characterized by absence of CD1a and CD8 expression and weak CD5 expression. At least 25% of ETP-ALL cells also express one or more of the following myeloid or stem-cell markers: CD117, CD34, HLA-DR, CD13, CD33, CD11b and CD65. Interestingly, they also pointed out that for patients with T-ALL, a diagnosis of ETP-ALL should be a stronger predictor of the outcome than is flow cytometric-based minimal residual disease [13]. We also found some ETP-ALL cases in our present study. The exact number of these immunophenotypic cases could not be indicated because not all of the myeloid or stem-cell markers reviewed above were used to diagnose our de novo ALL cases. However, six of 164 cases diagnosed using all these markers met the criteria for ETP-ALL. This frequency, 3.7%, was much less than the 12.6% reported by Campana et al. [13]. The difference in its frequency and correlation with the outcome should be ascertained in a future study.

Next, we classified B-lineage ALL into three categories, i.e., early pre-B ALL, pre-B ALL and mature B-ALL, according to the degree of B lymphoid differentiation of leukemic cells. Most cases of early pre-B ALL were positive for the common ALL antigen (CD10), CD34, HLA-DR and TdT. However, these antigens are not lineage specific. Although the immunoglobulin heavy chains are usually rearranged in these leukemic blasts, immunoglobulins were not detected. Early pre-B ALL can be conclusively defined as expression of at least two of the following four early B cell markers: CD19, CD20, CD22 and CD79a (Table 2). Pre-B ALL can be generally distinguished from transitional pre-B ALL based on their respective immunophenotypic characteristics [1, 10, 15]. However, in this study, we combined these two phenotypes as pre-B ALL, because discrimination of them might not be so important in the clinic [15, 21]. Pre-B ALL, including transitional pre-B ALL, can be defined as expression of cytoplasmic immunoglobulin μ heavy chains without κ or λ light chains and the presence of at least two of the following markers: CD19, CD20, CD22 and CD79a (Table 2). Additionally, B-ALL can be defined as expression of surface membrane immunoglobulin κ or λ light chains and at least two of the following markers: CD19, CD20, CD22 and CD79a (Table 2). Since, in rare instances, surface immunoglobulin μ heavy chains are absent in B-ALL cases, these markers are excluded from the definition of this immunophenotype [20].

Aberrant expression of one or more immunologic markers of another lineage might be observed in cases with mixed-lineage leukemia, which include myeloid antigen-positive ALL (B-lineage or T-lineage), lymphoid antigen-positive AML and true mixed-lineage leukemia [10]. Although our study included myeloid antigen-positive ALL, we did not find either biclonal or oligoclonal leukemias, which consist of two or more morphologically or immunophenotypically distinct leukemic cell populations. Expression of aberrant myeloid antigens (MyAgs) reportedly occurs in 5–22% of pediatric patients with de novo ALL [24–29]. We chose CD13 and CD33 as MyAgs, because they have been the most common antigens in MyAg-positive ALL. In our study, CD13 and CD33 were expressed in 31.7 and 26.5%, respectively, of de novo childhood ALL cases. Moreover, the frequency of CD13 expression was 33.3% in B-lineage ALL compared with 20.7% in T-ALL, while CD33 expression was 28.1% in B-lineage ALL versus 15.2% in T-ALL. These MyAgs were significantly more frequently associated with B-lineage ALL than with T-ALL ($p < 0.001$). In addition, the expression of these MyAgs was more frequent in early pre-B ALL cases than in pre-B ALL cases ($p < 0.001$). These incidences of MyAg expression in our study are in line with the data reported in the literature [24–29].

Recently, several notable studies investigated differences of race and ethnicity in the immunophenotypic subsets of childhood ALL [30–32]. Bhatia et al. [30] analyzed 8,762 children with de novo ALL who were categorized according to five groups: white, black, Hispanic, Asian and others. They showed that there was a significantly greater incidence of black children (25%) with T-ALL compared with Asian (19%), white (15%) and Hispanic (13%) children. In comparison, the frequency of T-ALL in our present report (the largest scale report in Japan to date), as representative data of East Asian children with ALL, was 13% of all cases, which is less than the 19% reported by Bhatia et al. [30]. This disparity cannot be readily explained. However, Kandan-Lottick et al. [32] pointed out that the reason might be that the Asian children analyzed by Bhatia et al. [30] were not Japanese, but from the Indian subcontinent and South Asia because they had been enrolled in the Children's Cancer Group Study.

