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Acute Myeloid Leukemia With *MLL* Rearrangement and CD4+/CD56+ Expression can be Misdiagnosed as Blastic Plasmacytoid Dendritic Cell Neoplasm: Two Case Reports

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Dear Editor,

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), characterized by co-expression of CD4 and CD56 without any other lineage-specific markers, is an aggressive tumor type that shows a high frequency of skin involvement and nodal or marrow infiltration with a propensity toward leukemic dissemination [1].This disease was formerly defined by the World Health Organization as blastic NK-cell lymphoma, and was later grouped with AML and related precursor neoplasms [2]. Here we report two AML cases with *KMT2A* (or *MLL*) rearrangements along with CD4+/CD56+ expression, which had the potential to be misdiagnosed as BPDCN.

A 59-yr-old man presented with erythematous papules and vesicles on his whole body for one week. Complete blood counts showed anemia (Hb, 80 g/L), thrombocytopenia (62×10^9 platelets/L), and many circulating plasmoblast-like cells (65%). Bone marrow examination showed hypercellular marrow (90%) mostly composed of plasmoblast-like cells with coarse nuclear chromatin, distinct nucleoli, and abundant basophilic cytoplasm (Fig. 1A). Flow cytometry revealed that the neoplastic cells were positive for CD4, CD33, CD38, CD56, CD117, and CD138 (Fig. 1B), and negative for other myeloid or lymphoid markers (Table 1). Skin lesions showed diffuse infiltration of medium- to large-sized agranular blastic cells with CD4 and CD56 co-expression (Fig. 1C). Bone marrow and skin were negative for CD123 immunohistochemical stain. The chromosome study revealed 45,X,-Y[9]/46,XY[11] without 11q23 abnormalities. Multiplex, nested reverse transcription (RT)-PCR was performed for screening and detection of 28 chromosomal translocations using the HemaVision kit (DNA Technology, Research Park, Aarhus, Denmark), and the presence of *MLL-MLLT10* rearrangement was demonstrated. It was confirmed by direct sequencing

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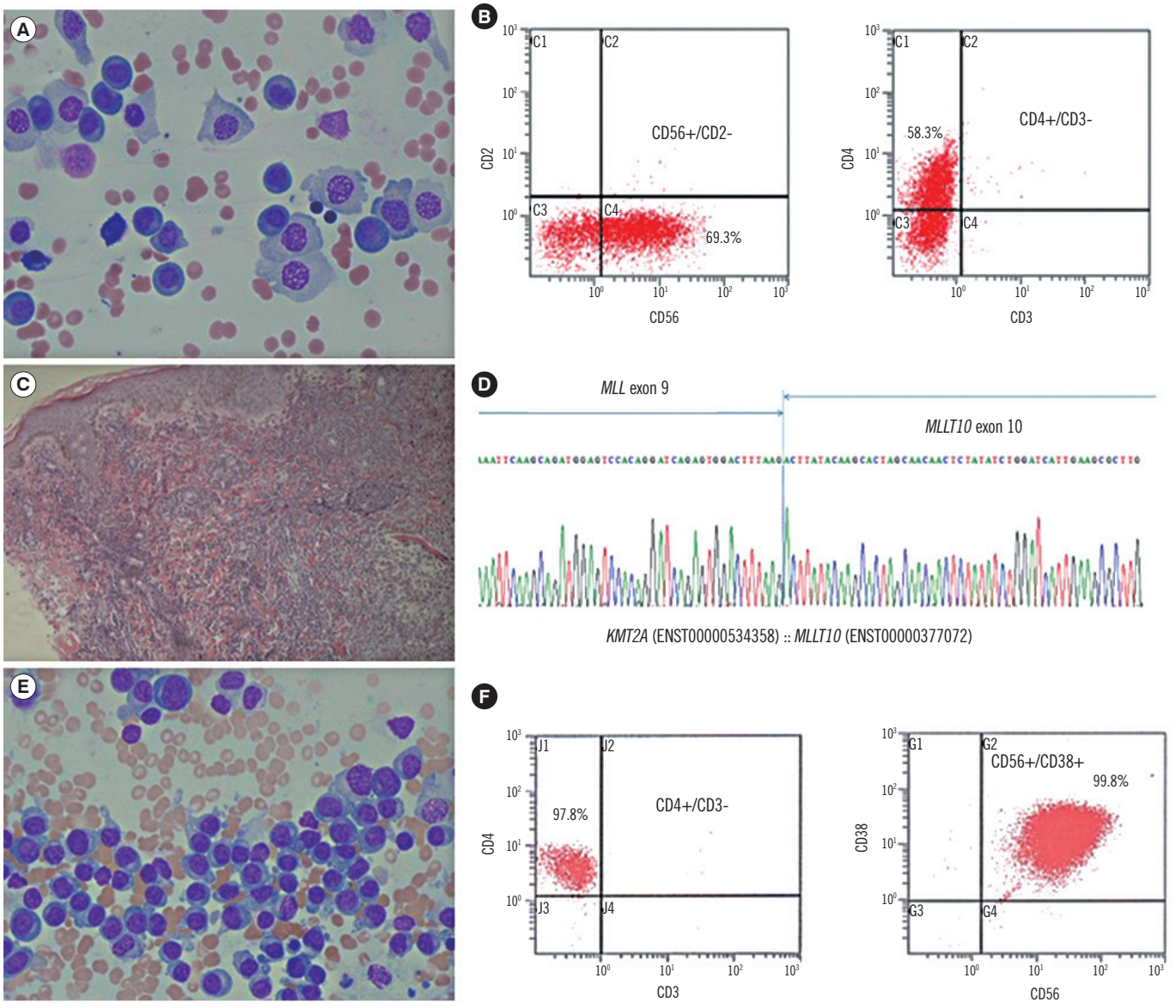

