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Case Report

A Patient with Hepatic Angiosarcoma and Kasabach–Merritt Syndrome Effectively Controlled by Weekly Paclitaxel Therapy

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Abstract

Angiosarcoma accounts for <2% of all soft-tissue sarcomas, and weekly paclitaxel treatment offers clinical benefits and good tolerance. Kasabach–Merritt syndrome (KMS) is a consumptive coagulopathy status associated with vascular tumors. We report a case of hepatic angiosarcoma complicated with KMS who achieved good control in about 2 months under weekly paclitaxel. We also discuss the presentation, diagnosis, and treatment of angiosarcoma with KMS and bone marrow involvement.

Keywords: Angiosarcoma, disseminated intravascular coagulation, Kasabach–Merritt syndrome, weekly paclitaxel

Introduction

Angiosarcoma represents a rare subtype of soft-tissue sarcoma (STS), accounting for <2% of all STSs.[1] Angiosarcoma can occur in any anatomical location but is most commonly found in the head-and-neck skin, breast, liver, heart, and other visceral organs.[2] Although angiosarcoma is commonly treated with the same regimen used by other STS subtypes, paclitaxel has been suggested as another treatment option specifically for angiosarcoma patients based on Phase II studies.[3]

Kasabach–Merritt syndrome (KMS) was originally reported in 1940 as the association between a rapidly enlarging capillary hemangioma and profound thrombocytopenia in an infant. Since then, this term has been used to describe a consumptive coagulopathy associated with vascular tumors.[4] KMS has been reported in angiosarcoma, but recovery from KMS in the metastatic setting is rare.

Herein, we report a case of hepatic angiosarcoma complicated with KMS who achieved good control in about 2 months under weekly paclitaxel. We also discuss the presentation, diagnosis, and treatment of angiosarcoma with KMS and bone marrow involvement.

Case Report

A 48-year-old woman was evaluated at National Taiwan University Hospital (NTUH) for abdominal distention and poor appetite. About 1 month before this presentation, she suffered

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from abdominal distention, poor appetite, chest discomfort, and shortness of breath. She was admitted to another hospital in Taipei about 2 weeks before this presentation, where contrast-enhanced computerized tomography (CT) showed hepatosplenomegaly with many hepatic and splenic hypodense tumors. To find the primary cancer origin, esophagogastroduodenoscopy and colonoscopy were done, but only benign lesions were found. Laboratory tests showed severe disseminated intravascular coagulation (DIC) with a prolonged prothrombin time (23.7 s) and a very low platelet count (23,000/μL). A CT-guided biopsy for the liver tumors was planned but repeatedly postponed due to an excessive bleeding risk. She was then transferred to NTUH for subsequent treatment.

On examination, her consciousness was clear and her vital signs were stable. A physical examination was unremarkable except for hepatomegaly and multiple skin ecchymoses; the Eastern Cooperative Oncology Group performance score was 3. Her weight was 90 kg, height 164 cm, and body surface area 2.02 m^2. Laboratory test results were notable for a hemoglobin level of 8.3 g/dL (reference range: 10.8–14.9 g/dL), a platelet count of 17,000/μL (reference range: 150,000–361,000/μL), and a prothrombin time of 24.0 s (reference range: 9.8–11.5 s). The normoblast count was 2 per 100 white cells (reference range, zero), whereas no blasts or immature myeloid cells were seen. The white cell count was within the normal range (7100/μL; reference range: 3540–9060/μL). The fibrinogen level was lower than 30 mg/dL (reference range: 205.3–372.8) and the d-dimer level was higher than 35.2 μg/mL (reference range: <0.56). Contrast-enhanced abdominal magnetic resonance imaging (MRI) showed hepatosplenomegaly with numerous hemorrhagic cystic tumors in the liver and spleen [Figure 1a-e], and liver angiosarcoma was suspected.

Due to severe DIC, repeated and heavy component therapy was given from the day after arrival. Indirect hyperbilirubinemia (total bilirubin: 2.89 mg/dL, reference range: 0.3–1; direct bilirubin: 0.80 mg/dL, reference range: 0.03–0.18) with a very high level of lactate dehydrogenase (LDH; 2181 U/L, reference range: 140–271) was also recorded. Bone marrow involvement of angiosarcoma was suspected because of severe DIC.[5] Because of persistent coagulopathy, bone marrow aspiration and biopsy were arranged instead of liver biopsy. The imprint smear of bone marrow cytology showed focal aggregation of small round cells, compatible with cancer nests [Figure 2]. Because she also had DIC with severe thrombocytopenia and hemolytic anemia, a diagnosis of hepatic angiosarcoma, complicated with KMS, was made.

Reviewing her medical history, she also had hypertension and latent hepatitis B virus (HBV) infection. Her HBV viral load was 1230 IU/mL. Adequate HBV prophylaxis was given during the chemotherapy course.

For angiosarcoma treatment, the planned regimen was paclitaxel 80 mg/m^2 (total about 160 mg) intravenously for 60 min once per day on days 1, 8, and 15 of a 28-day cycle.