In conclusion, based on the results of our large, retrospective study of antigen expression in 1,774 children with newly diagnosed ALL enrolled between 1997 and 2007, we have formulated clinically useful guidelines for flow cytometric immunophenotypic criteria for the diagnosis and classification of pediatric ALL in the JPLSG. The JPLSG was established in 2003 to create a research base for multi-center clinical trials for promotion of evidence-based medicine in pediatric hematologic malignancies. The JPLSG unifies several pediatric leukemia study groups, including the Japan Association of Childhood Leukemia Study (JACLS), the Tokyo Children's Cancer Study Group (TCCSG), the Japanese Children's Cancer and Leukemia Study Group (JCCLSG) and the Kyushu Yamaguchi Children's Cancer Study Group (KYCCSG), which had been functioning in Japan since the 1970s. The patients analyzed in this study have been treated according to different clinical protocols in each study group, and some of

them have not been clinically observed long enough. In addition, the central reference flow cytometry laboratories of the JPLSG received samples and made immunophenotypic diagnoses even during the intervals between clinical studies. Therefore, in this study we did not concern ourselves with possible associations of antigen expression with the clinical, hematological or biological features, or attempt to determine the prognostic importance of antigen expression for the decision of treatments. Nevertheless, flow cytometric data generated by extensive use of our newly proposed immunological criteria together with common diagnostic panels developed according to the present analysis may be valuable for achieving more precise characterization of the leukemic blasts in each individual patient. This information, combined with the molecular and clinical features presented in the next standard clinical protocol for childhood ALL that will be issued by the JPLSG, will also contribute to the development of personalized medicine, the so-called tailor-made therapy, for each patient.

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LETTER TO THE EDITOR

Flow cytometric analysis of de novo acute myeloid leukemia in childhood: report from the Japanese Pediatric Leukemia/ Lymphoma Study Group

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Immunophenotypic analysis has become a powerful tool for the correct identification of leukemic cell lineage. Our study evaluates the diagnostic utility of flow cytometric immunophenotyping of pediatric AML. We retrospectively collected data of immunophenotype from 375 cases of de novo AML studied from 1997 to 2007 at central laboratory institutions of the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG): Department of Pediatrics and Developmental Science, Mie University Graduate School of Medicine; Department of Pediatrics, Osaka University Graduate School of Medicine; Center for Clinical Research, National Center for Child Health and Development; and Department of Pediatrics, Aichi Medical University. The diagnosis of AML was made according to the French-American-British (FAB) classification based on morphology and enzyme cytochemical analysis as follows: M0 (acute myeloid leukemia without differentiation, $n = 11$), M1 (acute myelocytic leukemia with little differentiation, $n = 41$), M2 (acute myelocytic leukemia with differentiation, $n = 113$), M4 (acute myelomonocytic leukemia, $n = 47$), M5 (acute monocytic leukemia, $n = 54$), M6 (acute erythroleukemia, $n = 6$), and M7 (acute megakaryoblastic leukemia, $n = 61$).

Mononuclear cells of bone marrow or peripheral blood samples were stained with various combinations of fluorescein isothiocyanate (FITC)- and phycoerythrin (PE)-labeled monoclonal antibodies against the following antigens: CD4, CD7, CD13, CD14, CD15, CD19, CD33, CD34, CD36, CD41, CD42b, CD45, CD56, CD61, CD65, CD117, glycophorin A (GPA: CD235a), and HLA-DR. Cytoplasmic MPO was also detected by anti-MPO antibody after permeabilization. Two-color flow cytometric immunophenotyping was performed by collecting 10,000 ungated list mode events. An antigen was considered as

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positive, if more than 30% of the gated cells showed specific labeling above that of controls, or if positive subpopulation was distinctively identified even in <30% positive cases.

The result is summarized in Table 1. Cytoplasmic MPO expression was found in less than half of cases with M0 (45.5%), which is consistent with other reports [1, 2]. However, M0 blasts expressed CD33 (90.0%) and CD117 (90.9%), and, less frequently, CD34 (72.7%), suggesting myeloid lineage. The low expression of CD13 as compared to CD33 in our study may reflect a more mature myeloid profile in pediatric cases [1, 3]. CD7, expressed in more than half cases, is known to be expressed in a proportion of AML-M0 and M1 cases [3–5], consistent with the fact that CD7 is expressed during early stages of normal myeloid differentiation [6]. CD56 was also expressed in nearly half of cases, but only one case co-expressed CD7 and CD56 consistent with NK/myeloid-cell precursor acute leukemic cells [7].

M1 and M2 blasts expressed CD34, CD117, HLA-DR, MPO, CD13, CD33, and HLA-DR in more than 80% of cases, and less commonly CD15 and CD65. CD7 was detected in 51.2% of M1 cases, while its expression was repressed in M2. CD19, detected in 24.8% of M2 cases, was reported to be detected in 78–81% of M2 cases with t(8;21) translocation [8, 9].

M3 cells expressed CD13, CD33, and MPO at high frequency, as for M1 or M2 cells. However, the frequency of CD117 expression was 76.7%, lower than for M1 or M2 cells. A striking feature is that the expression of CD34 and HLA-DR was low, at 14.3 and 4.8%, respectively. The lack of CD34 and HLA-DR was a feature of M3 blasts [4, 5, 10].