Fig. 1. Morphological features, flow cytometric analysis, immunohistochemical stain, and genetic study of the two cases of CD4+/CD56+ AML. (A) Plasmoblast-like neoplastic cells in the first case (Wright Giemsa stain, 400×, Bone marrow); (B) Immunophenotyping features with CD56 and CD4 coexpression in the first case; (C) Skin biopsy showing diffuse infiltration of medium- to large-sized agranular blastic cells into the dermis in the first case (Hematoxylin and Eosin stain, 100×, Skin lesion); (D) The *MLL-MLLT10* rearrangement confirmed by direct sequencing in the first case; (E) Plasmacytoid cells in the second case (Wright Giemsa stain; ×400, Bone marrow); and (F) The immunophenotyping features with CD4 and CD56 coexpression in the second case.

(Fig. 1D). Fluorescence *in situ* hybridization for *MLL* rearrangement revealed nuc ish(5′MLLx3,3′MLLx2)(5′MLL con 3′MLLx2)[170/200], suggesting the presence of an atypical *MLL* breakpoint. Although the lineage antigens expressed here were not specific to AML, he was diagnosed as having AML with *MLL* rearrangement in bone marrow and skin.

A 30-yr-old woman presented with multiple lymphadenopathy for three weeks. Laboratory analysis revealed anemia (Hb, 81 g/L), thrombocytopenia (82×10^9 platelets/L), and leukocytosis (16.77×10^9 white blood cells/L) with circulating plasmacytoid cells (63%). Neither skin lesion nor monoclonal gammopathy was present. Bone marrow analysis showed hypercellular marrow (100%) with leukemic cells containing abundant basophilic cytoplasm (Fig. 1E). Flow cytometry revealed that the neoplastic cells were positive for CD4, CD7, CD33, CD38, CD56, and CD64, (Fig. 1F), and were negative for other markers (Table 1).

Table 1. The clinicopathologic characteristics of CD4+/CD56+ hematologic malignancies carrying the *MLL* rearrangement

	Case 1	Case 2	Case 3	Case 4	Case 5
Reference	[3]	[4]	[5]	First case in this study	Second case in this study
Diagnosis	CD4+/CD56+ hematodermic malignancy	BPDCN with *MLL-ENL* rearrangement	BPDCN with *MLL* rearrangement	AML with *MLL* rearrangement	AML with *MLL* rearrangement
Age/gender	50/F	45/M	8/F	59/M	30/F
Race	China	Japan	Korea	Korea	Korea
Chief complaint	Not described	Multiple disseminated skin nodules	Mild fatigue and petechiae on extremities	Multiple skin rash	Multiple lymphadenopathy
Skin lesion	Yes	Yes	No	Yes	No
Circulating tumor cells	No	Yes	Yes	Yes	Yes
Bone marrow involvement	Yes	Yes	Yes	Yes	Yes
Flow cytometric positivity	CD4, CD45, CD56	CD4, CD11c, CD33, CD45RA, CD56, CD68, CD117, CD123, HLA-DR	CD4, CD15, CD33, CD56, CD64, CD117, HLA-DR, TdT	CD4, CD33, CD38, CD45, CD56, CD117, CD138	CD4, CD7, CD33, CD38, CD45, CD56, CD64, HLA-DR
Flow cytometric negativity	CD2, CD3, CD5, CD7, CD8, CD10, CD13, CD14, CD19, CD20, CD22, CD23, CD34, HLA-DR, MPO	CD3, cCD3, CD5, CD7, CD8, CD10, CD11b, CD13, CD19, CD20, CD34, cMPO	CD2, CD3, cCD3, CD5, CD7, CD10, CD13, CD14, CD16, CD19, CD20, cCD22, CD34, cMPO	CD2, CD3, CD5, CD7, CD10, CD13, CD14, CD19, CD20, CD34, cMPO, TdT	CD3, CD5, CD8, CD10, CD11b, CD13, CD14, CD19, CD20, CD34, cCD79a, CD117, CD138, cMPO, kappa, lambda, TdT
Karyotype	46, XX,t(4;9;11)(q12;p22;q23) [18]/46, XX [10]	49, XY, +add(1)(p13), +8, +8,t(11;19)(q23;p13.3) [20]	48,XX,+8,t(11;19)(q23;p13.3),+19[20]	45,X,-Y[9]/46,XY[11]	46,XX,t(9;11)(p22;q23),t(9;21)(q12;p11.2)[20]
FISH, *MLL* gene rearrangement	Detected	Detected	Detected	Detected atypical MLL breakpoint	Detected
RT-PCR for *MLL*	*MLL-MLLT3*	*MLL-ELN*	*MLL-MLLT1*	*MLL-MLLT10*	*MLL-MLLT3*
Treatment	CHOP combination chemotherapy and allogeneic bone marrow transplantation	After failure of CHOP chemotherapy, acute leukemia-type chemotherapy was done	Induction chemotherapy (daunorubicin, vincristine, prednisolone, and cytarabin)	Induction chemotherapy (daunorubicin and cytarabin)	Induction chemotherapy (daunorubicin and cytarabin) and allogeneic stem cell transplantation

