

Immunohistochemical diagnosis of primary cardiac leiomyosarcoma in a Latin American patient

Ruben Blachman-Braun,¹
 Carlos Manuel Aboitiz-Rivera,²
 Alberto Aranda-Fraustro,³
 Adrián Ransom-Rodríguez,⁴
 Mario Enrique Baltazares-Lipp,²
 Jorge Manuel Catrip-Torres,⁵
 Jesús Octavio Martínez-Reding⁶

¹Centro de Investigación en Ciencias de la Salud, Facultad de Ciencias de la Salud, Universidad Anáhuac México Norte;

²Echocardiography and Hemodynamics Service, Instituto Nacional de Enfermedades Respiratorias, Tlalpan, Mexico City; ³Department of Pathology, Instituto Nacional de Cardiología Ignacio Chavez, Mexico City; ⁴Department of Hepatopancreatobiliary Surgery, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; ⁵Department of Cardiovascular Surgery and ⁶Department of Cardiology, Instituto Nacional de Cardiología Ignacio Chavez, Mexico City, Mexico

Abstract

Primary cardiac malignancies are rare entities. Although sarcomas enclosed the main group of malignant heart neoplasms, primary cardiac leiomyosarcomas are extremely rare and constitutes less than 8% of cardiac tumors. Leiomyosarcoma usually originates from the pulmonary veins and have a worm-like shaped structure. In this article, we present a case of a 40-year-old Hispanic man diagnosed with a cardiac tumor who underwent surgical resection, during pathological examination the tissue samples were consistent with a malignancy of mesenchymal origin that contained irregular bundles of spindle cells. Subsequent immunohistochemical study categorized the mass as a primary heart leiomyosarcoma with positive smooth muscle actin and muscle specific actin. As usual in this type of malignancy, patient's clinical status declined overtime, recurrence was diagnosed two months after surgery, and four months after the procedure the patient was discharge for palliative care.

Introduction

Heart tumors are rare entities. The most

common origin of cardiac tumors are metastases, which are 40 to 100 times more frequent than primary cardiac tumors. The main source of cardiac metastases are lung, breast and renal cancer. The estimated frequency of primary tumors of the heart ranges from 0.0017% to 0.33%, of which 75% are benign. Sarcomas are the more prevalent heart malignant neoplasms and the most frequent subtype of cardiac sarcoma is angiosarcoma, followed by undifferentiated high-grade pleomorphic sarcoma (myxofibrosarcoma) and rhabdomyosarcoma.^{1,2} Generally, tumors in right heart chambers correlates with angiosarcomas, while other sarcomas are found in the left heart.³

Primary cardiac leiomyosarcoma is considered when a leiomyosarcoma arises from one of the heart chambers (usually left atrium), those type of tumors are extremely rare and constitutes less than 8% of cardiac tumors.^{2,4} In relation to population distribution, they typically occurs in the fourth decade of life, without gender predilection and often remains asymptomatic until advanced stages.⁵

In this article, we present the third case,^{6,7} to our knowledge, of a Latin American patient with this type of tumor, in addition a literature review of the histopathological and clinical aspects of this entity are provided.

Case Report

A 40-year-old Hispanic man with history of 10 months progressively worsening dyspnea which was exacerbated during exercise. Suddenly during physical activity, the patient presented a syncopal episode, so he was referred for cardiologic evaluation where transeophageal echocardiography was performed, reporting a left atrial mass (46×47 mm) protruding through the mitral valve orifice during ventricular diastole (Figure 1A) with pulmonary artery systolic pressure of 105 mmHg, consistent with severe pulmonary hypertension and a left ventricular ejection fraction of 62%. Posteriorly, a complementary computed tomography (CT) scan confirmed the diagnosis (Figure 1B).

