

[ CASE REPORT ]

## Dramatic Recovery from Cardiovascular Collapse: Paclitaxel as an Urgent Treatment for Primary Cardiac Angiosarcoma

Toshio Suzuki<sup>1</sup>, Yoshiyuki Yamamoto<sup>1,2</sup>, Noriaki Sakamoto<sup>3</sup>, Hideo Suzuki<sup>1,2</sup>, Kazuko Tajiri<sup>4</sup>,  
Tomoko Ishizu<sup>4</sup>, Yasuhiro Fujisawa<sup>5</sup>, Masayuki Noguchi<sup>3</sup>, Masaki Ieda<sup>4</sup>,  
Yuji Hiramatsu<sup>6</sup> and Ikuo Sekine<sup>1</sup>

### Abstract:

We herein report three patients with cardiac angiosarcoma who were directly admitted to the intensive-care unit for hemodynamic instability with circulatory collapse. Using a multidisciplinary cardio-oncologic approach, we diagnosed their condition as angiosarcoma by an invasive biopsy and urgently started weekly paclitaxel administration despite their poor performance status. Their vital signs were soon stabilized, leading to the patients' discharge from the hospital. Although no treatment guidelines for cardiac angiosarcoma have been established, chemotherapy with paclitaxel can be an option for cases presenting with hemodynamic instability.

**Key words:** cardiac angiosarcoma, paclitaxel, chemotherapy, rare malignant tumor, hemodynamic instability, cardio-oncology

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### Introduction

Angiosarcoma arises from atypical vascular endothelial cells growing along pre-existing vascular channels, sinusoidal or cavernous spaces throughout the body (1). The most common phenotype is a cutaneous one, accounting for about half of all cases (2). Deep soft tissues account for only 10% of the origination of all angiosarcomas, and even rarer sources of origin include parenchymal organs, such as the breast, bone, spleen, liver and heart (1, 3, 4). Among these, cardiac angiosarcoma is extremely rare with a poor prognosis.

Primary cardiac angiosarcoma is the most aggressive form of angiosarcoma, showing a rapid and infiltrating growth into the myocardial wall and heart chambers (5-7). It usually

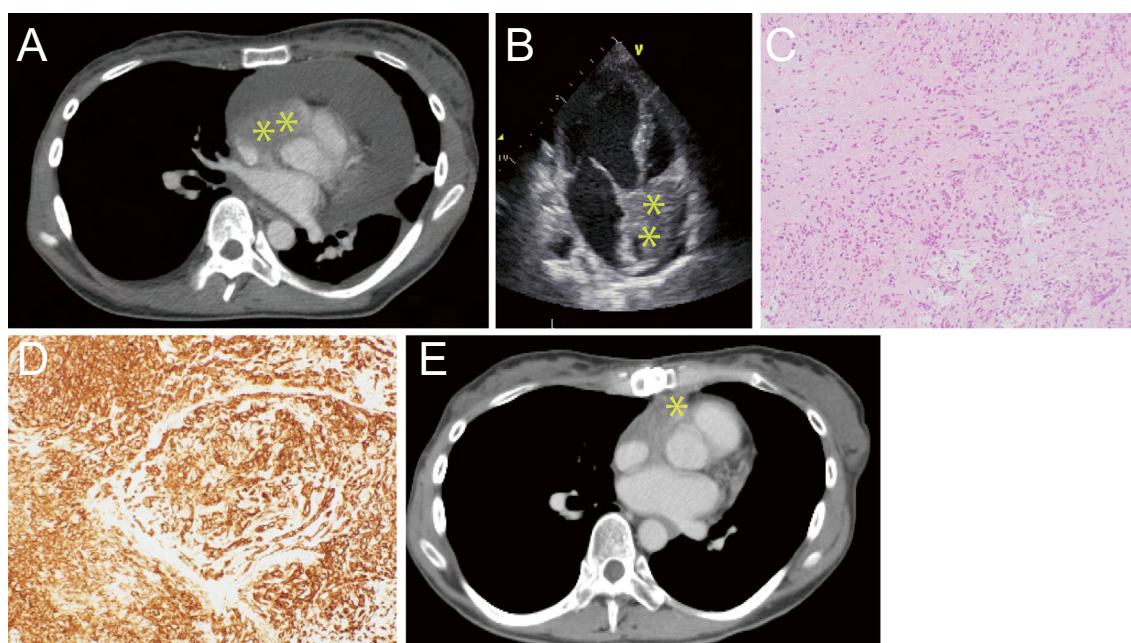
remains clinically silent until the tumor obstructs the intracardial blood flow or induces cardiac tamponade. However, once the symptoms become apparent, the tumor may cause sudden death by hemodynamic instability with circulatory collapse. Even though the tumor is localized, many patients lose the opportunity to receive surgical intervention because it may carry very high risks (8). For these patients, chemotherapy remains the only active treatment that can combat an otherwise fatal prognosis. However, due to the rarity of this condition, we have found no evidence supporting the use of specific regimens for these patients. There are no studies showing whether or not chemotherapy can be safely administered and resolve the hemodynamic instability in these patients.

