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Case and Review

Long-Term Survival due to Chemotherapy including Paclitaxel in a Patient with Metastatic Primary Splenic Angiosarcoma

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Keywords
Angiosarcoma · Hepatic metastasis · Bone metastasis · Paclitaxel · Chemotherapy

Abstract
A primary splenic angiosarcoma is a rare type of soft tissue sarcoma and is associated with an extremely poor prognosis. In this study, we describe the case of a patient who was diagnosed with metastatic primary splenic angiosarcoma and survived for about 2 years. A 62-year-old female was referred to us for the treatment of splenic angiosarcoma with disseminated intravascular coagulation (DIC) and multiple liver and bone metastases. Paclitaxel therapy resulted in recovery from DIC and enabled her to continue sequential treatment through to sixth-line chemotherapy. We reviewed all splenic angiosarcoma case reports which were described as stage IV to date and compared with our case. From these data, we found that the median overall survival was 105 days, and the prognosis of splenic angiosarcoma of stage IV was worse than conventional case series. Splenectomy was performed in more patients than chemotherapy as a treatment. Moreover, various chemotherapeutic regimens were used. These data suggest that administering chemotherapy including paclitaxel to patients with splenic angiosarcoma might improve their prognosis.

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Introduction

Angiosarcoma is a rare form of sarcoma, accounting for <1% of visceral and soft tissue sarcomas [1]. However, the most common primary tumors of the spleen are lymphoma and angiosarcoma [2]. Splenic angiosarcoma is known to have an extremely poor prognosis due to its high metastatic rate [3]. In this study, we report the case of a patient who had primary splenic angiosarcoma with multiple metastases and survived for roughly 2 years following chemotherapy that included paclitaxel (PTX).

Case Report

A 62-year-old female visited a nearby doctor complaining of left flank and back pain 3 months prior to visiting our hospital. Laboratory data at the initial consultation showed a decreased platelet count and increased level of C-reactive protein. Moreover, splenomegaly was detected by abdominal ultrasound. Consequently, the patient was referred to another doctor. Contrast-enhanced CT revealed multiple low-density areas in the liver and spleen, and she was therefore diagnosed with liver and splenic abscesses and treated with antibiotics. However, her abdominal masses did not resolve, and a liver biopsy was subsequently performed. The liver biopsy revealed angiosarcoma (Fig. 1), so she was transferred to our hospital for further examination and treatment.

At that time, the patient showed no objective symptoms except for palpable liver of 3 fingers' breadth at the epigastric region. Laboratory data on admission showed a low platelet count, normal liver and kidney function, mildly increased C-reactive protein, and increased fibrinogen and fibrin degradation products (Table 1). Contrast-enhanced CT showed enlargement of the spleen (11 × 7 cm) with tissue replaced by irregularly shaped low-density areas. Multiple tumors, which were poorly enhanced, were evident in both lobes of the liver (Fig. 2). Pelvic MRI showed multiple metastases in the sacral and lumbar vertebrae (Fig. 3). According to these findings, the patient was diagnosed with splenic angiosarcoma with multiple liver and bone metastases, cStage IV (T2bN0M1, American Joint Committee on Cancer, Cancer Staging Manual, seventh edition). Moreover, the patient had disseminated intravascular coagulation (DIC, based on the Japanese Association for Acute Medicine criteria) [4]. Therefore, it was judged that chemotherapy should be instituted as soon as possible.

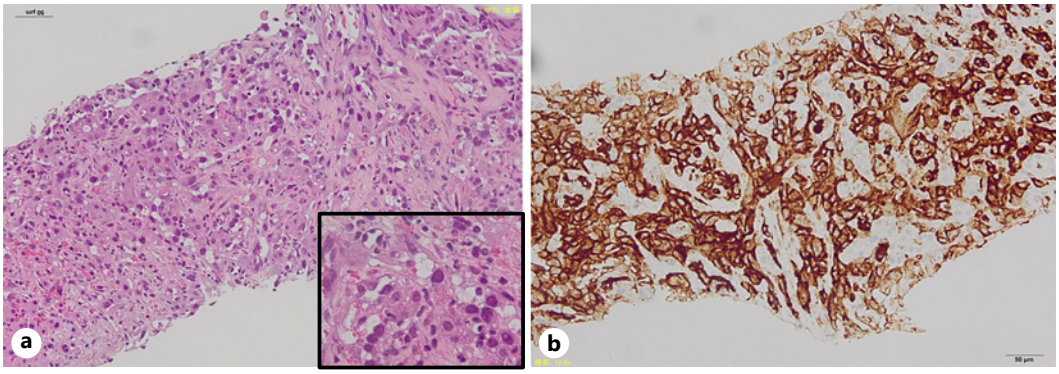

Fig. 1. Tumor tissue was acquired by biopsy of liver metastases. Microscopic examination showed that atypical cells proliferated and developed into lumen-like or slit-shaped structures with necrosis (**a**, magnification, ×126 and ×252). Immunohistochemical staining showed that atypical cells were positive for CD31 (**b**, magnification, ×126) and D2-40 (not shown). Based upon these findings, a diagnosis of angiosarcoma was reached.

