www.journalofcancerology.com PERMANYER J Cancerol. 2017;4:10-6

JOURNAL OF CANCEROLOGY CLINICAL CASE

Primary Cardiac Synovial Sarcoma

Omar Peña-Curiel[1], David José Heredia-Vázquez[2], Mario Cuellar-Hübbe[1], Ángel Herrera-Gómez[1], Humberto Martínez-Hernández[3] and Jorge Luis Martínez-Tlahuel[1]*

[1]Instituto Nacional de Cancerología INCan; [2]Hospital "Juárez" de México; [3]Instituto Nacional de Cardiología. Mexico City, Mexico

ABSTRACT

Introduction: Synovial sarcomas are a common entity of soft tissue sarcomas, presenting in the extremities characterized by translocation t (X; 18)(p11.2;q11.2). Primary cardiac synovial sarcoma is a rare entity and has only been reported as case reports. **Case presentation:** A 26-year-old man presented to a cardiology clinic with signs and symptoms of acute heart failure. On echocardiogram, a left ventricular mass was found. He underwent heart surgery and on pathology assessment, a liposarcoma was diagnosed and was treated as such with doxorubicin and external radiotherapy. After six months, the tumor recurred locally and was referred to our institution. On pathologic review of the specimen, cardiac synovial sarcoma was diagnosed. He underwent a ventriculoplasty with an incomplete resection due to technical difficulties. **Conclusion:** Cardiac neoplasms are a rare group of diseases, representing less than 0.3% of all neoplasms; moreover, cardiac synovial sarcoma has only been described as isolated case reports. We highlight the issues of the differential diagnosis of soft tissue sarcoma due to the different treatment options and prognosis. Although most primary heart masses are benign, we stress to not discard the malignant pathology, and the early referral to a high specialty center for treatment.
(J CANCEROL. 2017;4:10-6)
Corresponding author: Jorge Luis Martínez-Tlahuel, dr.jorgetlahuel@gmail.com

Key words: Synovial sarcoma. Primary of myocardial. Translocation.

Correspondence to:
*Jorge Luis Martínez-Tlahuel
Médico Adscrito al Departamento de Oncología Médica
Instituto Nacional de Cancerología
Avenida San Fernando, 22
Col. Sección XVI, Del. Tlalpan
C.P. 14080, Ciudad de México, México
E-mail: dr.jorgetlahuel@gmail.com

Received for publication: 12-04-2016
Accepted for publication: 02-11-2016

RESUMEN

Introducción: El sarcoma sinovial es un tumor frecuente de los tejidos blandos de las extremidades. Genéticamente se caracteriza por la translocación t(X;18)(p11.2;q11.2). Su localización en el músculo cardíaco es rara. **Presentación**: Hombre de 26 años de edad que acudió a recibir atención hospitalaria con cuadro sintomático de insuficiencia cardíaca aguda. Un ecocardiograma mostró un tumor ventricular izquierdo, por lo que se le realizó cirugía cardíaca y estudio histopatológico que fue informado como liposarcoma. Con este diagnóstico recibió tratamiento con doxorubicina y radioterapia externa. Seis meses después, el tumor recurrió localmente, por lo que fue referido al Instituto Nacional de Cancerología de México. La revisión de laminillas informó un sarcoma sinovial cardíaco. Se realizó ventrículoplastia y resección incompleta del tumor por problemas técnicos. **Conclusión:** Los tumores primarios del corazón son raros (0.3%) y el caso que presentamos es aún más raro. Aun cuando las mayoría de los casos informados son benignos, deben ser referidos a los centros hospitalarios altamente especializados para su tratamiento.

Palabras clave: Sarcoma sinovial primario de miocardio. Traslocación.

INTRODUCTION

Cardiac synovial sarcoma is an extremely rare disease presentation with an overall poor prognosis due to the technical difficulties encountered during the surgical procedures. As with extremity synovial sarcoma, treatment modalities include surgery, radiotherapy, and combined chemo-radiotherapy for localized disease. Upon recurrence, the five-year survival is less than 30%, making it of prime importance to pursue a correct diagnosis and treatment at presentation.

CASE PRESENTATION

A 26-year-old previously healthy man presented to a family clinic with insidious onset of fatigue and epigastric pain. He was empirically treated for gastro-esophageal reflux disease with proton-pump inhibitors and lifestyle changes with little symptomatic relief. After a month of treatment, he noticed peripheral edema, palpitations, and shortness of breath on exertion that progressed to resting dyspnea. He was admitted at a tertiary specialty center to the cardiology department where he was diagnosed with severe congestive heart failure. Physical examination revealed jugular vein distension, resting tachycardia, a third heart sound (S3, gallop), wet rales on pulmonary sounds, and peripheral edema. An echocardiogram revealed a left ventricular wall tumor at the cardiac apex that compromised heart mobility. A full body tomographic scan was undertaken to rule-out systemic disease, which did not show metastases in any organ.

