J Clin Exp Hematopathol
Vol. 48, No. 2, Nov. 2008

Case Study

A Peculiar Case of Acute Myeloid Leukemia Mimicking Plasmacytoid Dendritic Precursor Cell Leukemia

Fuminori Sano,[1] Taizo Tasaka,[2] Hirotake Nishimura,[3] Takashi Akiyama,[3] Yasutaka Kubo,[1] Yoshiko Matsuhashi,[1] Hideho Wada,[1] Takashi Sugihara,[1] Mitsunori Yamakawa,[4] and Yoshito Sadahira[3]

Differential diagnosis between plasmacytoid dendritic precursor cell leukemia (pDC leukemia) and acute myeloid leukemia (AML) with monocytic differentiation is difficult due to shared clinicopathological features ; however, such diagnosis is critical because the two leukemias are treated differently. Here we report a peculiar case of AML mimicking pDC leukemia. A 22-year-old man presented with leukocytopenia and bone marrow involvement of atypical plasmacytoid cells with a prominent nucleolus. In spite of positive cytochemical staining for NaF-sensitive naphthyl butyrate esterase, this case was diagnosed as pDC leukemia because the abnormal cells were positive for CD4, CD56, and CD123, and negative for myeloperoxidase and lysozyme. The patient achieved complete remission after 4 courses of combination chemotherapy, but relapsed four months later with leukemic manifestation and skin involvement. The morphology of the leukemia cells became myelomonoblastic, and some were immunohistochemically positive for lysozyme, suggesting AML. Although the patient received allogenic stem cell transplantation twice, he died of progressive disease. This case demonstrates the importance of cytochemical staining for naphthyl butyrate esterase in differential diagnosis between AML and pDC leukemia coexpressing CD4, CD56, and CD123. 〔*J Clin Exp Hematopathol 48(2) : 65-69, 2008*〕

Keywords: dendritic precursor cell leukemia, acute myeloid leukemia, naphthyl butyrate esterase staining

INTRODUCTION

Plasmacytoid dendritic cell leukemia/lymphoma (pDC leukemia), is a recently recognized disease entity with distinct clinicopathologic and immunophenotypic features.[1-4] Clinically, this malignancy generally involves the skin, bone marrow, and blood, and is highly resistant to conventional chemotherapy. The neoplastic cells are $CD56^+$ and have the phenotypic characteristics of plasmacytoid dendritic cells : positive for CD4, CD11c, CD36, CD45RA, CD68, and CD74, and negative for the myeloid markers CD14 and CD16, the T-cell marker CD3, and the B-cell markers CD19 and CD20. $CD4^+/CD56^+$ hematodermic neoplasm, previously called blastic natural killer (NK) cell lymphoma, is now considered to be included in this entity as well.[5-7]

Acute myeloid leukemia (AML) cells with monocytic differentiation also frequently coexpress CD4 and CD56. Striking similarities are noted between this type of myeloid leukemia and pDC leukemia in clinical presentation, histology, immunophenotype and prognosis. Differentiation between the two conditions depends on detecting the absence of the classic myelomonocytic markers myeloperoxidase and lysozyme,[5,6] the presence of the pDC markers CD123, TCL1a, or BDCA-2 (3,4), or, more recently, expression of a specific gene.[8] Thus, the diagnosis of pDC leukemia may be exceedingly difficult without extensive phenotyping.

Here we report a peculiar case of AML which was initially diagnosed as pDC leukemia because neoplastic cells predominantly showed plasmacytoid morphology and a $myeloperoxidase^-$, $lysozyme^-$, $CD4^+$, $CD56^+$, and $CD123^+$ phenotype.

