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CASE REPORT

Hepatic Angiosarcoma with Kasabach-Merritt Phenomenon: A Case Report and Review of the Literature

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ABSTRACT

A 76-year-old woman was referred to our hospital due to massive gingival bleeding following teeth extraction. Laboratory findings suggested disseminated intravascular coagulopathy (DIC). Enhanced computed tomography and magnetic resonance imaging disclosed multiple hypervascular liver masses of 2-6 cm in diameter, the largest of which displaying an irregular enhancement pattern. We considered that her DIC was caused by the multiple liver masses and commenced repeated erythrocyte/fresh frozen plasma infusion and gabexate mesilate administration. However, the DIC proved uncontrollable and trans-arterial embolization could not be attempted. The patient eventually died 4 months after admission due to spontaneous hepatic tumor rupture and hepatic failure. Post-mortem hepatic tumor biopsy led to a final diagnosis of hepatic angiosarcoma with Kasabach-Merritt phenomenon (KMP). Among the 7 cases of hepatic angiosarcoma representing KMP found in the literature, mortality occurred within 4 months of the appearance of bleeding tendency primarily due to abdominal bleeding and hepatic failure. The possibility of hepatic angiosarcoma should be considered in patients with DIC and hypervascular liver tumors. Since treatment is uncertain and prognosis is poor, novel diagnostic and therapeutic advances are needed for angiosarcoma.

Key words. Kasabach-Merritt phenomenon. DIC. bleeding tendency. Liver. Angiosarcoma.

INTRODUCTION

Disseminated intravascular coagulopathy (DIC) is characterized by massive microthrombi appearing through various mechanisms.[1] Enhanced thrombolysis and consumption of coagulation factors in DIC lead to bleeding tendency, thrombocytopenia, hypofibrinogenemia, and increased circulating fibrinogen degradation product (FDP).[1] Although DIC is frequently accompanied by severe infection, leukemia, and cancer cell invasion of the bone marrow, some cases are caused by tumors of vascular origin, such as cavernous hemangioendothelioma.[1] Hepatic angiosarcoma is an uncommon malignant vascular tumor of the liver that is very rarely accompanied with DIC.[2] We herein report a case of hepatic angiosarcoma showing Kasabach-Merritt phenomenon (KMP), review its clinical features, and compare it with existing cases in the literature.

CASE REPORT

A 76-year-old woman was referred to our outpatient clinic due to bouts of persistent or massive gingival bleeding following teeth extraction two weeks prior. On admission, she had no history of drinking, blood transfusion, medicine or supplement regimen, or occupation handling vinyl chloride or heavy metals. She did not suffer from weight loss, general fatigue, anorexia, or abdominal fullness or pain. Physical examination showed no jaundice, purpura, lymphadenopathy, or splenomegaly, but a soft liver was palpable in the epigastric region. Laboratory findings revealed decreased platelet count (56,000/μL) and

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circulating fibrinogen level (124 μg/mL) with elevated FDP level (233 μg/mL), which were suggestive of DIC (Table 1). Microscopic examination of peripheral blood cells detected no atypical leukocytes or fragmented erythrocytes. Serum levels of lactate dehydrogenase and the tumor markers alpha fetoprotein, des-gamma-carboxy prothrombin, carcinoembryonic antigens, carbohydrate antigen, pro-gastrin-releasing peptide, and soluble interleukin 2 receptor were all within normal ranges (Table 1). Negative blood culture results and normal levels of serum C-reactive protein and procalcitonin indicated a low possibility of underlying severe infection or inflammation (Table 1).

Enhanced computed tomography (CT) disclosed multiple hypervascular liver masses of 2-6 cm in diameter (Figure 1A). On magnetic resonance imaging (MRI), the largest tumor was T1 hypointense and T2 hyperintense (Figure 1B). Dynamic contrast enhanced MRI revealed irregular areas of enhancement at the periphery (Figure 1C) that were hypoechoic on routine ultrasound (Figure 1D).