We herein report three consecutive cases of right atrium cardiac angiosarcoma diagnosed in advanced stage with ex-

<sup>1</sup>Department of Medical Oncology, Faculty of Medicine, University of Tsukuba, Japan, <sup>2</sup>Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Japan, <sup>3</sup>Department of Diagnostic Pathology, Faculty of Medicine, University of Tsukuba, Japan, <sup>4</sup>Department of Cardiology, Faculty of Medicine, University of Tsukuba, Japan, <sup>5</sup>Department of Dermatology, Faculty of Medicine, University of Tsukuba, Japan and <sup>6</sup>Department of Cardiovascular Surgery, Faculty of Medicine, University of Tsukuba, Japan

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Correspondence to Dr. Yoshiyuki Yamamoto, y-yamamoto@md.tsukuba.ac.jp



**Figure 1.** (A) Chest computed tomography showing massive pericardial effusion and a mass on the right atrium wall. (B) Transthoracic echocardiography after pericardial drainage showing a right atrial mass. (C) Histology of a biopsy sample from the cardiac tumor (Hematoxylin and Eosin staining: original  $\times 200$ ). (D) Histology of a biopsy sample from the cardiac tumor (CD31 immunohistochemical staining: original  $\times 200$ ). (E) Chest computed tomography showing a significant volume reduction of the pericardial effusion and right atrial mass six months after the initial paclitaxel treatment.

tremely unstable vital signs. The patients were all urgently hospitalized in the intensive-care unit (ICU). A multi-disciplinary team comprised of clinical oncologists, cardiologists and cardiovascular surgeons established prompt histological diagnoses by invasive biopsies. Despite the patients' poor performance status (PS), we urgently initiated paclitaxel chemotherapy. They all responded well, with a dramatic decrease in tumor size and an improved PS. As a result, chemotherapy resolved their cardiac emergency and led to their discharge.

## Case Reports

### Case 1

A 39-year-old woman was referred to our hospital with chest pain, dyspnea and recurrent vomiting that had persisted for one month.

