CASE REPORT

WILEY

Alveolar rhabdomyosarcoma with bone marrow metastasis causes disseminated intravascular coagulation

Yan Su | Xisi Wang | Jing Yang | Wen Zhao | Chao Duan | Mei Jin | Xiaoli Ma

Beijing Key Laboratory of Pediatric Hematology Oncology; National Discipline of Pediatrics, Ministry of Education; MOE Key Laboratory of Major Diseases in Children; Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

Correspondence
Xiaoli Ma, Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China.
Email: mxl1123@vip.sina.com

INTRODUCTION

Disseminated intravascular coagulation (DIC) is an abnormal activation of the coagulation cascade that occurs in response to different diseases. Tumors such as malignant hematological diseases and solid tumors are important causes of DIC. The incidence of DIC is reported to be 7% in patients with solid tumors.

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor in children. RMS includes embryonal, alveolar, spindle cell/sclerosing, and pleomorphic pathological subtypes according to the 2013 WHO Classification of Soft Tissue Tumors.[1] The primary sites of RMS include head, neck, body, limbs, and genitourinary system. Bone marrow (BM) metastasis is exceptionally rare in RMS. It is easy to make a clinical misdiagnosis. BM involvement is found in 15% of patients with alveolar RMS (ARMS), but only in 1.1% of patients with embryonal RMS.[2]

Severe DIC can occur in RMS with BM metastasis and has been seen in widespread ARMS with BM metastasis. Adequate control of DIC improves survival in children. Here we describe a child with widespread ARMS and BM metastasis with clinical presentation of severe hemorrhages resulting from DIC.

CASE REPORT

An 8-year-old boy was admitted to the Hematology Oncology Center of Beijing Children's Hospital (BCH) in June 2017 because of intermittent abdominal distension and left palmar pain for > 3 months following dorsum muscular soreness for > 10 days. He felt weak, dizzy, and had no appetite. He lost 4 kg weight during the previous 3 months. In two local hospitals, his BM aspirate showed infiltration of a large number of undifferentiated blast-like cells. These cells were distributed in piles, round, vacuolated, and oligoplasmatic, and had irregular nuclei, rough chromatin, and obscure nucleoli. He was suspected of having acute leukemia and neuroblastoma. There was no treatment available for him in local hospitals.

On physical examination in BCH, he was pale with no mucocutaneous hemorrhage. There were multiple small (2–5 mm) nodules in the subcutaneous tissue of his left palm and back. Slight hepato-splenomegaly was found on physical examination. Laboratory examination revealed 92.3 ng/mL neuron-specific enolase, normal urinary vanillylmandelic acid, 1188.7 ng/mL ferritin, 656.8 μmol/L uric acid and 2103 U/L lactate dehydrogenase (LDH). Complete blood cell analysis showed 5.8×10^9/L white cell count, 80 g/L hemoglobin, and 105×10^9/L platelet count. Coagulation examination showed 2.09 g/L fibrinogen,

19.004 mg/L D-dimer, and normal prothrombin time and activated partial thromboplastin time. Positron emission tomography–computed tomography showed that fluorodeoxyglucose metabolism diffusely increased in bones and locally increased in soft tissue of the anterior vertebral bodies. Ultrasound showed multiple tumor foci in the muscles and fat tissues of the left palm, pelvis, back, waist, thymus, and infraclavicular fossa. Magnetic resonance imaging (MRI) of the brain showed the T2 signal of the lateral cerebellar hemisphere close to the cranial plate, and the local cerebellum was compressed.

BM aspirate showed 76.5% undifferentiated tumor cells with irregular bodies, large nuclei, rough chromatin, and less and vacuolated cytoplasm (Figure 1). The flow cytometry immunophenotype of BM showed 52.23% of the cells expressed CD56 and CD81, which was indicative of malignant tumor cells of non-epithelial, non-hematopoietic origin. BM chromosome analysis demonstrated complex abnormalities including 47,XY, +der(2)t(2;13)(q35:q14), t(2;13)[14]/46,XY[6] (Figure 2). BM biopsy revealed focal oval cells among bone trabecula and morphology-matched ARMS metastatic to BM. The immunohistochemical panel showed desmin (+), MyoD1 (+), CD56 (+), myogenin (+), Syn (−), CgA (−), TH (−), LCA (−), TdT (−), CD117 (−), PAX-5 (−), ALK (−), P53 (−), Ki-67 (70% +). Fluorescence in situ hybridization was positive for *PAX-FKH*R gene of BM.
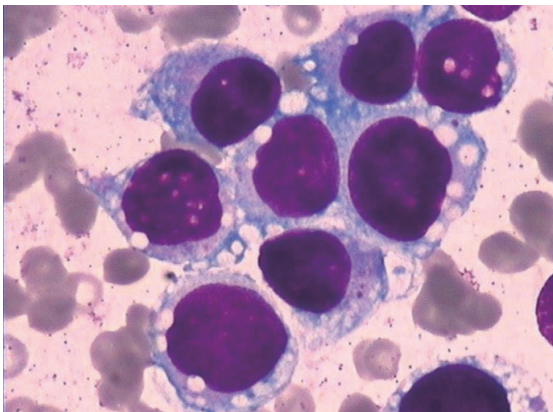

