

Case Report

Primary Cardiac Epithelioid Angiosarcoma with Sustained Remission following Surgical Resection: A Case Report

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Keywords

Epithelioid angiosarcoma · Primary cardiac angiosarcoma · Atrial fibrillation · Gc protein-derived macrophage-activating factor

Abstract

Epithelioid angiosarcoma is an extremely rare subtype of cardiac angiosarcoma that is highly aggressive and associated with poor prognosis. Due to its rare nature, the epidemiology and pathogenesis of this disease are not well-known. Thus, effective diagnostic and treatment modalities are limited. Here, we report a case of a primary epithelioid angiosarcoma in a patient who was treated successfully with surgical resection. A 45-year-old woman who initially presented with chronic systemic symptoms and severe anemia and subsequently developed new-onset atrial fibrillation with rapid ventricular rate was found to have a right-sided cardiac mass with a large pericardial effusion. Several years prior to presentation, she was treated for localized papillary thyroid cancer with Gc protein-derived macrophage-activating factor (Gc-MAF) therapy after declining thyroidectomy. After initial workup of her cardiac mass, including a transthoracic echocardiogram and cardiac MRI, she was transferred to an outside hospital where her mass was surgically resected. She was found to have stage IIIA high-grade epithelioid angiosarcoma involving the inferior vena cava, right atrium, and pericardium. She subsequently had complete resolution of her pericardial effusion and anemia and continues to have good

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performance status 16 months after her excellent surgical outcome without evidence of recurrence. This unique case contributes to our knowledge of epithelioid cardiac angiosarcoma, of which limited number of cases has been reported. It highlights a favorable outcome following surgical resection of a rare, life-threatening primary cardiac tumor.

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Introduction

Primary cardiac tumors are extremely rare with overall estimated incidence ranging from 0.001% to 0.03%. In comparison, metastases to the heart and pericardium are more common. The majority of primary cardiac tumors are benign, and nearly half of them are cardiac myxomas. Approximately, 25% of primary cardiac tumors are malignant, of which angiosarcoma and undifferentiated sarcoma make up a significant percentage of cases [1, 2]. Notably, while most of the primary tumors of the left atrium are benign, half of right atrial tumors are malignant [3]. In published case reports and series of primary cardiac angiosarcoma, patients have presented with chest pain, congestive heart failure, syncope, fatigue, palpitations, and dyspnea. However, there is no consistent symptomatology or specific physical exam findings, making the diagnosis clinically challenging even with advances in diagnostic imaging [4, 5]. Due to the nature of its aggressive and high-grade pathology, predilection for early metastasis, and diagnostic challenges, prognosis is poor with a mean survival of nine to 12 months at time of diagnosis [6]. Therefore, early diagnosis and treatment are critical. Epithelioid angiosarcoma, a particularly rare subtype of angiosarcoma that is uncommonly reported, especially when arising from the heart or the great vessels, is a highly aggressive tumor with poor prognosis [7, 8].

Herein, we report a case of primary cardiac epithelioid angiosarcoma in a patient who presented with constitutional symptoms, severe anemia, and atrial fibrillation and achieved a highly favorable outcome following surgical resection of her tumor. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000530113>).

Case Presentation

A 45-year-old female with iron deficiency anemia and unresected stage I papillary thyroid carcinoma presented to the emergency department with chronic fatigue, night sweats, body aches, and joint pain and was subsequently found to have anemia with a hemoglobin of 6.6. She denied chest pain, weight loss, hematochezia, melena, or hematemesis. Due to a positive Hemoccult test and prior history of Barrett's esophagus, she was admitted to the hospital for blood transfusion and expedited gastrointestinal evaluation. However, on the second day of hospitalization, she experienced palpitations and was found to be in atrial fibrillation with rapid ventricular response sustaining heart rates up to 150. She was hemodynamically stable and responded to intravenous metoprolol. She spontaneously converted back to normal sinus rhythm later that day.