Based on the above findings, we considered the possibility of a tumor of vascular origin, such as hemangioendothelioma or angiosarcoma. In spite of repeated packed red blood cell and fresh frozen plasma transfusion along with gabexate mesilate administration, the patient's gingival bleeding did not stop and alveolar hemorrhage appeared 43 days after admission. A relationship between the multiple liver tumors and DIC was suspected, but primary liver tumor treatment, such as trans-arterial embolization (TAE), could not be attempted due to the patient's poor general condition and uncontrollable systemic bleeding tendency; bleeding would persist for several days following routine blood sampling from the peripheral vein. Spontaneous hepatic tumor rupture and hepatic failure eventually occurred and she died 120 days after admission.

Post-mortem hepatic tumor biopsy revealed various pathological findings. Liver parenchyma with mild invasion of tumor cells exhibited dilated hepatic sinusoids lined by hypertrophied endothelial cells displaying atypical hyperchromatic nuclei (Figure 2A). In severely involved areas, these bizarre cells had proliferated in dilated sinusoids, causing liver cell plate atrophy (Figure 2B and C) and forming clusters in areas which the hepatocytes had disappeared entirely (Figure 2D). Immunohistochemical analysis revealed CD31 and CD34 positivity in tumor cells, leading to the final diagnosis of hepatic angiosarcoma (Figure 2E and F).

DISCUSSION

Hepatic angiosarcoma is a malignant mesenchymal tumor with a very low incidence of 0.14-0.25 per million inhabitants that represents 1.8% of all primary liver tumors.[3] Several etiological factors have been implicated in this disease, including exposure to thorotrast, vinyl chloride, copper, radium, sex steroids, and arsenic compounds.[4] Although the present case contained none of these elements, numerous other reports support the existence of hepatic angiosarcoma without such factors.[2]

The symptoms of hepatic angiosarcoma are largely nonspecific. Abdominal pain is the most common complaint, followed next by weakness, fatigue, and weight loss.[2] Moreover, there are no physical or laboratory findings characteristic of this disease. The lack of specific findings makes accurate diagnosis of hepatic angiosarcoma difficult.

Table 1. Laboratory data on admission.

Biochemistry			Hematology			Tumor markers		
TP	6.9	g/dL	WBC	6870	/μL	AFP	5	ng/mL
ALB	4	g/dL	RBC	383×10^4	/μL	DCP	17	mAU/mL
T-bil	1.0	mg/dL	Hemoglobin	11.5	g/dL	CEA	0.6	ng/mL
AST	44	IU/l	Platelet count	56,000	/μL	CA19-9	4	U/mL
ALT	38	IU/l	Coagulation			ProGRP	40.5	pg/mL
LDH	231	IU/l	PT-INR	1.38	INR	sIL-2R	180	U/mL
ALP	338	IU/l	APTT	30.6	sec			
γGTP	125	IU/l	FDP D-dimer	113	μg/mL	Blood culture	negative	
BUN	22.8	mg/dL	FDP	233	μg/mL			
Cre	0.7	mg/dL	Fibrinogen	124	mg/dL			
CRP	0.26	mg/dL	TAT	> 60	ng/mL			
Procalcitonin	0.2	ng/mL	PIC	11.9	μg/mL			

AFP: alpha fetoprotein. ALB: albumin. ALP: alkaline phosphatase. ALT: alanine transaminase. APTT: activated partial thromboplastin time. AST: aspartate aminotransferase. BUN: blood urea nitrogen. CA19-9: carbohydrate antigen 19-9. CEA: carcinoembryonic antigen. Cre. creatinine. CRP: C-reactive protein. DCP: des-gamma-carboxy prothrombin. FDP: fibrinogen degradation product. γGTP: gamma-glutamyltranspeptidase. LDH: lactate dehydrogenase. PIC: plasmin-α2 plasmin inhibitor complex. ProGRP: pro-gastrin-releasing peptide. PT-INR: international normalized ratio of prothrombin time. RBC: red blood cells. sIL-2R: soluble interleukin 2 receptor. TAT: thrombin-antithrombin complex. T-bil: total bilirubin. TP: total protein. WBC: white blood cells.

