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【 CASE REPORT 】

The First Case of Non-leukemic Sarcoma Composed of Mixed-phenotype Acute Leukemia, B/myeloid, Not Otherwise Specified

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Abstract:
Isolated sarcoma with features of mixed-phenotype acute leukemia (MPAL) is an extremely rare disease and it can be easily misdiagnosed as lymphoma or other malignancies. We herein report the case of a 61-year-old woman with non-leukemic sarcoma of the right pleura, pretracheal lymph node, and supraclavicular lymph node with features of MPAL, B/myeloid, not otherwise specified, which was first misdiagnosed as diffuse large B cell lymphoma. After performing a detailed re-examination of the biopsy specimens, few scattered eosinophilic myelocytes allowed us to reach a correct diagnosis of MPAL and the patient was thereafter successfully treated by intensified chemotherapy followed by cord blood transplantation.

Key words: sarcoma, mixed-phenotype acute leukemia, diagnosis, stem cell transplantation, chemotherapy

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Introduction

Biphenotypic leukemia was first reported in the 1980s as a type of leukemia that could not be classified as either acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) and which expressed both myeloid and lymphoid markers (1). The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms established a new definition of mixed-phenotype acute leukemia (MPAL) including bilineal and biphenotypic acute leukemias (2). MPAL is a rare type of leukemia, accounting for 0.6-2.4% of all acute leukemias (3, 4), and recently several reports have been published about its prognosis and treatment.

An extramedullary tumor consisting of immature myeloid cells is defined as myeloid sarcoma (MS), accounting for 2.5-9.1% of all acute leukemias (5), whereas there is no disease entity known as non-leukemic sarcoma with features of MPAL, which thus seems to be extremely rare and most cases are probably incorrectly diagnosed as non-Hodgkin lymphoma.

Case Report

A 61-year-old woman, who had been receiving regular aromatase inhibitor treatment for 20 months after undergong a definitive operation and post-operative including field radiation therapy for right-sided breast cancer, underwent follow-up chest computed tomography (CT). A mediastinal mass with right pleural thickness was thus identified which compressively extended into the thoracic spine. A positron emission tomography CT (PET-CT) scan revealed abnormal fluorodeoxyglucose (FDG) accumulation in the lesion of the right pleura (SUVmax: 6.1), the right pretracheal lymph node (SUVmax: 10.0), and the right supraclavicular lymph node (SUVmax: 4.3) (Figure a and b).

The laboratory findings were as follows: white blood cell

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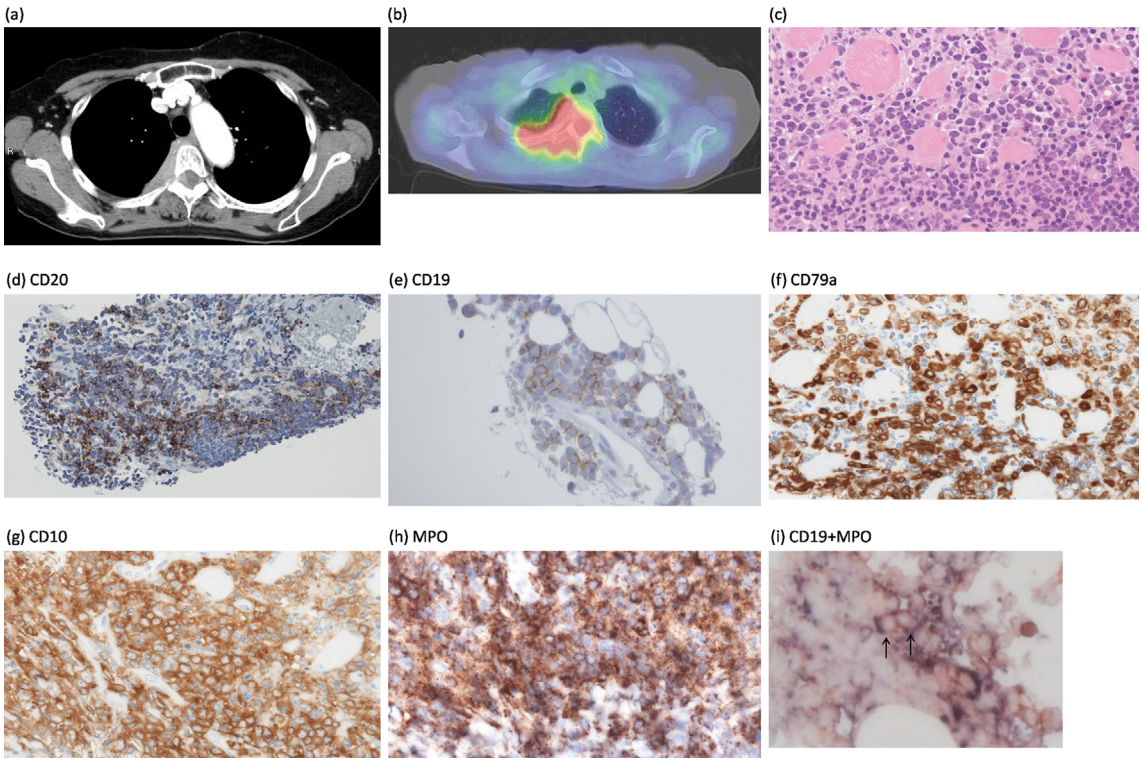

