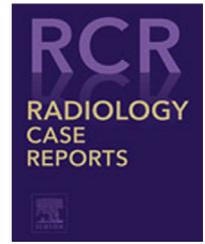
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Case Report

Primary cardiac epithelioid angiosarcoma: A case report [☆]

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ABSTRACT

Primary cardiac angiosarcoma is an extremely rare, high-grade malignancy. Here, we describe the case of a 44-year-old male patient with a heart tumor in the left atrium wall, which caused a large amount of pericardial effusion that invaded the surrounding area and is visible on transthoracic echocardiography, computed tomography, and magnetic resonance imaging. The postoperative histopathological results confirmed this case as a primary cardiac epithelioid angiosarcoma.

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Introduction

Primary cardiac cancer is an extremely rare cancer because of the highly differentiated tissues that make up the heart, in which angiosarcoma is the most common histopathological type [1]. A study of over 500 cases of surgically operated

cardiac tumors revealed that the majority of tumors were benign (75%). The remaining 25% were identified as malignant, of which 95% were primary cardiac tumors, and the most common histological form was angiosarcoma (accounting for 30%) [2].

Primary cardiac angiosarcoma is an epithelial cell tumor that is usually localized at the right atrium (78%–93%), rapidly

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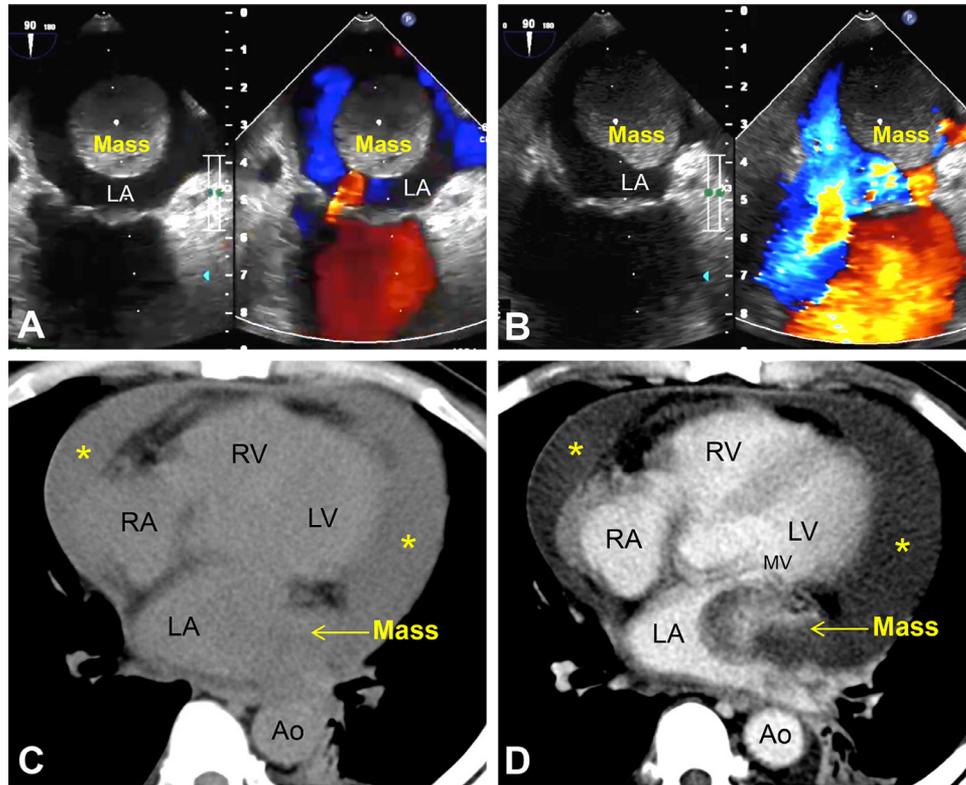


Fig. 1 – Transthoracic echocardiography (A, B): Two chamber views showed a hyperechoic mass originating from the left atrium and mild mitral valve regurgitation. Chest CT axial images at the precontrast (C) and arterial phases (D) showed a left atrial chamber mass (yellow arrow) that heterogeneously enhances and infiltrates the posterior left atrial wall and involves the mitral valve with an extension into the left atrium and pericardial effusion (asterisks). MV: mitral valve, RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle, Ao: descending aorta.

growing, invading the surrounding myocardium, or growing into the right atrium lumen, invading the vena cava and tricuspid valve. The tumor was found in the left atrium or ventricle with diverse clinical manifestations and a prognosis of high mortality in the remaining few cases [2].

