A case report of primary cardiac intimal sarcoma presenting with atrial fibrillation and a left atrial mass

Karen Ho1, Kavya Yatham1, Rommel Seno1,2, and Omar Sultan1,3*

1Department of Medicine, University of Saskatchewan College of Medicine, 103 Hospital Drive, Saskatoon, SK, Canada S7N 0W8; 2Department of Pathology and Laboratory Medicine, Saskatchewan Health Authority, 4101 Dewdney Avenue, Regina, SK, Canada S4T 1A5; and 3Department of Cardiology, Saskatchewan Health Authority, 1440 14th Avenue, Regina, SK, Canada S4P 0W5

Received 10 May 2021; first decision 9 June 2021; accepted 5 October 2021; online publish-ahead-of-print 7 October 2021

Background
Intimal sarcoma is an exceedingly rare type of primary cardiac tumour. It is characterized by poorly differentiated spindle-shaped cells that can mimic smooth muscle and is strongly associated with MDM2 genetic amplification. Owing to its rarity and non-distinctive histological features, diagnosis remains a significant challenge.

Case summary
In this case report, we describe a case of primary cardiac intimal sarcoma in a 37-year-old woman who presented with atrial fibrillation (AF) and a left atrial mass. Despite having a histological sample from an excised left atrial mass, the diagnosis was not made until she presented with back pain secondary to metastatic disease to the spine.

Discussion
Primary cardiac intimal sarcoma is an extremely rare diagnosis. The mainstay management of intimal cardiac sarcoma is aggressive surgical resection. Unfortunately, the prognosis of cardiac sarcomas remains very poor, with a mean survival between 3 months and 1 year. This case of cardiac intimal sarcoma highlights the difficulty in establishing a diagnosis, particularly given the unusual presentation of AF.

Keywords
Intimal sarcoma • Cardio-oncology • Cardiac tumour • Atrial fibrillation • Case report

ESC Curriculum
2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 5.3 Atrial fibrillation • 6.8 Cardiac tumours

Introduction
Intimal sarcoma is an exceedingly rare type of primary cardiac tumour. It is characterized by poorly differentiated spindle-shaped cells that can mimic smooth muscle and is strongly associated with MDM2 genetic amplification. Owing to its rarity and non-distinctive histological features, diagnosis remains a significant challenge. In this case report, we describe a case of primary cardiac intimal sarcoma in a 37-year-old woman who presented with atrial fibrillation (AF).
Timeline

| Date       | Event Description                                                                 |
|------------|----------------------------------------------------------------------------------|
| February 2017 | The patient was referred to the electrophysiology service for management of paroxysmal atrial fibrillation. |
| March 2017 | An attempt at pulmonary vein isolation was attempted, but the procedure was aborted due to an extremely thick septum. |
| June 2017 | Transeosophageal echocardiogram revealed a sheet-like mass lining the left atrium, suspicious for a thrombus. |
| June 2018 | A cardiac magnetic resonance imaging (MRI) characterized a 4.7 x 1.3 cm mass in the atrium, believed to be an atrial myxoma. |
| January 2019 | The patient underwent radical excision of the left atrial mass. She was discharged on postoperative day #6. |
| April 2019 | Repeat cardiac MRI revealed complete resection of the left atrial mass, believed to be an organizing thrombus. |
| May 2020 | The patient presented with back pain secondary to T10 and L1 pathological fractures. She underwent vertebral body biopsies and vertebroplasty. Initial pathology suggested a diagnosis of metastatic leiomyosarcoma. |
| June 2020 | Repeat MRI revealed interval increase in the spinal canal encroachment at T10 and L1 vertebral bodies. She underwent surgical decompression and instrumental fusion of the affected vertebral levels. |
| August 2020 | Pathological review of the left atrial mass and vertebral biopsies confirmed the diagnosis of high-grade intimal sarcoma. |
| September 2020 | The patient underwent 6 weeks of stereotactic body radiation therapy. |
| February 2021 | The patient presented with shortness of breath secondary to a large right pleural effusion. Repeat MRI shows progression of an anterior paraspinal soft tissue mass at the T10 and L1 level. |
| February 2021 | The patient was started on an anthracycline-based chemotherapy regimen, including Adriamycin/Ifosfamide mesna for palliation. |

Case presentation

A 37-year-old woman was referred to the cardiac electrophysiology service for management of paroxysmal AF. Her past medical history was significant for a remote cholecystectomy. Cardiovascular and respiratory examination did not reveal any abnormal finding. A pulmonary vein isolation ablation was attempted, but an extremely thick inter-atrial septum precluded transseptal puncture and access to the left atrium. The patient’s AF was managed with propafenone in the interim.

