Bone Marrow Metastasis of Rhabdomyosarcoma Mimicking Acute Leukemia: A Case Report and Review of the Literature

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Abstract

Bone marrow metastasis of rhabdomyosarcoma has been reported to be difficult to distinguish from acute leukemia. We herein describe a case of rhabdomyosarcoma with bone marrow metastasis mimicking acute lymphoblastic leukemia. A 29-year-old woman was admitted with thrombocytopenia, blast-like cells in the peripheral blood and a coagulation disorder. Bone marrow aspirates showed 94.8% blast-like cell infiltration (CD45⁺, myeloperoxidase⁺, and CD56⁺), and CT scan revealed the presence of an infiltrating mass in the nasal cavity. Based on a biopsy of the nasal cavity, the patient was diagnosed with rhabdomyosarcoma exhibiting bone marrow metastasis. She received chemotherapy, followed by radiation therapy, and has since remained alive for 26 months, as of the last follow-up.

Key words: rhabdomyosarcoma, alveolar, bone marrow metastasis, acute leukemia, disseminated intravascular coagulation, VDC EI

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Introduction

Some rare malignant diseases exhibit clinical features and bone marrow aspirate morphology similar to that of acute leukemia. For instance, rhabdomyosarcoma, neuroblastoma (1), medulloblastoma (2), anaplastic oligodendroglioma (3), small cell carcinoma, Ewing's sarcoma and neuroendocrine tumors have been reported to display an acute leukemia-like morphology in bone marrow aspirates after metastasizing to the bone marrow. Among these lesions, rhabdomyosarcoma, a soft tissue sarcoma that is primarily observed in childhood and adolescence (4, 5), is particularly difficult to distinguish from acute leukemia based on bone marrow aspirate morphology. Indeed, some cases have been diagnosed and treated as leukemia due to the presence of blast-like cells in bone marrow aspirates (4, 6-10). We herein describe a case of alveolar rhab-

domyosarcoma in the nasal cavity with bone marrow metastasis mimicking acute lymphoblastic leukemia.

Case Report

A 29-year-old woman presented with epistaxis in August 2011. She first felt glabellar pain in early September and later experienced a headache, fever and malaise. In October, her chest pain worsened, and she visited an orthopedic clinic. A CT scan revealed a fractured sternum, and the laboratory data showed thrombocytopenia and the appearance of abnormal blast-like cells in the peripheral blood. The patient was then referred to our hospital.

On admission, a physical examination revealed pallor and swelling of the sternum. Purpuric lesions and hematomas were also observed in the left forearm and both lower extremities. The laboratory findings are described in Tables 1 and 2, as follows: white blood cells=6.6×10⁹/L with

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Table 1. Laboratory Data

Peripheral blood		Blood chemistry		Blood coagulation	
WBC	6,600/ μ L	TP	7.1 g/dL	PT	12.6 sec
Blast	1%	Alb	4.2 g/dL	PT-INR	1.15
Myelo	6%	BUN	11.5 mg/dL	APTT	30.5 sec
Meta	5%	Cr	0.73 mg/dL	Fibrinogen	212 mg/dL
Stab	20%	UA	8.1 mg/dL	D-dimer	43.4 μ g/mL
Seg	39%	T-bil	0.5 mg/dL	FDP	93 μ g/mL
Eos	0%	D-bil	0.2 mg/dL	ATIII	139%
Baso	0%	AST	49 IU/L	TAT	>60.0 ng/mL
Mono	1%	ALT	20 IU/L	PIC	9.1 μ g/mL
Lymp	27%	LDH	983 IU/L		
Aty-L	1%	LDH1	17%		
RBC	401 $\times 10^4$	LDH2	37%		
Hgb	12.3 g/dL	LDH3	30%		
MCV	90 fL	LDH4	11%		
MCHC	34.2%	LDH5	5%		
Ret	3.0 $\times 10^4$ / μ L	ALP	112 IU/L		
Plt	5.6/ 10^4 / μ L	CRP	0.04 mg/dL

