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(CASE REPORT)

Primary Cardiac Angiosarcoma: A Case Report of an Uncommon Tumor and a Brief Review of the Literature

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Abstract

Primary cardiac angiosarcoma (CAS) is a rare, malignant, aggressive, vascular tumor that commonly causes nonspecific cardiac symptoms and thus is a challenging diagnosis. A 56-year-old man with a history of hypertension and hyperlipidemia reported a three-month history of increased exertional dyspnea, periodic non-pleuritic chest pain, and fatigue. At two outpatient visits, routine laboratory studies and electrocardiograms were unremarkable. Nonsteroidal anti-inflammatories were ineffective in relieving symptoms. His symptoms progressed to heart palpitations and loss of exercise capacity. Trans-thoracic echocardiography (TTE) demonstrated a 3.5 cm heterogeneous mass at the right atrial free wall. A multilobulated, heterogeneous-enhancing mass with hemorrhage and necrosis was seen on cardiac magnetic resonance imaging (MRI), which is indicative of a primary cardiac malignancy.

The surgically excised tumor was positive by using immunohistochemical (IHC) studies for CD31, ERG, factor VIII, and FLI-1, consistent with high-grade cardiac angiosarcoma. Adjuvant chemotherapy was also administered. At nine months, bilateral metastatic lung nodules were identified. Palliative care was introduced, and the patient was put on secondary taxane-based chemotherapy. His condition deteriorated rapidly, and the patient passed away 15 months after diagnosis. The case emphasizes the importance of considering primary cardiac tumors as part of the possible causes of a patient's presentation of persistent, nonspecific cardiac symptoms.

Keywords: Cardiac angiosarcoma; Positron emission tomography; Immunohistochemistry; Chemotherapy

1. Introduction

Primary cardiac angiosarcoma (PCAS) is an exceedingly rare yet highly aggressive malignant vascular neoplasm arising from the heart's endothelial cells [1]. Despite its rarity, with an incidence estimated at 0.0001% to 0.0003% in autopsies, it is the most common primary malignant cardiac tumor in adults, accounting for nearly one-third of all primary cardiac malignancies [2] [3]. PCAS predominantly affects young to middle-aged adults, with a notable male predilection, and most frequently arises in the right atrium, often infiltrating the atrial wall, pericardium, and adjacent cardiac tissues. [2] [3]

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The insidious nature of PCAS often leads to a delayed diagnosis. Early symptoms are typically nonspecific, mimicking more common cardiac conditions such as dyspnea, chest pain, or congestive heart failure, which contributes to frequent misdiagnosis and progression to advanced stages [2] [4]. Definitive diagnosis necessitates a tissue biopsy, often obtained via open cardiac biopsy, which carries significant risks including tumor friability, hemorrhage, and potential perforation [5] [3]. Imaging modalities, particularly transthoracic echocardiography, are sensitive for initial detection, but laboratory markers are generally unremarkable [6].

Due to its rarity, there are few defined treatment guidelines or randomized clinical trials for PCAS, rendering its management highly contentious [7]. Current therapeutic approaches typically involve surgical resection when feasible, often complemented by chemotherapy (e.g., taxanes, which may be used pre-operatively to shrink the tumor) and radiotherapy [8]. However, the aggressive infiltrative nature of PCAS, coupled with its propensity for early metastasis, often results in poor patient outcomes [7] [8]. This case report aims to highlight the aggressive characteristics of cardiac angiosarcoma, the adverse prognostic implications of positive surgical margins, and the temporary effectiveness of current systemic therapy, thereby contributing to the limited literature and enhancing clinician awareness regarding diagnostic challenges and prospective management options for patients with limited cardiac reserves.

2. Clinical presentation

2.1. Initial clinical presentation, history, and physical examination

A 56-year-old male was admitted to the hospital with a 3-month history of progressive exertional dyspnea, intermittent non-pleuritic chest pain, and fatigue. Initially, these symptoms were mild and were explained as deconditioning and possible anxiety. He was assessed in an ambulatory clinic setting on two occasions, and routine laboratory tests and electrocardiograms were unremarkable. A brief trial of nonsteroidal anti-inflammatory drugs was given for suspected musculoskeletal chest pain with minimal symptomatic improvement. Over the next few weeks, he developed worsening shortness of breath, episodic heart palpitations, and decreased exercise tolerance, which led to a cardiology referral. Transthoracic echocardiography (TTE) was performed in the setting of suspected structural heart disease. It demonstrated an underlying large right atrium cardiac mass leading to his expedited hospital admission.