He underwent open heart surgery and during the procedure it was reported that the tumor has an apparent origin on the left inferior pulmonary vein lumen, lateral to the ligament of Marshall; the mass was attached to left atrium wall in several locations and to the inferior right pulmonary vein, suggesting auricular invasion. Therefore, it was difficult to precise the real origin, nonetheless, the wide base of the tumor was in the left pulmonary vein and its projection follow blood directionality. Tumor resection, mitral valve replacement for mechanic valve (26 mm) and auricular reconstruction were achieved without complica-

Correspondence: Ruben Blachman-Braun, Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud, Universidad Anáhuac México, Av. Universidad Anáhuac No 46, Colonia Lomas Anáhuac, Huixquilucan, Edo. de México, CP 52786, México. Tel.: +52.55.56270210. E-mail: rubenblachman@gmail.com

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tions. Next day after surgery a major mediastinal bleeding episode occurred, which was resolved during surgical reintervention. After discharge, patient was referred to the National Institute of Oncology (Instituto Nacional de Cancerología, INCAN) for multidisciplinary treatment.

The pathologist described a 6×5×3 cm mass in a C letter (worm-like) shaped structure with a red-brown irregular surface (Figure 2). Then a longitudinal section was performed, showing a white internal surface with several small areas of hemorrhagic appearance. Histological analysis was consistent with malignancy of mesenchymal origin, the tumor contained irregular bundles of spindle cells, with a high atypical mitotic rate, some of the cells have large vesiculated nuclei and others were multinucleated, suggesting sarcoma (Figure 3A-D). In the immunohistochemical study, neoplastic cells were focally positive for smooth muscle actin (SMA) (Figure 3E), positive for vimentin and muscle specific actin (MSA) (Figure 3F), and negative for desmin, S100 proteins, CD 31, epithelial membrane antigen and factor VIII.

Overall, the pathological analysis was consistent with a vascular leiomyosarcoma. Moreover, tumor cell free surgical margins were not achieved; the mitral valve leaflets were slightly thickened.

Two months after surgery, the patient was admitted with hemoptysis and dyspnea. A CT scan revealed the recurrence of an auricular mass of 29×33×39 mm involving the lumen of left inferior pulmonary vein. Then, a magnetic resonance imaging (RMI) scan confirms the presence of an infiltrative lesion in the inferior pulmonary vein with dilatation of the left chambers and biventricular systolic dysfunction. Additionally, the diagnosis of acute kidney injury was made. After oncological evaluation, it was concluded that adjunctive chemotherapy was not indicated due to the clinical status of the patient. In addition, the surgical team reported that surgery re-intervention would not be possible to achieve due to impossibility to completely remove the heart tumor. Three months after surgery the clinical status worsened, he presented signs of heart failure and was subsequently treated with continuous intravenous dobutamine drip. Four months after the surgery, the medical team in conjunction with the patient and his family, decided to discharge the patient to his home for palliative care.

Discussion

During patient clinical assessment, the diagnosis of a cardiac tumor remains a challenge because there are not pathognomonic clinical signs associated with this group of pathologies. However, diagnosis is usually incidental when imaging studies are indicated for symptomatology related to cardiovascular pathology. Frequently, cardiac sarcomas remains asymptomatic until advanced stages, often symptomatology is related to a mass effect that generates an outflow tract obstruction (*e.g.* dyspnea) or local invasion (*e.g.* heart failure).⁸ Patient's features may differ according to the anatomical location, size and the presence or degree of malignant invasion. Malignant neoplasms usually presents with cardiac obstructive symptoms, valve anomalies, constitutional symptoms, heart failure, arrhythmias, pericardial effusion and systemic embolization, manifestation due to metastasis; nevertheless, cases of asymptomatic cardiac neoplasms have been reported.^{1,9}

Moreover, at the time of diagnosis, primary heart malignancies (*e.g.* sarcomas) should be considered if the tumor is confined to the heart or pericardium, without evidence of extracardiac primary neoplasm.¹