Figure 1. May Giemsa stained bone marrow smears showing diffuse infiltration with a large number of large blast-like cells. **Figure 2.** (Enlarged image of Fig. 1). The cells were intermediate to large in size with large hyperchromatic and prominent nucleoli and vacuolation, similar to that observed in cases of acute lymphoid leukemia. **Figure 3.** Aspirate smears showing the absence of staining with peroxidase in the malignant cells.

blasts 1.0%, platelets= 56×10^9 /L, D-dimer= 43.4μ g/mL, fibrin degradation product (FDP)= 93μ g/mL. A bone marrow aspirate sampled obtained on admission showed 94.8% blast-like cells, which were essentially myeloperoxidase (MPO) negative (Fig. 1-3). These cells were intermediate to large in size, with prominent nucleoli and vacuolation, similar to that observed in cases of acute lymphoid leukemia. The results

of a flow cytometry analysis of the bone marrow aspirates obtained on admission were available on day 3, showing the blast-like cells to be CD56-positive, although they did not express CD45 or other lymphoid or myeloid antigens (Fig. 4). Based on an MRI examination performed on day 5, which showed a contrasted mass infiltrating from the right nasal cavity to the ethmoid sinus (Fig. 5), and an 18 F fluoro 2 deoxy D glucose (18 F-FDG)-positron emission tomography study performed on day 6, which demonstrated a high level of accumulation in the bone marrow, including the sternum, and extending from the right nasal cavity to the ethmoid sinus. A biopsy of the nasal cavity performed on day 6 after admission revealed proliferating cells with a high nuclear-cytoplasmic ratio with uniform solid nests arranged in palisades on Hematoxylin and Eosin staining, implying a diagnosis of alveolar rhabdomyosarcoma (Fig. 6- Hematoxylin and Eosin). Therefore, a tentative diagnosis of alveolar rhabdomyosarcoma of the nasal cavity with bone marrow metastasis was made.

After the biopsy, disseminated intravascular coagulation (DIC) rapidly worsened (i.e., the fibrinogen level decreased

Hematoxylin and Eosin

CD45

CD34

CD56

Figure 4. A bone marrow biopsy demonstrated that the tumor cells were positive for only CD56 and negative for both myeloid and lymphoid markers.

Figure 5. Magnetic resonance image showing a contrasted mass infiltrating from the right nasal cavity to the ethmoid sinus.

to 120 mg/dL, the D-dimer level increased to 255 $\mu\text{g/mL}$ and the FDP level increased to 580 $\mu\text{g/mL}$) on day 7, and it became difficult to control the bleeding from the site of the biopsy of the nasal tumor. Given the urgency to initiate treatment, before obtaining the definitive diagnosis, the patient was tentatively diagnosed with rhabdomyosarcoma

based on the results of a flow cytometry analysis of the bone marrow cells and the distinctive morphological pattern of the biopsied nasal cavity specimen. Treatment with alternating cycles of VDC [vincristine (VCR), doxorubicin (DXR), cyclophosphamide (CPA)] and etoposide, ifosphamide (EI) (11) followed by radiation therapy was initiated starting on day 8 after admission.

The treatment course is shown in Fig. 7. Specifically, the patient received VCR at a dose of 1.5 mg/m^2 (maximum dose: 2 mg), DXR at a dose of 37.5 $\text{mg/m}^2/\text{day}$ as a daily 18-hour infusion for two days and CPA at a dose of 600 $\text{mg/m}^2/\text{day}$ for two days with mesna at a dose of 360 $\text{mg/m}^2/\text{dose}$ for five doses each day at weeks 0, 6, 12, 18, 24 and 30. In addition, etoposide was administered at a dose of 100 $\text{mg/m}^2/\text{day}$ for five days with ifosfamide at a dose of 1,800 $\text{mg/m}^2/\text{day}$ for five days and mesna at a dose of 360 $\text{mg/m}^2/\text{dose}$ for five doses at weeks 3, 9, 15, 21, 27, 33, 36 and 39. Finally, VCR was also administered at weeks 1, 2, 7 and 8. Triple intrathecal chemotherapy was omitted, as there was no evidence of central nervous system (CNS) invasion. After week 12 (following four cycles of chemotherapy), the patient received irradiation as primary local therapy at a dose of 5,040 cGy in 28 fractions to the tumor, followed by an additional boost of 540 cGy.