He underwent tumor resection due to the high risk of cardiac tamponade. On surgical exploration, the tumor infiltrated the full myocardium thickness and thus was incompletely resected with positive macroscopic margins. The surgical procedure was completed without complications and the patient was discharged afterwards with full recovery.

Pathologic analyses of the surgical specimen showed uniform round, small-sized neoplastic cells, with oval hyper-chromatic nuclei, resembling liposarcoma and was diagnosed as such. No other study was performed.

After full recovery, he underwent systemic and local therapy with doxorubicin every twenty-one days for six cycles and external beam radiotherapy. A computed tomography (CT) scan after treatment showed partial response of the lesion and was left on surveillance afterwards. After a progression-free interval of six months, the patient's symptoms recurred.

The patient decided to continue care at our hospital. Upon arrival, pathologic review of the paraffin-embedded tissue reported a small, round-cell neoplasia, compatible with synovial sarcoma with divergent differentiation (biphasic). Immunohistochemistry was positive for Bcl-2, TLE-1, FLI-1, CD 99, vimentin and cytokeratins; and negative for SMA, CD 138, CD 34, CD31, desmin, EMA, myogenin, S-100, synaptophysin, and WT-1, supporting the diagnosis of synovial sarcoma (Fig. 1). On the basis of these findings, we undertook fluorescent in-situ hybridization (FISH) analyses to support the diagnosis, showing positivity to the translocation *t(X;18)* in 90% of the specimen's cells.

Heart magnetic resonance imaging and CT scan of the chest, abdomen, and pelvis were performed showing a hypo-intense lesion with peripheral enhancement at the heart apex of 5 x 3 cm in size with pericardial involvement (Fig. 2).

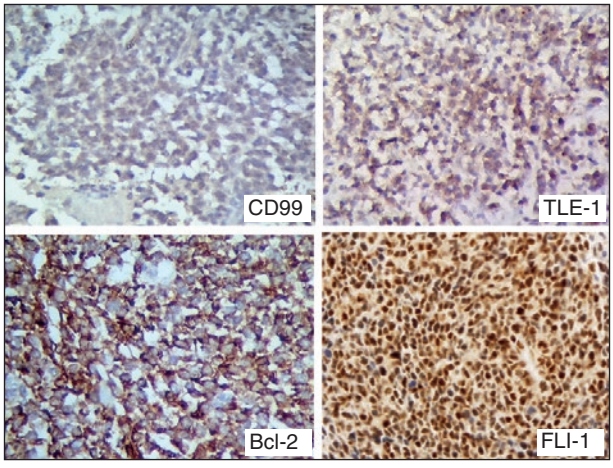

Figure 1. Hematoxylin and eosin and immunohistochemical microphotographs of the surgical specimen showing positivity to CD99, TLE-1, Bcl-2 and FLI-1.

He underwent tumor resection with ventriculoplasty with an extracorporeal pump yielding a 3.5 x 2.5 x 2 cm apex tumor with an incomplete resection due to technical difficulties. He had an optimal recovery from surgery and is currently taking beta-blockers, diuretics, and low-dose angiotensin-converting-enzyme (ACE) inhibitor for treatment of heart failure. On echocardiographic assessment afterwards, his left ventricular ejection fraction (LVEF) was reduced to 30%, thus limiting the possibility of continuing with systemic second-line treatment.

DISCUSSION

Synovial sarcomas are highly aggressive mesenchymal cancers that predominantly affect children and young adults. They represent between 5 to 10% of all soft-tissue sarcoma diagnoses and more than 90% occur on the extremities near the joint area[1]. Surgical resections with or without adjuvant radiotherapy and/or doxorubicin-based chemotherapy are the mainstays of treatment with only modest overall response rates[2]. The tissue of origin of synovial sarcoma is unknown as it has no precise normal tissue counterpart. The term "synovial sarcoma", which connotes histogenesis from the synovial chondrocyte lining in the joints, is a misnomer; in fact, synovial sarcomas can have both mesenchymal and epithelial resemblance and thus are said to be monophasic (only one differentiation), biphasic (both mesenchymal and epithelial differentiation), or poorly/undifferentiated tumor, based on immunohistochemical staining[3,4].

