immunophenotyping show blasts with CD19+, CD10+, CD34-, terminal deoxynucleotidyl transferase (TdT)-, and surface immunoglobulin (sIg) λ+.
Abbreviation: FAB, French-American-British classification.

(Fig. 1B). All other markers including myelomonocytic markers were not expressed. Conventional karyotyping of uncultured bone marrow aspirate showed a 3-way t(9;11;11) translocation among 9p22, 11q23, and 11p11.2 in 20 metaphase cells (Fig. 2A). FISH studies performed on bone marrow aspirates revealed a *MLL* translocation (Fig. 2B). In additional studies, there was no evidence of MYC rearrangements. Molecular analysis by reverse transcription (RT)-PCR also revealed a 367-bp sized amplicon corresponding to the *MLL* ex8-*MLLT3* (AF9) ex9 fusion transcript (Fig. 2C).

The patient received induction chemotherapy for ALL. A rapid response was observed with the resolution of leukocytosis, and complete remission (CR) was documented after the induction phase. Sibling peripheral blood stem cell transplantation (PB-SCT) was performed after the consolidation phase. Minimal residual disease (MRD) evaluation at this time was negative and no evidence of relapse has been found during 8 months of follow-up.

The majority of B-lineage lymphoblastic leukemia cases present B cells of the pre-pre-B and pre-B stages, without surface immunoglobulin light chain expression. Mature B-cell phenotype is found in less than 2% of cases [13]. *MLL* translocation, particularly t(9;11), exists in a small number of these patients.

To date, more than 50 different translocation fusion partners of *MLL* have been identified [5]. Regardless of the variety of cytogenetic abnormalities, ALL with *MLL* gene rearrangement forms a distinct subset of acute leukemias. The three most frequent *MLL* rearrangements are t(4;11), t(9;11), and t(11;19) [17, 18]. However, the t(9;11), although common in *de novo* AML and therapy-related AML, is only rarely seen in B-cell lymphoblastic leukemias (B-ALL) [19, 20].

We found 13 previously reported cases of B-ALL with surface light chain expression and *MLL* rearrangements in children and the characteristics are summarized in Table 1. Among the 14 cases including the present case, 13 patients were children, and 9 had t(9;11). Interestingly, none of these patients showed t(4;11)(q21;q23), the most frequent *MLL* rearrangement found in B-ALL of children [18]. Rather, the t(9;11) was most frequently observed. In the present case, the three-way translocation t(9;11;11)(p22;q23;p11.2) bearing the *MLL*-AF9 fusion gene was detected by FISH and RT-PCR analyses.

The frequent association between the t(9;11) and surface light chain restriction suggests that ALL with this profile is a distinct subset of *MLL*-positive B-ALL. Reported cases showed variable response to treatment. Some patients showed poor prognosis with multiple relapses (like most patients with *MLL*+

