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Case Study

Alveolar Rhabdomyosarcoma Mimicking Nasal Lymphoma at The Initial Presentation

Tatsuya Ihara,[1] Daisuke Okamura,[1] Naoki Takahashi,[1] Mika Kohri,[1] Hidekazu Kayano,[2] Jun-ichi Tamaru,[2] and Nozomi Niitsu[1]

Rhabdomyosarcoma is exceedingly rare in adults. A 62-year-old woman was referred to our hospital because of general pain. Computed tomography revealed a solid tumor in the right nasal cavity. Histopathological examination showed solid proliferation of atypical small round cells, having cytologic features reminiscent of lymphomas, and lacking the fibrovascular stroma. The cells were CD56$^+$, desmin$^+$, vimentin$^+$, HHF35$^+$, myogenin$^+$ and MyoD1$^+$. The patient was positive for the *PAX3-FKHR* fusion gene. The patient was diagnosed as having alveolar rhabdomyosarcoma. We conclude that rhabdomyosarcoma should be included in the differential diagnoses of CD56$^+$ small round cell tumor, and immunohistochemical and cytogenetic studies should be performed. 〔*J Clin Exp Hematopathol 48(2) : 61-64, 2008*〕

Keywords: alveolar rhabdomyosarcoma, *PAX3-FKHR* gene, nasal lymphoma, CD56

INTRODUCTION

Rhabdomyosarcoma is exceedingly rare in adults ; soft tissue sarcoma makes up less than 1% of all adult malignancies, and rhabdomyosarcoma accounts for 3% of all soft tissue sarcomas.[1] The most common sites of rhabdomyosarcoma are the head and neck, the genitourinary tract, and the extremities.[2] The two major subtypes of rhabdomyosarcoma seen in the extremities are embryonal and alveolar, which have distinct histopathological appearances. The alveolar variant is seen in approximately 20% of rhabdomyosarcomas. Recently, there have been case reports of alveolar rhabdomyosarcoma masquerading as hematological malignancies.[3,4]

We report a patient with alveolar rhabdomyosarcoma that required differentiation from nasal cavity primary lymphoma.

CASE REPORT

A 62-year-old woman was referred to our hospital because of general pain that had progressively worsened over the previous two months. Physical examination showed lymph node swelling of the cervical lymph nodes to a diameter of up to 1 cm. Computed tomography (CT) revealed a solid tumor in the right nasal cavity. Complete blood count was within normal limits and there were no abnormal cells. Laboratory examination showed a lactate dehydrogenase (LDH) level of 1,230 IU/L and a soluble interleukin-2 receptor (sIL-2R) level of 680 U/mL. On bone scintigraphy, a body of vertebra, rib, and the right hip joint showed abnormal accumulation. Histopathological examination of nasal tumor biopsy specimens showed diffusely arranged, small round tumor cells, proliferation of cells having a variant form, and also apoptotic cells (Figs. 1A, 1B). Histological examination of the specimen biopsied from the nasal tumor showed solid proliferation of atypical small round cells having cytologic features reminiscent of lymphomas, and lacking the fibrovascular stroma. The neoplastic cells were diffusely proliferating without any characteristic features such as alveolar structure or angiocentric proliferation pattern. Upon immunohistochemical staining, the proliferating cells were phenotypically characterized as being CD2$^-$, CD3ε^-, CD20$^-$, CD16$^-$, CD56$^+$ (Fig. 1C), desmin$^+$ (Fig. 1D), vimentin$^+$, HHF35$^+$ (Fig. 1E), myogenin$^+$ (Fig. 1F) and MyoD1$^+$. Serum IgG antibody titer to Epstein-Barr virus (EBV) viral capsid antigen (VCA) and antibody titer to EBV nuclear antigen (EBNA) were elevated, but no positive signals for EBV-encoded small nonpolyadenylated RNA (EBER) were detected in the tumor cells by *in situ* hybridization. A bone marrow aspirate contained 38.8% undifferentiated tumor cells with large nuclei and blue vacuolated cytoplasm (Fig. 2A). Histopathologic studies of bone

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[1]Department of Hematology, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Saitama, Japan
[2]Department of Pathology, Saitama Medical University, Saitama, Japan
Address correspondence and reprint request to Nozomi Niitsu, M.D., Department of Hematology, Comprehensive Cancer Center International Medical Center, Saitama Medical University 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
E-mail nniitsu@saitama-med.ac.jp