The patient had a history of previously treated hypertension and hyperlipidemia. He had no recorded evidence of prior malignancy, radiation exposure , or chronic immunosuppression. He was an ex-smoker with a 15-pack-year history who stopped smoking 10 years earlier. There was no family history of malignancy or inherited medical syndromes. Systems review was not significant for fever, night sweats, or hemoptysis on presentation.

Physical examination showed the patient was slightly short of breath. Physical examination showed borderline tachycardia without hypotension (respiratory rate, 102 beats per minute, and blood pressure, normal)—no Jugular venous distention. Cardiovascular examination revealed a normal rate and rhythm, with a soft systolic murmur at the left sternal border, but no rubs or gallops. On pulmonary auscultation, soft bibasilar crackles were noted. Peripheral edema, cyanosis, or clubbing were absent. He had no palpable abdominal masses, lymphadenopathy, or skin lesions. The working diagnosis based on the clinical course was of an intracardiac condition with early hemodynamic compromise.

2.2. Diagnostic workup

Laboratory data were unremarkable except for mild normocytic anemia and slightly increased inflammatory markers, including C-reactive protein, on the day of admission. Cardiac enzymes were unremarkable. TTE demonstrated a 3.5-cm heterogeneous mass originating from the right atrial free wall, partially extended into the atrium cavity without hemodynamic compromise. Cardiac MRI indicated a multilobulated, infiltrative mass with heterogeneous enhancement, areas of hemorrhage, and necrosis, which were suspicious for a malignant primary cardiac tumor.

Chest, abdomen, and pelvis computed tomography (CT) at diagnosis was negative for distant metastatic disease. Positron emission tomography (PET) revealed marked intense FDG-uptake contained mainly within the cardiac mass. Differential considerations on imaging included primary cardiac angiosarcoma, undifferentiated pleomorphic sarcoma, lymphoma, and, less likely, atrial myxoma, given aggressive radiologic features. Tissue diagnosis was pursued owing to the mass's size, location, and concern for malignancy.

2.3. Tumor board discussion, diagnosis, and treatment

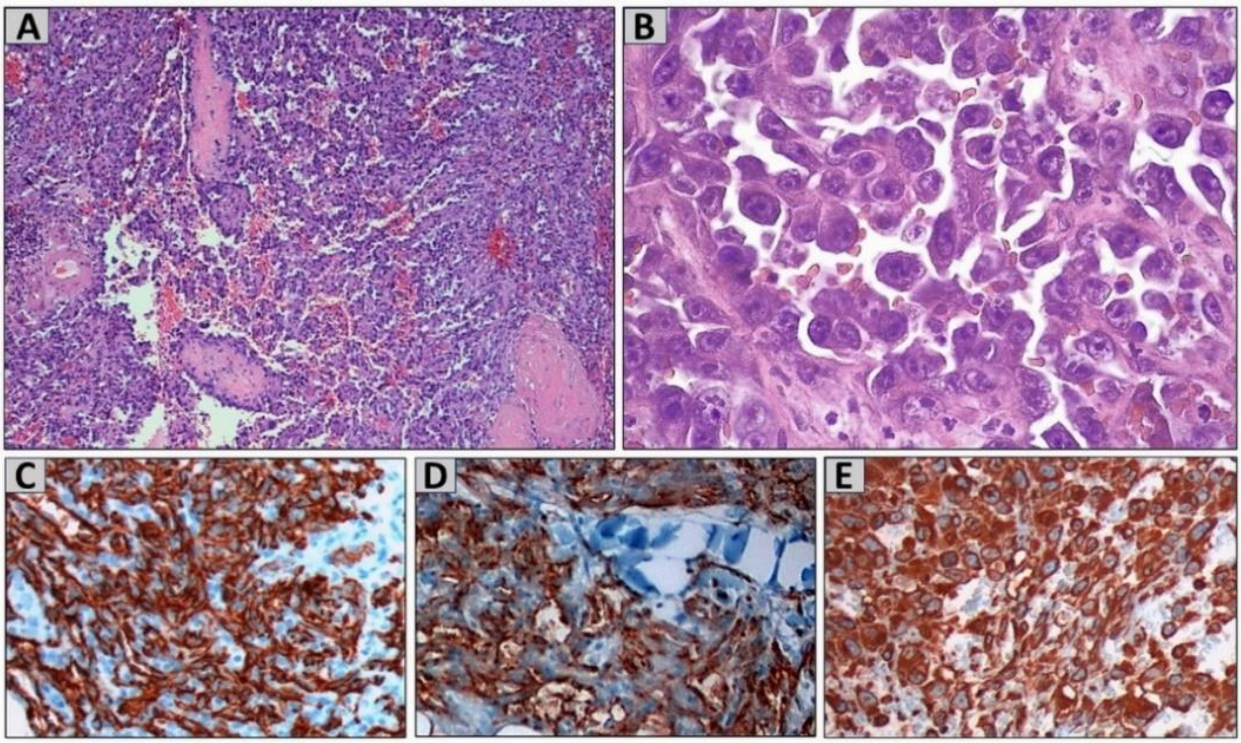
The case was discussed at a multidisciplinary tumor board discussion with the involvement of cardiothoracic surgery, oncology, radiology, pathology, and cardiology. Points of discussion included the role of preoperative biopsy versus

