

PRIMARY LEFT ATRIAL ANGIOSARCOMA MIMICKING PERICARDITIS: A CASE REPORT AND REVIEW OF THE LITERATURE

Trinh Le Huy✉, Pham Duy Manh
Hanoi Medical University

A 45-year-old male presented with symptoms mimicking pericarditis, including rapidly worsening dyspnea and retrosternal chest pain. On imaging workup, an abnormal mass of 50x53 mm in size was detected at the left atrium, which partially obstructed blood flow through the mitral valve. PET/CT was done in searching for the probable site of origin but revealed no abnormal uptake lesions. The tumorectomy and excision of the posterior wall of the left atrium were then performed with curative intent. The postoperative histology of the tumor was in favor of a spindle cell sarcoma, originating from the left atrium, grade 2, which was confirmed as epithelioid angiosarcoma by immunohistochemistry. The patient denied adjuvant radiation, thus we treated him with six cycles of Paclitaxel monotherapy, which was completed six months ago. At present, he is doing well with no signs of recurrence on the imaging technique. This paper illustrates the rarity of cardiac angiosarcoma, its complex presentation, and a brief review of available treatment options for this devastating disease.

Keywords: primary cardiac tumor, angiosarcoma.

I. INTRODUCTION

Primary cardiac tumors are extremely rare, occurring at a frequency of 0.02% in autopsy series and most of them are benign.¹ Of all malignant cardiac tumors, cardiac angiosarcoma is the most aggressive entity with dismal prognosis and no available treatment consensus.¹ Clinical presentation varies from mild chest pain to congestive heart failure, depending on the size, location and growth rate of the tumor. Patients tend to present in the late course of the disease with symptoms of local infiltration within the cardiac wall, the atrioventricular valves, the pericardium or the superior or inferior vena cava. Here we report a case of a left atrium angiosarcoma patient with symptoms mimicking pericarditis and

his treatment course. We also aim to review the literature about diagnosis and available treatment options in this fatal disease.

II. CASE PRESENTATION

A 45-year-old male with a history of type II diabetes presented at 108 Military Central Hospital with dyspnea and retrosternal chest pain that progressed for about one week. His symptoms deteriorated over time, especially on exertion. Chest radiography revealed an enlarged heart that raised suspicion of pericardial effusion, which was then confirmed by cardiac ultrasound. Electrocardiogram (ECG) revealed flattened T-waves. The patient underwent pericardiocentesis to control symptoms and provide specimens for cytology, but no malignant cell was detected.

MRI of the chest was performed, which revealed an abnormal mass of 50x53 mm in size. The mass occupied the left atrium cavity and invaded the parietal pericardium. This

Corresponding author: Trinh Le Huy

Hanoi Medical University

Email: tringlehuy@hmu.edu.vn

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mass is also attached to the posterolateral mitral valve leaflet, partially obstructing blood flow passing the valve. This scan also showed no invasion of the tumor to other adjacent structures. (**Figure 1**) PET/CT was used in searching for a probable site of origin, but there were no abnormal PET/CT uptake lesions.

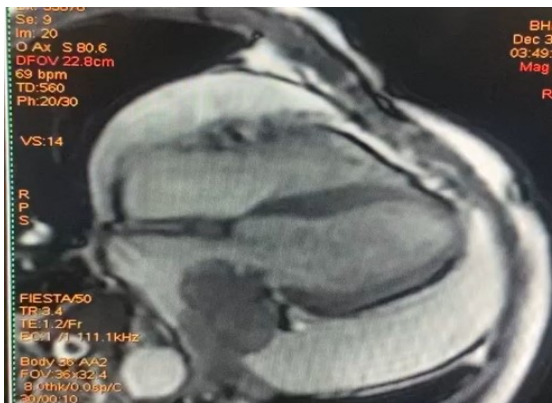


Figure 1. Left atrial tumor invaded the parietal pericardium

Due to the inability to diagnose, we decided to perform the surgery with curative intent after controlling his symptoms by pericardiocentesis. The tumorectomy and excision of the posterior wall of the left atrium were then performed. Intraoperatively, the tumor did not invade nearby structures and was shapely removed by sharp dissection. The tumor was 5x6 cm in size, solid, and irregular borders. No abnormal lymph nodes were detected.

