

Case Report

---

# Multifocal Epithelioid Hemangioendothelioma Complicated with Disseminated Intravascular Coagulation

Hiroaki Kimura<sup>a</sup> Norio Yamamoto<sup>b</sup> Katsuhiro Hayashi<sup>b</sup>  
Takashi Higuchi<sup>a, b</sup> Hiroyuki Tsuchiya<sup>b</sup>

<sup>a</sup>Department of Orthopaedic Surgery, Kanazawa Red Cross Hospital, Kanazawa, Japan;

<sup>b</sup>Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan

## Keywords

Epithelioid hemangioendothelioma · Disseminated intravascular coagulation · Angiosarcoma

## Abstract

Epithelioid hemangioendothelioma (EHE) is a rare malignant vascular neoplasm that requires long-term management. Several reports describe disseminated intravascular coagulation (DIC) associated with angiosarcoma, but no association with EHE has been reported. We encountered a patient with DIC complicated by multifocal EHE. The patient was an 83-year-old woman with spinal lesions, small lung nodules, and a soft tissue mass in the right buttock. The tumor was biopsied and diagnosed as EHE. The patient received pain control therapy without antitumor therapy. One month later, DIC developed with tumor progression. DIC subsided with nafamostat mesylate infusion, and oral apixaban was administered. DIC was managed for 5 months until the patient died of brain metastases. This is the first report of a patient with DIC complicated by EHE. It should be noted that progression of EHE can cause DIC. We were able to manage DIC using anticoagulant agents.

© 2021 The Author(s).

Published by S. Karger AG, Basel

## Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor derived from vascular or pro-endothelial cells, and it has an epithelioid and histiocytic appearance. It represents <1% of all vascular tumors [1]. The term epithelioid hemangioendothelioma was introduced in 1982 by Weiss and Enzinger [2] to describe a vascular tumor of the bone and soft tissue with characteristics of both hemangioma and angiosarcoma. According to the latest World Health Organization (WHO 2020 5th Edition) classification, EHE is a malignant vascular neoplasm composed of epithelioid endothelial cells within myxohyaline stroma, most often characterized by *wwtr1-camta1* or *yap1-tfe3* gene fusion [3]. Unlike angiosarcoma, it is often characterized by a slow clinical course and an ability to control the disease, even without therapy. EHE arising in the lung or bone or with the *yap1-tfe3* fusion gene has a worse prognosis, and patients often present with metastatic disease [4].

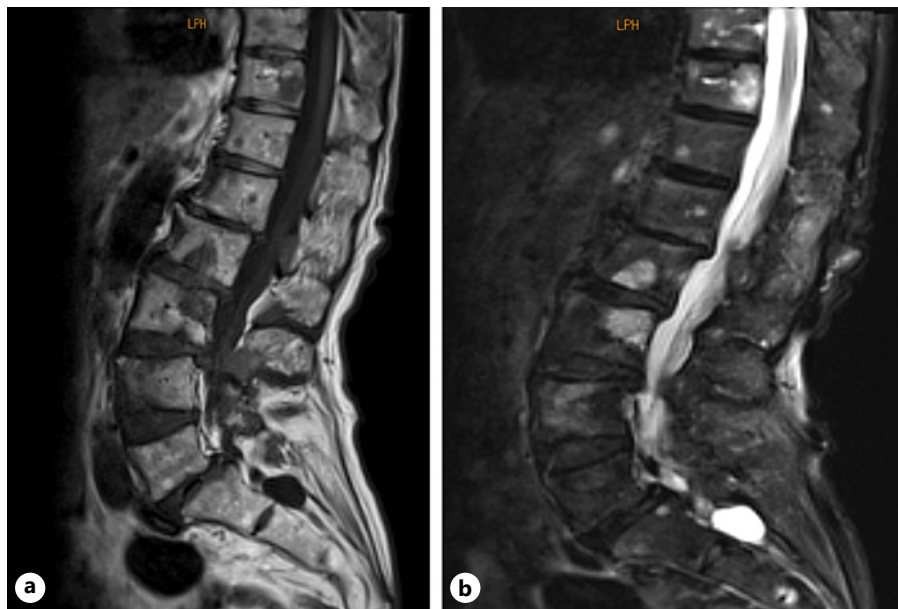
EHE most commonly occurs in the soft tissues, lungs, and liver. However, EHE is a highly heterogeneous tumor that can reportedly occur throughout the body [5]. Visceral and bone lesions are often multifocal and may be metastatic at presentation [6, 7]. When encountering these cases, it can be difficult to determine if the tumor is multicentric or a primary lesion with metastases in other tissues. Metastatic lesions may be distinguishable from multicentric primary tumors due to poor differentiation and loss of epithelial marker expression at metastatic sites [8]. Due to its rarity, EHE has no standard treatment, and few therapeutic options are available. When the lesion is localized, surgical resection or follow-up only is recommended, depending on the patient's symptoms. Other recommendations include radiotherapy for unresectable localized EHE, adjunctive therapy for when sufficient margins cannot be secured for surgery, and systemic chemotherapy for advanced conditions. However, its effects have been reported to be limited [9, 10].