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Table 1. Laboratory data on admission

Hematology			Blood chemistry			Tumor marker		
WBC	8,000	/μL	AST	15	IU/L	CEA	0.7	ng/mL
Neutro	66.2	%	ALT	9	IU/L	CA19-9	5	ng/mL
Lympho	26.0	%	LDH	284	IU/L	AFP	5	ng/mL
Mono	2.9	%	T-BIL	0.6	mg/dL	CA125	20	U/mL
Eosino	2.2	%	ALP	364	IU/L	Coagulation		
Baso	0.8	%	γ-GTP	113	IU/L			
RBC	456	$\times 10^4$/μL	CK	40	IU/L	PT	11.4	s
Hb	11.8	g/dL	TP	7.7	g/dL	PT-INR	0.96	
HCT	37.4	%	ALB	4.1	g/dL	APTT	29.1	s
MCV	82.1	fL	BUN	12	mg/dL	Fib	345	mg/dL
MCH	25.8	pg	CRE	0.53	mg/dL	AT III	132.5	%
MCHC	31.4	%	Na	144	mEq/L	FDP	42	μg/mL
PLT	6.7	$\times 10^4$/μL	K	3.8	mEq/L	D-dimer	35.7	μg/mL
Serology			Cl	105	mEq/L	TAT	14.1	ng/mL
			Ca	9.3	mEq/L	PIC	2.2	μg/mL
CRP	0.93	mg/dL	AMY	48	IU/L			
HBs Ag	(-)							
HCV Ab	(-)							

WBC, white blood cell; Neutro, neutrophil; Lympho, lymphocyte; Mono, monocyte; Eosino, eosinophil; Baso, basophil; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; PLT, platelet; CRP, C-reactive protein; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; T-Bil: total bilirubin; ALP, alkaline phosphatase; ?-GTP, gamma glutamyl transpeptidase; CK, creatine kinase; TP, total protein; ALB, albumin; BUN, urea nitrogen; CRE, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; AMY, amylase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AFP, alpha-fetoprotein; CA125, carbohydrate antigen 125; PT, prothrombin time; PT-INR, PT-international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; AT ?, antithrombin 3; FDP, fibrin and fibrinogen degradation products; D-dimer, fibrin and fibrinogen degradation products fragment D-dimer; TAT, thrombin-antithrombin 3 complex; PIC, alpha 2 plasmin inhibitor-plasmin complex.

PTX administered weekly was used as the first-line chemotherapy. Weekly PTX therapy was continued for 10 months (11 cycles). The best overall response was a partial response (reduction rate of 37%) (Fig. 2). Subsequent second-line chemotherapy consisted of doxorubicin for 4 months (6 cycles), pazopanib for 1 month, docetaxel for 4 months (6 cycles), gemcitabine plus docetaxel for 2 months (2 cycles), and ifosfamide for 2 months (2 cycles) successively. However, chemotherapy was ultimately ineffective, and the patient died of liver failure approximately 23 months after referral to our hospital.

Discussion

In this study, we report the case of a patient who had primary splenic angiosarcoma with distant metastases and survived for 23 months due to chemotherapy. Until now, the largest series of splenic angiosarcoma were reported by Li et al. [5]with 110 patients in China and

