Case Study

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

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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.
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 × 10^6/μL, hemoglobin concentration of 14.2 g/dL, and platelet count of 21.6 × 10^9/μL were within the normal range. Biochemical values were within normal limits, except for slightly elevated serum ferritin 170 mg/dL, 247.8 mg/dL, and 282.3 mg/dL, respectively. Soluble normal ranges. IgG, IgA, and IgM concentrations were 1,195 ng/mL. Serum and urinary lysozyme values were below the normal limits, except for slightly elevated serum ferritin 170 mg/dL, 247.8 mg/dL, and 282.3 mg/dL, respectively. Biochemical values were within normal limits. Soluble interleukin-2 receptor (sIL-2R) showed a slight elevation (369 mg/dL, 247.8 mg/dL, and 282.3 mg/dL, respectively. Soluble normal ranges. IgG, IgA, and IgM concentrations were 1,195 ng/mL. Serum and urinary lysozyme values were below the normal limits, except for slightly elevated serum ferritin 170 mg/dL, 247.8 mg/dL, and 282.3 mg/dL, respectively. 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. While the cells were cytochemically positive for naphthyl butyrate esterase reactions, they showed slight antigenicalteration. While the cells were cytochemically positive for naphthyl butyrate esterase reactions, they showed slight antigenicalteration. While the cells were cytochemically positive for naphthyl butyrate esterase reactions, they showed slight antigenicalteration.

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, CD45R0, 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 blasts 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), Cα1 (TCR), and Jγ (TCR). EBER-1 in situ hybridization showed no positive signals; therefore, the diagnosis of plasmacytoid 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...
DISCUSSION

The diagnosis of pDC leukemia is challenging because of the diagnostic overlap with myeloid leukemia. 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. 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 butyrate esterase and the diagnosis was changed to AML regardless of the expression of CD123 and TCL-1. 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. 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 butyrate esterase, which has been reported to be specific to the monocytic lineage. This enzyme is a key

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-chloroacetate esterase 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.
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.
cytotoxic marker for AML with monocytic lineage, as recommended by the French-American-British (FAB) leukemia study group. Although it has not been confirmed that the presence of naphthyl butyrate 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. 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. 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.

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. 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