Unexplainable DIC may be a clue in identifying hepatic tumors of vascular origin. In 1940, Kasabach and Merritt described a new syndrome in a boy with kaposiform hemangioendothelioma, severe thrombocytopenia, anemia, and consumption coagulopathy.[3] KMP with angiosarcoma was later detected in the skin,[4] breast,[5] and bone.[6] Recently, ultrastructural examination of kaposiform hemangioendothelioma samples with KMP revealed trapping of

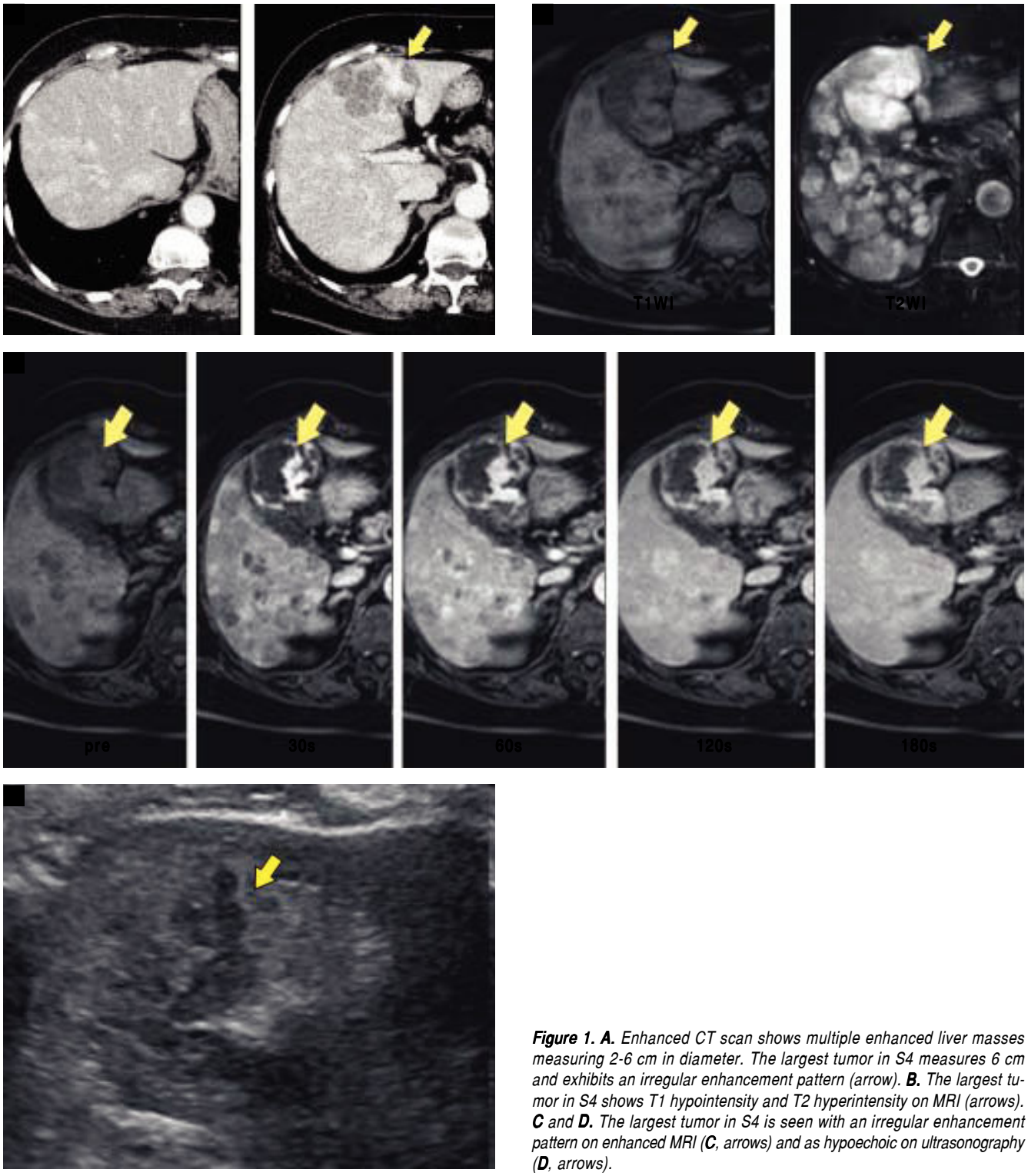

Figure 1. A. *Enhanced CT scan shows multiple enhanced liver masses measuring 2-6 cm in diameter. The largest tumor in S4 measures 6 cm and exhibits an irregular enhancement pattern (arrow).* ***B.*** *The largest tumor in S4 shows T1 hypointensity and T2 hyperintensity on MRI (arrows).* ***C*** *and* ***D.*** *The largest tumor in S4 is seen with an irregular enhancement pattern on enhanced MRI (**C**, arrows) and as hypoechoic on ultrasonography (**D**, arrows).*

