JACC: CASE REPORTS VOL. 3, NO. 5, 2021

MINI-FOCUS ISSUE: CARDIO-ONCOLOGY

INTERMEDIATE

CASE REPORT: CLINICAL CASE

An Unusual Cause of Functional Mitral Stenosis

A Left Atrial Intimal Sarcoma

Jamie E. Diamond, MD, MPH,[a] Michael Y. Mi, MD,[a] Paul A. VanderLaan, MD, PhD,[b] Louis Chu, MD,[c] Eli V. Gelfand, MD[a]

ABSTRACT

Primary cardiac tumors are rare, with an incidence of <0.1% in postmortem series; sarcomas comprise 75% of these. Cardiac sarcomas may be life-threatening at the time of presentation. We describe a left atrial intimal sarcoma presenting with constitutional symptoms, obstructive shock, and systemic emboli, and treated with proton beam therapy. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:829–33) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 51-year-old woman presented with 1 day of sudden-onset fatigue, subjective fever, headache, and dyspnea with minimal exertion.

On physical examination, the patient was tachycardic to 104 beats/min, blood pressure was 111/73 mm Hg, oxygen saturation was 94% on 2 l/min oxygen by nasal cannula, and temperature was 36.9°C. Cardiac examination was notable for regular tachycardia and no audible murmurs. Diffusely decreased breath sounds and rales in the bilateral lower lung fields were noted. Laboratory studies showed elevated inflammatory markers, including a white blood cell count of 13.7 × 10^3/μl with 81%

LEARNING OBJECTIVES

- To highlight the triad of symptoms common to intracardiac cavitary masses including constitutional, embolic, and obstructive phenomena.
- To describe the rare clinical entity of a cardiac left atrial intimal sarcoma.
- To review an alternate cause of mitral stenosis physiology.
- To emphasize novel treatment modalities as emerging therapeutics for intracardiac intimal sarcomas including proton beam therapy and therapies targeting MDM2 cytogenetics.

From the [a]Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; [b]Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; and the [c]Department of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 13, 2020; revised manuscript received January 26, 2021, accepted February 28, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.02.043