Complications of consumptive coagulopathies, including disseminated intravascular coagulation (DIC), have been reported with angiosarcoma, which is a more aggressive and high-grade malignant type of EHE. However, there are no previous reports of DIC arising in patients with EHE. In angiosarcoma patients, any clinical response to cancer chemotherapy saw coincident improvement in coagulopathy. Conversely, tumor progression led to worsening of DIC. While treatment of DIC is usually targeted to the underlying cause, challenges arise when there is no available treatment option for the underlying cause [11].

This is the first report of a patient with DIC complicated by multifocal EHE. We highlight that oral anticoagulant agents controlled DIC in this patient, even though she did not receive any antitumor therapy and the disease progressed.

## Case Report/Case Presentation

The patient was an 83-year-old woman who was referred to our institution from a nearby clinic for further investigation of lower back pain. Magnetic resonance imaging (MRI) showed multiple spinal lesions from the thoracic spine to the lumbar spine, suggesting spinal metastases (shown in Fig. 1). She did not have any past illness or family history of malignancy. Laboratory studies revealed slight anemia and elevated serum lactic acid dehydrogenase and serum calcium levels. The levels for tumor markers, including CEA, SCC, CA19-9, and sIL-2, were within the normal range. A computed tomography scan from the chest to the pelvis revealed multiple small lung nodules which were suspected to be lung metastases; however, no primary malignant lesion was detected. Multiple osteolytic lesions were detected from the thoracic spine to the pelvic bone, and a soft tissue mass was also detected in the subcutaneous tissue of the right buttock (shown in Fig. 2). Although it was found to be a malignant disease



**Fig. 1.** MRI showing multiple spinal lesions with low intensity on T1-weighted images (a) and high intensity on STIR images (b). There was no extraosseous extension of the tumor with nerve compression. MRI, magnetic resonance imaging.