upfront surgical resection, along with their risks and benefits. Because of the risk of cardiac perforation and embolization, it was generally agreed that surgical excision should be performed with diagnostic and therapeutic conclusion.

Pathologic examination revealed a high-grade angiosarcoma including atypical endothelial cells showing irregular vascular channels, significant nuclear pleomorphism, and a high mitosis rate. The tumor cells were strongly positive for CD31, Factor 8 (FVIII), ERG transcription factor, and FLI-1 by immunohistochemistry, supporting endothelial differentiation. The Ki-67 proliferation index was significantly high. (Figure 2 A, B, C, D, E) Molecular testing was not available at that time and was not performed.

The patient underwent surgical excision by median sternotomy under cardiopulmonary bypass. Partial right atrial resection and reconstruction with the use of a pericardial patch were carried out. Total resection with free margins was possible, but wide margins were not feasible, since tumor infiltration into atrial tissue would have risked cardiac function. There were no postoperative complications, and the patient was extubated within 24 h. Final pathology confirmed the diagnosis of high-grade primary cardiac angiosarcoma with focal microscopic disease at the resection margin, indicative of R1 resection. Lymphovascular invasion was present. The surgical team decided that an additional surgical procedure for a free margin would not be possible on an anatomical basis without expected morbidity.

The patient subsequently underwent adjuvant chemotherapy with an anthracycline-based regimen, and radiation therapy was delayed due to concerns related to cardiac toxicity. He underwent therapy with an acceptable tolerance and side effects.



1A Low power view showing atypical endothelial cells showing irregular vascular channels (H&E stain X20); 1B High power view showing pleomorphic, highly atypical endothelial cells and increased mitosis (H&E stain X60); 1C Tumor cells positive for CD31; 1D Tumor cells positive for Factor 8 (FVIII); 1E Tumor cells positive for Vimentin

Figure 1 Microscopic features of the excised cardiac angiosarcoma

2.4. Disease progression at 9 months

After 9 months of surgery, follow-up images showed several bilateral pulmonary nodules compatible with metastases. Simultaneously, cardiac imaging revealed tumor recurrence at the right atrial resection site, producing partial obstruction of venous inflow. The patient manifested insidious onset of progressive dyspnea, lower extremity edema, and signs of right-sided CHF. With disease progression, the treatment intent was changed to palliative therapy. However, because angiosarcoma is known to be sensitive to taxane-based chemotherapy [9], second-line chemotherapy

was started. Emphasis was placed on supportive care , including diuretics and symptom-directed therapy. The patient refused any additional treatment.

2.5. Follow-up and outcome

While on palliative therapy, the patient's disease advanced, and he developed deteriorating cardiopulmonary status. His functional status worsened in the latter months. He was placed in hospice and died 15 months after his initial diagnosis. This case emphasized the aggressive nature of cardiac angiosarcoma, the negative prognostic effect of surgical margin positivity, and the transient efficacy of present systemic therapies.