The clinical presentation of this tumor is nonspecific and depends on how the tumor invades the myocardium and surrounding tissues. The most common symptoms are dyspnea, fatigue, weight loss, and myocardial ischemia-related symptoms [2]. A statistical study by Sachdeva et al. [3] in clinical cases of left atrial angiosarcomas published in PUBMED, SCOPUS, and WEB OF SCIENCE until June 2021 revealed that the left atrial angiosarcoma was more common in females (12/19 cases, 63%). The mean age was 59.26 ± 12.21 years. The most common clinical symptoms were dyspnea that increased with exertion (11/19, 58%) and chest pain (5/19, 26%). Myocardial ischemia was the initial presentation in 11% of cases (2/19) and congestive heart failure in 26% (5/19). Clinical manifestations are frequently associated with tamponade or heart failure due to obstruction and compression. The tumor is usually at an advanced stage and is difficult to be surgically removed when presenting clinically. Pericardial effusion accompanied by a significant hemorrhage is quite common [4]. The rate of distant metastases is up to 89% of the cases, and the common metastasis includes mediastinal lymph nodes, lungs, liver, and bones [5].

Early primary cardiac angiosarcoma diagnosis remained limited due to its rarity, inadequate experience of doctors, and small tumor, thereby causing few symptoms. Diagnostic imaging always plays an important role in cardiac tumor assessment. Transthoracic or transesophageal echocardiography (TTE or TEE) helps detect tumors at an early stage when they are still small. Computed tomography (CT) and magnetic resonance imaging (MRI) help assess tumor morphology, structure, and invasive characteristics, thereby providing diagnosis, differential diagnosis, and prognosis. However, the definitive diagnosis depends on the pathology.

Surgical excision followed by chemotherapy is the treatment of choice in most cases. Cardiac sarcoma prognosis is very poor, and few patients could survive for >12 months, even when they got radical surgery and aggressive chemotherapy, according to a statistical report. Death was reported in 58% of patients [3].

Here, we present a case of primary cardiac angiosarcoma of epithelioid origin that is localized in a rare location (the left atrium), detected on TTE, CT, and MRI, and subsequently confirmed by pathology.

Case report

A 44-year-old male patient had a 10-year history of type 2 diabetes, without a history of cough, cyanosis, or syncope. The