The differential diagnosis of the classic appearance of a monotonous small round-cell neoplasia is vast and includes Ewing's sarcoma, primitive neuroectodermal tumor, rhabdomyosarcoma, non-Hodgkin's lymphoma, retinoblastoma, neuroblas-

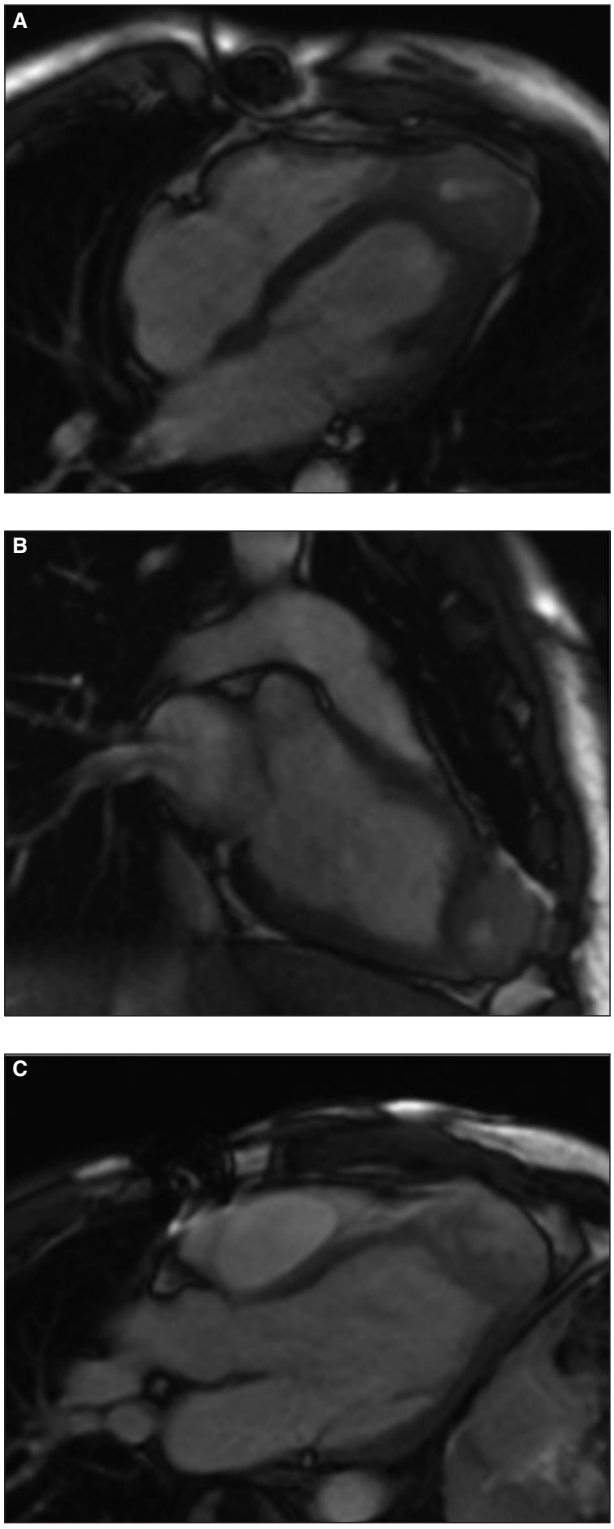

Figure 2. Cardiac magnetic resonance imaging showing a 5 x 3 cm hypo-intense lesion with pericardial involvement and apex compression in echo gradient sequences in the four **(A)** and two-chamber **(B)** axis that also shows heterogeneous gadolinium enhancement **(C)**.

toma, hepatoblastoma, and Wilms' tumor[5]. Ancillary diagnostic methods like immunohistochemistry (IHC), polymerase chain reaction (PCR), and FISH help in identifying specific genetic mutations common in a wide array of sarcomas and characteristic of them.

For the diagnosis of synovial sarcoma to be made, microscopic analysis of the tissue with the typical appearance of a small-round cell tumor (spindle-cell), with IHC positive for epithelial membrane antigens such as cytokeratins 7 and 19 (monophasic), together with IHC positive for mesenchymal antigens such as vimentin and Bcl-2 (biphasic), and other positive markers like protein S-100, CD99 and CD 34 have been reported as the mainstay for the correct diagnosis[6]. Furthermore, the translocation *t(X;18)*, which leads to the expression of the unique SYT-SSX fusion protein, is present in virtually all synovial sarcoma cases[7].

Primary cardiac synovial sarcoma is an extremely uncommon presentation that carries a dismal prognosis. The clinical presentation of cardiac synovial sarcoma includes a broad array of signs and symptoms typical of heart disease, including dyspnea, cough, edema, chest pain, and fatigue as reported in the literature review by Zhang, et al.[8]; others have reported fever, pericardial effusion, weight loss, and cyanosis as part of the clinical spectrum (Table 1). In our case report, we present a previously healthy man in his third decade of life presenting with insidious onset of shortness of breath and limb swelling due to heart failure caused by left ventricular out-flow obstruction from the tumor, which is in accordance to other clinicians' experience with this atypical tumor. Upon arrival to our center, both immunohistochemical analysis and FISH were consistent with the diagnosis of cardiac synovial sarcoma and a multidisciplinary team underwent treatment planning.

