

# Comprehensive treatment of unresectable cardiac angiosarcoma: A case report and review of literature

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**Abstract.** Cardiac angiosarcoma is a rare but lethal tumor that is difficult to diagnose and treat, due to its rapid local relapse and high incidence of systemic metastasis. The prognosis of cardiac angiosarcoma is dismal, with a mean life expectancy of only a few months. We herein report a case of unresectable angiosarcoma arising from the right atrium. The patient received first-line chemotherapy with weekly paclitaxel, and second-line therapy with vinorelbine and bevacizumab upon disease progression. The progression-free survival was 6 months and the overall survival was 7 months. The patient eventually succumbed to respiratory failure. A study of the present case and a review of the relevant literature suggest that treatment decisions for unresectable locally advanced or metastatic cardiac angiosarcoma are difficult, as the published literature on this disease mainly consists of case reports without sufficient data. Therefore, further clinical trials specific to the treatment of unresectable cardiac angiosarcoma are warranted.

## Introduction

Primary cardiac neoplasms are rare, with an incidence of ~0.2%. Primary cardiac angiosarcoma (PCA) comprises 2% of all primary cardiac neoplasms (including benign tumors) and is the most common primary malignant cardiac tumor (1,2). PCA typically presents between the third and fifth decades of life, most often arising in the right atrium (RA) and infiltrating the pericardium, which may cause right-sided heart failure or tamponade, usually with superimposed systemic signs, such as fever, night sweats, chills, fatigue and weight loss. Pericardiocentesis yields bloody fluid that often does not

contain malignant cells, even when the tumor cells have invaded the pericardium (3). Diagnostic assessment includes tissue biopsy followed by histological confirmation, transthoracic echocardiography (TTE) to determine the tumor dimensions, pericardial status and cardiac function, computed tomography (CT) imaging to exclude metastatic disease, magnetic resonance imaging (MRI) to depict the extracardiac extent of the disease and delineate the extent of the primary lesion; positron emission tomography (PET) imaging may also be useful for detecting metastases when radical surgery is planned (2,4). However, even radical surgery often yields unsatisfactory results, as >90% of the patients succumb to the disease within 1 year (5). Comprehensive treatment includes neoadjuvant or adjuvant chemotherapy, radiotherapy or targeted therapy with complete surgical resection; even orthotopic heart transplantation may prove beneficial for the patients (6). We herein report a case of unresectable PCA originating in the RA. The patient received first-line chemotherapy with weekly paclitaxel, and second-line therapy with vinorelbine and bevacizumab when the disease progressed. The relevant literature was also reviewed, to compare and summarize the treatment of unresectable locally advanced or metastatic PCA.

## Case report

In June 2015, a healthy 41-year-old Chinese woman complained of a 2-month progressive shortness of breath and chest discomfort for no apparent reason, which was relieved by rest. There was no precordialgia, no radiating back pain, no headache or dizziness, and no edema in the lower extremities. The previous medical history revealed that the patient had presented with unexplained pericardial effusion and underwent pericardiocentesis; however, analysis of the pericardial fluid failed to determine the etiology. On auscultation, there were no heart murmurs or lung rales, with the exception of a pericardial rub. The results of the laboratory tests were as follows: Carbohydrate antigen (CA)125 435.70 U/ml (normal, <35.00 U/ml), CA199 12.70 U/ml (normal, <35.00 U/ml), carcinoembryonic antigen (CEA) 1.69 ng/ml (normal, <5.00 ng/ml) and neuron-specific enolase 32.51 ng/ml (normal, <17.00 ng/ml). TTE revealed a large mass (6.7x3.7 cm), originating from the free wall of the RA, of which the lower part entered the right ventricle (RV) during diastole (Fig. 1A), accompanied by a massive pericardial effusion. Chest X-ray