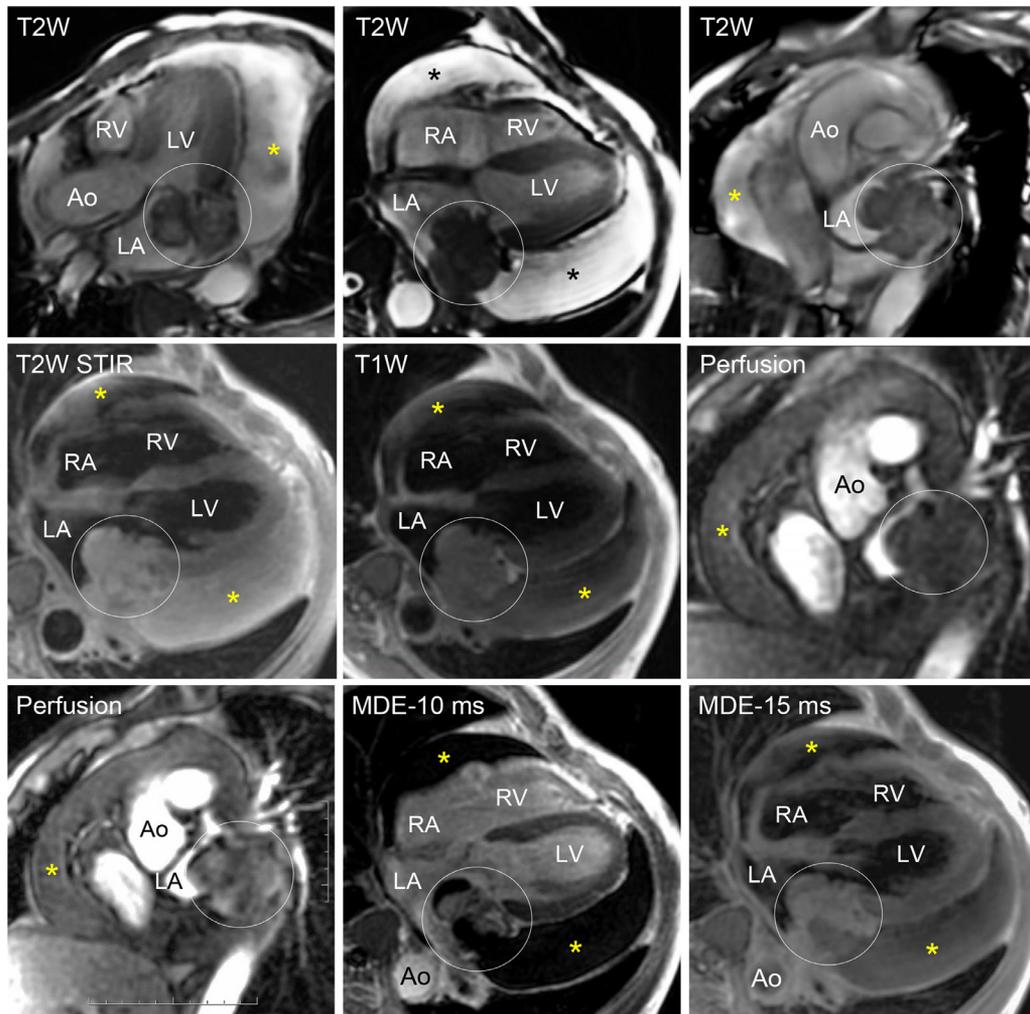


Fig. 2 – Cardiac MRI showed a cardiac tumor (circle), dimensions: 5.3 × 4.9 × 5.0 cm in the left atrium with pericardial effusion (asterisks). The tumor origin rose from the posterior left atrial wall, adhered to the posterior mitral valve, and extended into the lung hilum (T2W and T1W images). The lesion demonstrated late and heterogeneous enhancement (Perfusion and MDE images). Ao: aorta, RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle, MDE: myocardial delayed enhancement, STIR: short tau inversion recovery.

patient has been experiencing shortness of breath, chest pain, and fatigue for approximately 10 days. A chest X-ray revealed an enlarged heart. The electrocardiogram (ECG) showed a normal sinus rhythm, without evidence of acute ischemia. Blood tests showed red blood cells of 4.39 T/L, hemoglobin of 132 g/L, white blood cells of 9.07 G/L, and platelet of 259 G/L. A TTE revealed a hyperechoic homogeneous mass in the left atrium lumen, 5.0 × 4.9 × 4.6 cm in size, with an extensive pericardial effusion and normal left and right ventricular function (Fig. 1A, B). Pericardiocentesis was performed, which aspirated approximately 560 ml of blood fluid. The pericardial fluid test was negative for tuberculosis and other malignancies, protein quantification was 50.8 g/l, and glucose was 10.3 mmol/l.

A chest CT scan was performed on an Aquilion One 320-slice CT scanner (Toshiba, Japan) with a tube voltage of 120kV, tube current of 50 mA, tube rotation time of 0.35 s, a field of view of 400, and slice thickness of 0.5 mm, and breath-holding.

An 18-gauge needle was inserted into the antecubital vein to administer a nonionic contrast agent bolus, Xenetic vial at 300 mg/100 ml (Guerbet, France), with a dose of 1.5 ml/kg, at a speed of 5 ml/s, by a Medrad Stellant injector (Bayer) USA, followed by a 30 ml saline flush at the same speed. The delayed time for the acquisition scanning after the contrast injection was based on the maximum contrast agent appearance at the aortic arch (test bolus), usually 20 and 60 s for the arterial and portal venous phases, respectively. At those moments, the contrast agent was filled into the heart chambers helping to visualize the tumor boundary and its contrast-enhanced parenchyma.