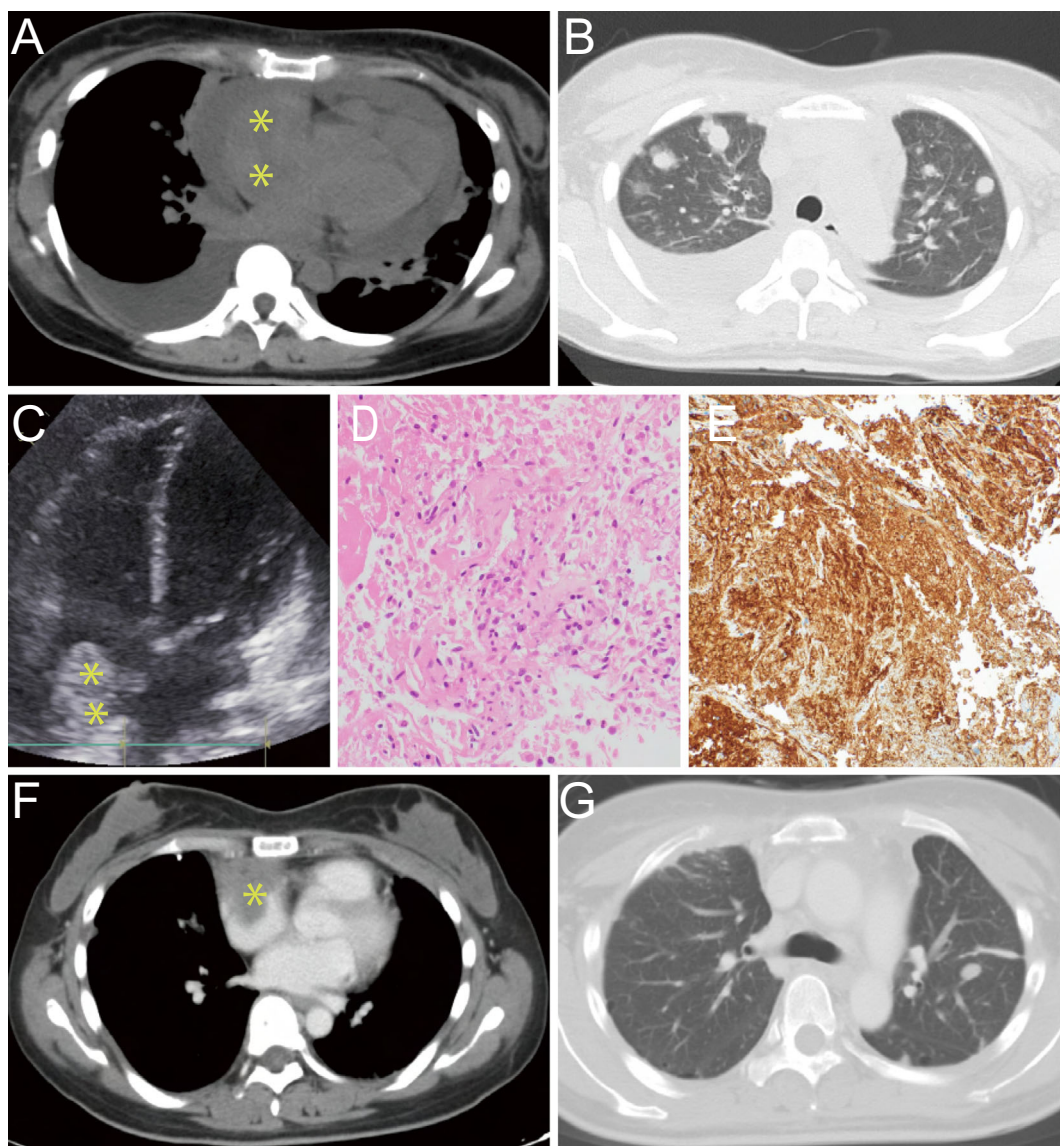
A physical examination on admission showed an Eastern Cooperative Oncology Group (ECOG) PS of 4, blood pressure 82/62 mm Hg, heart rate 127 bpm with pulsus paradoxus, distended jugular veins, and orthopnea. Computed tomography (CT) of the chest (Fig. 1A) and transthoracic echocardiography (Fig. 1B) revealed a broad base right atrium space-occupying lesion (maximum diameter: 65 mm), pericardial dissemination, massive pericardial effusion, and congestive liver, showing cardiac tamponade (Fig. 1A) without any other metastasis. Since pericardiocentesis failed to

control the cardiac tamponade and the cytology of the effusion was negative for malignancy, open surgical drainage and a biopsy were performed immediately. The tumor morphology showed spindle cell (sarcomatoid) proliferation and a focal vascular structure. The tumor was positive for endothelial markers (CD31 and CD34) and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and negative for CD20, CD3, thyroid transcription factor-1 (TTF-1), carcinoembryonic antigen (CEA) and CD68, which established the histological diagnosis of angiosarcoma (Fig. 1C, D). Since surgical removal was considered difficult, we started weekly paclitaxel treatment [100 mg/m<sup>2</sup> body surface area (BSA), on days 1, 8, 15, 22, 29 and 36 of a 7-week cycle, as approved in Japan]. As a result, the vital signs became normal as the pericardial effusion disappeared within 7 days.

The patient was discharged from the hospital the next month (ECOG-PS of 1) and completed the chemotherapy regimen in the outpatient clinic. Even though she achieved partial response of the tumor (Fig. 1E: 15 mm), she died of her disease 14.3 months after the first paclitaxel administration, despite paclitaxel rechallenge and second-line trabectedin.

### Case 2

A 39-year-old woman complained of dyspnea for 1 month and chest pain for 2 weeks. Upon arrival at the hospital, her ECOG-PS was 4, and she was in shock with a systolic blood pressure of 70 mm Hg and a heart rate of 130 bpm.



