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CD4+CD56+CD68+ Hematopoietic Tumor of Probable Plasmacytoid Monocyte Derivation with Weak Expression of Cytoplasmic CD3

Hematopoietic neoplasm coexpressing CD4 and CD56 includes a subset of acute myeloid leukemia with myelomonocytic differentiation, plasmacytoid monocyte tumor, and other immature hematopoietic neoplasms of undefined origin. Herein, we report a CD4+CD56+CD68+ hematopoietic tumor that was thought to be a tumor of plasmacytoid monocytes. This case is unique in the absence of accompanying myelomonocytic leukemia and the faint expression of cCD3 on the tumor cells. The patient was a 22-yr old man presented with multiple lymphadenopathy and an involvement of the bone marrow. Tumor cells were large and monomorphic with an angulated eosinophilic cytoplasm of moderate amount. Nuclei of most tumor cells were eccentric and round with one or two prominent nucleoli. Rough endoplasmic reticulum was prominent in electron microscopic examination. Tumor cells expressed CD4, CD7, CD10, CD45RB, CD56, CD68, and HLA-DR and were negative for CD1a, CD2, sCD3, CD5, CD13, CD14, CD20, CD33, CD34, CD43, CD45RA, TIA-1, S-100, and TdT. cCD3 was not detected in the immunostaining using paraffin tissue, but was faintly expressed in flow cytometry and immunostaining using a touch imprint slide. T-cell receptor gene rearrangement analysis and EBV in situ hybridization showed negative results. Cytochemically, myeloperoxidase, Sudan black B, and alpha naphthyl butyrate esterase were all negative.

Key Words : *Plasmacytoid Monocytes; Antigens, CD56; Antigens, CD3*

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INTRODUCTION

Plasmacytoid monocytes (PM) represent a rare cell type in human lymph nodes, and was originally referred to as plasmacytoid T cells based on their plasma cell-like morphology, expression of CD4, and localization in the T-dependent areas of the lymph nodes (1-3). Subsequently, they were renamed plasmacytoid monocytes because so-called plasmacytoid T cells share major immunophenotypic features with cells of the mononuclear-phagocytic system (4, 5).

PM in the lymph nodes is increased in certain conditions, such as Kikuchi's lymphadenitis, Castleman's disease, and Hodgkin's disease (4, 6, 7). Tumorous proliferations of PM are very rare. Less than 10 cases have been reported and they were seen almost exclusively in lymph nodes. Interestingly, reported cases previously were all associated with myeloproliferative disease that usually had a monocytic component (8-10).

Immunophenotypic characteristics of reactive or neoplastic PMs are consistent expressions of CD4, CD43, CD45, CD68, and HLA-DR with weak expression of CD10 (8, 9). Other markers associated with T, B, and myeloid cells, and monocytes are mostly negative. Expression of CD56 in PM has not been given much attention except recent two reports that described PMs associated with CD56+ chronic myelomonocytic leukemia and cutaneous CD4+CD56+CD68+ neoplasm, respectively (10, 11).

Herein, we report a novel CD45RB+CD4+CD68+CD10+ CD56+ malignant neoplasm of the lymph node, which is most consistent with PM. However the tumor cells weakly expressed cCD3, which has never been described in PM.

CASE REPORT

Clinical History

A 22-yr-old male patient was admitted with multiple lymphadenopathy of the inguinal, cervical, and preauricular lymph nodes, the largest of which measured 4 cm in diameter. A computed tomographic scan of the abdomen revealed diffuse hepatosplenomegaly and enlarged paraaortic, common iliac, and external iliac lymph nodes. Peripheral blood findings were hemoglobin (Hb) 15.3 g/dL, and white blood cells (WBC) 7.4 $\times 10^3/\mu$L with normal differential counts except for increased