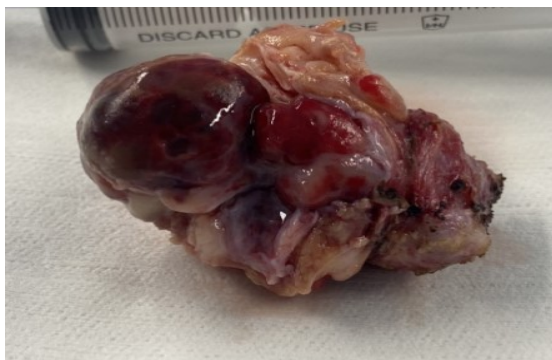


Figure 2. The gross characteristic of the left atrium tumor

Histopathologic examination showed a spindle cell sarcoma with hyperchromatic nuclei, multiple mitotic figures, and areas of haemorrhage and necrosis. In this case, endothelial differentiation is typical microscopically by formation of irregular anastomosing vascular spaces lined by spindle-shaped cells with malignant appearing. So histopathologic examination should favor angiosarcoma and be confirmed by IHC, which showed positive staining for CD31, CD34, SMA, ERG, Vim, VIII factor, and negative staining for CD117, S100, Desmin, Myogenin, CK, Caldesmon, Muc4. These two results led to a final diagnosis of spindle cell sarcoma favor angiosarcoma.² (**Figure 3**)

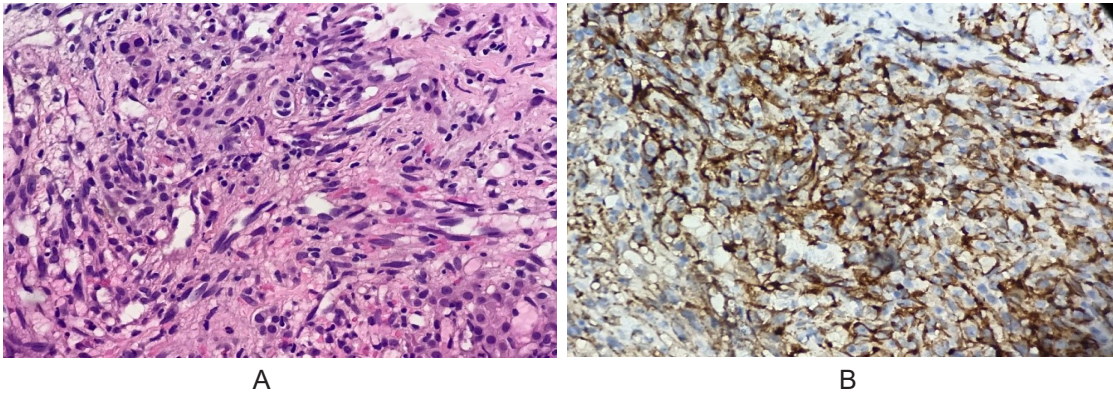


Figure 3. (A) Histologic photomicrograph (HE stain, original magnification 20×); the tumor consists of spindle-shaped cells with pleomorphic nuclei lining anastomosing vascular spaces. These findings support the diagnosis of angiosarcoma. (B) Immunohistochemistry photomicrograph (CD31 stain, original magnification 40×); the tumor cells are positive for the endothelial marker CD31, which confirms the vascular nature of the tumor

Thus, the final diagnosis was a stage IIIA angiosarcoma (pT3N0M0). After recovering from surgery, he was transferred to Hanoi Medical University Hospital for further treatment. Due to the high incidence of recurrence if left untreated, we decided to give him postoperative radiation. However, he denied radiation for fear of heart failure after treatment. Alternatively, we gave him Paclitaxel as adjuvant chemotherapy. He completed 6 cycles of chemotherapy six months ago. At present, he is doing well with no sign of recurrence on the imaging technique.