Received : February 1, 2008
Revised : April 9, 2008
Accepted : May 7, 2008
[1] Division of Hematology, Department of Medicine, Kawasaki Medical School, Kurashiki, Japan
[2] Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Kurashiki, Japan
[3] Department of Pathology, Kawasaki Medical School, Kurashiki, Japan
[4] Department of Pathology, Yamagata University School of Medicine, Yamagata, Japan
Address correspondence and reprint request to Yoshito Sadahira, M.D., Department of Pathology, Kawasaki Medical School, 577, Matsushima, Kurashiki, Okayama 701-0192, Japan
E-mail : sadapath@med.kawasaki-m.ac.jp

CLINICAL SUMMARY

A 22-year-old man was admitted to our hospital due to progressive leukocytopenia, which had been discovered by chance. The patient had no specific symptoms on admission and no particular family or past history. On admission, no abnormalities of the lymph nodes were noted, and the liver and spleen sizes were normal. Laboratory data revealed a decreased white blood cell count of 1,940/μL (band form of neutrophils, 0% ; segmented form of neutrophils, 43% ; monocytes, 2% ; lymphocytes, 55% ; atypical cells, 0%). Red blood cell count of $439 \times 10^4/\mu$L, hemoglobin concentration of 14.2 g/dL, and platelet count of $21.6 \times 10^4/\mu$L were within the normal range. Biochemical values were within normal limits, except for slightly elevated serum ferritin 170 ng/mL. Serum and urinary lysozyme values were below the normal ranges. IgG, IgA, and IgM concentrations were 1,195 mg/dL, 247.8 mg/dL, and 282.3 mg/dL, respectively. Soluble interleukin-2 receptor (sIL-2R) showed a slight elevation (369 U/mL), but concentrations of interferon (IFN)-α, IFN-β, IFN-γ, IL-3, and IL-10 were within normal ranges.

Tumor scintigraphy and bone scintigram revealed isotope accumulation in the sternal and clavicular bones. Bone marrow aspiration was performed and the findings are listed below (see Pathological Findings). The patient was treated with 4 courses of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone. After the initial course of chemotherapy, he achieved complete remission, which was confirmed by scintigraph and bone marrow aspiration ; however, he relapsed four months later. Delayed recovery from myelosuppression after chemotherapy was observed. Bone marrow aspiration revealed that the bone marrow was occupied by monoblast-like cells which were positive for naphthyl butyrate esterase reactions. Abnormal cells soon appeared in the peripheral blood. Generalized lymph node swelling and hepatosplenomegaly were also observed. Elevated serum lactate dehydrogenase and sIL-2R were also observed but serum lysozyme value was within the normal range. Disseminated intravascular coagulation was also complicated with leukocyte elevation. Initially, the patient was treated with a combination of idarubicin and cytosine arabinoside (ara-C) as induction chemotherapy, which was ineffective. Next, he was treated with high-dose ara-C, which also failed. Bone marrow transplantation from an HLA-identical brother was performed and the patient achieved complete remission that lasted for two months. After the second relapse, the disease became refractory to chemotherapy, including high-dose regimens. Finally, he received a haploidentical HLA bone marrow transplantation from his father, which failed due to engraftment failure.

PATHOLOGICAL FINDINGS

Morphologic analysis of bone marrow aspirates on the patient's first admission demonstrated hypercellular marrow with a high count of abnormal cells. The cells were homogeneous and medium in size and showed an intermediate nucleus-cytoplasm ratio. The cytoplasm displayed basophilia, with small cytoplasmic vacuoles and no granulation. The nucleus was eccentric and regular in shape with a prominent nucleolus (Fig. 1a). Mitotic figure was absent. Cytochemical tests revealed that the abnormal cells were negative for myeloperoxidase and naphthol ASD chloroacetate esterase, but positive for naphthyl butyrate esterase reactions (Fig. 1b). Flow cytometric analysis clearly highlighted an immunophenotypic feature : positive for CD4, CD11a, CD11c, CD33, CD38, CD44, CD45RA, CD49d, CD56, CD68, CD123 (90%), and HLA-DR, but negative for CD1, CD2, CD3, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD16, CD19, CD20, CD25, CD30, CD34, CD36, CD40, CD45RO, CD49e, CD54, CD57, CD62L, CD71, and CD126. On paraffin-embedded sections of a bone marrow aspiration clot, the number of hematopoietic cells was decreased and the number of blastic cells with plasmacytoid features was increased (Fig. 1c). Immunohistochemistry revealed that the plasmacytoid cells were positive for CD4, CD43, CD45, CD45RA, CD56, and CD68 (KP-1, PG-M1, Ki-M1p), but negative for CD3, CD79a, CD20, CD30, CD34, CD138, CD163, S-100 protein, T-cell intracellular antigen-1, TdT, myeloperoxidase, and lysozyme. Chromosomal analysis showed a normal male karyotype. Southern blotting analysis indicated no rearrangement of the *immunoglobulin heavy-chain* (*IgH*) gene or *T-cell receptor* (*TCR*) gene using JH (IgH), Cβ1 (TCR), and Jγ (TCR). EBER-1 *in situ* hybridization showed no positive signals ; therefore, the diagnosis of pDC leukemia was made.