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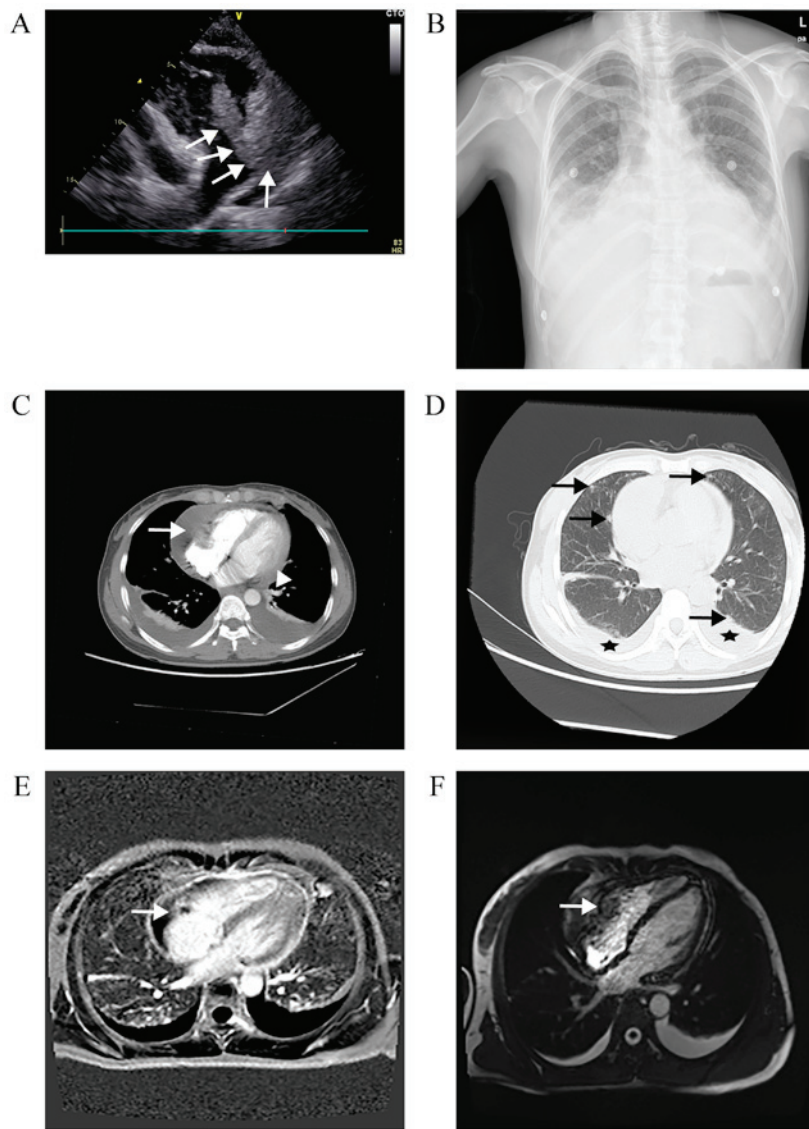


Figure 1. Imaging examinations. (A) Echocardiography demonstrated a dense lobed structure at the free wall of RA (arrows). (B) Chest X-ray revealed increased cardiothoracic ratio and costophrenic angle blunting. (C and D) Computed tomography revealed an inhomogeneous irregularly shaped mass infiltrating the RA (white arrow) and scattered pulmonary nodules (black arrows), pericardial effusion (white arrowhead) and bilateral pleural effusion (black asterisks). (E) Magnetic resonance imaging scan revealed that the tumor (arrow) had an isointense to high-intensity signal on T1-weighted images and (F) an isointense to low-intensity signal on T2-weighted images (white arrows). RA, right atrium.

revealed expansion of the heart shadow (cardiothoracic ratio, 70%) and bilateral pleural effusion (blunting of the bilateral costophrenic angle; Fig. 1B). A CT scan confirmed the presence of a heterogeneous irregularly shaped mass infiltrating the RA, and also detected bilateral pulmonary nodules (Fig. 1C and D). On MRI, the mass exhibited heterogeneous signal intensity enhancement on T1-weighted images, and flow void on T2-weighted images (Fig. 1E and F). The  $^{18}\text{F}$ -fluorodeoxyglucose uptake in the tumor reached a standardized uptake value of 13.6 (Fig. 2B). PET-CT also revealed tumor metastasis to multiple organs, including the lungs and bones (Fig. 2A and C-G). CT-guided percutaneous biopsy of a left ilium metastasis revealed poorly differentiated spindle-shaped tumor cells with slit-like or irregular vascular channels containing red blood cells (RBCs; hematoxylin and eosin staining; magnification, x400). Immunohistochemically, the tumor cells were positive for CD31 and CD34 (magnification, x400; Fig. 3). Taken together, these findings confirmed the diagnosis of metastatic PCA (T2N1M1).