FIGURE 1 Bone marrow biopsy (Wright stain × 1000) showed 76.5% undifferentiated tumor cells with irregular bodies, large nuclei, rough chromatin, and less and vacuolated cytoplasm.

The patient was diagnosed with ARMS with BM metastasis. He also had multiple metastases in the muscle, fat tissue, bone, and intracranially, but the primary tumor site was unknown.

The patient underwent BM biopsy on day 2 of hospitalization. He experienced persistent oozing at the site of puncture. The red blood cells and fresh frozen plasma were discontinuously infused because of postoperative hemorrhage. On day 8 of admission, the patient received VAC chemotherapy (vincristine, actinomycin-D and cyclophosphamide) according to the CCCG-RMS-2016 protocol. On day 2 of chemotherapy, the patient had massive epistaxis and hematemesis. D-dimers increased to > 69 mg/L. His hemoglobin concentration and platelet count decreased to 42 g/L and 5×10^9/L, respectively. Uric acid increased to 680.2 μmol/L and LDH increased to 6156 U/L. DIC was diagnosed.
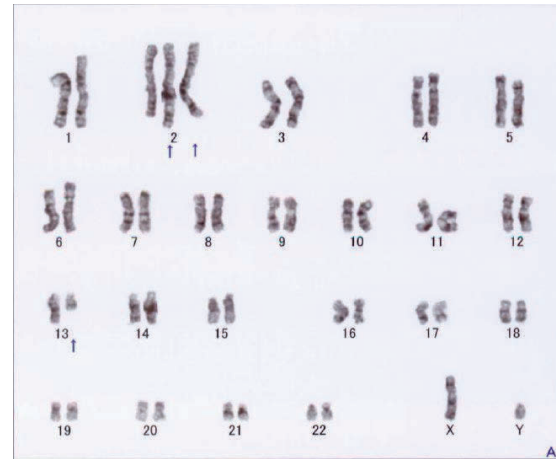

FIGURE 2 Bone marrow chromosome analysis demonstrated complex abnormalities including 47,XY, +der(2)t(2;13)(q35:q14), and t(2;13) [14]/46,XY[6].

As a result of severe bleeding and deterioration of coagulation indexes, the patient required repeat blood product transfusions, comprising 15 U red blood cell concentrate, 4.7 L fresh frozen plasma, 8 U single donor platelets, 16 g fibrinogen concentrates, and 2700 U prothrombin complex concentrate (PCC). On day 10 of chemotherapy, the DIC parameters and bleeding tendency started to improve. On day 14 of chemotherapy, DIC was completely corrected (Figure 3). The patient continued to receive alternate chemotherapy with VAC and VI (vincristine and irinotecan). BM showed disappearance of tumor cells after two cycles of chemotherapy in August 2017. The imaging suggested that the tumors were reduced and some of them disappeared. The left palmar tumor was resected surgically in October 2017. After eight cycles of chemotherapy, the patient received radiotherapy of the tumor area in the left palm and T11 and L5–S3 vertebrae from December 2017 to January 2018.

After radiotherapy, the disease progressed with BM relapse and multiple areas of new bone destruction and a tumor focus at the right tibia. The chemotherapy protocol was changed to VDC (vincristine, doxorubicin and cyclophosphamide) and IE (ifosfamide and etoposide), alternately. After two cycles of chemotherapy, the BM showed complete remission. The alternate chemotherapy with VDC and IE was continued. In April 2018, after 13 cycles of chemotherapy, the patient presented with disturbance of consciousness and then convulsive seizure. Brain MRI showed round lesions in the left frontotemporal lobe and right parietal lobe, and long T1 and T2 signals
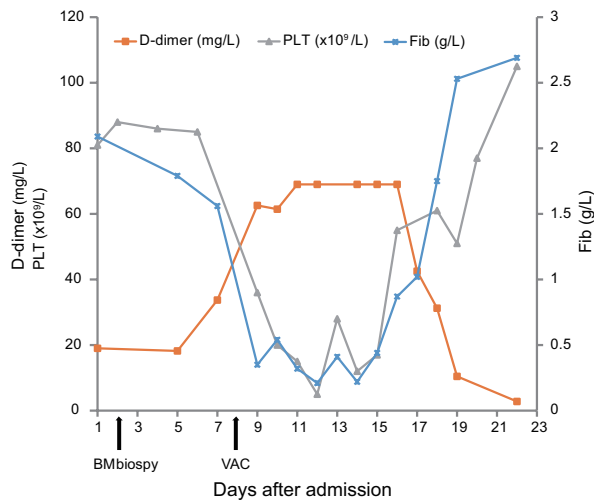
FIGURE 3 Disseminated intravascular coagulation (DIC) parameters and clinical course of the patient. VAC, vincristine, actinomycin-D and cyclophosphamide; PLT, platelet; Fib, fibrinogen; BM, bone marrow.