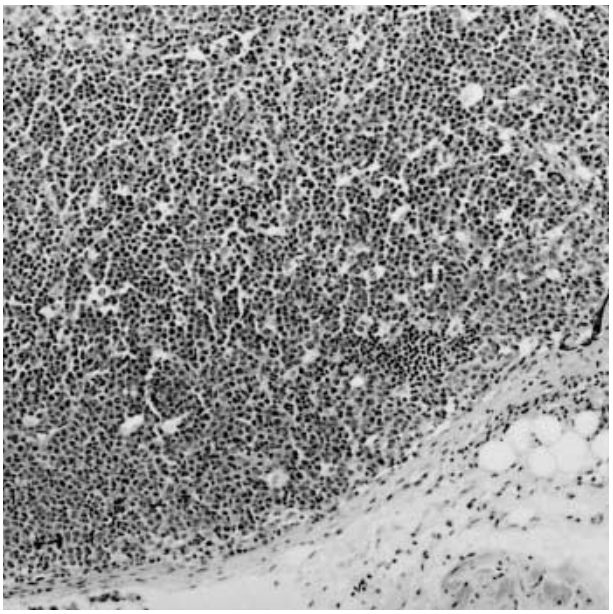

Fig. 1. Lymph node showing diffuse infiltration of tumor cells and some starry-sky macrophages (H&E, ×100).

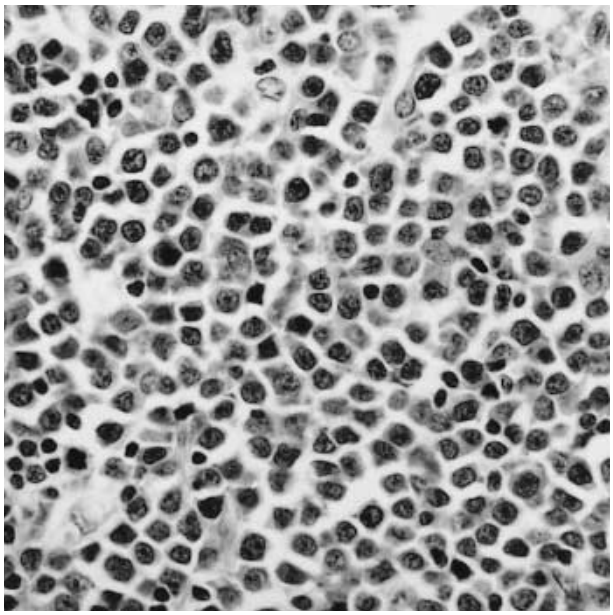

Fig. 2. Medium- to large-sized tumor cells with eccentric position of nuclei and occasional prominent nucleoli (H&E, ×400).

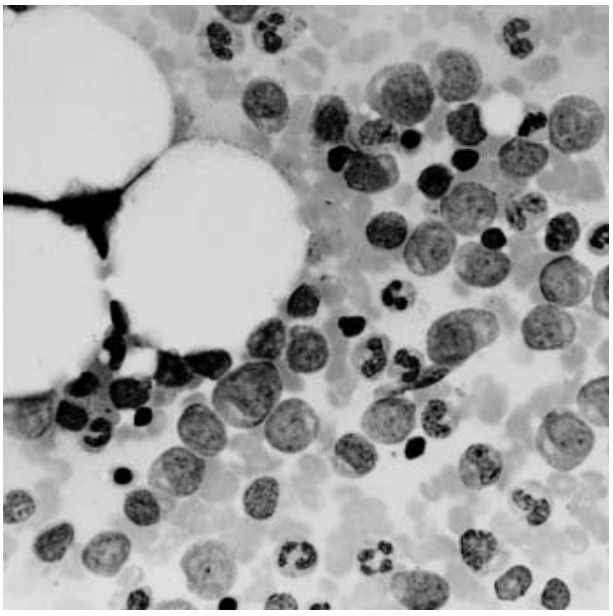

Fig. 3. Tumor cells in bone marrow smear exhibit eccentrically located nuclei with prominent Golgi zone (Giemsa, ×1,000).