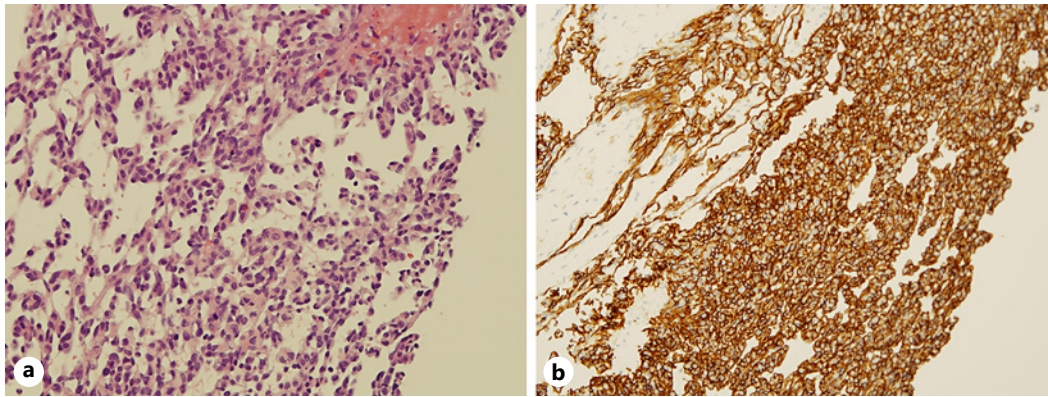


**Fig. 2.** CT revealed a high-density soft tissue mass in the subcutaneous tissue of the right buttock. CT, computed tomography.

with multiple metastases, it was difficult to determine the primary lesion and diagnose based on imaging alone.

To determine the pathological diagnosis of the lesions, a biopsy of the subcutaneous mass of the right buttock was performed. Histological examination showed that the tumor had an alveolar structure with nuclear irregularities with very few mitoses. Round or spindle tumor cells were surrounded by vascular lumen. Immunohistochemistry revealed that the tumor cells were diffusely positive for the vascular endothelium marker CD34 and the epithelial marker CK, and negative for AE1/AE3, which corresponds to EHE (shown in Fig. 3). Due to her age and the nature of the tumor, the patient received only pain control therapy without antitumor therapy.

One month after the patient first presented to our hospital, she had spontaneous subcutaneous hematomas on the left forearm and right thigh. Subsequent work-up revealed a



**Fig. 3.** Needle biopsy specimens were collected from the subcutaneous mass of the right buttock. The specimens consisted of round or spindle tumor cells surrounded by vascular lumens. Alveolar structures with nuclear irregularities and very few mitoses were observed. **a** HE staining. **b** Immunohistochemistry revealed that the tumor cells were positive for the vascular endothelium marker CD34.

hemoglobin level of 9.1 g/dL, platelet count of  $3.7 \times 10^4/\mu\text{L}$ , fibrinogen value of 62.9 mg/dL, fibrin degradation products (FDP) D-dimer level of 86.3  $\mu\text{g}/\text{mL}$ , partial thromboplastin time international normalized ratio (PT-INR) of 1.12, antithrombin 3 activity of 65%, thrombin-antithrombin 3 complex of 121.9 ng/mL, creatinine level of 1.11 mg/dL, and blood urea nitrogen (BUN) level of 39.1 mg/dL (Table 1). Computed tomography showed acute tumor progression of the lung and spinal lesions. We diagnosed DIC complicated by tumor progression.

She was admitted immediately and treated with 100 mg daily of nafamostat mesylate infusion for the first week after DIC diagnosis to reduce the consumption of coagulation factors induced by thrombosis. Subsidence of DIC was confirmed 1 week after starting nafamostat mesylate with normalization of the platelet count and fibrinogen concentration to  $16.5 \times 10^4/\mu\text{L}$  and 284 mg/dL, respectively. However, we expected DIC recurrence if anticoagulant therapy was ended because the progression of the tumor lesion was the underlying cause of this DIC. In general, the introduction of chemotherapy should be considered to control tumor growth. However, considering the patient's age and general condition, it was difficult to administer a cytotoxic anticancer drug, such as doxorubicin or paclitaxel. Continuation of anticoagulant therapy was essential to maintain the improvement in DIC. Considering the continuity of the treatment and activity of daily life (ADL) improvement, nafamostat mesylate infusion was then transitioned to 2.5 mg oral apixaban twice daily. Two weeks after administration of oral apixaban, subsidence of DIC was confirmed with a platelet count of  $28.9 \times 10^4/\mu\text{L}$  and fibrinogen concentration of 540 mg/dL. Finally, DIC could be continuously controlled without antitumor treatment for 5 months until the patient died of brain metastases.