ABBREVIATIONS AND ACRONYMS

CT = computerized tomography

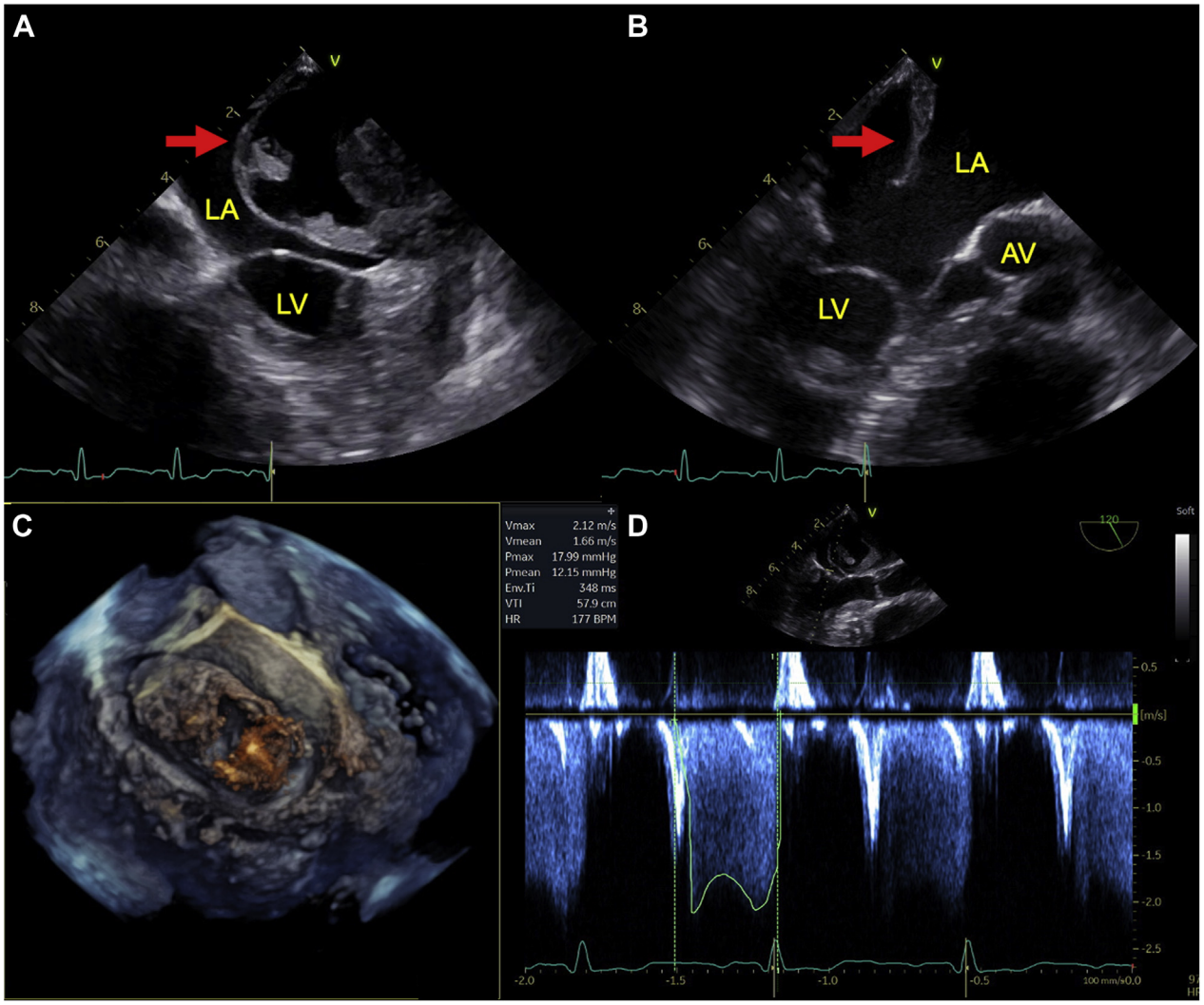
MDM2 = mouse double minute 2 homolog

MRI = magnetic resonance imaging

neutrophil predominance, C-reactive protein of 100.8 mg/l, lactic acid dehydrogenase of 337 U/l, and ferritin of 274 ng/ml. Chest radiograph revealed diffuse bilateral interstitial infiltrates.

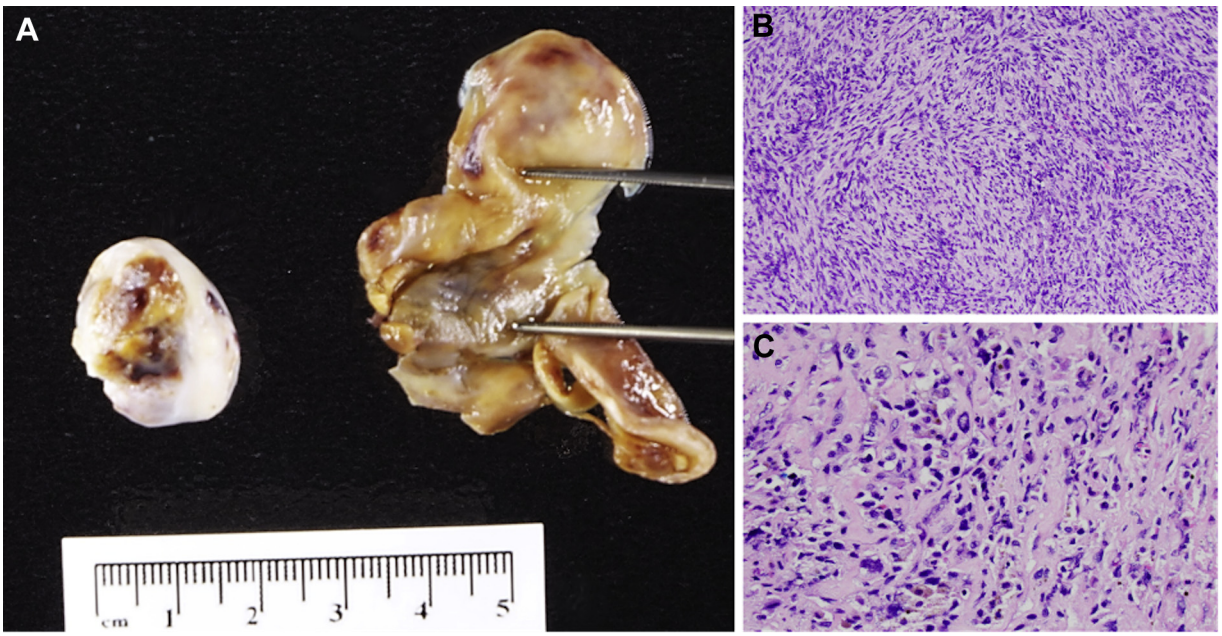
During the subsequent 72 h, her clinical course rapidly progressed with hypoxemic respiratory failure requiring endotracheal intubation and mechanical ventilation. Transthoracic echocardiogram performed to evaluate for the cause of heart failure symptoms revealed a left atrial mass with intermittent obstruction of left ventricular inflow, right ventricular dilation with mildly reduced systolic function, mild mitral and aortic regurgitation, severe tricuspid regurgitation, and severe pulmonary hypertension. Due to obstructive shock impairing cardiac output she was initiated on vasopressors. The patient was transferred to our hospital for consideration of advanced therapies. Hypotension precipitated acute tubular necrosis and renal failure requiring continuous renal replacement therapy. Due to refractory hypoxemia caused by obstruction of pulmonary venous return, she required paralysis and prone positioning.