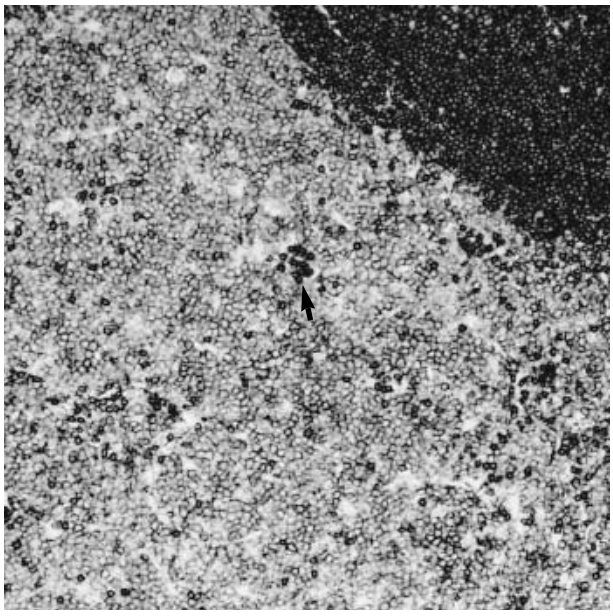

Fig. 4. Immunostaining with CD45 antibody. Note the weak staining of tumor cells compared to small reactive lymphocytes (arrow) (PAP, ×100).

monocytes (8.2%). The level of LDH (676 IU/L) increased. The bone marrow was positive. After biopsy of the cervical lymph node, he received one cycle of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy without response. Then high dose CHOP chemotherapy was given, which attained complete remission. Subsequently the patient underwent peripheral blood stem cell transplantation, however, the tumor recurred in the bone marrow four months later.

Pathologic Findings

The biopsy of the cervical lymph node showed effacement of nodal architecture by diffuse infiltration of monomorphic tumor cells that were medium to large size with an angulated eosinophilic cytoplasm of moderate amount. Nuclei of most tumor cells were eccentric and round with one or two promi-

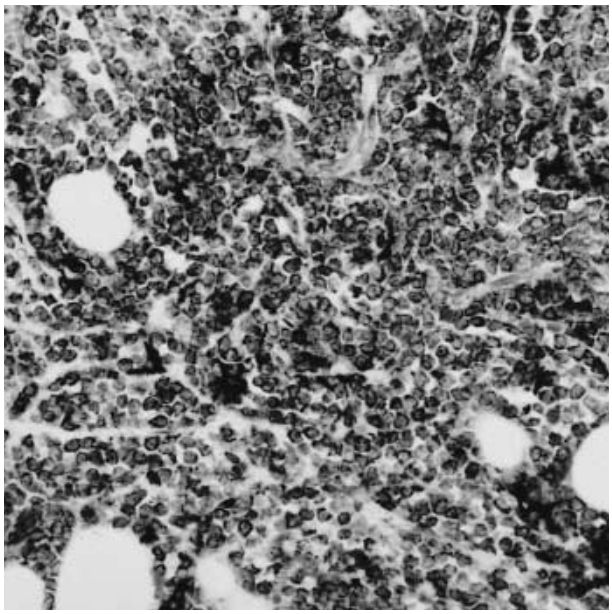

Fig. 5. Immunostaining with anti-CD68 antibody. Almost all tumor cells are positive (×250).

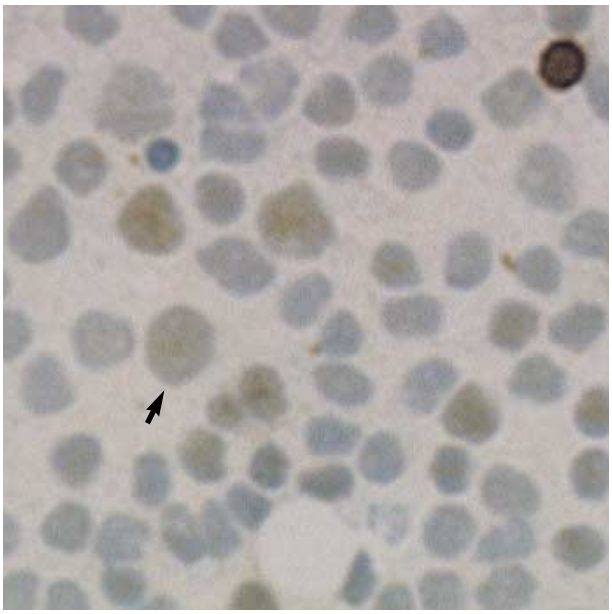

Fig. 7. Immunostaining with polyclonal anti-CD3 antibody using touch imprint slide; the reactive T cells are strongly positive, whereas the tumor cells are weak positive (arrow) (×1,000).

nent nucleoli. Those cytologic features were reminiscent of plasma cells or tumor cells of plasmacytoid immunoblastic lymphoma. Some tumor cells showed slightly irregular nucleus without conspicuous nucleoli. There were frequent mitotic figures with many phagocytosing histiocytes between tumor cells, imparting a starry sky appearance (Fig. 1, 2).