### Discussion/Conclusion

DIC is often observed as a complication of advanced disease in several different malignancies. High-grade angiosarcoma is known to be associated with DIC in some cases, but there are no previous reports of DIC occurrence in EHE. Farid et al. reported that 17% of angiosarcoma patients who stabilized after systemic antineoplastic therapy and chemotherapy developed DIC, but no EHE patients did [12]. To our knowledge, this is the first report of a patient with EHE complicated by DIC.

**Table 1.** Patient test results

Laboratory measurement	Initial presentation (day 1)	DIC onset (day 28)	1 week after DIC treatment with nafamostat (day 35)	2 weeks after initiation of DOAC (day 50)
WBC	6,700	6,000	12,440	8,680
Hb, g/dL	11.2	9.1	8.4	7.2
Plt × 10 <sup>4</sup>	11.8	3.7	30.2	29.1
PT-INR	0.97	1.12	0.98	1.10
APTT, s	29.1	31.4	27.9	36.0
Fibrinogen	N/A	62.9	374	540
D-dimer, µg/mL	N/A	52.7	18.0	5.9
AT III, %	N/A	65	N/A	N/A
TAT, ng/mL	N/A	121.9	N/A	N/A
Cr, mg/dL	0.80	1.11	1.10	0.69
BUN, mg/dL	18.1	39.1	29	20.1
UA, mg/dL	5.4	7.4	5.8	5.2
Ca, mg/dL (corrected for albumin)	10.1	13.1	9.2	8.2

DIC, disseminated intravascular coagulation; Ca, calcium.

Several theories have been proposed to explain how angiosarcomas may trigger DIC, including exposure of the endothelial basement membrane, release of clotting factors triggered by a decreased blood flow inducing blood cell trapping and lysis, and release of thromboplastin and tissue factors induced by local inflammation or malignant endothelial cells [13]. In this case, we speculated that EHE tumor activity increased and DIC developed by the same mechanism as angiosarcoma.

DIC is classified into 3 types according to the ratio of fibrinolysis to coagulation: fibrinolysis-suppressing type, fibrinolytic equilibrium type, and fibrinolysis-enhancing type. DIC in solid tumors is usually considered to be the fibrinolytic equilibrium type, but in some malignancies such as prostate cancer and malignant melanoma, fibrinolysis-promoting substances are produced in addition to tissue factors, which may result in fibrinolysis-enhancing type DIC. This case was also considered to be fibrinolysis-enhancing type DIC because of the increased bleeding tendency and high FDP D-dimer. Although there are no reports on a relationship between sarcoma and DIC classification, it is highly possible that in this case, a malignant tumor derived from vascular endothelial cells produced a fibrinolysis-promoting substance, which led to fibrinolysis-enhancing type DIC. Gavexate mesylate is often used for the treatment of DIC. But in this case, considering the pathological state of hyperfibrinolysis, the use of nafamostat mesylate, which can suppress not only the coagulation system but also fibrinolysis activation, was started and DIC improved.

Management of DIC associated with malignant tumors requires additional treatment along with chemotherapy and surgery for the underlying disease. Rosen et al. reported that after controlling DIC by administering tranexamic acid and heparin for hepatic angiosarcoma complicated by DIC, chemotherapy, including taxane-based chemotherapy, doxorubicin, and daily enoxaparin administration controlled the condition over time [14]. Honda et al. [11] reported a cardiac angiosarcoma patient with multiple liver and bone metastases complicated by DIC, which was stabilized by the administration of fresh frozen plasma and recombinant thrombomodulin- $\alpha$ . The patient was then administered nab-paclitaxel regularly,

which led to successful stabilization of the tumor and DIC over a long period of time. However, in situations where there is no effective treatment for the underlying disease like in this case, controlling DIC over a long period is often difficult. It has recently been reported that DOAC is effective for the treatment and control of chronic DIC. Since EHE is a slow-growing tumor that is not effectively treated with chemotherapy, it is expected that once DIC develops, it will easily become a chronic condition. In this case, it was possible to control DIC over a long period of time while maintaining ADL by switching antithrombotic therapy from infusion of nafamostat mesylate to oral administration of apixaban.