In the subsequent stage, the morphology of leukemia cells in aspiration changed from a plasmacytoid to a myelomonoblastic configuration : the nucleus was located in the center and had slight indentation, with fine chromatin (Fig. 1d). While the cells were cytochemically positive for naphthyl butyrate esterase reactions, they showed slight antigenic alteration, that is, positivity for CD7, CD13, and CD34. Histological study of the skin involvement showed that leukemia cells were diffusely distributed from the dermis to subcutaneous tissue (Fig. 2a). Immunohistochemical study revealed that some of these leukemia cells were positive for lysozyme as well as CD4 and CD56 (Fig. 2b, 2c, 2d) ; therefore, the diagnosis of acute myeloblastic leukemia (M5a of FAB classification) was made.

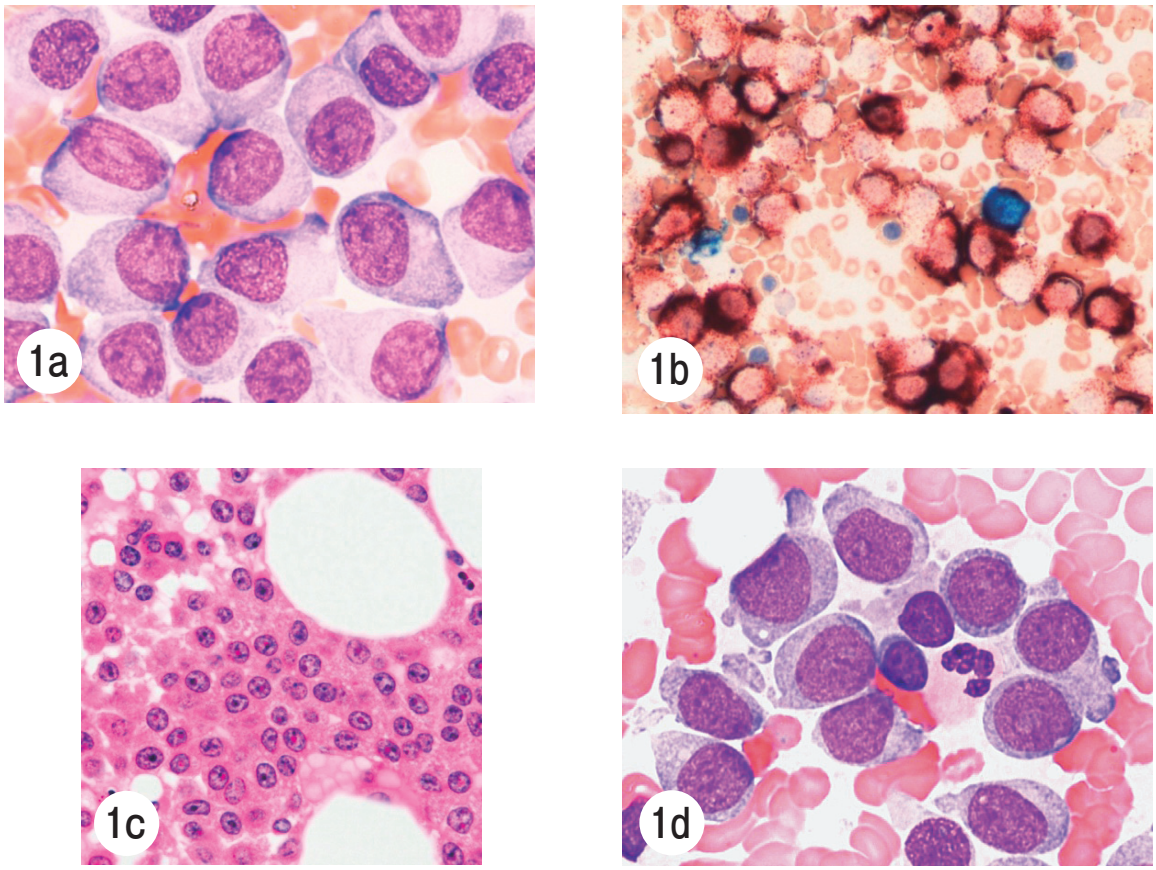
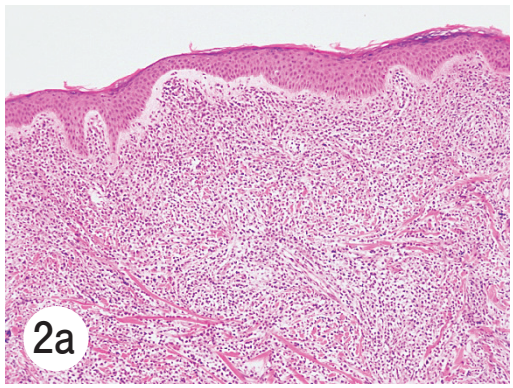