FIGURE 1 Transesophageal Echocardiographic Images of Left Atrial Mass



(A) Multilobulated mass **(solid red arrow)** attached to the left atrial (LA) ridge. **(B)** Separate fibrinous attachment **(solid red arrow)** attached to the LA roof. **(C)** Three-dimensional visualization of the LA mass. **(D)** Severe diastolic left ventricular (LV) inflow obstruction with a transmitral gradient of 12 mm Hg. AV = aortic valve.

FIGURE 2 Surgical Gross Pathology and Histology



(A) Gross image of the resected tissue demonstrating a solid pedunculated white/tan nodule measuring 2.1 × 2.0 cm with smooth surfaces and central necrosis on cut section, and an additional fragment of tan/red smooth-walled cyst wall measuring 5.0 × 3.5 cm. **(B)** Histological evaluation highlights the cytologically malignant spindle cell neoplasm with a fascicular growth pattern (hematoxylin and eosin stain, 200× original magnification). **(C)** Other areas showed tumor cells with a varied epithelioid morphology and marked tumor cell pleomorphism (hematoxylin and eosin stain, 400x original magnification).

MEDICAL HISTORY

Before presentation she had nonalcoholic fatty liver disease, obesity, and osteoarthritis of the knees. She was a former smoker with a 2 pack-year smoking history.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient's left atrial mass included primary cardiac tumor (cardiac myxoma, papillary fibroelastoma, or malignant sarcoma), metastatic tumor, organizing thrombus, vegetation, bronchogenic cyst, or hydatid cyst.

INVESTIGATIONS

Transesophageal echocardiogram performed to better characterize the left atrial mass showed a 4.0- × 3.6-cm multilobulated mass with both solid and cystic components attached to the left lateral atrial ridge (**Figures 1A and 1C,** Video 1). There was a smaller, separate fibrinous attachment to the roof of the left atrium (**Figure 1B,** Video 2). The larger mass obstructed the mitral valve inflow with a mean gradient of 12 mm Hg (**Figure 1D**). Testing for novel coronavirus disease-2019, echinococcus, tuberculosis, and cultures for bacteria and fungi were unrevealing.

MANAGEMENT

After improvement in respiratory status the patient had a slow neurological recovery off of sedation. A contrast-enhanced magnetic resonance imaging (MRI) study of the brain demonstrated multiple embolic lesions. Recurrent paroxysmal atrial fibrillation with rapid ventricular rate precipitated hemodynamic compromise requiring initiation of amiodarone. Although initially deferred due to hemodynamic instability and unclear neurological prognosis, after extubation and shared decision making with the patient, her family, cardiac surgery, and cardiac intensive care teams, the patient underwent surgical resection of the left atrial mass. Gross pathological findings confirmed a solid pedunculated tan tumor with smooth surfaces and central necrosis and an additional red smooth-walled cyst (**Figure 2A**). Histological evaluation revealed a pleomorphic malignant neoplasm, ranging from areas with a spindle cell morphology showing orderly fascicular growth

JACC: CASE REPORTS, VOL. 3, NO. 5, 2021
MAY 2021:829–33

along with other areas showing epithelioid cells with marked nuclear atypia (**Figures 2B and 2C**). The overall tumor morphology and accompanying diagnostic immunohistochemical stain work-up was consistent with an intimal sarcoma. Resection margins were involved. Chest tomography (CT) of the abdomen and pelvis showed no evidence of metastases.

DISCUSSION

Primary cardiac tumors are rare (incidence <0.03%) and only one-quarter are malignant (1). The majority of primary malignant cardiac tumors are mesenchymal-origin sarcomas (2). Intimal (spindle cell) sarcoma is a rare, highly aggressive undifferentiated sarcoma arising from intimal subendothelial cells of the great vessels or the heart (3). Pathological findings include atypical, tightly packed spindle-shaped cells with varying degrees of necrosis, hemorrhage, cellular atypia, pleomorphism, and mitotic activity (1,2). Intimal sarcomas typically harbor amplification of the mouse double minute 2 homolog (MDM2) gene (1,4), as was the case with this tumor.