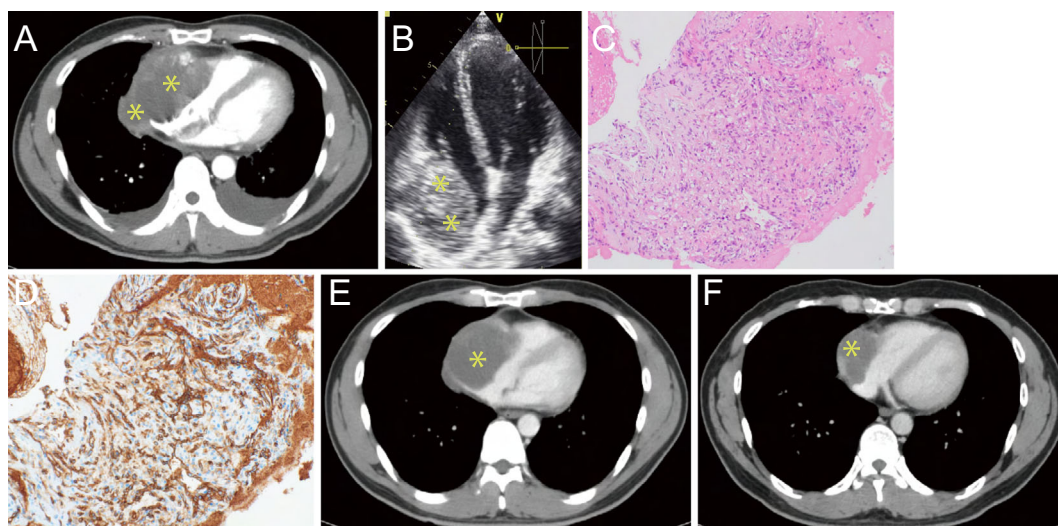
**Figure 2.** (A, B) Chest computed tomography showing massive pericardial effusion and a mass on the right atrium wall (A) along with multiple metastatic pulmonary tumors (B). (C) Transthoracic echocardiography after cardiocentesis showing right atrial mass. (D) Histology of a biopsy sample from the cardiac tumor (Hematoxylin and Eosin staining; original  $\times 200$ ). (E) Histology of a biopsy sample from the cardiac tumor (CD31 immunohistochemical staining; original  $\times 200$ ). (F, G) Chest computed tomography showing a significant volume reduction of the pericardial effusion and right atrial mass (F) as well as of the pulmonary metastasis. (G) the month after the initiation of the paclitaxel treatment.

CT (Fig. 2A, B) and transthoracic echocardiography (Fig. 2C) revealed a 58-mm mass in the right atrium (Fig. 2A, C) with massive pericardial effusion (Fig. 2A), multiple nodules in both lungs with bilateral pleural effusion (Fig. 2B), and multiple nodules in the liver. Due to her critical condition, she was directly transferred to the ICU. Percutaneous aspiration of the pericardial and right pleural effusions contributed to the transient resolution of the vital instability, but both reappeared within two days, along with cardiac tamponade. Cytology examinations of the pericardial and pleural effusions were negative for malignancy. A subsequent endocardial biopsy showed tumor cells negative for pan-cytokeratin but positive for CD31 and CD34

(Fig. 2C, D), and we diagnosed this case as cardiac angiosarcoma.

With weekly paclitaxel treatment ( $100 \text{ mg/m}^2$  BSA), the refractory pericardial effusion and the cardiac tamponade disappeared within 7 days, and the patient was discharged from the hospital (ECOG-PS of 1). CT performed the following month confirmed a partial response (Fig. 2E: 40 mm, Fig. 2F). After disease progression, second-line trabectedin and subsequent eribulin treatment were not effective, and the patient ultimately died 7.5 months after the first administration of paclitaxel.





**Figure 3.** (A) Chest computed tomography showing a massive mass on the right atrium wall. (B) Transthoracic echocardiography after cardiocentesis showing suspected blood-flow obstruction in the right atrium. (C) Histology of a biopsy sample from the cardiac tumor (Hematoxylin and Eosin staining: original  $\times 200$ ). (D) Histology of a biopsy sample from the cardiac tumor (CD31 immunohistochemical staining: original  $\times 200$ ). (E) Chest computed tomography showing a significant volume reduction of the right atrial mass the month after the initiation of the paclitaxel treatment. (F) Chest computed tomography at six months after the initial paclitaxel treatment showing more tumor size reduction than in (E).

### Case 3

A 38-year-old man presented to the emergency room with rapidly progressing chest pain and nausea, with an ECOG-PS of 4. He was found to be in deep shock, with a systolic blood pressure of 70 mm Hg and a heart rate of 120 bpm. Laboratory tests revealed only an elevated C-reactive protein (CRP: 24.6 mg/dL); all other results were within the normal range, including brain natriuretic peptide, creatine kinase and troponin T. CT showed cardiac tamponade and a right atrium mass (Fig. 3A: 100 mm) as well as multiple bone metastases. Transthoracic echocardiography after cardiocentesis revealed suspected blood-flow obstruction in the right atrium (Fig. 3B). We made a diagnosis of cardiac angiosarcoma by a biopsy of the right atrial mass via right heart catheterization (Fig. 3C, D).