In order to reduce the potential for tumor lysis syndrome,

Hematoxylin and Eosin

CD56

Desmin

Figure 6. Biopsy of the nasal cavity. Immunohistochemistry showed most tumor cells to be highly positive for CD56 and partially positive for desmin.

Induction								
week	0	1	2	3	6	7	8	9
	V	V	V	E	V	V	V	E
	D			I	D			I
	C				C			
Consolidation								
week	12*	15	18#					
	V	E	V					
	D	I	C					
	C							
Maintenance								
week	21	24	27	30	33	36	39	
	E	V	E	V	E	V	E	
	I	D	I	D	I	D	I	
		C		C		C		

Figure 7. V: VCR 1.5 mg/m² (max 2 mg). D: DXR 37.5 mg/m² 2 days. C: CPA 600 mg/m²/day 2 days. E: Etoposide 100 mg/m²/day 5 days. I: Ifosfamide 1,800 mg/m² 5 days. *: Patients receiving irradiation to the nasal tumor as primary local therapy began treatment at week 12 after completing DXR at a dose of 5,040 cGy/28 Frac followed by an additional boost of 540 cGy/3 Frac. #: At week 18, DXR was omitted due to the administration of additional radiation therapy.

the first doses of VCR, DXR and CPA were administered separately over the course of a few days. An immunohistochemical study of a nasal specimen performed after the start of chemotherapy revealed the following findings: most tumor cells were highly positive for CD56, partially positive for desmin, positive for Periodic acid-Schiff (PAS) stain and negative for oxidase PAS (Fig. 6). The patient was ultimately diagnosed with rhabdomyosarcoma and bone marrow metastasis and clinically ranked as having Intergroup Rhabdomyosarcoma Study Group (IRSG) Stage IV disease (i.e., a high risk and poor prognosis) (12). A chromosome analysis demonstrated the presence of complex abnormalities (Table 1). Although the DIC was treated, and the patient was transfused with red blood cell concentrate (RCC), fresh frozen plasma (FFP) and platelet concentrate (PC), the DIC parameters peaked on day 11 after admission, with a fibrinogen level of <30 mg/dL and an FDP level of >800 µg/mL. After three weeks of treatment, the bone marrow exhibited a complete response. The total dose of transfusion required during this period was 28 units of RCC, 540 units of PC and 120 units of FFP. After the first course of treatment, the patient's hematological toxicities included grade 4 neutropenia, grade 4 thrombocytopenia and grade 2 anemia, requiring no further transfusions. No signs of infection were documented, and the only non-hematological toxicity was

Table 2. Laboratory Data

Bone marrow aspiration		Cytogenetic analysis
NCC	120,000/ μ L	n, XXX, -X, -1, add(2)(q33)x2,
MgK	13/ μ L	-3,-7,add(9)(p11)x2,-11,-13,-13,-14,-15,+22,+mar
M/E	16.0	(n : 81=[1/20], 82=[1/20], 83=[1/20], 84=[4/20], 85=[10/20],
Blast-like	94.8%	86=[1/20], 87=[1/20])
Metamyelo	0.2%	Specific staining
Stab	0.2%	MPO (-)
Seg	2.8%	PAS (+)
Lympho	1.4%	Immunostaining
M-Series	3.2%	CD56 (+)
N-PolyErb1	0.2%	CD45 (-)
Er-series	0.2%	CD34 (-)
Macrophage	0.2%	

grade 2 nausea.