The chest CT demonstrated an infiltrating, spreading tumor that invades the pericardial cavity, pericardium, and left lung hilum, at approximately 4.0 × 4.7 × 4.2 cm in size, isodense with the pericardial fluid in precontrast phase. The tumor enhancement was heterogeneous after contrast injection, and pericardial effusion was extensive (Fig. 1C, D). No



Fig. 3 – Postoperative macroscopic image of the tumor, with an irregular border and size of 5 cm × 7 cm.

distant metastases were found when other screening methods were applied.

Cardiac MRI was conducted on a 3 Tesla MR Revolution (GE), with Dotarem gadolinium (Guerbet, France) and the following imaging protocols: (1) routine functional views of the heart, including short axis (SA), 2 chamber (2CB), 3 chamber (3CB), 4 chamber (4CB), and left ventricular outflow tract using the Fast Imaging Employing Steady-state Acquisition (FIESTA) CINE sequence; (2) cardiac structure signal intensity characterization assessed by 2 sequences, such as SA, 2CB, 4CB T1W double-Inversion Recovery Fast Spin-echo (IR FSE) and SA, 2CB, 4CB T2W triple-IR FSE; (3) first-pass perfusion imaging, using a Fast Gradient Echo time course rest perfusion sequence on SA and 4CB planes, with 0.05–0.1 mmol/kg of Dotarem; (4) myocardial early enhancement that is performed on SA and 4CB planes, following 0.1–0.2 mmol/kg of Dotarem, within the first 2 min of gadolinium administration; (5) myocardial delayed enhancement that is started by acquiring CINE IR—the test Time to Inversion images on SA and 4CB planes, at 10 and 15 min after gadolinium administration.

Cardiac MRI showed a large tumor (5.3 × 4.9 × 5.0 cm), heterogeneously hypointense on pre-contrast T1W and T2W images, developed from the posterior left atrial wall and attached to the posterior mitral valve leaflet and the left lung hilum. No enhancement was found in the early phase of the perfusion sequence; however, it was heterogeneously enhanced in the subsequent phase and the late phases (Late gadolinium enhancement [LGE] in 10 and 15 min; Fig. 2).

Surgery was performed on the patient to remove the heart tumor. The tumor was approached via mediastinal endoscopic surgery with the assistance of the cardiopulmonary bypass (CPB) system. Sondergaard's plane was dissected to reveal the left atrium. The tumor measured approximately 5 cm × 7 cm and had a rough surface (Fig. 3). It developed from the posterior free wall of the left atrium approximately 0.5 cm from the mitral valve and invaded the lumen, and also the posterior left lung hilum. We completely removed the tumor and a portion of the left atrium.

The histopathological slides of H&E staining showed that tumor tissue included major solid sheets and some irregularly shaped vascular channels. Tumor vascularity was uneven, ramified, and staghorn. Tumor cells were plump, spindle-shaped with quite pleomorphic nuclei and mitosis. The

groups of spindle crowded cells were with unclear endothelial vasoformative patterns. Immunohistochemistry was stained to differentiate from other sarcomas. Tumor cells were positive with vascular markers, such as CD34, CD31, ERG, and additionally scattered EMA referred to as epithelial origin. Epithelioid angiosarcoma was histologically confirmed (Fig. 4).

The patient made a remarkable recovery after >1 month of intensive treatment (adjuvant chemotherapy) and is still living a healthy life with his family, without signs of metastasis, 6 months postoperatively.

Discussion

As previously mentioned, primary cardiac angiosarcoma is a type of vascular tumor that develops from endothelial cells, presents as malignant, and is extremely rare and mostly occurs in the right atrium. Small tumors are usually asymptomatic or with nonspecific symptoms, such as dyspnea, fatigue, weight loss, or myocardial ischemia, which makes its early detection difficult. The tumor causes clinical symptoms corresponding to its invasion area as it grows larger. Tumors can invade the right atrial wall or lumen, the tricuspid valve, and even the superior vena cava, pericardium, coronary vessels, and ventricles. A study on 46 patients by Butany [6] revealed that chest pain and dyspnea as the most common clinical symptoms.