The immunohistochemistry results were as follows: CD31 (Fig. 3D), CD34 and  $\alpha$ -SMA were positive, and CD68 was negative. After the cardiovascular surgeons decided that total surgical resection was impossible, chemotherapy with weekly paclitaxel (100 mg/m<sup>2</sup> BSA) was initiated. The treatment was well tolerated, and the vital signs soon stabilized. Chest CT performed the following month revealed significant regression of the tumor (Fig. 3E: 78 mm). Amazingly, the CRP levels rapidly improved to almost the normal range (0.60 mg/dL) by 7 days after paclitaxel initiation. He was discharged from the hospital (ECOG-PS of 1) and continued the chemotherapy in the outpatient clinic. At the time of this manuscript preparation, the patient is continuing the treatment with a partial response for 6 months (Fig. 3F: 55 mm).

### Discussion

We described here three cardiac angiosarcoma patients who were urgently admitted to the ICU due to refractory cardiac tamponade and quickly diagnosed by a multidisciplinary team comprising clinical oncologists, cardiologists, and cardiovascular surgeons. Although chemotherapy is generally not indicated in patients with a poor PS, we decided to administer weekly paclitaxel treatment, considering the efficacy of this regimen for angiosarcoma of other origin, toxicity of weekly paclitaxel, and the patients' devastating conditions, as all of them would have died within a few weeks if we had chosen best supportive care. All our patients quickly recovered following the initiation of the weekly paclitaxel chemotherapy. Our experience indicates that the weekly paclitaxel regimen is well tolerated for adverse events, including myelosuppression, and is therefore suitable for patients with a poor PS.

Treatment options for extra-cardiac angiosarcoma include surgical resection, radiation therapy and chemotherapy (9). However, in most cases of cardiac angiosarcoma, surgical resection is not an option, as patients are usually admitted to the hospital in the late stages of the disease. In addition, the beating heart and respiratory movements make it difficult for the radiation beam aimed at the tumor to avoid irradiating normal heart tissue. Thus, chemotherapy remains the best option for unresectable situations. For resectable cases, surgical resection combined with chemotherapy and local radiotherapy might be useful. Fukunaga et al. recently reported a three-year survival in a patient with primary cardiac

angiosarcoma, who received surgical resection followed by chemoradiotherapy (10).

Thus far, there are no established chemotherapy guidelines for cardiac angiosarcoma. Anthracyclines with or without ifosfamide have been used for extra-cardiac angiosarcomas as a first-line chemotherapy (11). However, for patients with heart failure caused by cardiac angiosarcoma, anthracyclines are not indicated due to their cardiac toxicity (12). Similarly, due to the hepatic toxicity, trabectedin, a second-line drug for sarcoma, is not recommended for patients with cardiac tamponade or blood-flow obstruction in the right atrium followed by severe hepatic congestion. In addition to their anti-tumor activity by suppressing tubulin elongation (13), taxanes work as angiogenesis inhibitors (14), which may explain the rapid response in cases of angiosarcoma. Although taxanes have been reported to be effective against angiosarcomas (13, 15, 16), no randomized control trials evaluating their efficacy against cardiac angiosarcomas have been conducted. The famous prospective multicentric phase II clinical trial for metastatic or locally advanced angiosarcoma, ANGIOTAX, established the efficacy of weekly paclitaxel treatment, reporting an overall response rate of 18.5% at 2 months, median time to progression of 4 months and overall survival of 7.6 months (16). However, this study did not include cardiac angiosarcomas. The efficacy of this regimen may vary among the rare types of angiosarcomas, especially in the most aggressive histotype, cardiac angiosarcomas.

Another approach targeting angiogenesis is the blockade of the vascular endothelial growth factor (VEGF)/receptor (VEGFR) pathway, which may be an attractive alternative regimen (17, 18). Activation of the VEGF-angiogenesis pathway drives tumor formation of angiosarcoma (19). Pazopanib, a multi-kinase inhibitor active against VEGFR1, VEGFR-2 and VEGFR-3 is currently a treatment option for angiosarcomas (20). However, there are no prospective studies yet regarding its activity against angiosarcoma.

In conclusion, the outcomes of these three cases of cardiac angiosarcoma suggest that paclitaxel treatment following a challenging invasive biopsy is a promising treatment strategy despite a poor PS if surgical resection is technically difficult. These three experiences should encourage clinicians to break free of the medical myth that chemotherapy is not beneficial in patients with a poor PS. Further multi-institutional retrospective studies and prospective clinical trials in cooperation with cardiologists and oncologists need to be conducted.

**The authors state that they have no Conflict of Interest (COI).**

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