The bone marrow aspiration smear with trephine biopsy

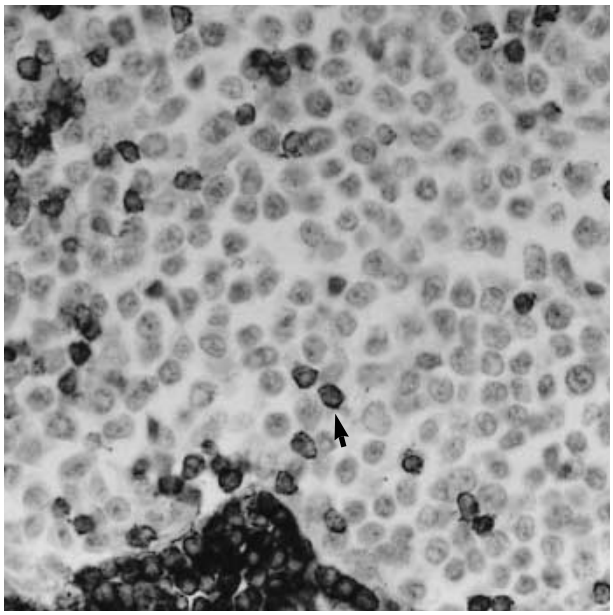

Fig. 6. Immunostaining with polyclonal anti-CD3 antibody using paraffin-embedded section; the reactive T cells (arrow) are positive, whereas the tumor cells are negative (×400).

showed medium- to large-sized tumor cells accounting for 57.6% of all nucleated cells (Fig. 3). Erythroid and granulocytic precursors were rare with normal number of megakaryocytes.

Immunohistochemical Findings

Paraffin section immunohistochemistry of the lymph node showed that tumor cells were positive for leukocyte common antigen, CD56 (Monosan, The Netherlands) and CD68 (KP1) (DAKO, Denmark); negative for CD20 (DAKO, Denmark), polyclonal CD3 (DAKO, Denmark), TIA-1 (Coulter, Hialeah, FL), S-100 (Dako, Denmark), CD1a (Novocastra, U.K.), CD43 (Dako, Denmark), CD45RA (Dako, Denmark), and TdT (DAKO, Denmark) (Fig. 4-6). Polyclonal CD3 immunostaining on touch imprint slide of bone marrow showed weak positivity of tumor cells (Fig. 7).

Cytochemical Stains of Bone Marrow Smear

Tumor cells were negative for myeloperoxidase, Sudan black B, and alpha naphthyl butyrate esterase and stained positively for PAS in block pattern.

Flow Cytometric Analysis

Flow cytometric analysis of bone marrow aspiration specimen was performed. PermaCyte-FPTM WBL3010 kit (Bio-Ergonomics, MN, U.S.A.) was used for analysis of cytoplasmic CD3 expression. There was lymphoid light scatter with dim to moderate CD45 expression which included 3% CD33+ cells, 3% CD13+ cells, 3% CD14+ cells, 25% CD7+ cells, 1% CD5+ cells, 1% CD2+ cells, 11% CD19+ cells, 40%