Transthoracic and transeosophageal echocardiogram revealed a clot-like mass lining almost the entire left atrium, extending into the left atrial appendage (Figures 1–6). A second opinion from a specialist in echocardiography concluded that the differential diagnoses included thrombus, fat, or tumour, and recommended a cardiac magnetic resonance imaging (CMR) for further characterization. Cardiac magnetic resonance imaging revealed a sheet-like mass adherent to the septal side of the left atrial cavity, measuring 4.7 x 1.3 cm (Figure 7). The mass is isointense to myocardium on pre-contrast T1 imaging, mildly hyperintense to myocardium on the T2-weighted sequence and hyperintense on Short-T1 Inversion Recovery (Figures 7–9). Based on the signal characteristics and enhancement, although the elongated sessile appearance was noted to be atypical, the conclusion was that the mass was most in keeping with an atrial myxoma. The patient underwent open cardiac surgery and excision of the atrial
mass (Figure 10). Intra-operatively, the mass was noted to be very fibrotic and densely adherent throughout the left atrial wall extending down towards the mitral leaflets and into each of the pulmonary vein orifices. A frozen section of the mass, after haematoxylin and eosin staining, revealed dense fibrous tissue, with areas of fibrin undergoing organization. As well, there were areas of chronic inflammation and somewhat atypical but reactive appearing stromal cells (Figure 11A and B). There was no cardiac myxoma cells forming ring structures, or other structures that would be diagnostic of an atrial myxoma. Although there is some uncertainty, the tissue was thought to be in keeping with a mural thrombus undergoing organization.

Sixteen months post-surgery, the patient presented to the hospital with severe back pain. A magnetic resonance imaging revealed aggressive lytic pathologic fractures involving the T10 and L1 vertebral bodies, with a paravertebral soft tissue mass at L1, concerning for metastatic disease. The primary malignancy, however, was unclear. The patient underwent vertebral body biopsies revealing a malignant spindle cell tumour suggestive of smooth muscle differentiation (Figure 11C and D). The tumour cells were positive for muscle markers, desmin, and smooth muscle actin (SMA), pointing towards a leiomyosarcoma. Mammogram, Papanicoulou test, and computed tomography of the chest, abdomen, and pelvis did not identify a primary malignancy.

Due to the lack of a primary malignancy identified and the atypical appearance of the cardiac mass resected a year ago, both the cardiac and vertebral biopsies were sent for further analyses. The atrial mass had foci of moderately atypical spindle-shaped cells with mitotic activity that raised concern for spindle cell sarcoma. The T10 vertebral body also showed similar atypical spindle cells. A series of immunohistochemistry analyses revealed strong nuclear expression of MDM2, with patchy SMA and pankeratin expression. Fluorescence in situ hybridization (FISH) analysis demonstrated convincing evidence of MDM2 genetic amplification, with an MDM2/CEP12 ratio of 7.8.
These findings supported the diagnosis of an intimal sarcoma of atrial origin, with subsequent metastases to the vertebral bodies. The patient received 6 weeks of stereotactic body radiation but returned 7 months later with a large pleural effusion and progression of the anterior paraspinal mass. Her case was discussed at Tumour Boards and an anthracycline-based regimen, including Adriamycin/Ifosfamide mesna, and Dacarbazine was initiated for palliation.