It was at this time that the patient revealed she had experienced palpitations and occasional syncope episodes over the past 2 years and shared more of her past medical history. Four years before this hospital admission, she was diagnosed with stage I papillary thyroid carcinoma based on thyroid ultrasound and biopsy; however, she declined surgical treatment

and opted for active surveillance. Three years prior, she pursued alternative therapy in Mexico with intravenous nutritional supplements and subcutaneous Gc protein-derived macrophage-activating factor (Gc-MAF) injections called Sunivera Immunotherapy™. After starting this experimental treatment, she developed a generalized erythematous rash that resolved when she paused treatment. She was prompted to continue treatments and subsequently experienced full-body pain, chills, nausea, and flushing. Two years prior to presentation, she again self-discontinued treatments and reported these symptoms but was again encouraged to complete one more month of injections to finish the 3-month regimen. After completing the full course of treatment, she began experiencing episodes of heart palpitations with associated dyspnea and syncope in addition to the previously mentioned constitutional symptoms. For the ensuing 2 years leading up to the hospitalization, she continued to have these symptoms, which she attributed to the experimental immunotherapy that never resolved or improved after discontinuing treatments. During this time, she saw integrative health providers and followed-up periodically with the clinic in Mexico but did not have a comprehensive diagnostic evaluation of her recurrent syncope.

Based on this new information, CT imaging and transthoracic echocardiogram were performed and demonstrated a 6.6 × 5.2 cm mass inferior to the heart with a circumferential moderate to large pericardial effusion (Fig. 1a). Cardiac ejection fraction was estimated as 70%, and there was no sign of tamponade physiology or atrial enlargement. MRI also similarly confirmed the presence of this heterogeneous mass posterior to the heart and abutting the right atrium and right ventricle (Fig. 1b). In addition to anemia, other significant laboratory findings included a C-reactive protein level of 110.0 mg/L, erythrocyte sedimentation rate (ESR) of 127 mm/h, thrombocytosis to 686,000/μL, ferritin level of 144 ng/mL, iron level of 11 μg/dL with transferrin saturation at 4.0%, and a negative troponin level. She was treated with intravenous ferric gluconate and red blood cell transfusions with adequate response. Her gastrointestinal workup was postponed in light of this new cardiac mass that was thought to be the cause of her chronic constitutional symptoms, as well as intermittent palpitations and syncope.

During her second week of hospitalization, the patient was transferred to an outside hospital for higher level of care where her mass was surgically resected by a cardiothoracic surgery team. On gross examination, the mass measured 8.5 × 7.0 × 5.2 cm and had a heterogeneous surface with attached areas of pericardium and inferior vena cava (Fig. 2a). Cut sections of the mass revealed a yellow, firm, whorled surface with a 2.5 × 2.3 × 1.7 cm area of necrosis and hemorrhage. On microscopic examination, the tumor was composed of sheets of atypical polygonal cells with vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm (Fig. 2b). These cells were admixed with delicate blood vessels, angulated vascular channels and areas of hemorrhage and demonstrated invasion into adjacent atrial muscle (Fig. 2c). Atypical mitotic figures were also identified (Fig. 2d). On immunohistochemical (IHC) analysis, the neoplastic cells were positive for vimentin, CD31, CD34, and calretinin and weakly positive for pancytokeratin with a Ki-67 index of 10% (Fig. 2e–h). In addition, CAMTA1 IHC showed negative nuclear staining. The margins were negative for tumor, and PET CT scan did not show evidence of metastatic disease. Given tumor size, high grade, and lack of metastases, the staging was determined to be IIIA, T2bN0M0, according to the Eighth Edition of the American Joint Committee on Cancer (AJCC) Staging System [9].

The patient had no complication in her postoperative course and no recurrence of atrial fibrillation. She was discharged on aspirin, metoprolol, and furosemide and had complete resolution of her anemia on subsequent laboratory studies. Her last transthoracic echocardiogram 4 months after surgery demonstrated complete resolution of the