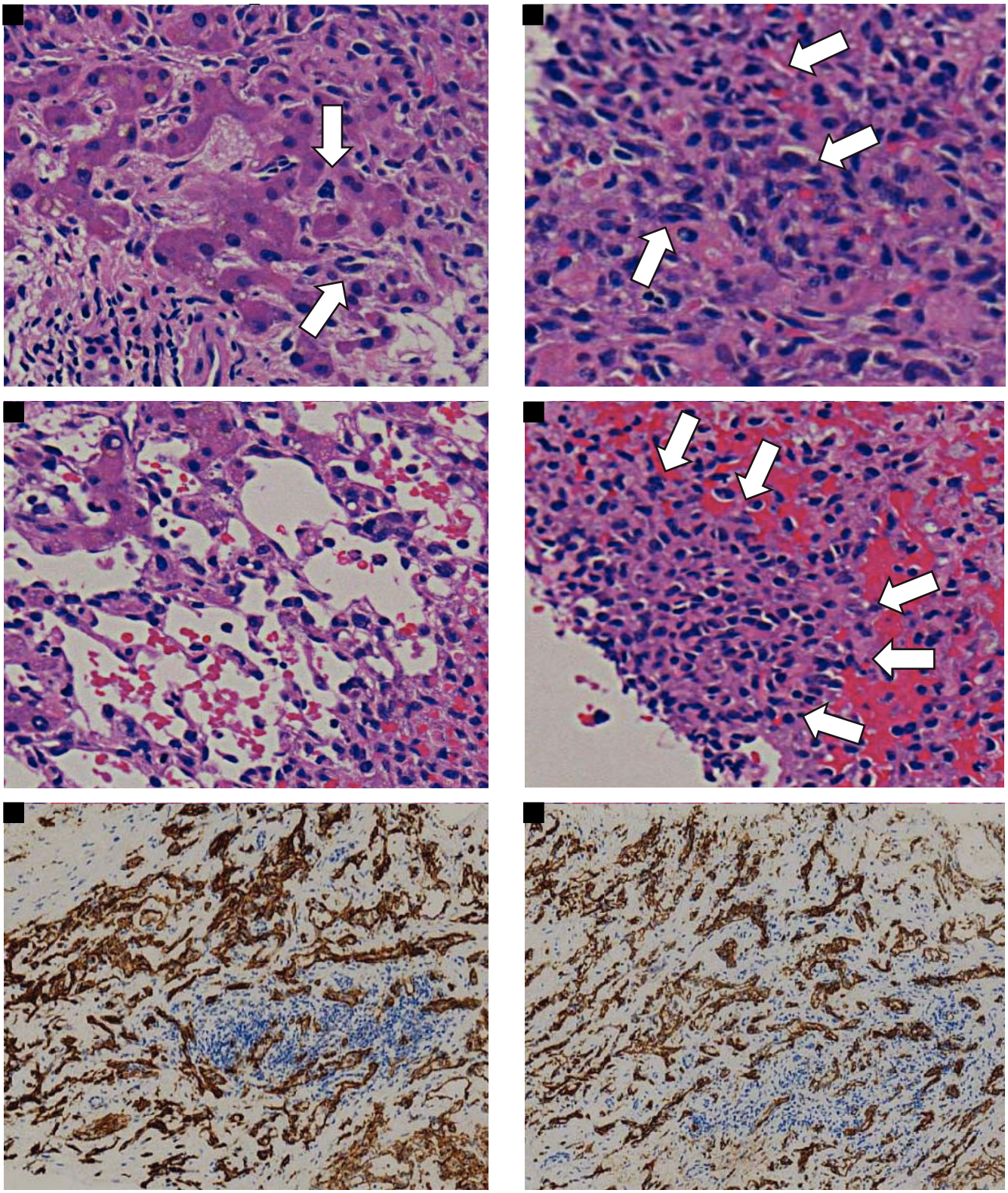

Figure 2. A. *Areas with mild tumor cell invasion show dilated hepatic sinusoids lined by hypertrophied endothelial cells with atypical hyperchromatic nuclei (arrows).* ***B*** *and* ***C.*** *With progressive involvement, the sinusoids dilate and fill with malignant endothelial cells (****B****, arrows) with liver cell plate atrophy* ***(C)****.* ***D.*** *Areas in which hepatocytes have entirely disappeared sometimes exhibit solid malignant cell growth (arrows).* ***E*** *and* ***F.*** *Immunohistochemical analysis. The tumor cells are positive for the endothelial markers CD31 (E) and CD34* ***(F)****.*

Table 2. Case reports of hepatic angiosarcoma with Kasabach-Merritt phenomenon.

Case (Ref)	Age	Sex	Chief Complaint(s)	Platelet count (/μL)	FDP (μg/mL)	Fibrinogen (mg/dL)	Size (cm)	Treatment	Cause of death	Survival time (months)
1 (12)	71	M	Purpura abdominal pain	38,000	80	70	15	TAE	Abdominal bleeding, liver failure	0.7
2 (13)	70	M	Gingival bleeding	ND	ND	ND	15	TAE	Abdominal bleeding	4
3 (14)	70	M	Gingival bleeding, Purpura	30,000	58.5	125	8	TAE	Abdominal bleeding	2
4 (10)	70	M	Abdominal pain	50,000	ND	110	ND	Supportive care	Abdominal bleeding	3
5 (11)	70's	F	Purpura, appetite loss	15,000	25.9	ND	5	Supportive care	Liver failure	1
6 (16)	70's	F	Abdominal pain	42,000	ND	ND	18	Hepatectomy	ND	ND
7 (9)	87	M	Asymptomatic	31,000	ND	ND	15	Supportive care	Congestive heart failure	ND
Our case	76	F	Gingival bleeding	56,000	233	124	6	Supportive care	Abdominal bleeding, liver failure	4

F: female. FDP: fibrinogen degradation product. M: male. ND: not described. Ref: reference. TAE: transcatheter arterial embolization.

platelets, erythrocytes, lymphocytes, and macrophages in tumor cells and intra-tumoral channels.[7] Many thrombi were generated and a large amount of platelets and coagulation factors were consumed in the tumor, leading to DIC.[7] Judging from the clinical course and pathological biopsy findings in the present case, we considered that the DIC caused by multiple hepatic angiosarcoma was KMP.