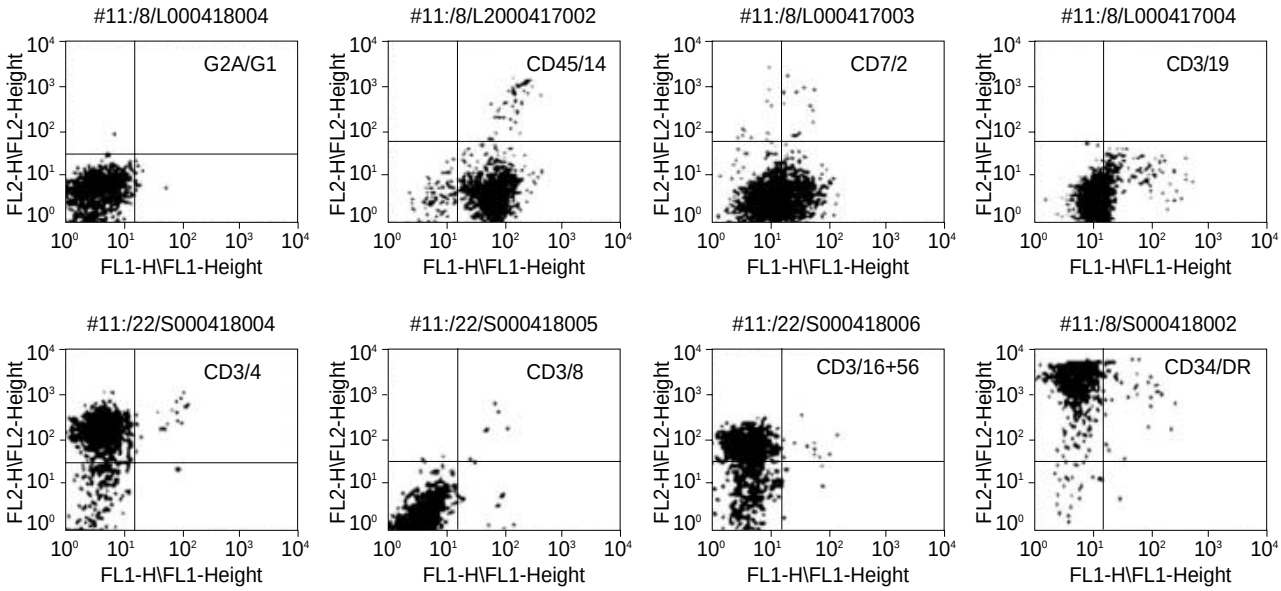

Fig. 8. Flow cytometric study of bone marrow aspirate. Tumor cells express CD45, CD4, CD56, and HLA-DR with dim expression of CD7.

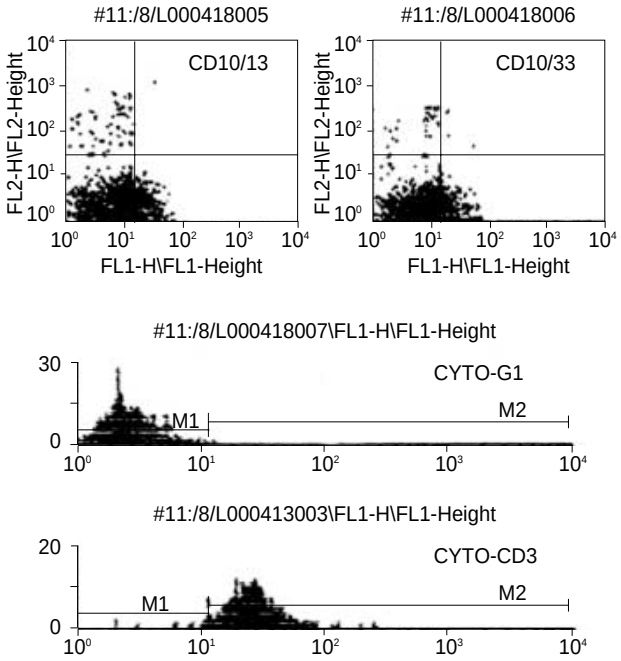

Fig. 9. Flow cytometric study showing dim expression of CD10 and cytoplasmic expression of CD3.