III. DISCUSSION

Primary cardiac tumors are not commonly encountered with the reported prevalence ranges from only 0.3% to 0.7% of all cardiac tumors.¹ Approximately one-quarter of all primary heart and pericardial tumors are malignant, and, of these, 75% are sarcomas.^{1,3} Of all primary cardiac sarcoma, angiosarcomas accounted for the highest percentage and most commonly located at the right atrium, followed by the left atrium.¹ This rare disease has a dismal prognosis with the survival rate at one year after diagnosis is only about 10% if left untreated.¹

In patients with primary malignant cardiac tumors, clinical presentation varies depending on the tumor location, size, and growth rate rather than the histologic subtypes.^{1,3} These characteristics could lead to congestive heart failure from intracardiac obstruction, systemic embolization, and arrhythmias due to conduction disturbances.³ Right-sided cardiac tumors tend to appear as infiltrative masses that grow in an outward pattern, thus do not present with congestive heart failure in the early stages. In contrast, left atrial sarcomas tend to be more solid and less infiltrative than right-sided sarcomas. Consequently, left-sided tumors often lead to blood-flow obstruction and substantial, life-threatening congestive heart failure.^{3,4} Our patients with left atrial tumor also presented with signs of dyspnea that gradually deteriorated, especially whenever exertion, which was concordant with symptoms of heart failure.

Regarding diagnosis, initially, pericarditis was suspected due to the rapid worsening of retrosternal pain and the presence of flattened T-waves on ECG. The 4 ECG stages of pericarditis include: 1) diffuse ST elevation

and/or PR depression, 2) normalization of ST- and PR-segments, 3) diffuse T-wave inversions with isoelectric ST-segments, and 4) normalization of the ECG. This patient had flattened T-waves after one week of symptom onset, which was consistent with ECG changes in stage 2.⁵ However, flattened T-waves could present in other abnormal statuses, including hypokalemia and ischemic heart disease. Thus, further investigations needed to be performed. We began with pericardiocentesis to both alleviate symptoms and collect specimens for cytology, but no conclusion could be made. Besides, imaging workup was also performed simultaneously, which showed an abnormal left atrial mass on echocardiogram. In this particular case, imaging is crucial to locate the abnormal mass within heart chambers, finding suspicious signs of myocardial invasion, and evaluating its mobility, which is useful in determining embolic potential and prognosis.⁴ In primary cardiac angiosarcoma, a combination of echocardiogram, cardiac magnetic resonance, and positron emission tomography has been proved to be the best method to fully evaluate the tumor and its progression throughout the body.¹ Echocardiography has the advantage of being a readily available technique that can be done at the patient's bedside without any contraindications. However, it is sometimes difficult to define whether the tumor has invaded nearby structures. Magnetic resonance imaging (MRI) has the benefit of providing more precise characterization of the tumor, including the tumor size, compression of the cardiac chambers or the great vessels, pericardial involvement, and signs of necrosis. PET/CT has potential in finding more accessible sites that could be safely biopsied, instead of proceeding to surgery without a final diagnosis. Imaging workup is also potential in excluding

other differential diagnoses, including angina pectoris, constrictive pericarditis, mediastinitis, mesothelioma, restrictive cardiomyopathy, and atrial myxoma, which is much more common than cardiac sarcoma. However, unfortunately, all preoperative workup findings were negative, and the interventional radiologists refused to perform transthoracic needle biopsy due to technical limitation. Thus, the patient had to undergo the surgery first to both solve the deteriorating symptoms and excising the entire tumor for pathology. This needs to be highlighted here since neoadjuvant chemotherapy in predefined cardiac sarcoma is gaining more attention, especially in patients whose initial resection could not achieve R0 resection.⁶ In a study of 27 patients diagnosed with cardiac sarcoma (11 patients had angiosarcoma), perioperative chemotherapy (neoadjuvant, adjuvant, or both) resulted in a survival rate of 80.9% at 1 year and 61.6% at 2 years.⁷ Another study of 44 cardiac sarcoma patients, (including 30 angiosarcoma patients) also reported that participants receiving neoadjuvant chemotherapy had a higher rate of R0 resection and better mean overall survival (20 months vs 9.5 months in patients with immediate surgery).⁸ In our report, the patient had R0 resection and the final stage was pT3N0M0, which was suitable for immediate surgery, but then again, clinicians should attempt to have the final diagnosis if possible and consider neoadjuvant treatment if needed.