Although the patient's performance status score was 1 on the Eastern Cooperative Oncology Group scale, the tumor had metastasized to other internal organs and total excision of the cardiac tumor was anatomically impossible. Therefore, 90 mg/m<sup>2</sup> paclitaxel was administered intravenously on days 1, 8 and 15 of a 28-day cycle. Prior to the administration of paclitaxel, the patient received intravenous premedications, including dexamethasone 5 mg, cimetidine 400 mg and phenergan 25 mg. Standard antiemetics (mainly palonosetron 0.25 mg) were prescribed by the treating physician when clinically indicated. Cycles could not be initiated unless the granulocyte count was  $>1500/\mu\text{l}$  and the platelets were  $>100,000/\mu\text{l}$ . The treatment was well-tolerated by the patient, except for grade II neutropenia (white blood cells  $2.41 \times 10^9/\text{l}$ , neutrophils  $1.06 \times 10^9/\text{l}$ ) and prophylactic granulocyte colony-stimulating factor was administered at 150  $\mu\text{g}$ . In December 2015, TTE revealed a shrinkage in the cardiac tumor size (1.5x1.1 cm) and absorption of the pericardial effusion. A CT scan,

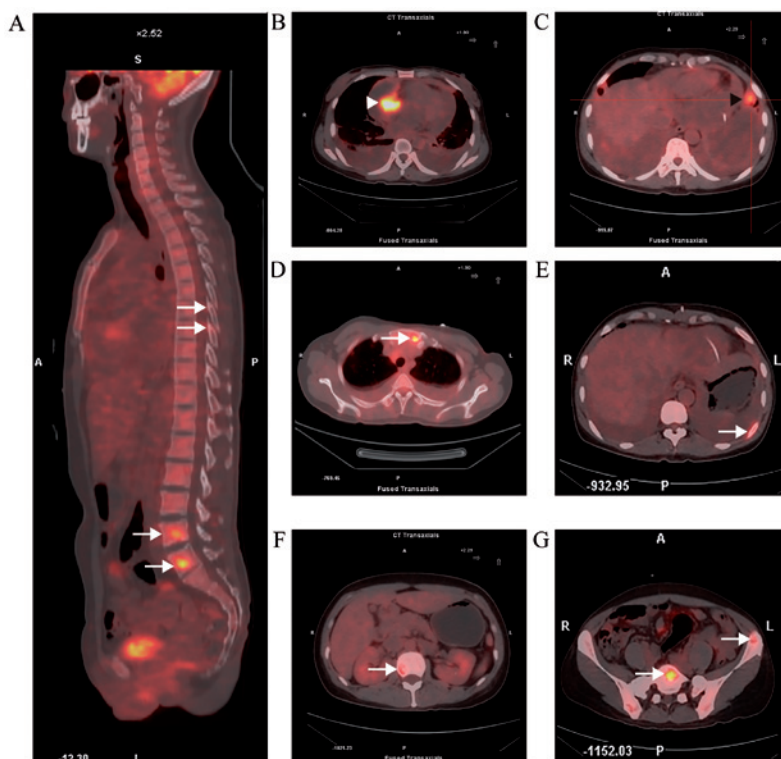


Figure 2. Positron emission tomography-computed tomography demonstrated multiple foci of abnormal activity in different organs and in the bones, including (A) the thoracic and lumbar vertebrae (white arrows), (B) heart (white arrowhead), (C) lung (black arrowhead), sacrum, ilium, (D) manubrium sterni (white arrow), (E) ribs (white arrow), (F) lumbar vertebrae (white arrow) and (G) sacrum and ilium (white arrow).

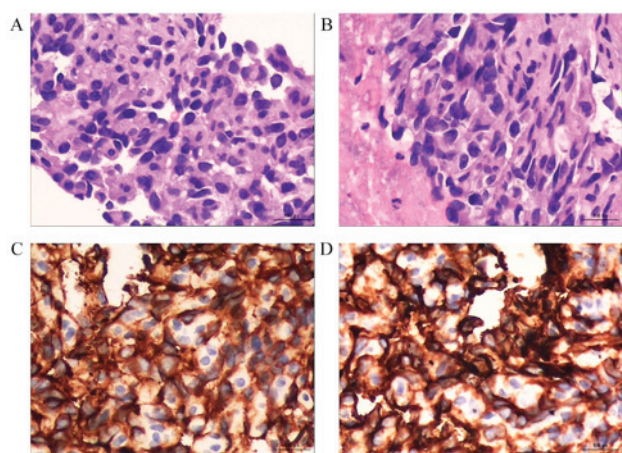


Figure 3. Pathological examination. (A and B) Hematoxylin and eosin stain (magnification, x400) of the biopsy specimen revealed poorly differentiated spindle-shaped tumor cells with slit-like or irregular vascular channels containing erythrocytes; (C) Immunohistochemical staining for CD31 revealed positive endothelial cells (magnification, x400); (D) Immunohistochemical staining for CD34 revealed positive endothelial cells (magnification, x400).