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

The first clinical diagnosis of cardiac angiosarcoma was documented in 1934. Significant advancements in its identification and diagnosis began with the advent of echocardiography in 1968, further enhanced by the subsequent development of computed tomography (CT) and magnetic resonance imaging (MRI) [10]. Despite these diagnostic improvements, PCAS remains an aggressive malignancy associated with a poor prognosis. This is largely attributed to its frequent and early metastasis to distant sites, particularly the lungs, lymph nodes, and liver [3]. The CAS predominantly affects individuals under 65 years of age, with a peak incidence between 20 and 50 years, and exhibits a male predominance, occurring 2-3 times more frequently in males than females [11].

Originating from the endothelial lining of cardiac blood vessels, PCAS typically presents in the right atrium or atrial septum [12]. Early symptoms are often absent or nonspecific; however, with disease progression, patients may develop dyspnea, chest pain, and heart failure. More specific symptoms can emerge with local infiltration of surrounding cardiac structures or the development of distant metastases [7]. Prognosis remains grim, with a typical survival range of approximately 14 months for surgically treated patients, and a significantly shorter median survival of 3.8 ± 2.5 months for those with untreated disease and metastasis [13].

While secondary tumors arising from metastasis are more prevalent, primary cardiac tumors represent a rare clinical entity. Metastatic tumors are estimated to be 20 to 40 times more common than primary cardiac tumors. The incidence of primary cardiac tumors is very rare, found in approximately 0.001% to 0.03% of autopsies. [14]. Among malignant primary cardiac tumors, angiosarcoma is the most common subtype. Although often idiopathic, several risk factors have been identified, including exposure to environmental carcinogens such as vinyl chloride, thorium dioxide, or arsenic, a history of radiation therapy, or chronic lymphedema, as well as certain genetic syndromes [3]. In PCAS, specific genetic alterations have been implicated, including those affecting the kinase insert domain receptor (KDR), cyclin-dependent kinase inhibitor 2A (CDKN2A), protection of telomeres 1 (POT1), phospholipase C gamma 1 (PLCG1), and KIT genes [15].

3.2. Pathogenesis, pathophysiology

The pathogenesis of PCAS is characterized by an interplay of profound cellular atypia and the dysregulation of key angiogenic signaling pathways, which together dictate its rapid clinical progression. [3] At the histopathologic level, PCAS is characterized by the proliferation of atypical endothelial cells that form irregular, anastomosing vascular channels. These cells display marked nuclear pleomorphism and a high mitotic rate, hallmarks of a high-grade malignancy. [17] The structural integrity of these neo-vessels is inherently poor, leading to frequent intratumoral hemorrhage and extensive necrosis. A markedly elevated Ki-67 proliferation index serves as a surrogate for the tumor's aggressive kinetics, correlating with its rapid infiltration of the myocardium and surrounding structures. [3]

The molecular pathogenesis of PCAS is centered on the subversion of normal angiogenic signaling. [18] The tumor is often driven by the overactivation of the vascular endothelial growth factor (VEGF) pathway. When this pathway is dysregulated, it triggers critical downstream cascades: The PI3K/AKT/mTOR pathway, which enhances cell survival and metabolic reprogramming, and the RAS/MAPK cascade, which fuels relentless cellular proliferation. In some instances, somatic mutations in genes such as PLCG1 or KDR (VEGFR2) further exacerbate this signaling, creating a self-sustaining cycle of growth and migration. [15]

The convergence of infiltrative growth, high-grade cellular activity, and vascular fragility explains the hallmark clinical presentations of PCAS. The "leaky" nature of the tumor’s neo-vessels frequently results in hemorrhagic pericardial effusion, often progressing to cardiac tamponade. [3] Additionally, the mass effect and myocardial invasion commonly

culminate in right-sided heart failure. Ultimately, the rapid local tissue destruction and early systemic metastasis are direct consequences of the tumor's underlying molecular drive and high proliferative capacity. [16]

3.3. Comparative analysis of our case with the existing literature (Clinical-radiology-pathology, lab, diagnosis-management-outcome)

The clinical presentation of our patient, a 56-year-old male with a 3-month history of progressive dyspnea and chest pain, aligned closely with the typical profile described in the literature. PCAS predominantly affected males in their fourth to sixth decades of life, often presenting with nonspecific symptoms that mimicked more common cardiac or pulmonary conditions [2]. Similar to many reported cases, our patient's initial laboratory and ECG findings were unremarkable, underscoring the diagnostic challenge and the frequent delay in identifying these rare malignancies until they reach an advanced stage.