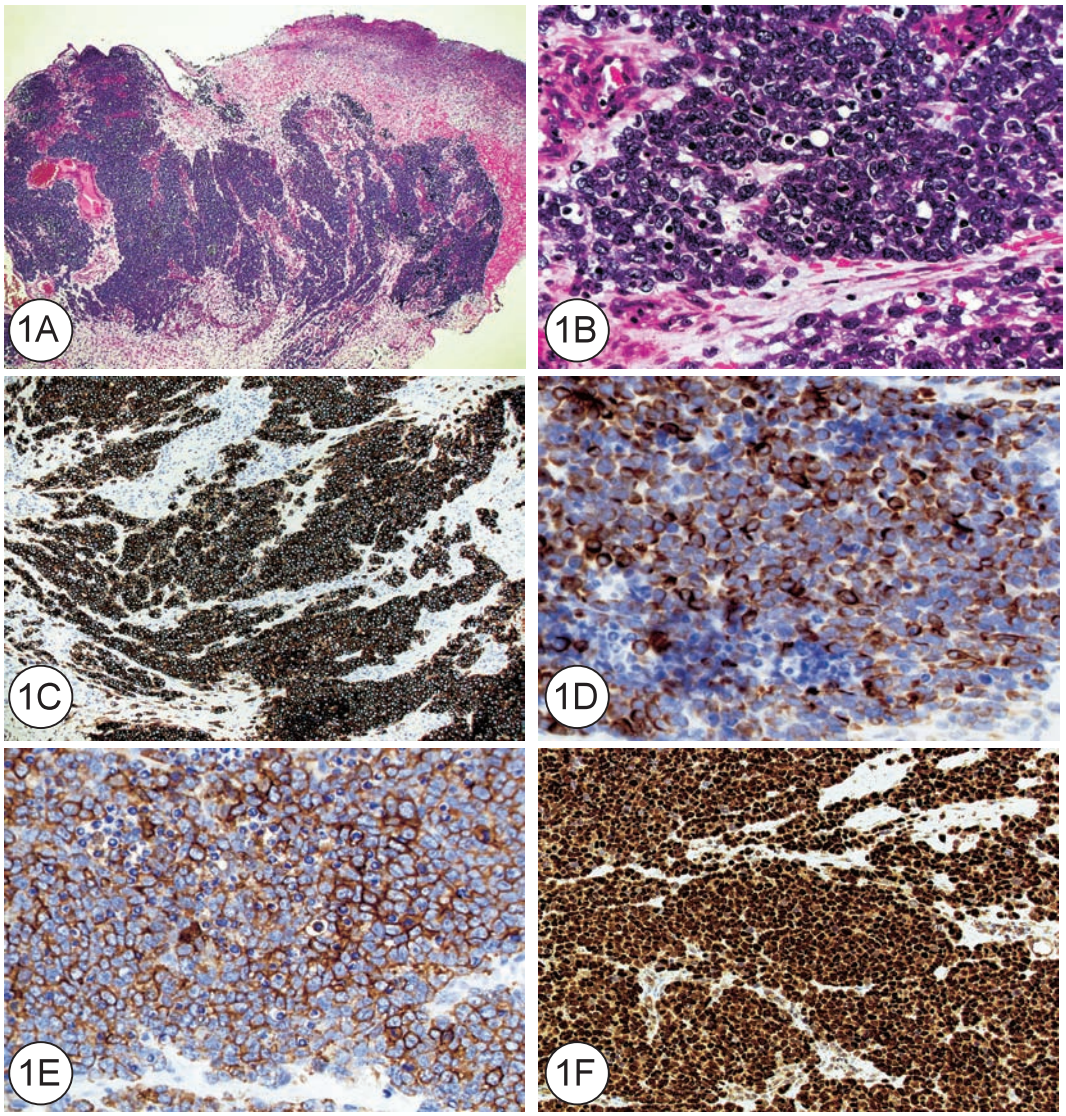

Fig. 1. Histopathologic and immunohistochemical features of the lymphoma. Nasal tumor biopsy specimens show diffusely arranged, small round tumor cells and proliferation of cells with variant form (***1A***, ***1B***). The tumor cells were CD56^{+} (***1C***), desmin^{+} (***1D***), HHF35^{+} (***1E***), and myogenin^{+} (***1F***). (***1A & 1B***), HE ; (***1C***)-(***1F***), immunoperoxidase stain with hematoxylin counterstain. (***1A***) x2 ; (***1B***) x40 ; (***1C & 1F***) x20 ; (***1D & 1E***) x40