however, revealed that the volume of the pulmonary nodules had increased and identified new foci in the liver (Fig. 4). On laboratory tests the CA125 level was 19.00 U/ml, the CA199 level was 37.60 U/ml and the CEA level was 8.13 ng/ml. Therefore, vinorelbine was selected as second-line treatment, with 25 mg/m<sup>2</sup> vinorelbine administered intravenously on days 1 and 8 of a 21-day cycle. In December 24, bevacizumab was added to the therapy scheme (vinorelbine 25 mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle following administration of

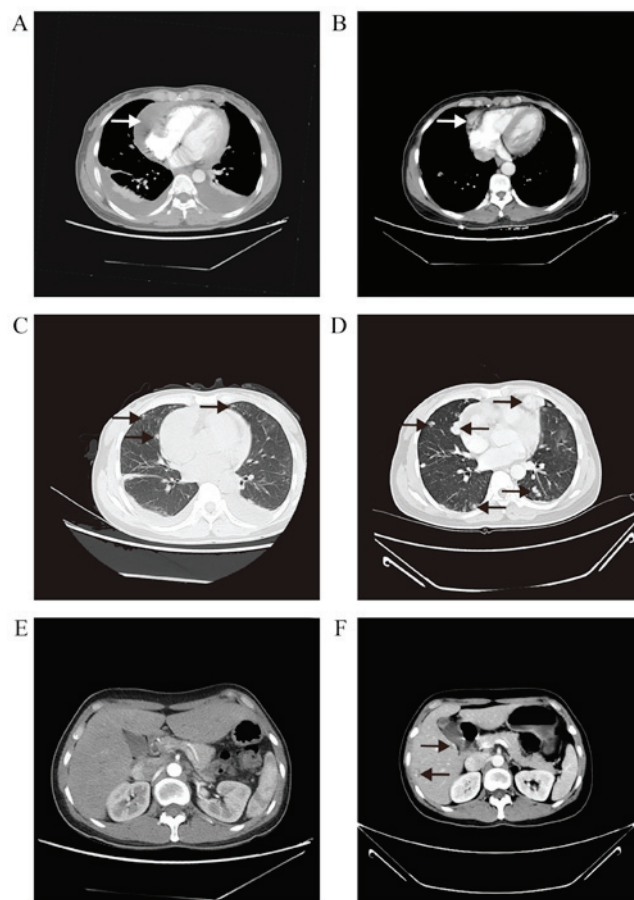


Figure 4. (A, C and E) Computed tomography scan of the heart (white arrow), lung and liver (black arrows) before treatment with weekly paclitaxel and (B, D and F) after the treatment.



Table I. Cases of unresectable cardiac angiosarcoma reported in the English literature identified through a PubMed search.

First author, year	Location	Pericardial extension	Treatment	Outcome (months)	(Refs.)
Ram Prabu, 2011	RA	Yes	Weekly paclitaxel (80 mg/m <sup>2</sup> )	PFS 16 <sup>a</sup>	(5)
Suderman, 2011	LA	Yes	Weekly docetaxel (25 mg/m <sup>2</sup> ) and radiotherapy	PFS 16, OS 22	(7)
Kodali, 2006	RA	Yes	Doxil 40-50 mg/m <sup>2</sup> q/4 weeks (line 1), MAID regimen <sup>b</sup> (line 2)	PFS 15, OS 16	(8)
Hata, 2011	RA	No	CRT (30 fractions of 2 Gy) with weekly carboplatin (area under the curve=2) and PTX (60 mg/m <sup>2</sup> )	PFS 5 <sup>a</sup>	(9)
Franceschini, 2013	RA	Yes	Epirubicin (60 mg/m <sup>2</sup> ), ifosfamide (3,000 mg/m <sup>2</sup> ) and radiotherapy 60 Gy	PFS 16 <sup>a</sup>	(10)
Fehr, 2010	RA	No	Doxorubicin (75 mg/m <sup>2</sup> ) and ifosfamide (7,500 mg/m <sup>2</sup> ) q/3 weeks (line 1), radiotherapy (22 fractions of 2 Gy) and weekly paclitaxel (80 mg/m <sup>2</sup> ) (line 2)	PFS 8.5, OS 12	(11)
Castilla, 2010	RA	No	Paclitaxel <sup>c</sup>	OS 9	(12)
Batzios, 2006	RV	No	Epirubicin 75 mg/m <sup>2</sup> , cisplatin 80 mg/m <sup>2</sup> and ifosfamide 2 gr/m <sup>2</sup> , plus uromitexan 800 mgx2		(13)
Aoka, 2004	RA	Yes	Trastuzumab 150 mg once weekly and imatinib 400 mg	PFS 6, OS 7	
Elsayad, 2016	RA	No	Carbon-ion radiotherapy 64 Gy and interleukin 2	PFS 5, OS 18 <sup>a</sup>	(14)
			Radiotherapy 55.8 Gy and weekly paclitaxel (50 mg/m <sup>2</sup> ) (line 1), doxorubicin and ifosfamide <sup>c</sup> (line 2) and pazopanib (maintenance therapy)	PFS 3, OS 16 <sup>a</sup>	(15,16)

