CD56-positive B cell precursor acute lymphoblastic leukemia harboring *KMT2A-AFF1* rearrangement developed in a pregnant woman successfully treated with allogeneic hematopoietic cell transplantation

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Although aberrant T/NK-cell antigen expression is observed approximately 10% of B cell precursor acute lymphoblastic leukemia (BCP-ALL), the bright positivity of CD56 is exceedingly rare [1–3]. Here, we describe the first reported case, at least to our knowledge, of *KMT2A-AFF1*-rearranged BCP-ALL that co-expressed CD34, CD19, cytoplasmic (cyt) CD79a, and CD56 without any other lineage markers developed in a pregnant woman and successfully treated by allogeneic hematopoietic cell transplantation.

A 33-year-old woman in her third trimester was referred to our department because of extreme hyperleukocytosis reaching $300 \times 10^9/\text{L}$ with 96% of leukemic blasts (Fig. 1a). Flow cytometric analysis of bone marrow leukemic cells revealed the bright surface expression of CD34 and CD56 as well as the positivity of CD19, CD38, and HLA-DR with partial expression of cyt CD79a, while CD3, CD10, cyt myeloperoxidase, cyt CD3, cyt CD22, and cyt μ heavy chain were found to be negative (Fig. 1b). CD4 was also negative (data not shown) and there was no morphological findings that suggest monocytic differentiation. Cytogenetic analysis

showed a 47, XX, +X, t(4;11)(q21;11q23.3) karyotype suggesting a diagnosis of *KMT2A*-rearranged BCP-ALL, which was confirmed by the molecular detection of *KMT2A-AFF1* fusion transcript. After delivery of a female newborn by Cesarean section at 32 weeks pregnant, she had started to receive intensive chemotherapy by use of the hyper-CVAD regimen [2], which led her disease to sustained molecular remission. The delivered infant did not show any hematologic abnormalities that denied the possibility of fetal cell-derived maternal leukemia. Considering the high-risk nature of *KMT2A-AFF1*-rearranged BCP-ALL with hyperleukocytosis, we decided to perform allogeneic peripheral blood stem-cell transplantation from her HLA identical sister using myeloablative conditioning consisting of fludarabine 120 mg/m², intravenous busulfan 12.8 mg/kg, and melphalan 140 mg/m² as a consolidative treatment. She has maintained molecular remission with good performance status with mild skin chronic GVHD more than 2 years after transplantation.

Aberrant expression of CD56 is commonly observed in acute myeloid leukemia, whereas its expression in lymphoblastic leukemia is a relatively rare event. BCP-ALL with *KMT2A-AFF1* is a common subtype of *KMT2A*-rearranged leukemia characterized by frequent occurrence in infants with dismal clinical course [4]. In a more recent study, *KMT2A-AFF1* was also shown to be the most prevalent translocation in adult patients with Philadelphia chromosome-negative BCP-ALL and associated with a worse outcome independent of age [5]. Although its etiology and cellular origin remain an enigma, *KMT2A-AFF1* fusion gene was shown to be present in primitive CD34+CD19– lymphoid progenitors [6]. Because those common lymphoid progenitors usually differentiate into innate lymphoid cells via expression of CD56 [7], aberrant CD56 expression in our patient might suggest the bidirectional differentiation potential of very early B cell

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A high-magnification micrograph of a blood smear. The field is populated with numerous erythrocytes, which appear as small, orange-red, circular cells. Interspersed among these are several large, purple-stained cells, likely leukocytes. These cells have large, dark purple nuclei and some show a thin rim of light blue cytoplasm. The background is a pale, off-white color, typical of a stained blood smear.

Fig. 1 Morphology and flow cytometric characterization of leukemic cells. **a** Light microscopic picture of bone marrow leukemic cells (May-Giemsa staining, $\times 1000$). Leukemic blasts were heterogeneous in size with strongly basophilic cytoplasm containing prominent Golgi areas; note that some blasts contained fine azurophilic granules. **b** Immunophenotypic characterization of leukemic cells. Bone marrow cells obtained at diagnosis were analyzed by four-color flow cytometry using FACSCANTO II (BD Bioscience, San Jose, CA, USA) using standard protocols described elsewhere. The panels of monoclonal antibodies used for analysis included CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD13, CD16, CD19, CD20, CD22, CD24, CD33, CD34, CD45RO, CD56, CD99, CD117, cyt myeloperoxidase, cyt CD3, cyt 22, cyt 79a, cyt immunoglobulin μ heavy chain, TdT, and HLA-DR. The surface expression of CD2, CD3, CD4, CD5, CD7, CD8, CD24, CD99, and CD117 was negative (data not shown)

progenitors characterized by CD34+CD10–CD19+ phenotype, a putative origin of *KMT2A-AFF1*-rearranged BCP-ALL. It is also important to note here that CD34+CD10–CD19+ B cell precursors might arise from distinct developmental pathways from CD34+CD10+CD19+ pro-B cells [8]. Because the promoter of CD56 gene contains sequences that allow binding of various transcription factors such as RUNX1, BTB3, Pax5, MMSET, and Cyclin D1 [9], more simple explanation of aberrant CD56 expression in this particular case might be dysregulated transcriptome of leukemic cells. Finally, although the prognostic impact of CD56 expression in *KMT2A-AFF1*-rearranged BCP-ALL has yet to be elucidated, our present experience suggests that sustained remission can be achieved by allogeneic hematopoietic cell transplantation performed at an appropriate timing.

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Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent for writing and publishing this report was obtained from the patient included in the study. T. Ichinohe has received speaker honoraria from Bristol-Myers Squibb, Celgene, Janssen Pharmaceutical K.K., and Kyowa Kirin Co. and research funding from Astellas Pharma, Chugai Pharmaceutical Co., CSL Behring, Eisai Co., FUJIFILM Wako Chemicals, Kyowa Kirin Co., Ono Pharmaceutical Co., Pfizer, Nippon Shinyaku Co., MSD, Otsuka Pharmaceutical Co., Repertoire Genesis Inc., Sumitomo Dainippon Pharma Co., Taiho Pharmaceutical Co., Takara Bio Inc., Takeda Pharmaceutical Co., and Zenyaku Kogyo Co. All other authors declare that they have no conflict of interest.

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