In addition to the imaging workup, detailed pathologic description, and immunohistochemistry (IHC) staining pattern is a must to establish the exact diagnosis. Angiosarcoma typically presents as abnormal, pleomorphic, malignant endothelial cells with few or even no vascular structures. In cases of vascular absence, IHC with vascular markers

including von Willebrand factor, CD34, CD31, and ERG would have an important role in diagnosis.⁹ In our case, the patient had positive staining for all the above-mentioned markers.

In terms of differential diagnosis, other diseases with pericardial effusion should be excluded since they have different treatments and prognosis. Tuberculous pericarditis is often mistakenly diagnosed in cases of hemorrhagic pericardial effusion, especially in endemic areas of tuberculosis (TB) like Vietnam. The tuberculous pathogenesis of pericarditis must be established by a thorough search for acid-fast bacilli in the sputum, lymph nodes, and pericardial fluid. Polymerase chain reaction (PCR) has also been utilized for detecting *M tuberculosis* DNA in pericardial fluid. Tuberculin skin testing is of little value in endemic countries like Vietnam, because of the high prevalence of primary TB, mass Bacillus Calmette–Guérin (BCG) immunization, and the likelihood of cross-sensitization from mycobacteria present in the environment.¹⁰ However, in clinical practice, a trial of empirical antituberculous might be used for exudative pericardial effusion, after other causes such as malignancy, uremia, and trauma have been excluded.

Due to the paucity of clinical data, treatment guidelines for cardiac angiosarcoma have not yet been established. At present, surgery remains the mainstay of treatment for stage I-III cardiac angiosarcoma. In a retrospective review of 54 patients who had undergone extensive resection for atrial sarcoma (with pericardial reconstruction), Reardon et al reported that patients with negative surgical margins had a survival benefit compared to patients with positive surgical margins (median survival, 27 vs 4 months, respectively).¹¹ The Mayo Clinic reviewed a 32-year period and found 34 patients who had undergone surgical resection

of primary cardiac sarcoma; the median survival time in patients with R0 resection was significantly longer than in group of R1 resection (17 months vs 6 months, respectively).¹² Also, the combined series from MD Anderson Cancer Center and the Texas Heart Institute found 21 patients over a 25-year period; those who underwent an R0 resection had a median survival time of 24 months compared to 10 months in those underwent R1 resection.¹³ These results emphasize the vital role of complete resection in improving oncologic outcomes. Therefore, though cardiac surgery remains a technical challenge, physicians need to consider surgery whenever possible.

After surgery, the role of radiation and chemotherapy in cardiac angiosarcoma is controversial given its rarity. Indeed, most therapeutic approaches in this rare disease are extrapolated from the multidisciplinary approach of other soft tissue sarcomas. Some clinicians would omit adjuvant radiation due to the potential cardiovascular complications including pericardial disease and cardiomyopathy, while others still have a preference for adjuvant treatment. In a case report of a right atrial sarcoma with R1 resection, the patient was treated with adjuvant concurrent chemoradiotherapy (CRT) 5000 cGys/30 fractions with five cycles of weekly docetaxel (25 mg/m²). He tolerated the treatment very well and had a progression-free survival of 12 months until progressing with liver metastases. He was then undergone hepatic metastasectomy and palliative chemotherapy with weekly paclitaxel for 16 weeks until the second progression.¹⁴ This finding indicated that even if patients could not have a complete resection, they still have clinical benefit from adjuvant therapy and both radiation and chemotherapy could be safely administered. In a metastatic setting, Taxane

monotherapy is also a good alternative to Anthracycline in patients who could not tolerate Anthracycline, such as heart disease patients. In a trial of 17 angiosarcoma patients, weekly paclitaxel regimen had shown effectiveness and tolerability with a median overall survival of 18.6 months.¹⁵ Thus, in our case, we decided to give the patient weekly adjuvant paclitaxel. The patient tolerated well and showed no signs of recurrence till the most recent check-up.