Our case was among the 5% where the tumor was located in the left atrium, which is a very rare location [3]. The tumor had grown, invaded the left atrial wall and posterior mitral valve leaflet, disrupted the pericardium, and infiltrated the left lung hilum causing a rapidly relapsing pericardial effusion. This made the surgical process difficult, despite meticulous planning.

Echocardiography is frequently the first choice, as it aids in quite accurately determining the tumor location and size and assessing the heart valves and pericardial structure [7]. The tumor morphology was observed on echocardiography, as well as the tumor's "leg" that attached to the left atrial septum and the posterior mitral valve wall, which led us to suspect a left atrial mucinous tumor. We could not comprehensively assess the invasion of adjacent tissues (extracardiac) due to the tumor's large size.

Chest X-ray often shows an enlarged heart, pulmonary congestion, or pericardial effusion. A CT scan helps comprehensively evaluate tumor morphology, invasiveness, and distant metastases with a prevalence rate of up to 89%, of which the most common is lung metastasis. Especially, CT helps differentiate primary cardiac sarcoma from other heart diseases, such as thrombosis, endocarditis, pericarditis, and other benign tumors. Contrast-enhanced CT scan provides additional information regarding contrast enhancement properties and tumor nature, heart wall, blood vessels, and lung parenchyma. Lesions can be missed in some cases if a contrast agent is not used [8]. Finding the tumor on plain CT images (without contrast) of this patient was difficult due to its co-density with the pericardial fluid and the left atrial blood (Fig. 1C). Only after contrast injection, a heterogeneously hyperdense mass could be seen (Fig. 1D). It was a widespread lesion that invaded the

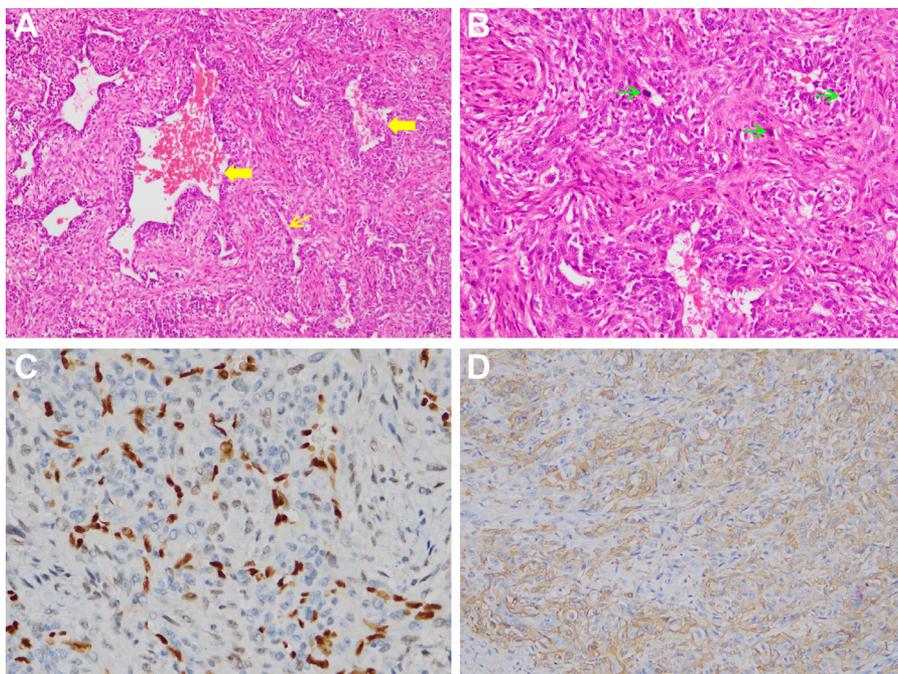


Fig. 4 – Histological cardiac angiosarcoma image. (A) Hematoxylin-eosin stain showed a high density of the spindle cells, interspersed uneven blood vessels (yellow bold arrows), and staghorn branched blood vessels (yellow thin arrows). **(B)** Higher magnification (400x) expressed large spindle cells with atypical nucleus and mitosis (green thin arrows), arranging haphazard clusters. **(C)** ERG-positive (in brown) in the tumor area with various densities. **(D)** CD34 immunostain of heart angiosarcoma showing positive vascular marker expression (200x).

left atrium and the left lung hilum, accompanied by a significant amount of pericardial effusion.