Due to the nonspecific physical/laboratory findings of hepatic angiosarcoma, imaging modalities play a critical role in its diagnosis. Angiosarcoma has various hallmark features in CT/MRI that reflect its heterogeneous histologic composition. When angiosarcoma appears as multiple nodular lesions, most include enhancement foci to enable distinction from benign hemangiomas showing nodular enhancement.[8] Hemorrhagic lesions may appear in cases of very large angiosarcoma.[9] Our patient exhibited irregular areas of enhancement at the periphery of the largest lesion. Although we could not obtain a specimen, we surmised that it corresponded to cavernous areas lined by malignant cells and ensuing hepatocyte atrophy.

There is uncertainty on how patients with KMP should be treated. The clinical features, treatment, and outcomes of 7 case reports of hepatic angiosarcoma with KMP are presented in table 2. Patient age ranged from 70 to 87 years and initial symptoms primarily included gingival bleeding, purpura, and abdominal pain. All cases possessed thrombocytopenia and large tumors of more than 5 cm in diameter. Tumor resection and TAE were considered risky because of uncontrollable bleeding tendency. Moreover, TAE was insufficient in most cases and required additional treatments. Survival was less than 4 months due to rapid tumor progression, with intraperitoneal bleeding and liver failure representing the main causes of death. Although there are no established therapeutic strategies for angiocarcinoma at present, several reports have demonstrated the potential of anti-angiogenic agents, such as anti-VEGF drugs, tyrosine kinase inhibitors, such as sunitinib, and combinations of such molecular targeted agents as sorafenib and sunitinib to be at least partially effective.[15] The establishment of novel therapeutic interventions is needed.