were seen in the lesions (Figure 4). Sixty percent tumor cells were seen in his BM smear. Temsirolimus, vinorelbine and cyclophosphamide, and then ICE (ifosfamide, carboplatin and etoposide) chemotherapy were given alternately. Despite chemotherapy, the patient eventually died 2 months later from disease progression.

DISCUSSION

RMS is the most common soft tissue sarcoma of childhood and adolescence. DIC is a rare occurrence in pediatric solid tumors. A review of the literature reveals that DIC appears to be associated with advanced ARMS with BM metastases.[3-5]

The clinical picture of widespread RMS with BM metastasis may resemble acute hematological malignancy and pose a diagnostic problem. BM aspirate may show infiltration of small blue round cells similar to lymphoblasts or myeloblasts. The condition can be misdiagnosed as acute leukemia.[3,4,6] The flow cytometry immunophenotype can help with diagnosis. RMS cells can express the immunological profile CD45−CD56+. However, this profile alone is not enough to identify the RMS cells as it is present in many types of non-hematopoietic small blue round cell tumors, including neuroblastoma, small cell carcinoma and Ewing's sarcoma. The CD45−CD56+ immunophenotype combined with the Myf4 transcript can be used to confirm infiltration of RMS cells in BM.[7] Furthermore, over 99% of cases of RMS have polyclonal desmin-positive cells, which helps with diagnosis. The present case was diagnosed with acute non-lymphocytic leukemia and neuroblastoma before he came to our hospital because of BM with undifferentiated blast-like cells. Through BM morphology, flow cytometry immunophenotype, immunohistochemistry, and chromosome and *PAX-FKHR* gene analysis, we were able to exclude the diagnosis of leukemia and neuroblastoma and made the final diagnosis of ARMS with BM metastasis.

Severe DIC can occur in ARMS with BM metastasis and may be triggered by biopsy or invasive surgery.[4,8] Exposure of the subendothelial tissue factor after trauma to the tumor blood vessels causes the release of cytokines with procoagulant activity. This can trigger DIC, which presents with wound bleeding and progressive deterioration of the coagulation index. The current case presented with persistent oozing at the site of puncture after BM biopsy. Aida et al[4] and Yoon et al[8] reported that DIC rapidly worsened after surgery or biopsy in patients with ARMS metastatic to BM. Therefore, invasive procedures and surgery require caution in these patients.

In children with metastatic RMS and massive DIC, prompt chemotherapy and aggressive supportive care are
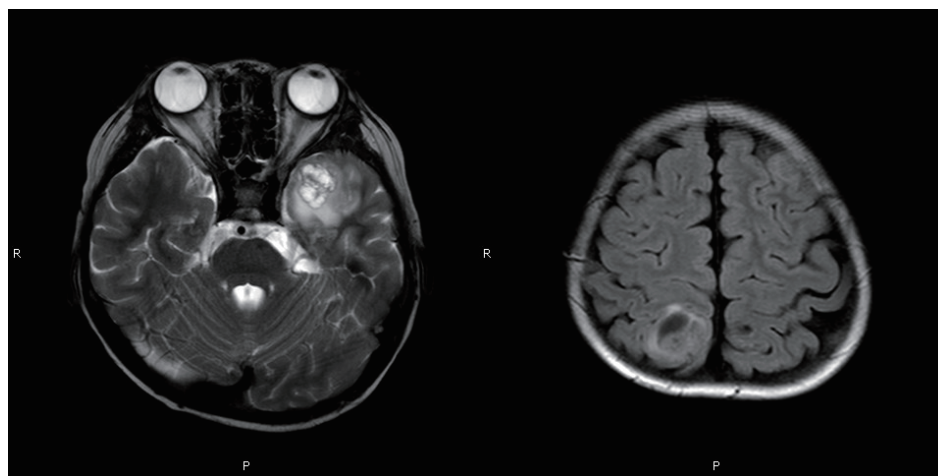

FIGURE 4 Brain magnetic resonance imaging showed round lesions in the left frontotemporal lobe and right parietal lobe and long T1 and T2 signals were seen in the lesions.

important to decrease malignancy-triggered procoagulant activity. Therefore, in order to control the massive acute bleeding in some cases, even if the definitive diagnosis is not obtained, urgent chemotherapy is initiated.[3] Usually, the laboratory parameters of DIC begin to resolve after 2 weeks of chemotherapy. Many experiences have shown that early chemotherapy is the fundamental measure for ending DIC.[3,4] In the present case, the DIC parameters and bleeding tendency started to improve after 2 weeks of chemotherapy.