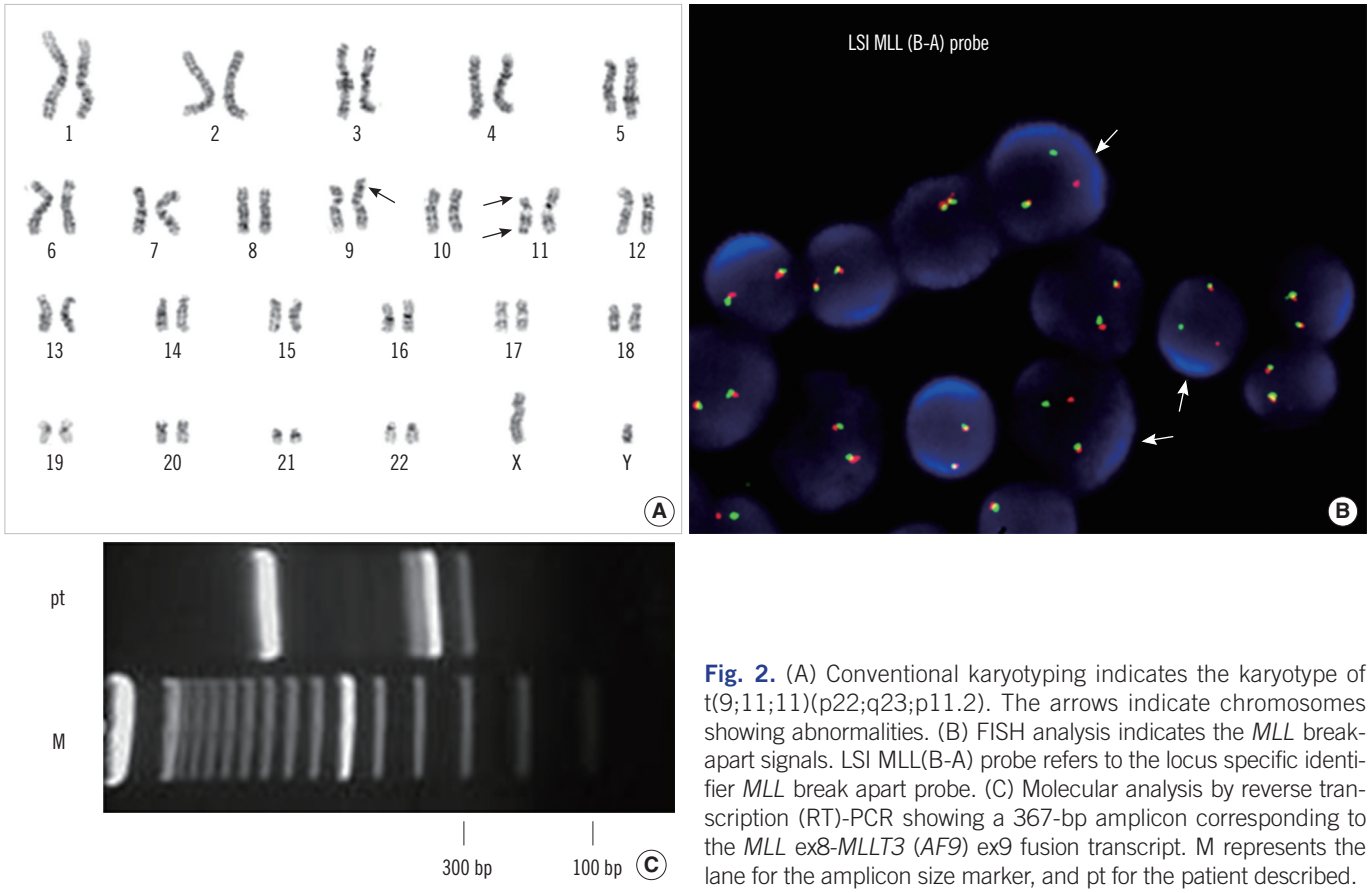


**Fig. 2.** (A) Conventional karyotyping indicates the karyotype of t(9;11;11)(p22;q23;p11.2). The arrows indicate chromosomes showing abnormalities. (B) FISH analysis indicates the *MLL* break-apart signals. LSI MLL(B-A) probe refers to the locus specific identifier *MLL* break apart probe. (C) Molecular analysis by reverse transcription (RT)-PCR showing a 367-bp amplicon corresponding to the *MLL* ex8-*MLLT3* (*AF9*) ex9 fusion transcript. M represents the lane for the amplicon size marker, and pt for the patient described.

**Table 1.** Lymphoblastic leukemia with surface light chain immunoglobulin expression and *MLL* rearrangement including t(9;11)

| Case No. | Age/Sex | Morphology | CD19 | CD20 | CD22 | CD34 | TdT | CD10 | sIg | Karyotype | FISH | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11 months/F | L1/L2 | + | + | + | - | NA | - | κ | 46,XX | *MLL* rearrangement | 13 |
| 2 | 12 months/F | L1 | + | + | + | - | - | - | λ | NA | *MLL* rearrangement | 12 |
| 3 | 23 months/F | L1 | + | + | + | - | NA | - | λ | t(9;11)(p21~22;q23)[4]/46,XX[12] | NA | 11 |
| 4 | 8 yr/F | L1 | + | + | NA | NA | + | - | λ | t(9;11)(p22;q23) | NA | 10 |
| 5 | 5 months/M | NA | + | - | NA | + | - | - | λ | NA | *MLL* rearrangement | 15 |
| 6 | 12 months/F | L1 | + | + | NA | - | - | + | λ | t(9;11)(p22;q23) | NA | 15 |
| 7 | 4 months/M | L1 | + | - | + | - | - | - | λ | t(9;11)(p21;q23) | NA | 15 |
| 8 | 8 months/F | Non-L3 | + | + | + | - | - | - | λ | t(9;11)(p21;q23) | NA | 15 |
| 9 | 5 months/M | Non-L3 | + | + | + | - | - | - | λ | 46,XX[20] | NA* | 16 |
| 10 | 13 months/F | Non-L3 | + | NA | + | - | - | - | κ | 46,XX[14] | *MLL*-AF9 rearrangement | 16 |
| 11 | 23 months/F | Non-L3 | + | + | + | - | - | - | λ | 46,XX[4]/46,XX, t(9;11)(p21~22;q23)[12] | NA | 16 |
| 12 | 8 months/M | Non-L3 | + | - | + | - | - | - | κ | 46,XY[10] | *MLL*-AF9 rearrangement | 16 |
| 13 | 67 yr/F | L2 | + | - | + | + | + | - | κ | 46,XX,t(2;11)(p21;q23) | NA | 14 |
| 14 | 4 months/M | L1 | + | - | + | - | - | + | λ | 46,XY[16]/46,XX,t(9;11;11)(p22;q23;p11.2)[4] | *MLL* rearrangement | index case |

**MLL*-AF10 fusion transcript by molecular study.
Abbreviations: TdT, terminal deoxynucleotidyl transferase; sIg, surface immunoglobulin; F, female; M, male; NA, not available.


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B-ALL), while others showed CR with no evidence of relapse. The patient described here received chemotherapy and PBSCT, and has so far shown no evidence of relapse. However, leukemias with *MLL* rearrangement are typically associated with a poor prognosis owing to the recurrent relapses, and Blin et al. [16] reported a rapid response to chemotherapy contrasted by the high incidence of relapse and poor overall prognosis in patients with this profile. Future identification of patients with this profile will allow us to expand our knowledge regarding prognostic significance and optimal treatment for this rare subgroup of patients.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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