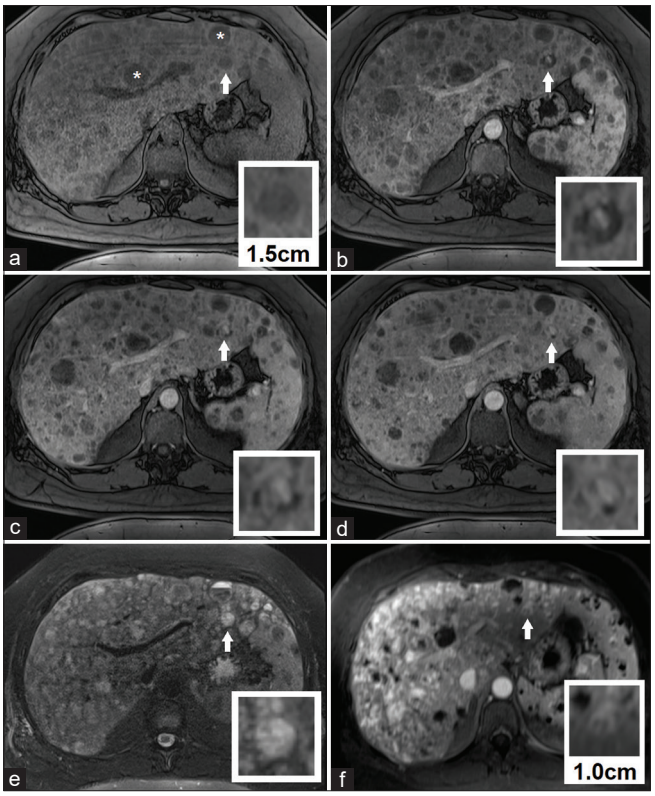

Figure 1: Serial magnetic resonance imaging of the abdomen. (a)~(e) Images at diagnosis: Hepatosplenomegaly with numerous diffuse hepatic and splenic tumors of various sizes. The arrows indicate a typical angiosarcoma tumor, which was hypointense on T1-weighted images and hyperintense on T2-weighted images, and had a progressive filling of enhancement under serial phases of contrast injection. The asterisks indicate tumors mixed with hemorrhages. (a) T1-weighted images without contrast. (b) T1-weighted images with contrast, arterial phase. (c) T1-weighted images with contrast, venous phase. (d) T1-weighted images with contrast, delayed phase. (e) T2-weighted images without contrast. (f) Image after paclitaxel treatment. The arrow indicates one of the tumors with decreased size

Because of her critical condition, a lower dose (a total 90 mg) of paclitaxel was given starting on the 3rd day of admission.

At the beginning of the chemotherapy cycle, she received up to 2 units of packed red blood cell (RBC), 12–24 units of apheresis platelets, and 20–40 units of cryoprecipitate daily. The need for heavy component therapy decreased markedly after day 4 (counting from the first dose of paclitaxel), and no packed RBCs were given afterward. The subsequent doses of paclitaxel were given on day 8 and day 15, and the dose on day 15 was escalated to 120 mg to improve hemogram and also better disease control. No cryoprecipitate was given after day 17, and the last day of platelet transfusion was on day 20, using human leukocyte antigen-matched platelets due to platelet transfusion refractoriness. The level of LDH decreased markedly and indirect hyperbilirubinemia improved [Figure 3].

On stable hemogram and resolved KMS, she was discharged on day 25, and weekly paclitaxel treatment was arranged at a clinic. Because leukopenia was recorded after the higher

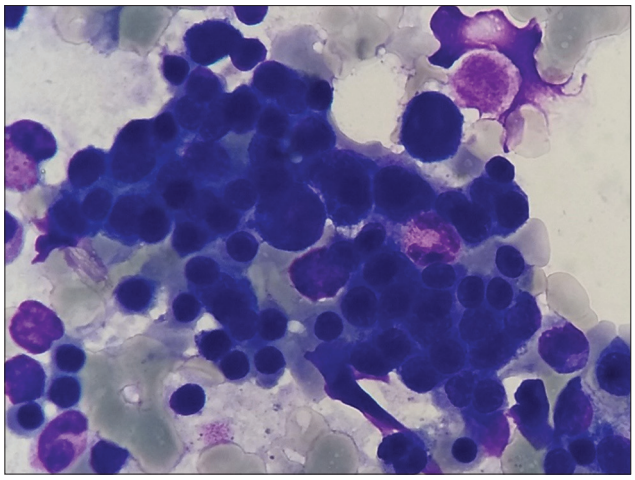

Figure 2: Bone marrow smear showed cancer nests (aggregation of small round cells) (Liu stain, original magnification × 1000)