Median presenting age of intimal sarcomas is 42 years with slight female predominance (1). Prognosis is poor with a mean survival <1 year due to diagnostic delay, therapeutic difficulty, and high metastatic potential of the tumor (5).

Presentation of intimal sarcoma varies and diagnostic suspicion must be high as symptoms and imaging can be nonspecific (2). Our patient demonstrated the classic triad of intracavitary cardiac masses with constitutional, embolic, and obstructive manifestations (2,6). These included her presentation with systemic symptoms and elevated inflammatory markers as well as brain MRI scan with evidence of emboli. In this case, mitral valve obstruction due to a large left atrial mass led to a marked decrease in left ventricular end-diastolic volume, stroke volume, and cardiac output. Left atrial hypertension contributed to the onset of atrial tachyarrhythmias and precipitated further hemodynamic compromise.

For diagnostic purposes, transesophageal echocardiography is a preferred modality for reliable demonstration of tumor size, location, and anatomic attachment, as well as mobility and estimation of embolization risk (5). Additional imaging modalities including MRI, CT, and positron emission tomography/CT may assist in forming a differential diagnosis and can reveal extracardiac metastases, which are present in up to 80% of patients at the time of diagnosis (5).

Complete resection of intimal sarcoma is the goal of therapy because clear margins approximately double life expectancy. However, feasibility of complete resection is often limited due to tumor involvement with contiguous vital cardiac structures (1). No evidence-based management guideline is available for treatment strategies. Data for chemotherapy and radiotherapy use is mixed (5,7,8). Novel treatment therapies including those aimed at MDM2 oncogene overexpression are under investigation (6). Proton beam therapy is an emerging treatment used to maximally spare uninvolved cardiac structures and was used in this case with a goal of improving long-term survival (8).

FOLLOW-UP

The patient had an uncomplicated postoperative recovery. Proton beam therapy was initiated with a plan for 37 fractions totaling 6,600 centiGray. Adjuvant chemotherapy was deferred.

CONCLUSIONS

Cardiac intimal sarcoma is a rare, aggressive disease entity with poor prognosis. Presentation varies but may include constitutional, embolic, and obstructive phenomena. Surgical excision with tumor-free margins is the mainstay of treatment but is often not feasible. Emerging treatments including proton therapy may decrease recurrence and improve survival.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. VanderLaan has received consulting fees from Gala Therapeutics, Caris Life Sciences, Flatiron Health, Intuitive Surgical, and Clearview Healthcare Partners. Dr. Gelfand is a Director of PharMate Inc. and is on the Advisory Board of Dyad Medical, all unrelated to the current work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Jamie E. Diamond, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Baker 4th Floor, Boston, Massachusetts 02215, USA. E-mail: jdiamon1@bidmc.harvard.edu.

REFERENCES

1. Grant L, Morgan I, Sumathi VP, Salmons N. Intimal sarcoma of the left atrium presenting with transient ischaemic attack – a case report and review of the literature. J Cardiol Cases 2020;21:89–92.

2. Mendes EM, Ferreira A, Felgueiras P, et al. Primary intimal sarcoma of the left atrium presenting with constitutional symptoms. Oxford Med Case Reports 2017;2017:109–12.

3. Ibrahim A, Luk A, Singhal P, et al. Primary intimal (spindle cell) sarcoma of the heart: a case report and review of the literature. Case Rep Med 2013;2013:461815.

4. Jimbo N, Komatsu M, Itoh T, Hirose T. MDM2 dual-color in situ hybridization (DISH) aids the diagnosis of intimal sarcomas. Cardiovasc Pathol 2019;43:107142.

5. Moeri-Schimmel R, Pras E, Desar I, Krol S, Braam P. Primary sarcoma of the heart: case report and literature review. J Cardiothorac Surg 2020;15:104.

6. Dewaele B, Floris G, Finalet-Ferreiro J, et al. Tumor and stem cell biology coactivated platelet-derived growth factor receptor α and epidermal growth factor receptor are potential therapeutic targets in intimal sarcoma. Cancer Res 2010;70:7304–14.

7. Valecha G, Pau D, Nalluri N, Liu Y, Mohammad F, Atallah JP. Primary intimal sarcoma of the left atrium: an incidental finding on routine echocardiography Case Report. Rare Tumors 2016;8:6389.

8. Aurelia A, Brun-Ly Valerie L, Sophie L, et al. Cardiac intimal sarcoma with complete response to thoracic radiotherapy-A case report. Arch Clin Med Case Rep 2020;4:483–90.

KEY WORDS acute heart failure, cancer, echocardiography, imaging, intimal sarcoma

APPENDIX For supplemental videos, please see the online version of this paper.