Early administration of chemotherapy and vigorous supportive care with blood product transfusion can control the massive bleeding in solid tumors with DIC.[3] The role of heparin therapy in malignancy-associated DIC is still controversial. Heparin is indicated in cases with a hypercoagulable period of DIC or obvious thromboembolic conditions. The red blood cells, fresh frozen plasma, and platelets should be transfused in patients with massive DIC with severe hemorrhage. The present case did not receive heparin therapy and only received repeated transfusions, comprising 15 U red blood cells, 4.7 L fresh frozen plasma, 8 U single donor platelets, 16 g fibrinogen concentrates, and 2700 U PCC. DIC was corrected by aggressive supportive therapy combined with effective chemotherapy.

The *PAX3-FKHR* or *PAX7-FKHR* gene fusions resulting from t(2;13)(q35;q14) or t(1;13)(p36;q14) translocations are seen in approximately 50% and 20% of ARMS patients, respectively. The incidence of BM involvement is significantly higher in *PAX3-FKHR* compared with *PAX7-FKHR* among patients with metastatic ARMS. The prognosis of ARMS with metastatic disease with *PAX3-FKHR* is poor. Sorensen et al[9] reported that the estimated 4-year overall survival rate in patients presenting with metastatic ARMS was 75% for *PAX7-FKHR* versus 8% for *PAX3-FKHR*. Most patients relapsed or died within two years. The cause of death is usually tumor progression, including brain metastasis.[4] In the present case, the patient had advanced BM metastatic ARMS with t(2;13)(q35:q14) chromosomal abnormality. He presented with widespread tumor foci including BM, spine, palm, back soft tissue, brain and bone. Despite intensive chemotherapy, surgery and radiotherapy, he died from repeated disease progression.

The clinical characteristics of widespread RMS with BM metastasis in children may resemble acute leukemia in morphology and pose a diagnostic problem. Physicians should consider the precise diagnosis according to the clinical findings, BM examination, flow cytometry, immunohistochemistry, and cytogenetic testing. BM metastatic RMS combined with DIC may present as severe hemorrhage. Timely systemic chemotherapy and aggressive supportive care are important to control this serious condition.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Jo VY, Fletcher CD. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. *Pathology*. 2014;46:95-104.
2. Weiss AR, Lyden ER, Anderson JR, et al. Histologic and clinical characteristics can guide staging evaluations for children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. *J Clin Oncol*. 2013;31:3226-3232.
3. Bien E, Maciejka-Kapuscinska L, Niedzwiecki M, et al. Childhood rhabdomyosarcoma metastatic to bone marrow presenting with disseminated intravascular coagulation and acute tumour lysis syndrome: review of the literature apropos of two cases. *Clin Exp Metastasis*. 2010;27:399-407.
4. Aida Y, Ueki T, Kirihara T, et al. Bone marrow metastasis of rhabdomyosarcoma mimicking acute leukemia: a case report and review of the literature. *Intern Med*. 2015;54:643-650.
5. Fiegl M, Weltermann A, Stindl R, Fonatsch C, Lechner K, Gisslinger H. Massive disseminated intravascular coagulation and hyperfibrinolysis in alveolar rhabdomyosarcoma: case report and review of the literature. *Ann Hematol*. 1999;78:335-338.
6. Kern JB, Hii A, Kruse MJ, et al. A leukemic presentation of alveolar rhabdomyosarcoma in a 52-year-old woman without an identifiable primary tumor. *Int J Surg Pathol*. 2015;23:75-77.
7. Bozzi F, Collini P, Aiello A, et al. Flow cytometric phenotype of rhabdomyosarcoma bone marrow metastatic cells and its implication in differential diagnosis with neuroblastoma. *Anticancer Res*. 2008;28:1565-1569.
8. Yoon BG, Baek HJ, Oh BS, Han DK, Choi YD, Kook H. Alveolar rhabdomyosarcoma with massive disseminated intravascular coagulopathy treated with systemic chemotherapy. *Korean J Pediatr*. 2015;58:505-508.
9. Sorensen PH, Lynch JC, Qualman SJ, et al. *PAX3-FKHR* and *PAX7-FKHR* gene fusions are prognostic indicators in alveolar rhabdomyosarcoma: a report from the children's oncology group. *J Clin Oncol*. 2002;20:2672-2679.