A CT scan performed after nine weeks revealed that the primary lesion had completely disappeared. The patient thereafter completed all treatment and remained free of relapse for 15 months until developing brain metastasis. She continues to be alive with persistent disease, as of 26 months at the last follow-up.

Discussion

Although rhabdomyosarcoma is known to spread throughout the body, it primarily originates as a primary lesion in the head and neck region (29.4 to 40%), followed by the genitourinary track (20 to 25%) and extremities (18 to 26.6%) (13-15). Fewer than 25% of patients have distant metastasis at diagnosis, which mainly occurs in the lungs (39%), bone marrow (32%), lymph nodes (30%), bones (27%), omentum/ascites (16%) and pleura (13%) (16). As in the present case, bone marrow metastasis of rhabdomyosarcoma of head and neck origin is not thought to be rare. However, the prognosis of metastatic cases is poor (17-19), with a five-year event-free survival rate of <30% (12), and outcomes are usually worse in adults than children (20, 21).

Bone marrow metastasis of rhabdomyosarcoma has been reported to be difficult to distinguish from acute leukemia, as both conditions exhibit diffuse involvement of blast-like cells (6, 8-10, 22-34). In general, bone marrow metastasis of carcinoma can be distinguished from hematologic malignancies according to the presence of mass formation. However, rhabdomyosarcoma is difficult to distinguish from acute leukemia owing to the presentation of a bone marrow infiltration pattern with a loosely arranged distribution. We reviewed previously reported cases of rhabdomyosarcoma with bone marrow metastasis in the literature and found that it was difficult to distinguish this condition from leukemia at the primary examination in most cases (key words on PubMed: "rhabdomyosarcoma and leukemia," "rhabdomyosarcoma and bone marrow metastasis"). Table 3 presents rhabdomyosarcoma cases published since 1990 (6-10, 22-37). Most of these cases were initially considered to be leukemia due to the presence of cytopenia and blast-like cells in the peripheral blood, as well as a high percentage of atypical blast-like cells in bone marrow aspirates. Although Fitz-

maurice reported a case in which a patient achieved a full remission with pulsed VAC (VCR, actinomycin D, CPA) and subsequently remained in good health until the end of chemotherapy (26), all other patients relapsed or died within two years (6-10, 22-37).

Some cases have been reported to have been treated based on an incorrect diagnosis. For instance, one patient was diagnosed with poorly differentiated malignoma of putative mesenchymal origin and treated with CPA+DXR+cisplatin (33). Another patient was diagnosed with very poorly differentiated leukemia and treated with methotrexate+prednisolone+VCR+L-asparaginase (8), while a third patient was diagnosed with acute myeloid leukemia, undifferentiated type, and treated with daunorubicin+cytarabine (10). In these cases, chemotherapy was initiated before obtaining a histological diagnosis due to the severity of the patients' conditions, and thus only findings for a morphological analysis and peroxidase staining of the bone marrow aspiration samples were available. Moreover, in some cases, no primary lesion was detected, which may have also led to an erroneous diagnosis.

In the present case, the patient's DIC status was not severe, and no bleeding was observed at the time of admission. Therefore, we were able to wait for the results of the flow cytometry analysis of the bone marrow cells, which revealed no lineage markers for myeloid, T or B cells. In addition, the presence of CD56-positive and CD45-negative cells in the present case suggests the possibility of neuroblastoma (38, 39), small cell carcinoma (40), rhabdomyosarcoma (38), Ewing's sarcoma (41) or a different type of neuroendocrine tumor (42). Furthermore, the tumor cells were positive for desmin on immunohistochemistry. Over 99% of cases of rhabdomyosarcoma stain positive for polyclonal desmin; this is the essential finding for diagnosing rhabdomyosarcoma (43-46) (Fig. 6).