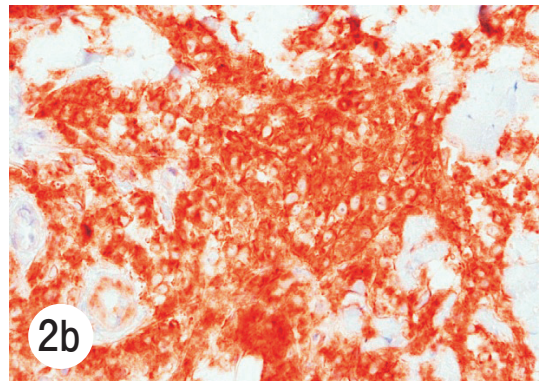
Fig. 1. Bone marrow specimens in initial (*1a*, *1b* & *1c*) and subsequent (*1d*) phases. (***1a***) Aspiration cytology. Note the regular-shaped eccentric round nucleus with prominent nucleoli and abundant cytoplasm. May-Giemsa, x400. (***1b***) Double cytochemical staining of aspiration for naphthol ASD-chroloacetate estrase and naphthyl butyrate esterase. Abnormal cells were positive for NaF-sensitive naphthyl butyrate esterase. x200. (***1c***) Hematoxylin & eosin staining of aspiration clot. Abnormal cells resembled myeloma cells. x200. (***1d***) Aspiration cytology. As compared with (*1a*), the size of abnormal cells varied and had an irregular nucleus with fine chromatin and slight indentation. May-Giemsa, x400.