In addition to chemotherapy, data from SARC028 trials suggest the promising effect of checkpoint inhibition in undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma.¹⁶ Numerous studies investigating the role of immunotherapy in soft tissue sarcoma are also currently ongoing, but many exclude rare subtypes such as angiosarcoma. Thus, further trials needed to be done to confirm the usefulness of immunotherapy in this rare disease.

IV. CONCLUSION

To summarize, primary cardiac angiosarcoma is a rare soft-tissue sarcoma associated with a dismal prognosis. Clinicians should be aware of this rare disease to be able to distinguish it from common disease like pericarditis. Surgical resection with an R0 margin remains the mainstay of treatment, followed by the role of radiation and chemotherapy in certain circumstances. Our case also indicates that unexplained pericardial effusion should prompt the clinician to seek for a malignant etiology, even when fluid cytology results are negative. Further randomized controlled trials are needed to investigate novel treatment options for this devastating condition.

REFERENCES

1. Leja MJ, Shah DJ, Reardon MJ. Primary cardiac tumors. *Tex Heart Inst J*. 2011;38(3):261-

262.

2. Burke A, Tavora F. The 2015 WHO Classification of Tumors of the Heart and Pericardium. *J Thorac Oncol*. 2016;11(4):441-452.

3. Gupta R, Meghrajani V, Desai R, Gupta N. Primary Malignant Cardiac Tumors: A Rare Disease With an Adventurous Journey. *J Am Heart Assoc*. 2020;9(10):e016032.

4. Yadav U, Mangla A. Primary pericardial angiosarcoma: case report and review of treatment options. *Ecancermedicalscience*. 2020;14:1056.

5. Marinella MA. Electrocardiographic manifestations and differential diagnosis of acute pericarditis. *Am Fam Physician*. 1998;57(4):699-704.

6. Mangla A, Yadav U. *Leiomyosarcoma*. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. <http://www.ncbi.nlm.nih.gov/books/NBK551667/>.

7. Bakaeen FG, Jaroszewski DE, Rice DC, et al. Outcomes after surgical resection of cardiac sarcoma in the multimodality treatment era. *J Thorac Cardiovasc Surg*. 2009;137(6):1454-1460.

8. Abu Saleh WK, Ramlawi B, Shapira OM, et al. Improved Outcomes With the Evolution of a Neoadjuvant Chemotherapy Approach to Right Heart Sarcoma. *Ann Thorac Surg*. 2017;104(1):90-96.

9. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol*. 2010;11(10):983-991.

10. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005;112(23):3608-3616.

11. Reardon MJ. Malignant tumor overview. *Methodist Debaquey Cardiovasc J*. 2010;6(3):35-37.

12. Simpson L, Kumar SK, Okuno SH, et al. Malignant primary cardiac tumors: review of a single institution experience. *Cancer*. 2008;112(11):2440-2446.

13. Putnam JB, Sweeney MS, Colon R,

Lanza LA, Frazier OH, Cooley DA. Primary cardiac sarcomas. *Ann Thorac Surg.* 1991;51(6):906-910.

14. Jang Y, Kim J, Shim JW, et al. Primary cardiac angiosarcoma: a prolonged response to surgical resection followed by concurrent chemoradiotherapy with docetaxel. *Springerplus.* 2016;5:648.

15. Apice G, Pizzolorusso A, Di Maio

M, et al. Confirmed Activity and Tolerability of Weekly Paclitaxel in the Treatment of Advanced Angiosarcoma. *Sarcoma.* 2016;2016:6862090.

16. Keung EZ, Burgess M, Salazar R, et al. Correlative Analyses of the SARC028 Trial Reveal an Association Between Sarcoma-Associated Immune Infiltrate and Response to Pembrolizumab. *Clin Cancer Res.* 2020;26(6):1258-1266.