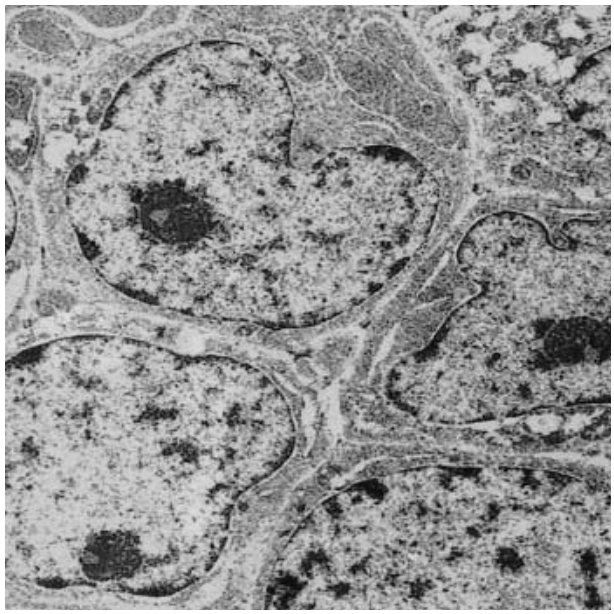

Fig. 10. Electron micrograph showing abundant lamellated rough endoplasmic reticulum in the cytoplasm (×5,000).

CD10+ cells, 3% TdT+ cells, 4% CD34+ cells, 98% HLA-DR+ cells, and 98% cCD3+ cells (Fig. 8, 9).

Cytogenetic Findings

Cytogenetic analyses were performed on bone marrow specimen. At diagnosis, 5 of 17 metaphases were abnormal, with the following clonal abnormalities: t(6;8)(p21.1; q24.1), add (10)(q22), monosomy 12, and a marker chromosome. The tumor at recurrence showed more complex chromosomal abnormality: 46, XY, add(1)(p36.1), add(3)(p12), add(4)(q21), add(5)(q13), t(6; 8)(p21.1; q24.1), add(9)(p22), add(10)(q22), -12, +mar[8]/45, idem,-13,-14[1].

EBV in Situ Hybridization Study

EBV in situ hybridization was performed using the fluorescein-conjugated EBER1 and 2 oligonucleotides (Dako SA). The result was negative.

T-Cell Receptor Gene Rearrangement Study

For polymerase chain reaction amplification of the T-cell receptor (TCR) gamma locus, DNA was prepared by standard proteinase K digestion and phenol/chloroform extraction. A seminested PCR was performed as described previously (12). No clonal rearrangement of TCR gene was demonstrated.

Electron Microscopic Study

Ultrastructurally, the tumor cells showed a round to oval nucleus with condensed chromatin as a narrow rim at the nuclear periphery. The cytoplasm contained a large amount of rough endoplasmic reticulum and polyribosomes (Fig. 10).

DISCUSSION

The immunophenotype of positive CD4 and CD68 with expression of CD10, and ultrastructural findings of abundant polyribosomes and rough endoplasmic reticulum in the present case do well fit into those of plasmacytoid monocyte described in the literature (1-10).

CD4 is a 56-kDa glycoprotein, the expression of which is best to define a subset of mature T-cells. CD4 expression is not only limited to mature T cells, but also expressed on hematopoietic progenitors at various stages of lineage commitment and has been observed on a number of human cell types including megakaryocytes, eosinophils, monocytes, and dendritic cells (13-15). On the other hand, CD68 represents a classical immunohistochemical marker molecule for cells of the monocyte/macrophage and dendritic cell system (16). But it also can be detected in some natural killer cells, γ/δ T cells, and activated CD4+ and CD8+ cells (17). Coexpression of CD4 and CD68 without expression of other myelomonocytic markers is characteristic of plasmacytoid monocytes.

The lineage and the function of plasmacytoid monocytes have remained an enigma. Recent immunological and hematologic studies suggested that PM belongs to the mononuclear-phagocytic system, probably a precursor of dendritic cells, which is specialized to support T-cell function (18). Rare PM-like cells in the blood, which share morphological and phenotypical features with PMs, express IL-3Rα (CD123) and give rise to dendritic cells after being cultured with IL-3 and stimulated with CD40 ligand. These cells migrate to the inflamed lymph nodes and promote the differentiation of type 2 T-helper cells. And they produce type 1 interferon that protects T-cells from antigen-induced cell death (19).

Tumorous proliferations of PM reported previously were associated almost exclusively with myeloproliferative disorder, especially myelomonocytic leukemia (5, 10). The occurrence of myelomonocytic leukemia in the blood and of tumoral growth of PM in the lymph node in a same patient suggests that PMs and the associated myelomonocytic leukemia cells represent the same neoplastic process (5). The present case was not accompanied by myelomonocytic leukemia defined by cytochemical and immunohistologic criteria. Instead, the tumor cells weakly expressed cCD3 that was not detected in paraffin tissue immunostaining, but detected in the flow cytometric analysis and immunostaining using touch imprint smear, suggesting that cCD3 existed at a level below for detection after fixation and embedding.