Many rhabdomyosarcoma cases involve the chromosomal translocation, t(2;13)(q35;q14), in which the PAX3 gene is fused to the FKHR(FOXO1) gene (47, 48). This chromosomal translocation is found in 55% of cases of alveolar rhabdomyosarcoma, while the t(1;13)(p36;q14) translocation, in which the PAX7 gene is fused to FOXO1, is detected in 22% of patients (49). These chromosomal translocations often serve as key findings for diagnosis. In the present

Table 3. A Systematic Review of Cases of Rhabdomyosarcoma with Bone Marrow Metastasis Reported in the Literature was Carried out by Searching PubMed-MEDLINE between 1990 and 2012 with the Following Search Terms: "Rhabdomyosarcoma and Leukemia," "Rhabdomyosarcoma and Bone Marrow Metastasis."

Year	Reference	Age/Sex	WBC/ μ L	Hb	Plt/ μ L	DIC	Bone marrow	Gene	First treatment	Outcome	OS
1991	30	14/F	15,000	7	29,000	N/A	isolated cells 70%	t(2;13)(q35;q14)	CBDCA+EPR+VCR+IFM+ETP	death	6month
		14/M	3,200	8.5	68,000	o	a populations of large cells	t(2;13)(q35;q14)	N/A	recurrence	N/A
1991	7	9/F	2,200	N/A	56,000	o	tumor cells 100%	t(2;13)(q37;q14)	CPA+VCR+EPR	death	5month
1991	35	8/M	8,500	10.1	207,000	N/A	atypical poorly differentiated cells	N/A	CBDCA+DXR+ACT+ETP+IFM	N/A	N/A
1991	26	19/M	4,400	9.7	10,000	N/A	atypical blasts 90%	N/A	VCR+DXR+CPA	CR	N/A
1991	29	16/M	decrease	decrease	decrease	N/A	diffuse involvement by blast cells	N/A	chemotherapy	death	3month
		24/M	decrease	decrease	decrease	N/A	diffuse involvement by blast cells	N/A	chemotherapy	death	3month
		36/M	decrease	decrease	decrease	N/A	diffuse involvement by blast cells	N/A	chemotherapy	death	3month
1996	23	18/F	16,300	7	64,000	o	complete substitution by atypical cells	N/A	chemotherapy	death	12month
1996	29	18/F	7,200			x	round nucleated blasts 90%	add(2)(q37)	VCR+DXR+CPA -VCR+DXR+CPA	recurrence	9month
1998	6	25/M	129,000	14.8	63,000	N/A	neoplastic cells>95%	Complex	DEX+DNR+Ara-C	N/A	N/A
1998	37	35/M	N/A	decrease	decrease	N/A		N/A	N/A	N/A	N/A
1998	33	68/F	6,030	8.5	15,000	o	poorly differentiated cells	t(2;13)(q35;q14)	CDDP+DXR+CPA	death	11days
1999	27	77/F	5,300	8	217,000	N/A	large blast-like cells	N/A	VCR+DXR+CPA	PR	N/A
2000	31	29/M	7,900	11.3	125,000	N/A	atypical blast-like cells	t(2;13)	MTX+VCR+DEX+ IFM+VM26+Ara/CPA+DXR	death	7month
2001	8	12/M	3,400	8.2	60,000	N/A	blasts 100%	t(2;13)(q35;q14)	MTX+PSL+VCR+L-ASP	death	3month
2002	28	16/M	WNR	WNR	WNR	N/A	primitive cells	t(2;13)(q35;q14)	chemotherapy	death	24month
2004	22	25/F	7,690	5.3	107,000	N/A	tumor cells 90%	N/A	chemotherapy	recurrence	4month
2004	24	13/M	6,500	11.6	10,000	N/A	numerous mononuclear blasts	t(2;13)(q35;q14)	chemotherapy	death	8month
2005	36	19/F	6,300	8.2	18,000	o	undifferentiated tumor cells 88.8%	t(2;13)(q35;q14)	resection	death	7month
2007	34	14/M	11,300	10.4	45,000	o	undifferentiated tumor cells 89.6%	PAX3/FKHR	IDA+Ara-C	death	8month
2007	10	13/M	17,000	6.5	20,000	N/A	immature cells	N/A	DNR+Ara-C	N/A	N/A
2008	9	25/M	10,500	10.4	150,000	N/A	blast-like abnormal cells 92%	N/A	HD chemotherapy followed by allogenic PBSCT	death	N/A
		6/M	8,170	9.1	79,000	N/A	abnormal cells 95%	Complex	Combination chemo therapy, local irradiation, resection	death	N/A
		10/M	3,900	6.5	40,000	N/A	blast like abnormal cells 94%	Complex	Combination chemo therapy, local irradiation	death	N/A
2010	25	13/F	800	7	70,000	N/A	infiltrate of large cells	PAX3/FOXO1	IFM+VCR+DXR+ACT-D	N/A	N/A