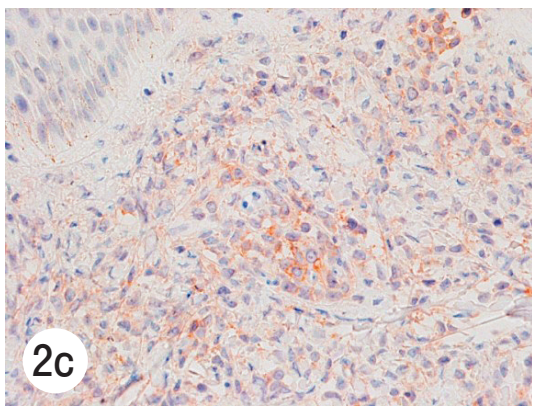
DISCUSSION

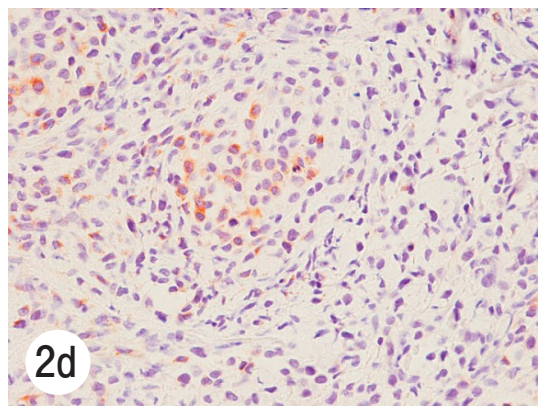
The diagnosis of pDC leukemia is challenging because of the diagnostic overlap with myeloid leukemia.[4] The present case was initially diagnosed as pDC leukemia because of the clinical, morphological, and phenotypical resemblance to pDC leukemia : first, neoplastic cells had basophilic cytoplasm and a rounded unevenly distributed nucleus with a prominent nucleolus located in the center ; second, they expressed antigens of dendritic cell lineage (CD4, CD11c, CD45RA, CD68, CD123, and HLA-DR) but not myeloid (CD13, CD11b, CD14, CD16, myeloperoxidase, and lysozyme) or lymphoid (CD3, CD19, and CD20) lineage. It has been reported that CD123 is a useful marker for pDC leukemia, and more recently, it was suggested that BDCA and TCL-1 as well as CD123 should be included in the diagnostic panel to distinguish pDC leukemia from myeloid leukemia.[3,4,9] However, a confusing case was recently described in which the initial diagnosis of $CD4^+$ / $CD56^+$ / $CD123^+$/ TCL-1^+ hematodermic neoplasm was made, but at relapse after chemotherapy, cells showed positive cytochemical staining for myeloperoxidase and naphthyl butyrare esterase and the diagnosis was changed to AML regardless of the expression of CD123 and TCL-1.[4] In addition, an unusual case of a 17-year-old adolescent, with overlapping features of pDC leukemia and AML co-expressing CD4, CD7, CD33, CD56, and pDC marker BDCA, was reported.[10] These cases are examples of borderline cases between pDC leukemia and AML.

One important point is that the neoplastic cells in the present case were consistently diffusely stained for NaF-sensitive naphthyl butyrare esterase, which has been reported to be specific to the monocytic lineage. This enzyme is a key









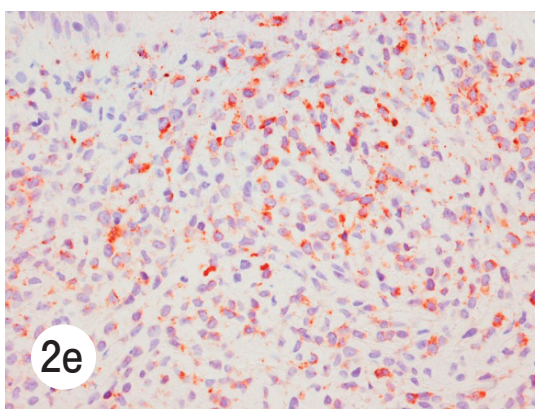


Fig. 2. Skin involvement in the second phase. (***2a***) Hematoxylin & eosin staining. Leukemic cells infiltrated diffusely in the dermis. x40. (***2b***) Leukemic cells were positive for CD4. (***2c***) Leukemic cells were positive for CD56. (***2d***) Some leukemic cells were positive for lysozyme. (***2e***) Leukemic cells were positive for CD68. (***2b***), (***2c***), & (***2d***), counterstained with hematoxylin, x100.

cytochemical marker for AML with monocytic lineage, as recommended by the French-American-British (FAB) leukemia study group.[11] Although it has not been confirmed that the presence of naphthyl butyrare esterase activity excludes the possibility of pDC leukemia, our case could have been diagnosed as AML from the initial phase according to current diagnostic criteria in the review by Garnache-Ottou *et al*.[3]

In the differential diagnosis, myeloid/NK cell acute leukemia and histiocytic sarcoma should also be considered. Myeloid/NK cell acute leukemias are characterized by the expression of such myeloid markers as CD11b, CD33, and myeloperoxidase antigen in conjunction with CD7 and CD56 expression.[12] In contrast, the current case lacked the expression of myeloperoxidase, CD7, and CD11b. In regard to histiocytic sarcoma, the present case could be differentiated from this entity because of its uniformity in cell morphology and its negativity for CD163.[13]

The initial chemotherapy for pDC leukemia seems to be effective, and no standard regimen for pDC leukemia has been developed. Relapses are frequently observed with an aggressive clinical course.[1] Only allogeneic haematopoietic cell transplantation can lead to complete remission after relapse. The clinical course of the present case was similar to that of pDC leukemia cases ; therefore, it was quite difficult to distinguish our present case from pDC leukemia by clinical parameters and the clinical course.

In summary, we have described a case of AML with plasmacytoid morphology and coexpression of CD4, CD56, and CD123. In this case, naphthol butyrate esterase appeared to be the most useful marker in differentiating acute myeloid leukemia from pDC leukemia.