Aside from T or natural killer cell lymphoma/leukemia, expression of cCD3 has never been described in other hematopoietic neoplasms including dendritic cell tumor. Dendritic cells are derived from both myeloid dendritic cell developmental pathway and lymphoid hematopoietic progenitors (18, 20, 21). Plasmacytoid monocytes have characteristic of lymphoid dendritic cells that are IL-3-dependent and express CD123 and initiate Th2 immune responses (18, 21). In the mouse, development of thymic dendritic cells and that of T-lineage are linked via a common precursor at an early stage of thymocyte development (22). In humans, dendritic cells, T and B cells, and natural killer cells could be differentiated from fetal marrow CD34+CD10+CD45RA+ common hematopoietic precursor cells (23). Moreover, conditional transformation of chicken bone marrow progenitors with v-rel estrogen receptor fusion gene induces dendritic cells expressing cCD3 and lymphoid transcription factor GATA-3 (24). Therefore, the expression of cCD3 in the plasmacytoid monocyte tumor appears to reflect ontogenic relation between T cells and plasmacytoid monocytes or "dedifferentiation" of neoplastic plasmacytoid monocyte toward common T and dendritic cell progenitor.

CD56 is an isoform of neural cell adhesion molecule involved in cell-to-cell interactions and characteristically expressed on normal NK cells and neoplasms of NK or NK-like T cell origin. CD56 is a useful marker in detecting NK-related cells, however, it is not lineage-specific, and seemingly aberrant expression of CD56 also has been identified in a variety of unrelated hematopoietic malignancies, including multiple myeloma (25) and in 46% of acute myelogenous leukemia (26).

Coexpression of CD56 and CD4 can be seen in a subset of acute myelogenous leukemia, especially in tumors with myelomonocytic differentiation (26). Recently a few reports described certain groups of hematopoietic neoplasia that coexpress CD56 and CD4. These tumors are TdT-negative blastic NK cell lymphoma (27), cutaneous monomorphous CD4+ CD56+ large cell lymphoma (28), and agranular CD4+ CD56+ hematodermic neoplasm, which commonly involve the skin at the time of presentation (29). Although these tumors show slight difference in their immunophenotype, they appear to be closely related.

TdT-negative blastic NK cell lymphoma described by DiGiuseppe et al. (27) showed very similar immunophenotype with the present case and lacked cCD3 by immunohistochemical stain using paraffin tissue and myelomonocytic markers by flow cytometry. The authors did not mention the expression of CD68. Morphologically, their cases displayed blas-

toid cytologic features, which were not observed in the present case.

Cutaneous monomorphic CD4- and CD56-positive large cell lymphomas reported by Nagatani et al. (28) shared similar immunophenotypic findings with the present case, but the tumor cells did not express CD68 (personal communication). Histologically, non-blastoid cytologic findings with prominent nucleoli were similar to the present case.

Agranular CD4+CD56+ hematodermic neoplasm described by Petrella et al. (29) is very similar to present case except cutaneous presentation. The tumor consisted of CD4+ CD56+ CD68+HLA-DR+ small- or medium-sized cells with several small- to medium-sized nucleoli. Other lineage markers including T, B, and NK cell markers were all negative. In the subsequent study, the authors demonstrated expression of CD123 in tumor cells and proposed that agranular CD4+ CD56+ hematodermic neoplasm could be the tumoral counterpart of CD56+ PM-like cells (11).

In conclusion, CD4+CD56+ neoplasms are heterogenous in nature and include myelomonocytic leukemia, plasmacytoid monocyte tumor, and other immature hematopoietic neoplasms. Plasmacytoid monocyte tumor can be differentiated from other CD4+CD56+ neoplasms by expression of CD68 and CD123 in the absence of myelomonocytic lineage markers, and electron microscopic demonstration of abundant rough endoplasmic reticulum would be an adjunctive to confirm the diagnosis.

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