In conclusion, we encountered a patient with DIC complicated by multifocal EHE. DIC was managed with oral anticoagulant agents for a long period without any antitumor treatment. It should be noted that disease progression of EHE can cause DIC.

### Statement of Ethics

This study was not required ethics approval by Ethics Committee of Kanazawa Red Cross Hospital. Written informed consent was obtained from next of kin for publication of the details of their medical case and any accompanying images.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Funding Sources

The authors have no funding sources for this study.

### Author Contributions

Hiroaki Kimura contributed to conceptualization, project administration, resources, data curation, investigation, and writing – original draft. Norio Yamamoto contributed to project administration and writing – review and editing. Katsuhiko Hayashi contributed to investigation and resources. Takashi Higuchi contributed to investigation, resources, and data curation. Hiroyuki Tsuchiya contributed to supervision and writing – review and editing.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

### References

- 1 Sardaro A, Bardoscia L, Petruzzelli MF, Portaluri M. Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor. *Oncol Rev.* 2014 Oct 13;8(2):259.
- 2 Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer.* 1982 Sep 1;50(5):970–81.

- 3 WHO Classification of Tumours Editorial Board. [World Health organization classification of soft tissue and bone tumours](#). 5th ed. Lyon: IARC Press; 2020.
- 4 Antonescu CR, Le Loarer F, Mosquera JM, Sboner A, Zhang L, Chen CL, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. [Genes Chromosomes Cancer](#). 2013 Aug;52(8):775–84.
- 5 Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. [Chest](#). 2011 Nov;140(5):1312–8.
- 6 Makhlof HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. [Cancer](#). 1999 Feb 1;85(3):562–82.
- 7 Kleer CG, Unni KK, McLeod RA. Epithelioid hemangioendothelioma of bone. [Am J Surg Pathol](#). 1996 Nov;20(11):1301–11.
- 8 Gómez-Arellano LI, Ferrari-Carballo T, Domínguez-Malagón HR. Multicentric epithelioid hemangioendothelioma of bone. Report of a case with radiologic-pathologic correlation. [Ann Diagn Pathol](#). 2012 Jan;16(1):43–7.
- 9 Rosenthal DI, Treat ME, Mankin HJ, Rosenberg AE, Jennings CL. Treatment of epithelioid hemangioendothelioma of bone using a novel combined approach. [Skeletal Radiol](#). 2001 Apr;30(4):219–22.
- 10 Kitaichi M, Nagai S, Nishimura K, Itoh H, Asamoto H, Izumi T, et al. Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. [Eur Respir J](#). 1998 Jul;12(1):89–96.
- 11 Honda K, Ando M, Sugiyama K, Mitani S, Masuishi T, Narita Y, et al. Successful treatment of cardiac angiosarcoma associated with disseminated intravascular coagulation with Nab-paclitaxel: a case report and review of the literature. [Case Rep Oncol](#). 2017 Sep 21;10(3):863–70.
- 12 Farid M, Ahn L, Brohl A, Cioffi A, Maki RG. Consumptive coagulopathy in angiosarcoma: a recurrent phenomenon? [Sarcoma](#). 2014;2014:617102.
- 13 Alliot C, Tribout B, Barrios M, Gontier MF. Angiosarcoma variant of Kasabach-Merritt syndrome. [Eur J Gastroenterol Hepatol](#). 2001 Jun;13(6):731–4.
- 14 Rosen EA, Vallurupalli M, Choy E, Lennerz JK, Kuter DJ. Management of disseminated intravascular coagulation in a patient with hepatic angiosarcoma: a case report. [Medicine](#). 2018 Nov;97(47):e13321.