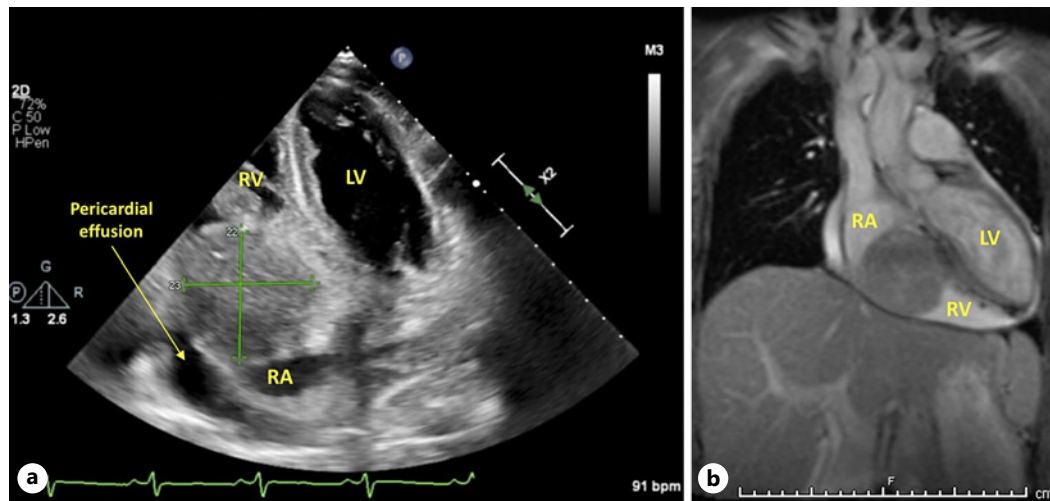


Fig. 1. Imaging studies of the cardiac mass **(a)** transthoracic echocardiography (TTE) revealed a moderate to large pericardial effusion circumferential to the heart, which was largest along the right-sided chambers and posteriorly. Within the pericardial space, posterior to the heart, and abutting the right atrium (RA) and ventricle (RV), was a large mass, measuring 5.5×5.9 cm, depicted in this apical view. The left ventricle (LV) was normal in size. **(b)** Cardiac MRI detected a heterogeneous mass inferior to the heart in the pericardial space that is intermediate in signal intensity on T1-weighted and T2-weighted images. This mass measured up to $5.9 \times 5.8 \times 6.2$ cm and displaced the heart superiorly.

pericardial effusion and normal cardiac function without recurrence of disease. Nine months after surgery, CT imaging showed no evidence of metastases, and thyroid ultrasound demonstrated stable, unchanged thyroid nodule. She was last seen in cardiology clinic around the same time with no recurrence of palpitations and dyspnea or chest pain on exertion. Despite discussion regarding the risk of recurrence and recommendations for adjuvant chemotherapy with her oncologist, the patient continued to decline further treatment. At the time of publication of this report, the patient continued to have excellent performance status without evidence of disease recurrence 16 months after her successful surgery.

Conclusion

Malignant epithelioid angiosarcoma of the heart is an exceedingly rare variant of cardiac angiosarcoma, which is a highly aggressive tumor preferentially affecting men in the fourth decade of life. Presenting with a range of symptoms including heart failure, dyspnea, and supraventricular arrhythmias, cardiac angiosarcoma patients have especially poor prognosis [10]. Pathogenesis of angiosarcoma is not well understood. Risk factors include chronic lymphedema, history of radiation, environmental carcinogens, such as vinyl chloride, thorium dioxide and arsenic, and several genetic syndromes such as Li-Fraumeni, though these largely pertain to cutaneous angiosarcomas [11]. Our patient did not have these documented risk factors, and her initial history only revealed vague constitutional symptoms with severe anemia, which was attributed to a possible gastrointestinal malignancy. It was not until the incidental episode of atrial fibrillation with rapid ventricular response that the medical team elicited further history of palpitations with associated dyspnea and syncope, which highlights the importance of a thorough review of systems.