CBDCA: carboplatin, EPR: epirubicin, VCR: vincristine, IFM: ifosfamide, ETP: etoposide, CPA: cyclophosphamide, DXR: doxorubicin, ACT: actinomycin, DEX: dexamethasone, DNR: daunorubicin, Ara-C: cytosine arabinoside, CDDP: cisplatin, MTX: methotrexate, VM26: teniposide, L-ASP: asparaginase, IDA: idarubicin, HD chemotherapy: high-dose chemotherapy, PBSCT: peripheral blood stem cell transplantation, ACT-D: actinomycin-D, N/A: not assessed

case, however, these translocations were not detected on a G-Band test, and we were unable to further examine the gene fusions.

Rhabdomyosarcoma has a poor prognosis, except in individuals with the following characteristics: an age of 1 to 10 years, an embryonal histology, the absence of bone or bone marrow involvement and two or fewer sites of metastases. In most cases, the patient relapses or dies despite being correctly diagnosed and treated. Indeed, only a few reported adult patients have been reported to maintain complete remission for more than one year (26). According to the IRSG, the VAC regimen is recommended for high-risk rhabdomyosarcoma patients (50). However, we did not have access to actinomycin-D at our hospital at the time of diagnosis in this case, and it would have taken several days to obtain the drug, whereas our patient required urgent chemotherapy. Moreover, there is no definitive or established standard therapy for treating high-risk rhabdomyosarcoma patients, and the VAC regimen appears to be unsatisfactory for those with an estimated overall survival of less than 30%. Arndt et al. reported the use of multi-agent therapy as an alternative to VDC/EI, followed by the administration of radiation therapy for the primary lesion, in intermediate-risk rhabdomyosarcoma patients with a five-year relapse-free survival rate of 82%. In that study, the therapy proved promising, given that the relative risk of failure for the VDC/EI study compared to the Fourth Intergroup RMS Study (IRS-IV) is 0.5 (51). Moreover, the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) is currently exploring the efficacy of VDC/EI therapy in addition to the application of interval compression of chemotherapy cycles and the administration of irinotecan in newly diagnosed patients with high-risk rhabdomyosarcoma. Accordingly, we chose multi-agent therapy for our patient.

In one report of a high-risk case, a long-term disease-free survival was achieved with allogeneic hematopoietic stem cell transplantation in order to induce a graft-versus-tumor effect (52). In our high-risk patient, the use of modified alternative VDC and EI therapy followed by radiation for the primary lesion successfully induced and maintained complete remission for 15 months.

In conclusion, the current patient exhibited bone marrow metastasis of rhabdomyosarcoma mimicking acute leukemia in morphology and presented with progressive deterioration following a nasal cavity tumor biopsy. However, a flow cytometry analysis of the bone marrow aspirate, as well as the morphology of the primary mass, as determined on staining with hematoxylin and eosin, aided the quick initiation of chemotherapy, resulting in complete remission. Therefore, physicians should consider rhabdomyosarcoma in the differential diagnosis of patients with DIC and blast-like cells in bone marrow aspirates showing negative staining for peroxidase. Moreover, if the patients is not in an urgent status (i.e., there are no signs of rapid progression of DIC or a severe bleeding tendency), clinicians should allow for a few days to perform a flow cytometry analysis of the bone mar-

row aspirates.

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

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