Figure. **The CT, PET-CT and pathological findings at diagnosis. (a) An enhanced computed tomography (CT) scan shows the right pleural mass with extensive erosion into the spinal canal from T1 through T5, in which the thoracic spinal code was compressed by the tumor. (b) The PET-CT scan shows a diffusely increased fluorodeoxyglucose uptake in the region of the right pleura, the right pretracheal lymph node, and the right supraclavicular lymph node, with a SUV max of 10.0. (c-h) Hematoxylin and Eosin staining illustrates the diffuse proliferation of large cells with a high N/C ratio and several cells have eosinophilic cytoplasm (c, ×400). Immunohistochemical staining shows the tumor cells to be partially positive for CD20 (d, ×100), weakly positive for CD19 (e, ×400), and strongly positive for CD79a, CD10, and myeloperoxidase (f-h, ×400). (i) Double staining of CD19 (blue) and myeloperoxidase (red) displays that the cytoplasm of the tumor cell coexpressed both lineage markers. CD19 is positive mainly in the peripheral area of the cytoplasm (×400).**

count, 3.6×10^9/L (lymphocytes, 29%; monocytes, 6%; eosinophils, 3%; basophils, 2%; neutrophils, 60%; and blasts 0%); hemoglobin, 10.3 g/dL; platelet count, 12.4×10^9/L; lactate dehydrogenase, 305 IU/L; ferritin, 106.7 ng/mL; antinuclear antibodies, negative, and soluble interleukin-2 receptor, 1,570 U/mL. A bone marrow analysis showed mild hypoplasia without an increase in the number of blast cells, dysplasia or any karyotype abnormality. There was also no invasion of other malignant cells or hemophagocytosis in the bone marrow. Thyrotropin and free T4 were 5.680 mIU/L and 0.99 ng/dL, respectively, indicating subclinical hypothyroidism. Based on these results, we surmised that her mildly decreased bone marrow function could be primarily attributed to subclinical hypothyroidism without any bone marrow invasion of malignant cells.

For diagnostic confirmation, a CT-guided needle biopsy of the thickened right pleura was performed. The biopsy specimen showed a dense diffuse infiltrate of large tumor cells with round to oval nuclei and a high nuclear/cytoplasm (N/C) ratio. A few scattered eosinophilic myelocytes were also present, but initially, we could not clearly distinguish them from the other tumor cells (Figure c). For the initial diagnosis, we performed an immunohistochemical analysis, which showed the atypical large cells to be positive for CD10, CD19, and CD79a, partially positive for CD20, but negative for CD3, CD5, and terminal deoxynucleotidyl transferase (TdT) (Figure d-g). Therefore, we misdiagnosed the patient to have diffuse large B cell lymphoma.