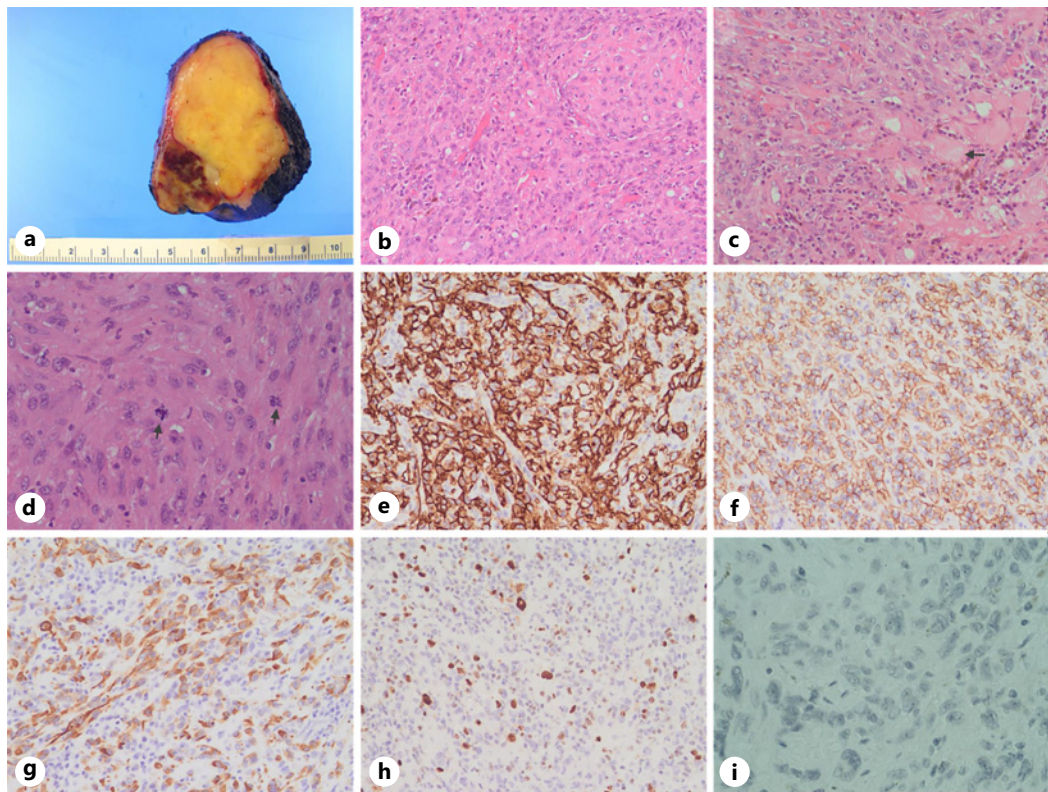


Fig. 2. Anatomic and histologic pathology of the epithelioid angiosarcoma (a) gross anatomical pathology demonstrated an ovoid-shaped, pink, and tan mass that measured $8.5 \times 7.0 \times 5.2$ cm with a heterogeneous surface. b–d Microscopic examination revealed epithelioid and vascular components, including nests and sheets of polygonal cells with vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm that were admixed with delicate blood vessels on H&E staining (b), as well as invasion in atrial muscle (c, black arrow) and atypical mitotic figures (d, black arrows, $\times 40$). e–i Immunohistochemistry revealed strong positive membranous staining for CD31 (e), positive staining for CD34 (f), focally positive staining for CKAE1/AE3 (pancytokeratin) (g), 10% positive staining for Ki-67 proliferation index (h), and negative nuclear staining for CAMTA1 (i, $\times 40$). $\times 20$ magnification unless otherwise noted.

Given the development of a rare cardiac tumor in a young female patient with no other risk factors, her prior experimental Gc-MAF therapy stands out as a unique exposure. However, direct association between Gc-MAF therapy and our patient's development of angiosarcoma cannot be definitively proven, due to the rarity of this tumor type and the lack of published data documenting toxicities in patients receiving Sunivera Immunotherapy™. Advertised as a proprietary therapy with no clinically observed side effects, it is important to note that Sunivera Immunotherapy™ is not FDA-regulated. While preclinical studies have shown promising results with macrophage-targeting methods, severe inflammatory toxicities may evolve from macrophage dysregulation, and macrophage-activating therapies are not yet a widely adopted mainstay of cancer treatment [12]. Based on a series of research studies conducted between 2008 and 2014, Gc-MAF therapy was postulated to activate macrophages and have curative benefit on a range of cancer types [13] – although three out of four of the original studies were later retracted by scientific journals due to questionable authenticity and study protocol irregularities. Recent molecular immune profiling of angiosarcomas has shown that macrophages are the predominant cell type in the immune infiltrate [14], but histologic morphology analysis of our particular case (Fig. 2) did

not show significant monocyte or macrophage infiltration. Given the side effects of this experimental anticancer therapy are unknown and may never be known, due to the nature of the institutions that administer these types of unregulated therapies, there remains a need for robust clinical studies to provide evidence of efficacy and the safety profile of Gc-MAF.