Discussion

Primary cardiac tumours are extremely uncommon, with an incidence of 0.001–0.03% based on post-mortem studies. Approximately a quarter of primary cardiac tumours are malignant, with the majority being sarcomas. Intimal sarcoma is a particularly rare subtype, usually encountered in great vessels like the pulmonary artery and aorta, but rarely in the heart.
The rarity of this condition and its non-distinctive histological differentiation create a challenge in diagnosing primary cardiac intimal sarcomas. Intimal sarcomas are poorly differentiated mesenchymal tumours, composed of spindle cells with variable degrees of atypia, mitotic activity, necrosis, and nuclear polymorphism. Most reported cases are immunohistochemically positive for vimentin and alpha-SMA. There exists significant heterogeneity and uncertainty regarding this diagnosis, with many simply described as undifferentiated pleomorphic sarcomas. A breakthrough was the discovery of MDM2 overexpression in intimal sarcomas. MDM2 is an oncogene that blocks p53 activity. Neuville et al. found that MDM2 overexpression is highly suggestive of the diagnosis of intimal sarcoma and helps to differentiate from other subtypes of cardiac tumours.

The diagnostic challenge of primary intimal cardiac sarcoma is highlighted in this case. The patient’s mass was initially thought to be an atrial myxoma on CMR, a differential that is commonly reported in case studies. Atrial myxomas tend to arise from the septum and have a stalk-like base with well-demarcated margins. Malignant tumours, on the other hand, tend to have poorly defined margins and are associated with infiltration into nearby structures. This case highlights that no imaging technique alone can be relied on to discern the nature of a cardiac mass, and an excisional biopsy should be undertaken, particularly in cases with an uncertain diagnosis. The histological findings of the cardiac tumour did not identify any myxoma cells but were thought to be in keeping with an organizing thrombus based on findings of fibrin. Interestingly, intimal sarcomas, often found in the pulmonary artery, are commonly mistaken as pulmonary embolisms. However, upon further histological review, although there are organizing thrombi present, there are also foci of moderately atypical spindle-shaped cells present, concerning for spindle cell sarcoma. The vertebral body biopsy was initially diagnosed as a leiomyosarcoma, another common differential. Leiomyosarcoma can present similarly to intimal sarcomas with striated spindle cells positive for markers such as vimentin and alpha SMA. Leiomyosarcomas, however, tend to be better differentiated, is positive for desmin or caldesmon, and is commonly found in the vena cava. Nonetheless, these features are non-specific and the diagnosis of intimal sarcoma relies heavily on the overexpression of MDM2. Rare diseases can be difficult to diagnose, and while not every specimen warrants advanced immunohistochemistry or molecular cytogenetic analyses, in cases with atypical presentation and uncertain diagnosis, further investigation is needed and may lead to earlier diagnosis.

One of the unique aspects of this case was its presentation—paroxysmal AF. Symptoms and signs from cardiac tumours can arise from intracardiac obstruction and systemic embolization. Although cardiac arrhythmias have been mentioned as a symptom, AF has not been reported in primary cardiac intimal sarcomas. Cases in the literature have described dyspnoea, myocardial infarction, and stroke as presenting symptoms. This case reminds clinicians that cardiac tumours can have a wide variety of presentations. As cardiac...
tumours, including intimal cardiac sarcomas, commonly arise in the left atrium, the development of AF in a patient should prompt investigation with an echocardiogram.

The mainstay management of intimal cardiac sarcoma is aggressive surgical resection with negative margins. Complete resection, however, is often not feasible due to late diagnosis and large tumour size. Nonetheless, a retrospective study of 124 patients found that surgical resection, whether complete or partial, was associated with prolonged survival. Although chemotherapy and radiotherapy have been reported to have limited benefit, a recent study by Frezza et al. found a real-world overall response rate of 38% with an anthracycline-based chemotherapy regimen. Unfortunately, the prognosis of cardiac sarcomas remains very poor, with mean survival between 3 months and 1 year. By the time, this case report was submitted, it would have been 48 months since this patient’s first presentation, which would make her one of the longer survivors of this disease.