A TEE has a higher resolution (1-3 mm) than that of an MRI (5-10 mm), but the MRI is better in determining tissue composition with its ability to distinguish between solid, liquid, blood, and fat [9]. Angiosarcoma is frequently visualized on MRI as a heterogeneous tumor with moderate signal intensity on T1-weighted images, a diffuse low signal on T2-weighted images, and high signal intensity on T2-STIR images. Contrast enhancement was not observed in the early phases after injection in this patient, but the tumor was heterogeneously enhanced in the subsequent phase and late phases (LGE: 10 min, 15 min).

Generally, diagnostic imaging plays a very important role in preoperative differential tumor diagnosis. Pericardial fluid cytology is positive in 75%-87% of cases. Pericardiocentesis-guided pericardial biopsy has a diagnostic value of 93.3%-97% [9]. The definitive diagnosis still depends on the pathological findings. Angiosarcoma is a highly malignant endothelial tumor that both locally infiltrates and metastasizes to distant organs, such as the lungs and brain. It has a poor prognosis, with a median survival of approximately 3.8 ± 2.5 months without surgical resection [6], and postoperative survival of 2-55 months, with a median of 14 months. Additionally, heart transplantation did not improve patient survival [10]. Some studies revealed that tumor location could influence prognosis. Blackmon and Reardon [1] reported that the right heart tumors are often large, easier to infiltrate and metastasize than

the left heart tumors, respond to adjuvant chemotherapy to shrink the tumor, and create favorable conditions for radical surgery and prolong postoperative survival time. Further, left-sided tumors are more likely to cause early heart failure, although less likely to infiltrate.

Various morphologic appearances may be arranged from lesions that are well-formed, anastomosing vessels to solid sheets of a high-grade epithelioid area with definitive vasof ormation and a spindle cell Kaposi-like area or poorly differentiated sarcoma. Atypical tumor cells include plump, polygonal, epithelioid, or spindle shapes with hyperchromatic, pleomorphic nuclei, and prominent nucleoli. Immunohistochemistry stain was useful to identify the diagnosis. Endoepithelial cell markers, including CD31, CD34, FLI1, ERG, VEGF, and factor VIII, express positivity with tumor cells [11–13]. Spindle cells show the positivity of diffuse membranous CD34 and focal nuclear ERG in this case (Figure 4). The CK and EMA markers express cytoplasm membrane in epithelial differentiated soft tumors. CK stain is positive ranging 78%-100% in epithelioid variant of angiosarcoma [14]. In our case, scatter or small focal areas are present in positive EMA although tumor cells are negative with CK.

A correlation study revealed that histological malignancy is not an independent factor in the survival of patients with cardiac sarcoma. However, radical resection combined with chemotherapy and repair or replacement of the valve when necessary has been shown to improve patient survival [14].

Conclusion

Cardiac angiosarcoma is an extremely rare, primary with high-grade malignancy, and epithelioid in origin. Imaging methods, such as TTE, contrast-enhanced CT, and MRI, play an important role in determining tumor location, size, contrast enhancement properties, and nature; in assessing the heart valves and pericardial structures. A definitive diagnosis must be based on pathological results. The prognosis for cardiac sarcoma is very poor, but the survival time can be increased up to a few years if the patient has no metastases and the tumor is surgically removed in combination with adjuvant chemotherapy.

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Ethical approval

This study was approved by the institutional review board of Hospital 108 in Vietnam. Informed consent was obtained from the study participants. All procedures performed in studies that involve human participants were under the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient consent

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