In conclusion, we report a rare case of hepatic angiosarcoma that had manifested as bleeding tendency. The possibility of hepatic angiosarcoma should be considered for patients with DIC and liver tumor.

ABBREVIATIONS

- CT: computed tomography.
- DIC: disseminated intravascular coagulopathy.
- FDP: fibrinogen degradation product.
- KMP: Kasabach-Merritt phenomenon.
- MRI: magnetic resonance imaging.

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CONFLICT OF INTEREST

No conflict of interest exists.

REFERENCES

1. Kaneko T, Wada H. Diagnostic criteria and laboratory tests for disseminated intravascular coagulation. *Journal of clinical and experimental hematopathology* 2011; 51: 67-76.

2. Locker GY, Doroshow JH, Zwelling LA, Chabner BA. The clinical features of hepatic angiosarcoma: a report of four cases and a review of the English literature. *Medicine* 1979; 58: 48-64.
3. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura. *Am J Dis Child* 1940; 59: 1063-70.
4. Imafuku S, Hosokawa C, Moroi Y, Furue M. Kasabach-Merritt syndrome associated with angiosarcoma of the scalp successfully treated with chemoradiotherapy. *Acta Dermato-venereologica* 2008; 88: 193-4.
5. Bernathova M, Jaschke W, Pechlahner C, Zelger B, Bodner G. Primary angiosarcoma of the breast associated Kasabach-Merritt syndrome during pregnancy. *Breast* 2006; 15: 255-8.
6. Choi JJ, Murphey MD. Angiomatous skeletal lesions. *Seminars in Musculoskeletal Radiology* 2000; 4: 103-12.
7. Yuan SM, Hong ZJ, Chen HN, Shen WM, Zhou XJ. Kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: ultrastructural observation and immunohistochemistry staining reveal the trapping of blood components. *Ultrastructural Pathology* 2013; 37: 452-5.
8. Koyama T, Fletcher JG, Johnson CD, Kuo MS, Notohara K, Burgart LJ. Primary hepatic angiosarcoma: findings at CT and MR imaging. *Radiology* 2002; 222: 667-73.
9. Habringer S, Boekstegers A, Weiss L, Hopfinger G, Meissnitzer T, Melchardt T, Egle A, et al. Kasabach-Merritt phenomenon in hepatic angiosarcoma. *British Journal of Haematology* 2014; 167: 716-8.
10. Alliot C, Tribout B, Barrios M, Gontier MF. Angiosarcoma variant of Kasabach-Merritt syndrome. *European Journal of Gastroenterology & Hepatology* 2001; 13: 731-4.
11. Homma M, Kushima M, Saito K. An autopsy case of angiosarcoma of the liver with aggressive course. *Division of Diagnostic Pathology* 2010; 27: 110-4.
12. Kudo M, Hirasa M, Takakuwa H. A case of hepatic hemangiosarcoma associated with kasabach-merritt syndrome and intraperitoneal bleeding. *Kanzo* 2016; 25: 1605-11.
13. Saito M, Watanabe Y, Fujita M. An autopsy case of hepatic angiosarcoma associated with Kasabach-Merritt syndrome and tumor rupture. *Shindanbyouri* 2000; 17: 369-71.
14. Tsuji K, Yoshida H, Sakurai Y. A case of angiosarcoma of the liver with Kasabach-Merritt syndorome and investigated on the tumor growth, retrospectively. *Kanzo* 2001; 42: 210-16.
15. Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. *Current Opinion in Oncology* 2010; 22: 351-5.
16. Gonzalez Rodriguez FJ, Dominguez Comesana E, Portela Serra JL, Lede Fernandez A, Pinon Cimadevila MA. Urgent surgery in a Kasabach-Merrit syndrome associated with a giant hepatic angiosarcoma. *Cirugia Espanola* 2014; 92: 370-2.

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