In conclusion, primary cardiac intimal sarcoma is a rare diagnosis. We described a case in a 37-year-old woman presenting with paroxysmal AF. Although there has been significant advancement in imaging technique, early detection of rare cardiac tumour remains a challenge. Despite having a histological sample from an excised left atrial mass, the diagnosis was not made until she presented with back pain secondary to metastatic disease to the spine. This case of cardiac intimal sarcoma highlights the difficulty in establishing the diagnosis, particularly given the unusual presentation.

Acknowledgements
We would like to thank Drs Ayman Abogudah (Cardiology), Colin Yeung (Cardiology), John Tsang (Cardiac Surgery), and Wojciech Dolata (Medical Oncology) for their contribution to this case.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: There is no conflict of interest to declare.

Funding: None declared.

References
1. Neuvillette A, Collin F, Bruneval P, Parrrens M, Thivolet F, Gomez-Brouchet A et al. Intimal sarcoma is the most frequent primary cardiac sarcoma: clinicopathologic and molecular retrospective analysis of 100 primary cardiac sarcomas. Am J Surg Pathol 2014;38:461–469.
2. Bussani R, Castrichini M, Restivo L, Fabris E, Porcari A, Ferro F et al. Cardiac tumors: diagnosis, prognosis, and treatment. Eur J Cardiothorac Surg 2020;58:1–13.
3. Moeni-Schimmel R, Pras E, Desar I, Krol S, Braam P. Primary sarcoma of the heart: case report and literature review. J Cardiothorac Surg 2020;15:1–6.
4. Ibrahim A, Lu K, Singhal P, Wan B, Zavodni A, Cusimano R et al. Primary intimal (spindle cell) sarcoma of the heart: a case report and review of the literature. Case Rep Med 2013;2013:461815.
5. Winther C, Timmermans-Wielenga V, Dauggaard S, Mortensen SA, Sander K, Andersen GB. Primary cardiac tumors: a clinicopathologic evaluation of four cases. Cardiovasc Pathol 2011;20:63–67.
6. Agaimy A, Rosch J, Weyand M, Streeker T. Primary and metastatic cardiac sarcomas: a 12-year experience at a German heart center. Int J Clin Exp Pathol 2012;5:928–938.
7. Cho GJ, Kim HJ, Kang JS. Primary cardiac sarcoma in pregnancy: a case report. J Korean Med Sci 2006;21:940–943.
8. Li Z, Hsieh T, Hi A. Recurrent cardiac intimal (spindle cell) sarcoma of the left atrium. J Cardiothorac Vasc Anesth 2013;27:103–107.
9. Modi A, Lipeviecius A, Moorjani N, Haw M. Prolonged survival with left atrial spindle cell sarcoma. Interact Cardiovasc Thorac Surg 2009;8:703–704.
10. Lu P, Yin B. Misdiagnosis of primary intimal sarcoma of the pulmonary artery as chronic pulmonary embolism: a case report. World J Clin Cases 2020;8:986–994.
11. Isambert N, Ray-Coquard I, Italiano A, Rios M, Kerbrat P, Gauthier M et al. Radiotherapy for primary cardiac sarcomas: a molecular retrospective analysis of 100 primary cardiac sarcomas. Eur J Cancer 2014;50:128–136.
12. Grebenc ML, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics 2001;20:1073–1103.
13. Frezza AM, Assi T, Lo Vullo S, Ben-Ami E, Dufresne A, Yonemori K et al. Systemic treatments in MDM2 positive intimal sarcoma: a multicentre experience with anthracycline, gemcitabine, and pazopanib within the World Sarcoma Network. Cancer 2020;126:98–104.
14. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. Lancet Oncol 2005;6:219–228.
15. Gupta A. Primary cardiac sarcomas. Expert Rev Cardiovasc Ther 2008;6:1295–1297.

Supplementary material
Supplementary material is available at European Heart Journal - Case Reports online.

Lead author biography
Dr Karen Ho is a 3rd-year Internal Medicine resident at the University of Saskatchewan in Canada. She completed her undergraduate degree at Johns Hopkins University in the USA and her medical degree at the University of Toronto in Canada. She will be pursuing a fellowship in Cardiology at Dalhousie University in Halifax, Canada. She has an interest in women’s heart health and quality improvement.