She began to experience intermittent pain on the right side of her upper back and progressive numbness in her extremities. Therefore, it was determined that therapy should be started immediately, initially in order to prevent her nervous system symptoms from worsening, and she underwent a single course of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone) chemotherapy plus rituximab as the initial treatment.

In our detailed re-examination during therapy, we noticed the existence of a few scattered eosinophilic myelocytes in the specimens, and decided to perform an additional immunohistochemical analysis. This analysis showed the myelocytes to be positive for myeloperoxidase (Figure h) and CD34, and negative for CD13 and CD33. Double staining

Table. Reported Case of Non-leukemic Sarcoma of Mixed Phenotype Acute Leukemia.

Case	Age	Site	Treatment	Outcome	2008 WHO classification	Reference
1	6-19*	Multiple lymph nodes	NA	NA	MPAL, T/myeloid	7
2	6-19*	Multiple lymph nodes	NA	NA	MPAL, T/myeloid	7
3	6-19*	Multiple lymph nodes	NA	NA	MPAL, T/myeloid	7
4	18	Cervical lymph node	HyperCVAD/MA	CR for 14 months	MPAL, T/myeloid	8
5	44	Left maxillary sinus, epipharynx, bilateral breast, umbilicus	AraC+MIT, AraC+DNR, AraC+ACR, BMT	Died 88 days after BMT	MPAL, MLL rearranged	9
6	61	Right pleura	HyperCVAD/MA, CBT	Alive 14 months after CBT	MPAL, B/myeloid	Our case

*Three cases in reference No.7 ranged in age from 6 to 19 years.

HyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone, MA: methotrexate, cytarabine, AraC: cytarabine, MIT: mitoxantrone, DNR: daunorubicin, ACR: aclarubisin, BMT: bone marrow transplantation, CBT: code blood transplantation, CR: complete remission, MPAL: mixed phenotype acute leukemia, NA: not available

of CD19 and myeloperoxidase revealed that the tumor cells coexpressed both lineage markers, which is a characteristic finding of biphenotypic acute leukemia (Figure i). An additional cytogenetic study was necessary, but it could not be performed because the sample volume was insufficient. Therefore, we performed dissection of the right pretracheal lymph node, which continued to be swollen after one cycle of chemotherapy, and obtained the same immunohistochemical results as described above. A cytogenetic study including a fluorescence *in situ* hybridization (FISH) analysis revealed a normal karyotype (46, XX) without any rearrangement of *BCR-ABL* or *MLL*. Based on these findings, we finally diagnosed this tumor to be non-leukemic sarcoma with features of MPAL, B/myeloid NOS according to the 2008 WHO classification.

After making the diagnosis, we treated her with an intensive chemotherapy regimen consisting of hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine) plus rituximab and intrathecal therapy for central nervous system prophylaxis, as previously described (6).

She achieved complete remission after 3 cycles of hyper-CVAD and 2 cycles of MA and underwent reduced intensity cord blood transplantation. The conditioning regimen consisted of fludarabine (25 mg/m^2 for 5 days), melphalan (80 mg/m^2 for 1 day), and total body irradiation (2 Gray for 2 days). The human leukocyte antigens between the patient and infused cord blood were matched at 4/8 alleles (5/8 antigens), and the total nucleated cells and CD34 positive cells were 2.7×10^7 and 0.6×10^5/kg recipient body weight, respectively. Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus and mycophenolate mofetil. She had no GVHD but developed human herpesvirus-6 encephalitis which improved after undergoing treatment with ganciclovir and thus suffered no major permanent damage. Now, at 19 months after transplantation, she is alive and continues to demonstrate complete remission.

Discussion

According to the 2008 WHO classification of hematopoietic and lymphoid tissues, MPAL was divided into five categories composed of two genetic categories, MPAL with t(9;22)(q34;q11.2) or *BCR/ABL1* and MPAL with t(v;11q23) or *MLL* rearrangement, and three other less-specific categories, B/myeloid not otherwise specified (NOS), T/myeloid NOS, and other rare type types of MPAL. Cases that meet the criteria for MPAL are not classified as MS. We diagnosed this case as MPAL, B/myeloid NOS because the tumor cells were positive on immunohistochemistry for myeloperoxidase, CD10, CD19, and CD79a without *BCR-ABL* or *MLL* rearrangement.