Furthermore, this case undeniably highlights a successful surgical outcome in a patient with primary cardiac sarcoma. Standard treatment of cardiac sarcomas involves resection of the mass, either complete excision in patients without distant metastases or palliative debulking [15]. In our patient with resection of her right-sided cardiac epithelioid angiosarcoma without adjuvant chemotherapy or radiation therapy, there continues to be no known metastases or recurrence of disease 9 months post-resection with overall survival greater than 16 months. This case, which shows excellent outcome in patient who had initially presented with arrhythmia, severe anemia, and multiple constitutional symptoms, adds to the growing body of research that reports successful surgery as a major prognostic factor in primary cardiac sarcoma [3].

Given this patient's excellent outcome following surgical resection, we carefully considered benign histologic mimics. Histologically, epithelioid angiosarcomas are characterized by pleomorphic plump epithelioid cells, and vasoformative foci as seen in conventional angiosarcoma may or may not be present. Endothelial differentiation must also be confirmed histologically or immunohistochemically with endothelial markers such as CD34, CD31, or ERG. In this case, vascular components such as angulated vessels and areas of delicate blood vessels were readily appreciated. Additionally, endothelial markers such as CD34 and CD31 were positive. Angiosarcomas can also be differentiated from other benign vascular proliferations by the presence of cytologic atypia, sheeted growth pattern, increased Ki-67 proliferation index ($\geq 10\%$), and infiltrative tumor borders [16]. In hemangioendotheliomas, our leading differential diagnosis, recurrent chromosomal translocations result in the formation of a WWTR1-CAMTA1 fusion gene that is seen in over 90% of cases [17]. This fusion is absent in epithelioid angiosarcoma, and nuclear CAMTA1 IHC expression is both sensitive and highly specific in distinguishing hemangioendothelioma from epithelioid angiosarcoma. It is true that a rare percentage of hemangioendotheliomas without the WWTR1-CAMTA1 fusion expresses a YAP1-TFE3 fusion gene, and we were unable to perform this test [18]. However, in our patient, the overt cytologic atypia, presence of endothelial differentiation, tumor invasion into the atrial muscle, and negative CAMTA1 IHC analysis are all features consistent with the diagnosis of epithelioid angiosarcoma.

In summary, we report a unique case of primary cardiac epithelioid angiosarcoma in a patient who was treated with experimental macrophage immunotherapy and presented with chronic systemic symptoms along with intermittent palpitations and syncope. This case contributes to the limited literature on cardiac epithelioid angiosarcoma, an extremely rare but aggressive tumor. It highlights the importance of a thorough history to uncover rare but life-threatening diagnoses. It also demonstrates a successful outcome following surgical resection in a patient with a primary cardiac mass even without adjuvant chemotherapy or radiation therapy.

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Statement of Ethics

This case is reported in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Case reports were granted exemption from requiring ethics approval at the University of California Los Angeles Medical Center.

Conflict of Interest Statement

A.S.S. reports research support from Blueprint Medicines, Deciphera, Eli Lilly, and Nanocarrier; consulting or speakers' bureau fees from Daiichi Sankyo, Eli Lilly, OncLive, Deciphera, Eisai, Roche, and Novartis, NanoCarrier, Certis Oncology Solutions. The rest of the authors declare that they have no competing interests.

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Author Contributions

M.M.T.K. and E.S. wrote the manuscript and compiled figures. A.Y.R.G. reviewed the pathology and provided histological images. M.M.T.K., E.S., A.Y.R.G., and N.A. were involved in the care of this patient. A.S.S. and N.A. provided comments and edits on the manuscript. All authors reviewed the manuscript.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries may be directed to the corresponding author.

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