Abbreviations: BPDCN, blastic plasmacytoid dendritic cell neoplasm; RT-PCR, reverse transcription-PCR; cMPO, cytoplasmic myeloperoxidase; TdT, terminal deoxynucleotidyl transferase; CHOP, cyclophosphamide, vincristine, epirubicin, and prednisolone.

The cytochemical stain for non-specific esterase in neoplastic cells was negative. Immunohistochemical stains of bone marrow biopsy specimens showed that the neoplastic cells were negative for CD123, CD138, kappa, and lambda. Lymph node biopsy analysis demonstrated that the neoplastic cells co-expressing CD4 and CD56 were negative for CD123. Cytogenetic analysis revealed 46,XX,t(9;11)(p22;q23),t(9;21)(q12;p11.2)[20]. The *MLL-MLLT3* rearrangement was detected by RT-PCR. Although adequate lineage-specific markers were not observed, she was diagnosed as having an AML with *MLL* rearrangement in bone marrow and lymph nodes.

So far, three cases of CD4+/CD56+ hematologic malignancies with *MLL* rearrangements have been reported as rare cases of BPDCN with *MLL* rearrangement (Table 1). The leukemic cells reported in the literature expressed the myeloid and monocytic markers CD33, CD117, CD11c, CD15, or CD64, which were not specific enough to identify a specific lineage [3-5]. These three cases did not express highly specific plasmacytoid dendritic cell-associated antigens, such as CD123, TCL1, CD2AP, or CD303 (BDCA2); therefore, additional immunohistochemical studies were necessary at their diagnosis. Variable expression of CD4 or CD56 in adult AML cases with *MLL* rearrangement has been reported [6], and BPDCN is often confused with monocytic leukemias. Based on the limited information on immunophenotypes of these cases, *MLL*-related monocytic leukemia would be a reasonable diagnosis (Table 1).

This study emphasizes that the diagnosis of BPDCN should only be considered after a full investigation of plasmacytoid dendritic cell markers, ensuring there is no expression of myeloid or monocytic markers on the blasts [7]. Since hematologic neo-

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plasms such as BPDCN, AML, extranodal NK/T cell lymphoma, nasal type, and mature T cell lymphomas with or without skin involvement may express CD56 with or without CD4, extensive immunohistochemical and genetic analyses are necessary before definitively diagnosing BPDCN or AML [8, 9].

In conclusion, CD4+/CD56+ hematologic malignancies can be suspected to be BPDCN, and clinicians should conduct a full analysis including flow cytometry for adequate myeloid/monocytic markers, immunohistochemical stain for highly specific plasmacytoid dendritic cell-associated antigens, cytogenetic, and genetic studies to make an exact diagnosis and determine effective treatment.

Authors' Disclosures of Potential Conflicts of Interest

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

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REFERENCES

1. Garnache-Ottou F, Feuillard J, Saas P. Plasmacytoid dendritic cell leukaemia/lymphoma: towards a well defined entity? Br J Haematol 2007;136:539-48.
2. Swerdlow SH, Campo E, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. France: IARC Press, 2008:145-7.
3. Leung R, Chow EE, Au WY, Chow C, Kwong YL, Lin SY, et al. CD4+/CD56+ hematologic malignancy with rearranged *MLL* gene. Hum Pathol 2006;37:247-9.
4. Toya T, Nishimoto N, Koya J, Nakagawa M, Nakamura F, Kandabashi K, et al. The first case of blastic plasmacytoid dendritic cell neoplasm with *MLL-ENL* rearrangement. Leuk Res 2012;36:117-8.
5. Yang N, Huh J, Chung WS, Cho MS, Ryu KH, Chung HS. *KMT2A (MLL)-MLLT1* rearrangement in blastic plasmacytoid dendritic cell neoplasm. Cancer Genet 2015;208:464-7.
6. Muñoz L, Nomdedéu JF, Villamor N, Guardia R, Colomer D, Ribera JM, et al. Acute myeloid leukemia with *MLL* rearrangements: clinicobiological features, prognostic impact and value of flow cytometry in the detection of residual leukemic cells. Leukemia 2003;17:76-82.
7. Rush PS, Bennett DD, Yang DT. Hematopathology HP 15-5. ASCP case reports 2015;HP 15-5:1-20.
8. Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. Ann Oncol 2004;15:1097-108.
9. Herling M and Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. Am J Clin Pathol 2007;127:687-700.