Radiologically, the TTE and cardiac MRI findings in our case were classic for PCAS. The literature described these tumors as heterogeneous, multilobulated masses, often with areas of hemorrhage and necrosis, typically arising from the right atrial free wall [11]. Our patient's MRI showed intense heterogeneous enhancement and infiltrative features, which were hallmarks of malignancy. While PET imaging in our case showed intense FDG uptake, this was a common finding in high-grade sarcomas. However, it lacked specificity for angiosarcoma versus other primary cardiac malignancies, such as undifferentiated pleomorphic sarcoma [11].

Pathologically, the diagnosis was confirmed by the presence of atypical endothelial cells forming irregular vascular channels, significant nuclear pleomorphism, and a high mitotic rate. The strong immunohistochemical expression of CD31, ERG, and FLI-1 in our patient was consistent with the "gold standard" for confirming endothelial differentiation in angiosarcomas [16].

Regarding management, our patient underwent surgical resection followed by adjuvant chemotherapy, which was the standard multimodal approach. However, achieving R0 resection (negative margins) was notoriously difficult in the heart due to anatomical constraints and the tumor's infiltrative nature. Our patient underwent an R1 resection (microscopic positive margins), a known negative prognostic factor. [7] The literature suggests that while R0 resection can significantly extend survival (median ~27 months), R1 resection often results in outcomes similar to partial resection, with median survival ranging from 10 to 14 months [19] [20]. Our patient's survival of 15 months was consistent with these findings, slightly exceeding the reported median for R1 resections, likely due to the temporary efficacy of the adjuvant anthracycline-based regimen. [7]

4. What have we learned from this case?

This case provided several critical insights into the management of primary cardiac angiosarcoma:

High Index of Suspicion: The initial misattribution of symptoms to deconditioning and anxiety underscored the need for a high index of suspicion in patients with persistent, unexplained cardiopulmonary symptoms, even when routine tests were normal. Early use of TTE was found to be life-saving in detecting structural abnormalities.

The Challenge of Surgical Margins: The transition from a seemingly successful surgical resection to an R1 margin status highlighted the extreme difficulty in achieving clear margins in the heart. This case reinforced that even with advanced surgical techniques, the infiltrative nature of PCAS often precluded R0 resection, necessitating a realistic discussion of prognosis with the patient.

Multidisciplinary Coordination: The successful navigation of diagnostic dilemmas (biopsy vs. upfront surgery) demonstrated the value of a multidisciplinary tumor board. In this case, the decision for upfront surgery avoided the risks of possible cardiac perforation associated with biopsy while providing both a diagnosis and therapeutic intervention.

Transient Efficacy of Systemic Therapy: While the patient initially tolerated and responded to chemotherapy, the recurrence at 9 months illustrated the transient nature of current systemic treatments. It underscored the need for more durable therapeutic options, perhaps through targeted therapies based on molecular profiling (e.g., VEGF inhibitors).

Abbreviations

- Cardiac angiosarcoma (CAS);
- Primary Cardiac Angiosarcoma (PCAS);
- Transthoracic echocardiography (TTE);
- Positron emission tomography (PET)

5. Conclusion

This case of primary cardiac angiosarcoma was presented to illustrate the formidable diagnostic and therapeutic challenges posed by this rare malignancy. By detailing the clinical course from nonspecific initial symptoms to the limitations of R1 surgical resection and subsequent recurrence, we hope this report contributes to the medical community's understanding of the disease's natural history and the prognostic impact of surgical margins. Furthermore, it underscores the necessity for a high clinical suspicion and a coordinated multidisciplinary approach. Ultimately, this case served as a call for continued research into more effective systemic and targeted therapies to improve the currently dismal outcomes for patients with advanced primary cardiac malignancies.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis. No patient contact or intervention was involved, and informed consent was not required in accordance with institutional policies.

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