<sup>a</sup>Time to data published. <sup>b</sup>MAID regimen: Mesna, adriamycin, ifosfamide and dacarbazine. <sup>c</sup>No detailed content on the treatment. OS, overall survival; PFS, progression-free survival; RA, right atrium; RV, right ventricle; LA, left atrium; CRT, chemoradiotherapy; PTX, paclitaxel.

bevacizumab 10 mg/kg on day 1). The patient complained of abdominal pain; thus, Oxycontin was administered at 30 mg/12 h to control the symptom. On January 8, 2016, the patient displayed anemia and respiratory failure (hemoglobin 56 g/l, RBC count  $2.16 \times 10^{12}$ , PaO<sub>2</sub> 9.18 kPa, PaCO<sub>2</sub> 4.63 kPa, SpO<sub>2</sub> 91.5%, actual base excess 18.9 mmol/l, standard base excess 19.4 mmol/l, D-dimer 40.00 mg/l, and fibrin degradation products 128.1 mg/l) and was unable to tolerate the chemotherapy; thus, a blood transfusion was performed, with oxygen inhalation and diprophyllyline injection. The patient succumbed to respiratory failure 7 months after diagnosis.

## Discussion

Due to the rapid local relapse and high incidence of systemic metastasis, PCA has a dismal prognosis, with a mean life expectancy of only a few months. The literature focusing on the treatment of unresectable PCA was reviewed. Although the relevant studies were scarce, several case reports and

results from phase II trials expanded our knowledge of this rare disease. A summary of most common locations, treatment modalities and outcome is presented in Table I. The cases included in the Table I were almost inoperable, which was undoubtedly among the key factors determining the patients' prognosis. Although there are currently no established guidelines for the treatment of angiosarcoma, no further subgroups have been identified by which adjuvant therapy could be recommended; as previously reported, chemotherapy, radiotherapy and targeted therapy are the most common choices for the treatment of unresectable PCA. In the present case, addition of radiotherapy to the second-line treatment was initially attempted, as several cases of PCA exhibited high sensitivity to radiotherapy (14-16); however, due to the patient's poor physical condition, radiotherapy had to be abandoned. Weekly paclitaxel has been reported to be effective in the treatment of unresectable angiosarcomas (including PCA), with a median progression-free survival (PFS) of 4 months and a median overall survival of 8 months (17). Vinorelbine

has demonstrated antitumor activity in angiosarcoma, as monotherapy or combined with gemcitabine (18,19). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that blocks the activity of vascular endothelial growth factor (VEGF)-A. A phase II trial concluded that bevacizumab is an effective and well-tolerated single-agent treatment for metastatic or locally advanced angiosarcoma (20). Several case reports demonstrated that combination therapy with bevacizumab and chemotherapy or radiotherapy may improve quality of life and survival in patients with metastatic angiosarcoma (21-25). In addition, another VEGF inhibitor, pazopanib, may prolong the PFS of metastatic non-adipocytic soft-tissue sarcoma after previous chemotherapy (26), particularly when used as maintenance therapy for PCA (16).

In conclusion, unresectable cardiac angiosarcomas are rare but lethal. In such cases, a multimodality approach including image-guided radiotherapy and targeted therapy may be considered, as the overall prognosis of these patients is poor. Further clinical trials focusing on the treatment of unresectable PCA are warranted.

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