Lestuzzi *et al.*, suggested that the diagnosis of cardiac masses could be estimated accord-

ing to echocardiographic appearance, in which most of benign tumors are narrow-based and originates from the left interauricular septum (*i.e.* myxoma) or valves (*i.e.* fibroelastoma) and most tumors with broad base or arising elsewhere are probably malignant (*e.g.* pulmonary vein: leiomyosarcoma).¹⁰ Heart leiomyosarcomas are usually diagnosed through imaging studies, in which echocardiography is the most frequent tool. However, there have been reports where transthoracic echocardiography had overlooked the diagnosis, especially when the tumor is located in the right ventricle outflow tract, thus, transesophageal echocardiography provide a better window to assess cardiac anatomy and a higher sensibility for cardiac tumors. Wang *et al.*, reported that the sensitivity of CT scan and RMI scan is 100%, and positron emission tomography is an inaccurate diagnostic tool.²

A left atrial mass is often associated with a benign myxoma on imaging study.¹¹ Hence, intravascular leiomyosarcoma may resemble a myxoma due to the similarity in the echocardiographic characteristics and location in the left atrium. However, establishing the origin of the tumor in the pulmonary veins might be the initial sign to differentiate a leiomyosarcoma from a myxoma.²

Frequently after surgical resection, the macroscopic characteristics of the cardiac leiomyosarcoma includes a tumor with a wide base, usually originated in the pulmonary veins¹² and with a worm-like (finger-like) shaped structure that grows following the directionality of blood flow (a frequent characteristic in intravenous leiomyomas),¹³ and could involve more than one chamber. The histopathological characteristics of vascular leiomyosarcoma are consistent with a mesenchymal origin tumor, in which malignant cells may appear spindle, epithelioid or pleomorphic.² Even though leiomyosarcoma can be found in almost all organs, the histology varies little among sites of origin.¹⁴

According to Carvalho *et al.*, muscle markers in leiomyosarcomas are the SMA, MSA and calponin, being the SMA the most sensitive (95%) followed by MSA and protease calponin (91% and 88%, respectively). Other less sensitive markers for sarcomas includes desmin (*i.e.* rhabdomyosarcoma), vimentin (mesenchymal origin), caldesmon and myosin (muscular origin), S100 proteins (neural crest origin), CD 68 (fibrohistiocytoma), CD 31, CD 34 and factor VIII (angiosarcoma) and epithelial membrane antigen (carcinoma metastases).^{8,14}

The clinical distinction between myxoma and sarcoma may be difficult. Moreover, from the pathological standpoint, distinguish between them can be easily made through histopathological studies; however, it's a challenge to differentiate between sarcomas types,

in which the diagnosis of leiomyosarcoma is made with positive markers for smooth muscle.¹⁵ From a study of 122 cases with primary cardiac sarcomas, Neville *et al.* found that all cases showed overexpression and amplification of MDM2, KIT, PDGFRA and EGFR as well as loss of CDKN2A, demonstrating a genetic association.³ As in the majority of case reports, our patient had positively reaction to SMA and MSA, both sensitive markers for leiomyosarcoma. Additionally, MDM2 was not obtained for this patient because it is used for the diagnosis of intima sarcoma, which is enclosed in the category of undifferentiated sarcoma.

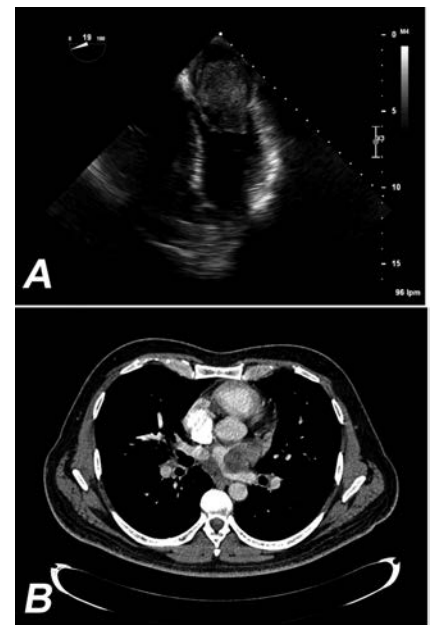


Figure 1. A) Transthoracic echocardiographic study showing the mass in the left atrium, which protrudes through mitral valve orifice during ventricle diastole. B) Thoracic computed tomography scan with contrast showing a mass in the left atrium lumen.