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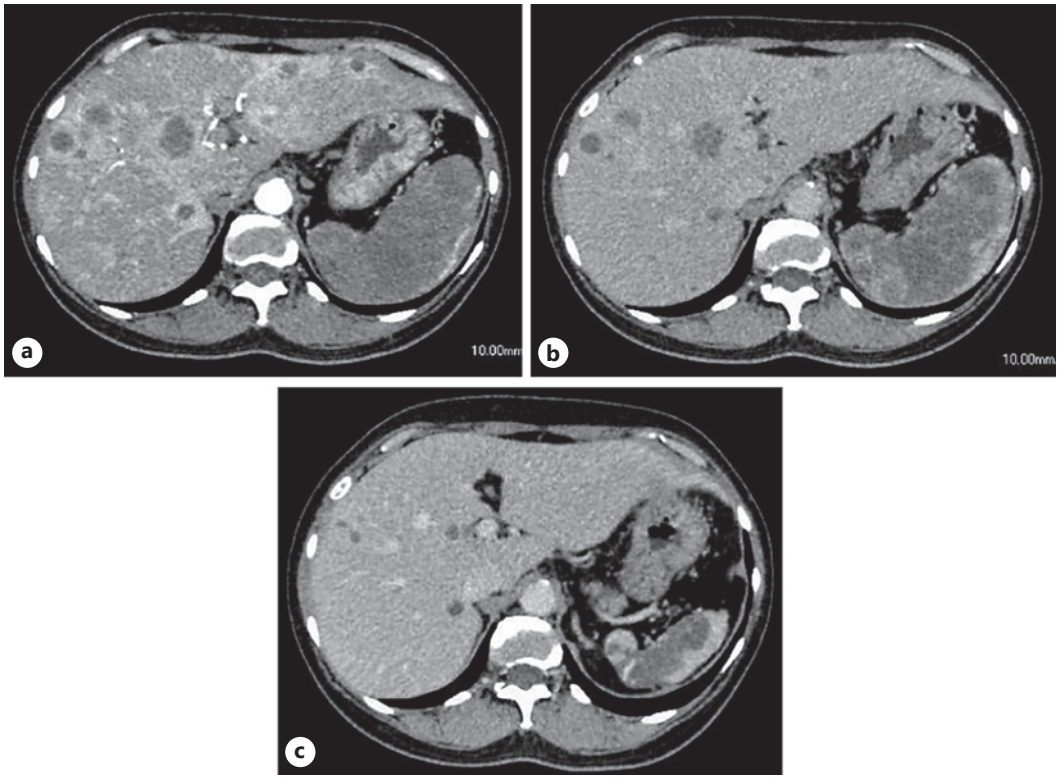

Fig. 2. An abdominal CE-CT. **a**, **b** The arterial phase and the equilibrium phase of CE-CT in the axial plane at the time of transfer to our hospital, respectively. The spleen was enlarged (11 × 7 cm) and mostly replaced by irregularly shaped low-density areas. In both lobes of the liver, there were multiple tumors which were poorly enhanced. **c** The equilibrium phase of CE-CT after chemotherapy. **b** Multiple liver metastases became markedly smaller due to treatment with 7 cycles of paclitaxel therapy compared with the size at the time of transfer to our hospital. The best overall response was a partial response (reduction rate of 37%). CE-CT, contrast-enhanced computed tomography.

Falk et al. [6] with 40 patients in the USA and Germany. Li et al. [5] retrieved the records of 110 patients with splenic angiosarcoma from the online Chinese databases (Wanfang, VIP, and CNKI) and the PubMed and Web of Science databases [5]. The 1-year survival rate was 19.1%, and the median overall survival time was 8.1 months. Age, gender, and radiation history showed no correlation with survival rate. However, by univariate analysis, the authors found that significant adverse predictors of survival were splenic rupture before surgery and large tumor size (>5 cm), while adjuvant chemotherapy was a favorable predictor. Furthermore, multivariate analysis revealed that splenic rupture and adjuvant chemotherapy were independent adverse and favorable predictors, respectively. Falk et al. [6] gathered information about 40 patients with splenic angiosarcoma from the Armed Forces Institute of Pathology (Washington, DC, USA) and the Department of Pathology, G.W. Goethe University (Frankfurt, Germany). Follow-up in 38 patients revealed that 30 (79%) were dead at a median interval of 6 months (range 0–48 months) and 8 were alive 5–21 months after diagnosis.

However, these 2 reports have a major limitation in that the stage of splenic angiosarcoma was not unified. Therefore, it is difficult to compare our case with these reports. In order to improve upon this problem, we reviewed all reports of splenic angiosarcoma cases which were stage IV on the diagnosis using PubMed (Table 2). These comprised 32 cases which occurred in patients aged 2–77 years (median 58 years); 13 males and 18 females. Eight of the 30 cases suffered splenic rupture, and none of the 27 cases experienced DIC. The metastatic