As far as we could determine based on a search of the pertinent literature, only five cases have been diagnosed as non-leukemic sarcoma with features of MPAL according to the 2008 WHO classification (7-9) (Table). One of them was diagnosed as MPAL with *MLL* rearranged, while the other four cases were diagnosed as MPAL, T/myeloid, NOS. To the best of our knowledge, this is the first description of non-leukemic sarcoma with features of MPAL, B/myeloid, NOS.

MPAL is rare and has been described to have an incidence of 0.35 cases per 1,000,000 person-years, comprising 0.6-2.4% of all leukemias (3, 4). Non-leukemic MS is also a rare disease with an incidence of 2 cases per 1,000,000 in adults (10). Although a part of MPAL or non-leukemic MS might contain extramedullary MPAL without leukemic cells in the peripheral blood and/or bone marrow, it is presumed that non-leukemic sarcoma with features of MPAL is extremely rare.

One reason for the very low frequency of non-leukemic sarcoma with features of MPAL may be the difficulty in obtaining a correct diagnosis. Insufficient immunohistochemical staining and/or flowcytometry analysis of the tumor cells could result in a misdiagnosis of non-leukemic sarcoma with

features of MPAL as malignant lymphoma or MS.

It seems to be a difficult problem for pathologists to distinguish MS from lymphoma and other malignancies. In a recent report published in 2013, 25% of all patients with non-leukemic MS were initially misdiagnosed (11). The histologic features of MS, which demonstrate a diffuse and infiltrative population of mononuclear cells, seem to make an accurate diagnosis difficult. Lymphoma typically demonstrates tissue-destructive invasion and coagulation necrosis found in the invading zone as well as in the tumor mass. In contrast, MS infiltrates tissue planes and relatively preserves the tissue architecture without demonstrating coagulation necrosis. Tumor cells in lymphoma have a coarsely clumped chromatin, thick nuclear membrane, and a lesser amount of amphophilic cytoplasm, whereas in MS, the neoplastic cells have larger and more prominent nucleoli and a moderate amount of eosinophilic cytoplasm with slight vacuoles or fine granules. Among these pathologic features, the most obvious diagnostic clue is eosinophilic cytoplasm, but tumor cells often do not have this distinctive feature (12).

In our case, although the initial diagnosis was diffuse large B cell lymphoma because myeloperoxidase staining is not routinely performed when lymphoma is suspected in our institution, the additional myeloperoxidase staining, undertaken after we noted the eosinophilic cytoplasm of the tumor cells, was the same as MS during the re-evaluation for diagnosis, thus leading to our final accurate assessment. In order to avoid an incorrect diagnosis, it is important to pay attention to the pathological characteristics as described above and select optimal immunohistochemical staining and/or flow cytometry markers.

Recent reviews have focused on several treatment approaches for MPAL and MS, but not for non-leukemic sarcoma with features of MPAL (3, 4). A recent review of MPAL reported the median overall survival and 5-year survival rate to be 18 months and 37%, respectively, and discussed the possibility that an ALL-directed regimen showed better outcomes compared with AML-type therapy (4). On the other hand, a recent report about MS stated that the general approach for MS is treatment with conventional AML-like chemotherapy, including the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) because it improved the overall survival (5). Based on these reports, we selected ALL type chemotherapy following allo-HSCT as one of the curative therapies for non-leukemic sarcoma with features of MPAL, B/myeloid NOS.

In conclusion, we encountered an extremely rare case of non-leukemic sarcoma with features of MPAL-mimicking lymphoma that followed a good clinical course with ALL-type chemotherapy including cord blood transplantation. The accumulation of additional cases is needed in order to evaluate the prognosis and select the appropriate treatment for this rare disease.

The authors state that they have no Conflict of Interest (COI).

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