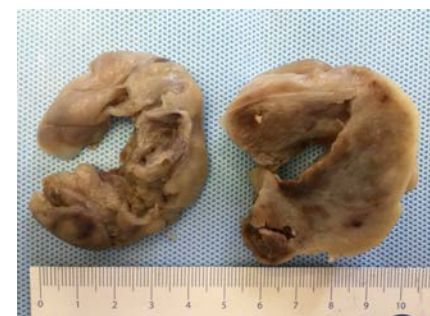


Figure 2. Left auricular tumor, with a worm-like shape and a red-brown irregular surface (left) and the internal surface with several small areas of hemorrhagic appearance (right).

Therefore, in this case, it was not necessary due to the fact that immunohistochemistry labeled this tumor as leiomyosarcoma.

Heart leiomyosarcoma treatment remains a challenge. Lv *et al.*, after analyzing 30 cases of vascular leiomyosarcoma with heart involvement, they stated that surgical resection should be the standard treatment, and surgery combined with adjunctive chemotherapy might be able to further prevent metastases and prolong survival. Although some authors do not support the use of radiotherapy because of its low sensitivity and possibly of direct myocardium damage,¹⁶ others have supported the use of adjunctive radiotherapy, which may increase life expectancy.² Even though surgical cardiac leiomyosarcoma resection is not a curative procedure, palliative surgery is usually undertaken due to the increased risk of mechanical obstruction, such as significant mitral or pulmonary stenosis.³ An orthotopic heart or heart and lungs transplantation should be considered when total body positron emission tomography and CT scans exclude metastases.¹⁷ Frequently, chemotherapy and radiotherapy are used in cases with incomplete sarcoma resection and patient who did not undergo surgical resection. Currently, there is not a standardized adjuvant therapy for this type tumors.^{3,18}

The prognosis of heart sarcomas is poor, even in absence of metastases; in the past it was thought that survival depended on the histological subtype. However, nowadays it is well known that favorable prognosis is mainly influenced by complete surgical resection, although sarcomas are often irresectable.³ Nevertheless, pathological diagnosis based on histopathological and immunohistochemical studies should be performed, as some subtypes presents a lower overall survival rates in comparison to others, leiomyosarcoma have a poor survival rate of 6 to 12 months without surgery and 24 months with surgery¹¹ when comparing with a benign atrial myxoma which have a relative good prognosis.¹⁹ Currently, the main risk factors associated with lower overall survival rates in heart leiomyosarcoma are age >50 years and inadequate surgical margins. In addition, the 5 year survival rate of local and metastatic recurrence is 25.4% and 14.7% respectively. Hence, the main metastatic sites include brain, bone, lungs and stomach.²

Even though the prevalence of cardiac leiomyosarcoma in Latin America is unknown and probably underreported, it is certainly extremely low, as the fact that in our knowledge, in the past 20 years only two similar cases has been reported. The first was in 1996, consisting of a 43-year-old Chilean⁶ woman who underwent open heart surgery, and was later was diagnosed as a primary cardiac leiomyosarcoma with vimentin and MSA positive tumor markers, as in this report. The sec-

ond case was a Mexican report published in 2002 in which a 31-year-old Mexican⁷ woman presented during surgery a large infiltrative tumor in the left atrium. Although both cases resembles this report in the early recurrence after surgery and poor prognosis, it's worth mentioning that this is the first report of a male patient in Latin America with this rare pathology.