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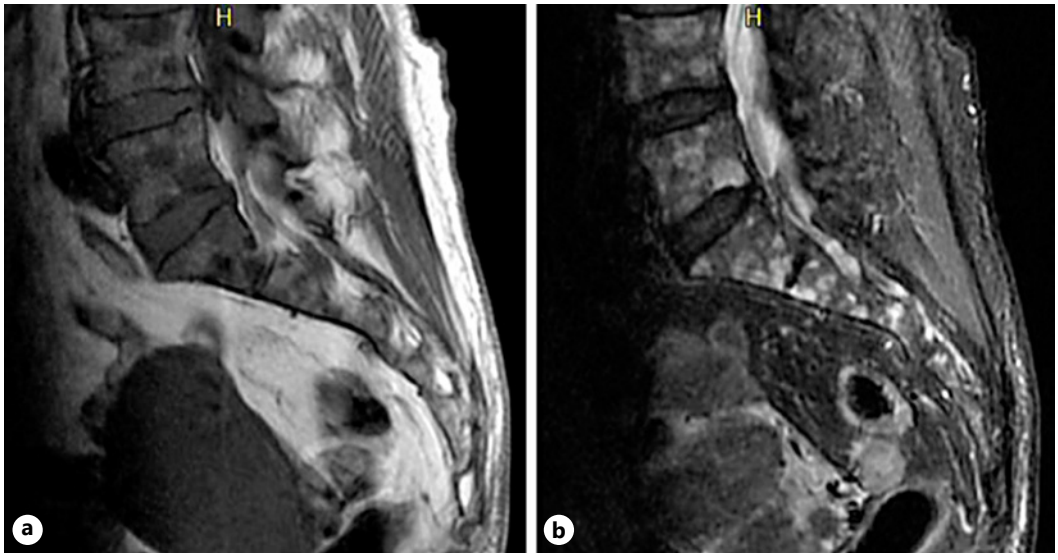

Fig. 3. A pelvic MRI at the time of transfer to our hospital. Multiple nodular abnormal signal areas with low intensity in the T1-weighed image (**a**) and high intensity in short-T1 inversion recovery images (**b**) were evident. These findings indicated that there were multiple bone metastases in the sacral and lumbar vertebrae. MRI, magnetic resonance imaging.

sites were the liver (26 cases), bone (5), lung (1), lymph node (1), bone marrow (4), and peritoneum (3). In spite of only 8 cases of splenic rupture, 22 of 26 cases had a splenectomy as not only an emergency operation but also a preventative operation. On the other hand, only 12 of 20 cases underwent chemotherapy. This is because many patients with splenic angiosarcoma are already not suitable for chemotherapy due to their poor condition at diagnosis. Only 1 patient underwent surgery after chemotherapy, but this case is thought to be a particular one. Overall survival was 1–960 days (median OS 105 days). Only 3 of 24 patients survived for >2 years, and 5 of 24 patients survived >1 year.

To compare our case with these reports, age, sex, presence/absence of splenic rupture, and metastatic site were not different. Although our case showed DIC inconsistent with these reports, it might have been difficult to evaluate DIC status using the same criteria without detailed blood tests results. As a therapy in our case, chemotherapy was chosen rather than preventative splenectomy because of the presence of multiple metastases. Prognosis in our case was considered quite good and a long-survived case compared with earlier reports of splenic angiosarcoma stage IV. With regard to the chemotherapy drugs used in these reports, these included anthracyclines, taxanes, gemcitabine, alkylating agents, pazopanib, and bevacizumab. Accordingly, there is no standardized chemotherapy regimen, and many varieties of drugs which overlap mostly with ours are administered for splenic angiosarcoma.

No effective systemic therapy for angiosarcoma with distant metastases has yet been established. National Comprehensive Cancer Network (NCCN) guidelines recommend PTX or anthracycline- or gemcitabine-based regimens as systemic therapies for angiosarcoma [7]. European Society for Medical Oncology (ESMO) guidelines for soft tissue and visceral sarcomas recommend taxane anticancer agents or gemcitabine, in combination with docetaxel if possible, as an alternative approach to the treatment of angiosarcoma. Furthermore, anthracyclines have also been recommended as the first-line chemotherapy for soft tissue sarcoma [8]. According to the Japanese Orthopaedic Association clinical practice guidelines for soft tissue sarcoma, doxorubicin and PTX are also effective for treating angiosarcoma [9].