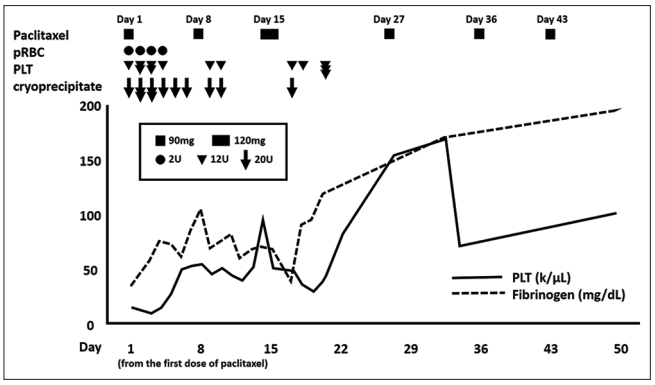

Figure 3: Graphic illustration of the time course of platelet and fibrinogen level in relation to the chemotherapy and component therapy. PRBC: Packed red blood cell, PLT: Platelet, U: Unit

paclitaxel dose (120 mg), a lower dose of 90 mg was prescribed. Without the support of component therapy, she had a nearly normal fibrinogen level of around 170–190 mg/dL and a mildly low platelet count of around 70,000–100,000/μL, probably due to the effect of chemotherapy. She continued to receive weekly paclitaxel from day 57 to day 81 with limited toxicity. A follow-up abdominal MRI on day 83 showed decreases in the sizes of the hepatic tumors [Figure 1f].

Unfortunately, around the same time, her fibrinogen level fell below 100 mg/dL and the LDH level increased again despite the weekly paclitaxel treatment. She was admitted, and salvage nivolumab, liposomal doxorubicin, and pazopanib were administered sequentially with no obvious response. Hepatic failure followed the refractory DIC, and she passed away on day 129.

Discussion

Angiosarcoma, although a rare disease, can originate from any soft-tissue structure or viscera.[6] Hepatic angiosarcoma accounts for 2% of all primary malignant neoplasms of the liver and is the second most common hepatic malignancy. Twenty-five percent of cases are associated with previous chemical exposure, such as thorotrast, androgenic steroids, arsenic, and vinyl chloride, and the remaining 75% have no known etiology.[7,8]

Patients usually present with abdominal pain, weight loss, or fatigue. Symptoms and signs of liver disease, such as nausea, vomiting, malaise, weakness, anorexia, hepatomegaly, and ascites, may also present.[9] Acute liver failure may occur in some patients.[8] As with the possible initial presentation of our case, tumor rupture with hemoperitoneum has been reported in 15%–27% of cases, and patients may also have DIC features.[10]

If hepatic angiosarcoma is accompanied with DIC, it is better described as KMS. Although the exact pathogenesis is not well-established, KMS is thought to be caused by platelet trapping by proliferating endothelial cells within the vascular tumor. This further causes the activation of platelets and consumption of coagulation factors.[4]

Because of the risks associated with a liver biopsy, imaging plays a key role in the diagnosis of hepatic angiosarcoma. The features of CT or MRI of angiosarcoma vary based on different morphological presentations. If the angiosarcoma presents as a dominant mass, early-phase images of dynamic contrast-enhanced CT or MRI typically show heterogeneous enhancement, followed by delayed phase images showing progressive enhancement. If the angiosarcoma presents with multiple nodular lesions, the typical pattern is hypoattenuation with focal enhancement. These features are clearly distinguishable from benign hemangiomas, which mostly present with nodular enhancement.[11] CT and MRI in our patient both highly suggested hepatic angiosarcoma. However, there was no window of opportunity for a liver biopsy due to persistent coagulopathy. In some cancer types, the presence of DIC is commonly associated with bone marrow metastasis.[12] A case of primary splenic angiosarcoma with bone marrow metastasis has been reported,[13] but no cases of hepatic angiosarcoma with bone marrow metastasis were found in the literature. In our case, the presence of KMS and coagulopathy forced us to consider bone marrow aspiration and biopsy as an alternative to confirm the diagnosis of angiosarcoma.

The therapeutic agents for angiosarcoma include paclitaxel, docetaxel, vinorelbine, sorafenib, sunitinib, bevacizumab, and all other systemic therapy options for STS. Due to the favorable results and low risk of bone marrow toxicity of a Phase II trial of weekly paclitaxel,[3] we adopted this regimen and titrated down the dosage due to the patient's critical condition. A lower dose was prescribed at first with a flat dose of 90 mg weekly with good control of DIC, then later titrated to 120 mg, and finally back to 90 mg weekly due to significant bone marrow suppression (please refer to the "Case Report" section above). The treatment effect lasted for about 2 months.

Published hepatic angiosarcoma case reports have reported very poor survival outcomes, with a survival of less than or

equal to 4 months. Rapid tumor progression with hepatic failure and severe bleeding were the main causes of death.[14] One case of metastatic angiosarcoma with KMS sequentially responsive to paclitaxel and then liposomal doxorubicin has been reported. Due to disease progression, gemcitabine and vinorelbine were given, and the patient achieved nearly complete remission.

In conclusion, we presented a rare case of hepatic angiosarcoma with KMS and bone marrow involvement. Although disease progression was inevitable, dose-reduced weekly paclitaxel generated an acceptable response period.

Ethical statement

The study was reviewed and has been approved by the IRB of NTUH hospital (Approval No. 202001026RINB obtained on Feb. 10th, 2020). The study was reviewed and has been approved by the IRB of NTUH hospital (Approval No. 202001026RINB). Informed written consent was waived by IRB.

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Conflicts of interest

There are no conflicts of interest.

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