marrow biopsy specimens showed diffusely arranged small tumor cells (Fig. 2B) ; the proliferating cells were immunophenotypically characterized as being CD3^{-}, CD20^{-}, CD16^{-}, and CD56^{+} (Fig. 2C). These cells lacked lineage markers of lymphoid or myeloid cells. The chromosome abnormality of the bone marrow was interpreted as 95, XXXX, i(1) (q10), +2, t(2;13)(q35;q14) x3, +5, - 9, +12, +20 [19/20] (Fig. 3). The patient was positive for the *PAX3-FKHR* fusion gene by the RT-PCR method. Based on these findings, the patient was diagnosed as having alveolar rhabdomyosarcoma. After she was admitted, her general condition rapidly worsened. Radiation therapy and steroid pulse therapy were administered, but she died on the 73rd day after onset.

DISCUSSION

The initial presentation of alveolar rhabdomyosarcoma with concurrent metastases to the bone marrow and lymph node, mimicking an acute leukemia/ lymphoma, is rare in adults. It can be confused with acute lymphoblastic leukemia or undifferentiated leukemia.[5] The present case was initially diagnosed as a CD56^{+} small round cell tumor. The differen-

tial diagnoses of a small round cell tumor with CD56 positivity include NK-cell tumor, rhabdomyosarcoma, small cell carcinoma, neuroblastoma, primary neuroectodermal tumor, malignant peripheral nerve sheath tumor, desmoplastic small round cell tumor, synovial sarcoma, and malignant melanoma. In order to make a differential diagnosis, immunohistochemical and cytogenetic studies are necessary. Desmin, vimentin, myoglobin, and MyoD1 are the most reliable markers of rhabdomyosarcoma.[4,6] On the other hand, cytogenetic analysis can help distinguish the subtypes of this tumor entity. The most common chromosomal rearrangements in alveolar rhabdomyosarcoma are t(2;13)(q35;q14), which is seen in 55% of cases, and t(1;13)(p36;q14), which is seen in about 22% of cases.[7] The translocations involve two *PAX* genes, *PAX3* and *PAX7*, which are located on chromosomes 2 and 1, respectively. These two chromosomal translocations are seen only in alveolar rhabdomyosarcoma. The PAX3-FKHR fusion protein inhibits differentiation of striated muscle, and it upregulates the expression of the anti-apoptotic protein, BCL-XL, leading to malignant transformation.[8] PAX3-FKHR upregulates expression of the *MET* gene, which encodes the receptor for hepatocyte growth factor (HGF), and the *CXCR4* gene, which encodes the receptor for stromal-derived factor-1 (SDF-1).[9,10] HGF and SDF1 are secreted in bone marrow and lymph node stroma, and the upregulated expression of MET in rhabdomyosarcoma cells induced by PAX3-FKHR and CXCR4 is thought to be one of the reasons why alveolar rhabdomyosarcoma cells readily migrate to bone marrow.

Sandberg *et al*.[5] have reviewed the rhabdomyosarcoma literature. All 26 cases were the alveolar type. The median age at presentation was 18 years (range, 3-68 years) with a male predominance. Cytogenetic analysis was performed in 14 cases and t(2;13)(q35;q14) was found in 9 cases. Cytogenetic analysis not only serves to demonstrate the presence or absence of t(2;13)(q35;q14), but may also reveal the presence of a specific karyotypic change associated with a substantial number of acute leukemias.[11]

The modern combination of surgery, radiation and chemotherapy has improved the prognosis of rhabdomyosarcoma, but alveolar rhabdomyosarcoma still shows more aggressive clinical behavior and worse prognosis than embryonal rhabdomyosarcoma.[12] Cases with bone marrow infiltration show a poor prognosis. Hematopoietic stem cell transplantation could effectively treat advanced rhabdomyosarcoma.[13]

In the present case, the primary tumor was located in the right nasal cavity and the patient's general condition rapidly worsened during the diagnostic work-up of alveolar rhabdomyosarcoma. Radiotherapy and steroid pulse therapy had no effect and the patient died. It is necessary to consider alveolar rhabdomyosarcoma in the differential diagnoses of tumors that do not express leukocyte antigens except CD56. For diagnosis, we performed immunostaining of tumor specimens to search for muscle-related proteins and chromosomal banding studies to search for chromosomal translocations, and it was necessary to search for a *PAX3-FKHR* chimera gene by the RT-PCR method.

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