REFERENCES

1 Feuillard J, Jacob MC, Valensi F, Maynadié M, Gressin R, Chaperot L, Arnoulet C, Brignole-Baudouin F, Drénou B, Duchayne E, Falkenrodt A, Garand R, Homolle E, Husson B, Kuhlein E, Le Calvez G, Sainty D, Sotto MF, Trimoreau F, Béné MC : Clinical and biologic features of CD4 (+) CD56 (+) malignancies. Blood 99 : 1556-1563, 2002

2 Garnache-Ottou F, Chaperot L, Biichle S, Ferrand C, Remy-Martin JP, Deconinck E, de Tailly PD, Bulabois B, Poulet J, Kuhlein E, Jacob MC, Salaun V, Arock M, Drenou B, Schillinger F, Seilles E, Tiberghien P, Bensa JC, Plumas J, Saas P : Expression of the myeloid-associated marker CD33 is not an exclusive factor for leukemic plasmacytoid dendritic cells. Blood 105 : 1256-1264, 2005

3 Garnache-Ottou F, Feuillard J, Saas P : Plasmacytoid dendritic cell leukaemia/ lymphoma : towards a well defined entity ? Br J Haematol 136 : 539-548, 2007

4 Herling M, Jones D : CD4+/CD56+ hematodermic tumor : The features of an evolving entity and its relationship to dendritic cells. Am J Clin Pathol 127 : 687-700, 2007

5 Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ : WHO-EORTC classification for cutaneous lymphomas. Blood 105 : 3768-3785, 2005

6 Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M, Meijer CJ, Courville P, Joly P, Grange F, De Muret A, Machet L, Dompmartin A, Bosq J, Durlach A, Bernard P, Dalac S, Dechelotte P, D'Incan M, Wechsler J, Teitell MA : Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms) : a review. Am J Clin Pathol 123 : 662-675, 2005

7 Assaf C, Gellrich S, Whittaker S, Robson A, Cerroni L, Massone C, Kerl H, Rose C, Chott A, Chimenti S, Hallermann C, Petrella T, Wechsler J, Bagot M, Hummel M, Bullani-Kerl K, Bekkenk MW, Kempf W, Meijer CJ, Willemze R, Sterry W : CD56-positive haematological neoplasms of the skin : a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer. J Clin Pathol 60 : 981-989, 2007

8 Dijkman R, van Doorn R, Szuhai K, Willemze R, Vermeer MH, Tensen CP : Gene-expression profiling and array-based CGH classify CD4+CD56+ hematodermic neoplasm and cutaneous myelomonocytic leukemia as distinct disease entities. Blood 109 : 1720-1727, 2007

9 Garnache-Ottou F, Jacob MC, Biichle S, Chaperot L, Trimoreau F, Plumas J, Tiberghien P, Saas P, Feuillard J : Identification of BDCA-2 and high levels of CD123 expression as useful markers for the diagnosis of plasmacytoid dendritic cell leukemia. Blood 106 : 3269, 2005 [abstract]

10 Anargyrou K, Paterakis G, Boutsis D, Politou M, Papadhimitriou SI, Siakandaris M, Vassiliadis J, Androulakis A, Meletis J, Rombos J, Tassiopoulou A, Vaiopoulos G : An unusual case of CD4+CD7+CD56+ acute leukemia with overlapping features of type 2 dendritic cell (DC2) and myeloid/ NK cell precursor acute leukemia. Eur J Haematol 71 : 294-298, 2003

11 Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C : Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. Br J Haematol 33 : 451-458, 1976

12 Suzuki R, Yamamoto K, Seto M, Kagami Y, Ogura M, Yatabe Y, Suchi T, Kodera Y, Morishima Y, Takahashi T, Saito H, Ueda R, Nakamura S : CD7+ and CD56+ myeloid/natural killer cell precursor acute leukemia : a distinct hematolymphoid disease entity. Blood 90 : 2417-2428, 1997

13 Mikami M, Sadahira Y, Suetsugu Y, Wada H, Sugihara T : Monocyte/macrophage-specific marker CD163+ histiocytic sarcoma : case report with clinical, morphologic, immunohistochemical, and molecular genetic studies. Int J Hematol 80 : 365-369, 2004