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Table 2. Summary of case reports with a diagnosis of primary splenic angiosarcoma, stage IV

	Reference	Age	Sex	Splenic rupture	DIC	Metastatic site	Splenectomy	Chemotherapy	Prognosis
1	Sözel and Yilmaz [10]	65	M	-	-	Liver	+	na	na
2	Zhao et al. [11]	44	M	+	-	Liver	na	na	9 h
3	Plantinga et al.[12]	67	F	-	-	Liver, bone marrow	na	na	6 days
4	Sharma et al. [13]	55	F	-	-	Liver	na	na	na
5	Yang et al. [14]	N.A.	F	-	-	Liver	+	-	35 days
6	Batouli et al. [15]	45	F	-	-	Liver, peritoneum	+	PTX	5 months
7	Chen et al. [16]	72	F	-	-	Liver	+	-	4 weeks
8	Krol et al. [17]	75	F	-	na	Liver	-	na	17 days
9	Xu et al. [18]	77	F	+	na	Liver	+	-	2 weeks
10	Serrano et al. [19]	3	F	-	-	Liver	+	GEM + DOC	5 months
11	Cho et al. [20]	na	na	na	na	Liver, bone	na	na	na
12	Anoun et al. [21]	25	F	-	-	Bone marrow, lymph node	+	+ (regimen not shown)	1 year
13	Kimura et al. [22]	77	F	-	-	Liver	+	-	38 days
14	Kamocki et al. [23]	54	M	+	na	Liver	+	na	3 months
15	Kamocki et al. [23]	77	F	-	-	Liver, peritoneum	+	-	1 month
16	Badiani et al. [24]	30	M	+	-	Peritoneum	+	na	na
17	Duan et al. [25]	65	M	+	-	Liver	+	na	6 months
18	Ferreira et al. [26]	30	M	-	-	Liver	+	Anthracycline, PTX, GEM + DOC	8 months
19	Ferreira et al. [26]	57	F	-	-	Liver	-	PTX, DXR, pazopanib	>2 years
20	Chen et al. [27]	2.5	M	-	-	Liver	+	CDDP, THP-ADM, VDS, IFM, VM-26 Operation CDDP, THP-ADM, VDS, IFM, VM-26 Radiotherapy	32 months
21	Takamatsu et al. [28]	60	F	+	-	Liver	-	-	13 days
22	Yoshida et al. [29]	56	M	+	-	Liver	na	-	6 days
23	Hadidy et al. [30]	15	M	-	-	Liver	+	Bmab, CDDP, liposomal DXR, IFM	5 months
24	Raffel et al. [31]	64	F	-	-	Bone	+	PTX	4 months
25	Suzuki et al. [32]	76	F	-	-	Liver, bone marrow	+	na	na
26	den Hoed et al. [33]	2	F	+	-	Liver	+	IFM, VCR, ACT-D	>2 years
27	Vaiphei et al. [34]	48	M	-	-	Liver, bone marrow	-	-	A few days
28	Karakas et al. [35]	63	F	-	-	Lung, bone	+	CPA, VCR, EPI	>1 year
29	Çermik et al. [36]	70	F	-	-	Bone	+	na	na
30	Hai et al. [37]	59	M	-	-	Liver	+	Anthracycline, taxane	na
31	Oztürk et al. [38]	49	M	na	na	Liver	na	na	na
32	Smith et al. [39]	63	M	-	-	Bone	+	CPA, DXR, MTX	13 months

DIC, disseminated intravascular coagulation; M, male; na, not available; F, female; PTX, paclitaxel; GEM, gemcitabine; DOC, docetaxel; DXR, doxorubicine; IFM, ifosfamide; CDDP, cisplatin; THP-ADM, pirarubicin; VDS, vindesine; Bmab, bevacizumab; CPA, cyclophosphamide; VCR, vincristine; ACT-D, actinomycin D; EPI, epirubicin; MTX, methotrexate.

PTX is a promising drug for the first-line therapy of angiosarcoma, and it had a therapeutic effect when given to our patient, resulting in a partial response. Our patient was thought to have a poor prognosis because of DIC and multiple liver and bone metastases at the time of transfer to our hospital. However, PTX therapy led to recovery from DIC and enabled the patient to proceed to additional systemic therapies. Subsequent therapy for angiosarcoma

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in this case consisted of a sequential regimen of anthracycline, a multikinase inhibitor for vascular endothelial growth factor receptors and platelet-derived growth factor receptors, and docetaxel combined with gemcitabine and ifosfamide, in accordance with NCCN and ESMO guidelines. It was very rare for a patient to survive for 23 months regardless of advanced stage of splenic angiosarcoma, but survival was improved in this case owing to aggressive chemotherapies.

Conclusion

Herein, we reported the case of a patient who had splenic angiosarcoma with distant metastases who had a long survival time due to the use of aggressive chemotherapies including PTX.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Tokushima University Hospital, Approval No. 3095. Written informed consent for publication was obtained from the patient's husband.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no funding sources.

Author Contributions

Hiroshi Miyamoto wrote this manuscript, and all other authors equally contributed to the patient's medical treatment and diagnosis.

Data Availability Statement

All data generated or analyzed during this study are included in this article or its online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000519211). Further enquiries can be directed to the corresponding author.

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