Leukemic cells of most M4 and M5 cases expressed monocyte markers, CD15 and CD65. The less common expression of CD14 has been reported by others, particularly in M5 cases [2, 5, 10]. M4 and M5 expressed CD33 at similarly high frequencies. The progenitor-associated antigens, CD34 and CD117, were seen in a lower proportion of M5 cases, which might reflect commitment to monocytic lineage. CD4 was expressed in 52.1% of M5 cases and 23.1% of M4 cases, in line with other reports [2, 10].

We observed only six M6 cases. Leukemic erythroblasts expressed CD36 and GPA in 66.7 and 83.3% of cases, respectively. Myeloid antigens (MPO, CD13, and CD33) and hematopoietic progenitor-associated markers (CD34 and CD117) were also expressed at variable frequencies. The expression of monocytic markers (CD14 and CD15) was absent, as well as megakaryocyte-associated antigens (CD41 and CD42b).

The expression frequencies of megakaryocyte-associated antigens, CD41 and CD42b in cases with M7, were

Table 1 Immunophenotypic profile of 375 de novo cases of acute myeloid leukemia

	CD34	CD117	HLADR	MPO	CD13	CD33	CD14	CD15	CD65	GPA	CD36	CD41	CD42b	CD61	CD7	CD4	CD19	CD56	CD45
M0 (11)	72.7 (11)	90.9 (11)	63.6 (11)	45.5 (11)	54.5 (11)	90.0 (11)	0 (11)	33.3 (9)	16.7 (6)	0 (11)	9.1 (11)	9.1 (11)	9.1 (11)	ND	54.5 (11)	9.1 (11)	9.1 (11)	45.5 (11)	90.0 (10)
M1 (41)	85.4 (41)	100 (36)	73.2 (41)	100 (41)	90.2 (41)	97.6 (41)	2.6 (39)	60.7 (28)	75.0 (20)	0 (37)	18.9 (37)	10.0 (40)	0 (36)	ND	51.2 (41)	2.7 (37)	7.3 (41)	19.5 (41)	90.9 (33)
M2 (113)	83.8 (111)	94.4 (89)	89.2 (111)	96.4 (84)	91.2 (113)	92.9 (113)	7.4 (108)	55.1 (89)	33.3 (63)	0 (93)	12.0 (92)	4.5 (112)	2.2 (92)	ND	14.3 (112)	0 (95)	24.8 (113)	36.4 (110)	97.3 (74)
M3 (42)	14.3 (42)	76.3 (38)	4.8 (42)	96.9 (32)	92.9 (42)	97.6 (42)	4.8 (42)	15.6 (32)	53.8 (26)	2.8 (36)	5.6 (36)	0 (42)	10.8 (37)	ND	0 (42)	2.7 (37)	2.4 (42)	7.1 (42)	85.2 (23)
M4 (47)	53.2 (47)	76.7 (43)	78.7 (47)	94.9 (39)	87.2 (47)	93.6 (47)	29.8 (47)	80.0 (30)	80.6 (31)	2.3 (43)	51.2 (43)	10.6 (47)	4.5 (44)	ND	8.5 (47)	23.1 (39)	2.1 (47)	15.2 (46)	94.4 (36)
M5 (54)	24.1 (54)	39.6 (48)	81.5 (54)	68.6 (35)	64.8 (54)	98.1 (54)	34.6 (52)	74.5 (47)	87.1 (31)	2.3 (43)	60.5 (43)	5.6 (54)	2.1 (48)	ND	3.7 (54)	52.1 (48)	1.9 (54)	57.4 (54)	93.8 (32)
M6 (6)	50.0 (6)	66.7 (6)	50.0 (6)	80.0 (5)	100 (6)	100 (6)	0 (6)	0 (4)	25.0 (4)	66.7 (6)	83.3 (6)	0 (6)	0 (6)	ND	33.3 (6)	16.7 (6)	0 (6)	0 (6)	60.0 (5)
M7 (61)	41.1 (56)	74.5 (51)	49.1 (57)	2.8 (36)	73.7 (57)	90.0 (60)	1.9 (53)	8.9 (45)	5.7 (35)	32.0 (30)	78.0 (50)	72.4 (58)	58.5 (53)	85.7 (14)	69.6 (56)	20.0 (50)	1.7 (58)	45.6 (57)	96.8 (31)

Values indicate proportion of positive cases (%); parentheses indicate evaluable cases, *ND* not done

72.4 and 58.5%, respectively. All cases expressed CD41 and/or CD42b. CD36 was expressed at a high frequency, but its expression was also seen in other subtypes (M4, M5, and M6). Myeloid antigens (CD13 and CD33) were expressed in most cases, but lack of MPO expression was observed. Hematopoietic progenitor-associated antigens (CD34 and CD117) were expressed in many cases, and CD7 was expressed in 69.6% of cases.

In conclusion, each subtype of AML possesses distinguishing features of antigen expression. Some antigens appear to be associated with certain subtypes, but are not necessarily specific. Uncommon expression must be interpreted in the context of the entire immunophenotyping profile for correct identification of AML subtypes.

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