Conclusions

Primary cardiac leiomyosarcoma is a rare entity, especially in Latin American patients. This type of tumor should be suspected when a

cardiac mass has its origin in the pulmonary veins with a wild base and multiple attachments to the auricular wall. In addition, the immunohistochemical analysis should include the most sensitive tumoral markers, SMA and MSA. Leiomyosarcoma has poor prognosis; treatment depend of patient hemodynamical and clinical status, and includes complete surgical excision and/or adjuvant chemotherapy and radiotherapy. However, surgery remains the cornerstone treatment associated with prolonged survival. Although the prognosis of cardiac leiomyosarcoma is poor and the rate of recurrence is high, we expect that further development of new chemotherapy and radiotherapy regimens will provide better prognosis for this group of patients.

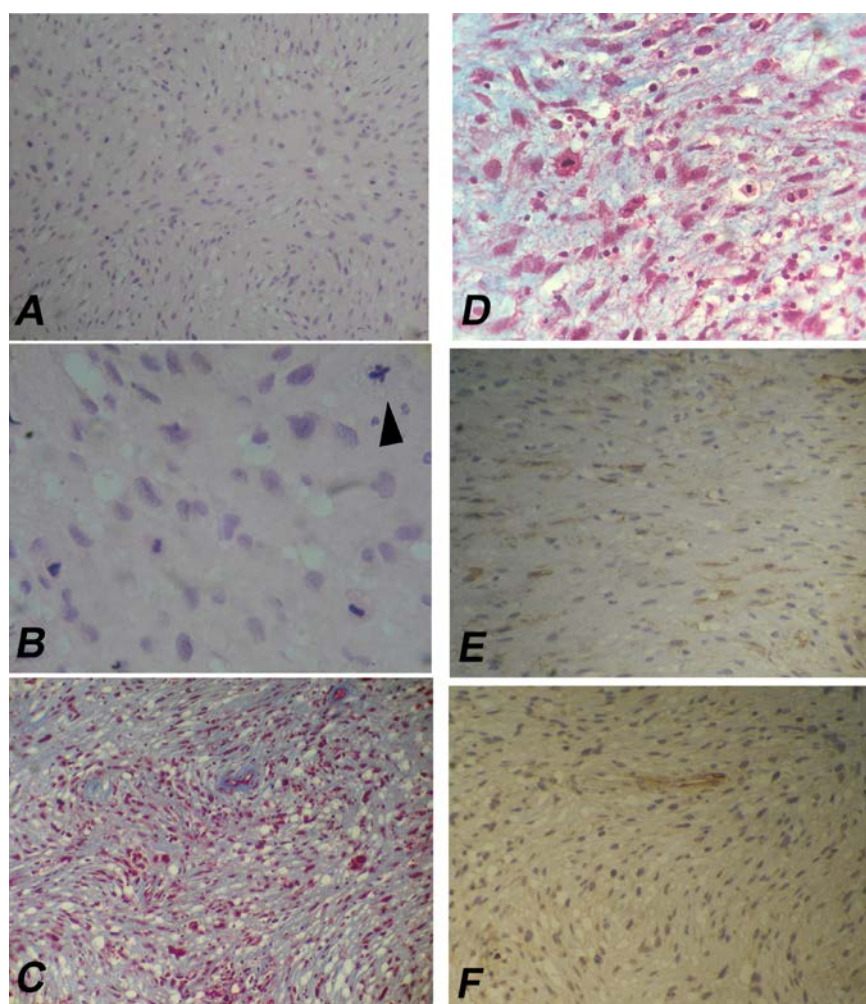


Figure 3. A) Histological analysis showing irregular bundles of spindle cells with a high atypical mitotic rate (Hematoxylin and Eosin 10×). B) Cells with large pleomorphic nuclei, with a high mitotic rate, in addition to abnormal mitosis (arrowhead) (Hematoxylin and Eosin 100×). C) Irregular bundles of spindle cells, the muscular cells stain with red and the collagen stroma stained in blue (Masson's trichrome 10×). D) Muscular cells with red cytoplasm and large pleomorphic nuclei (Masson's trichrome 100×). E) Immunohistochemical analysis showing SMA focally positive, in cytoplasm and nucleus of neoplastic cells (40×). F) MSA positive in neoplastic cells and vascular wall (40×).

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