Treatment of extremity synovial sarcoma includes maximal surgical resection with appropriate nega-

Table 1. Review of previously reported cardiac synovial sarcomas[8,13,15-21,22]

Author (year)	Presenting symptoms	Diagnosis	Treatment	Outcome
Koletsa, et al. 2004[15]	Facial edema, jugular vein distension, arterial hypertension	H&E: Monophasic, high-grade spindle-cells IHC: Vimentin, Bcl-2, CAM 5.2, CK AE-1/AE-3, EMA PCR: SYT-SSX1 fusion gene transcript	Surgery followed by radiotherapy; chemotherapy after recurrence	4 month follow-up; distant recurrence (lung, neck nodes)
Miller, et al. 2005[16]	Fatigue	H&E: Monophasic, plump spindle cells PCR: SYT-SSX1 fusion gene transcript	Surgery followed by chemotherapy	6 month follow-up (alive without recurrence)
Provenzano, et al. 2006[17]	Fever, fatigue, abdominal pain, and nocturnal dyspnea progressing over two weeks	H&E: Biphasic, spindle cell morphology	Surgery followed by chemotherapy	18 months follow-up (alive without recurrence)
Boulmay, et al. 2007[18]	Dyspnea, chest pain, exercise intolerance	IHC: CD99, Bcl-2 FISH: (X;18)(p11.2;q11.2)	Surgery only (complete resection)	5 year follow-up (alive without recurrence)
Yokouchi, et al. 2011[13]	Fever, palpitations dyspnea, pericardial effusion	H&E: Biphasic, spindle-cells with an ovoid nucleus ICH: BCL-2, CD56 PCR: SS18-SSX1 fusion gene transcript	Surgery followed by radiotherapy	9 month follow-up (alive without recurrence)
Zhang, et al. 2011[8]	Insidious productive cough, and hemoptysis	IHC: Syt+, CK5/6–, CD21/35–, S100–, Calretinin–, CK–, CD34–, Des–, EMA–, Melan-A–, CKpan–, SMA–, HMB45–, CD117–	Surgery only	6 month follow-up (alive without recurrence)
Khan, et al. 2014[19]	Dyspnea on minimal exertion, facial swelling, weight loss, and cyanosis	H&E Biphasic, spindle cells and glandular areas IHC: EMA+, CK7+ CK19+, CD99+, CD34+, Calretinin	Surgery and chemotherapy	3 month follow-up (alive without recurrence)
Yin, et al. 2013[20]	Dyspnea and syncope	H&E Biphasic, small round cell morphology IHC: Vimentin+, Bcl-2+ calretinin+, FLI-1+ FISH: rearrangement of SS18 in 88% of the neoplastic cells	Surgery only	3 month follow-up (alive without recurrence)
Huo, et al. 2015[21]	Pericardial effusion	H&E: Biphasic, mixture of spindle cell and epithelioid components IHC: CK 19+, S-100+, vimentin+, Bcl-2+, CD99+ FISH: SS18 rearrangement	Surgery followed by chemotherapy	No report on follow-up
Sharma, et al. 2015[22]	Shortness of breath	H&E Biphasic, pleomorphic spindle- cells admixed with round and polygonal cellular areas IHC: cytokeratin+, vimentin+, MIC-2+, and Bcl-2+, focal CD 34+, calretenin+	Surgery followed by chemo-radiotherapy	1 month follow-up (alive without recurrence)

FISH: fluorescent in-situ hybridization; H&E: hematoxylin and eosin; IHC: immunohistochemistry; PCR: polymerase chain reaction.

tive margins and adjuvant treatment with radiotherapy for close or positive surgical margins combined with anthracycline-based chemotherapy[9]. In patients with large tumors (> 8 cm), preoperative radiotherapy with or without chemotherapy has shown to prolong disease-free survival and overall survival in some reports[10]. The appropriate treatment of cardiac synovial sarcoma has not been established due to the rarity of this presentation. Based on previous reports, most patients undergo primary surgery and only a few were candidates for any type of adjuvant treatment. Our patient was treated with primary surgery with an incomplete resection followed by adjuvant treatment with radiotherapy and anthracycline-based chemotherapy. Upon recurrence, synovial sarcoma patients amenable to resection should be offered a surgical intervention followed by radiotherapy and/or chemotherapy if not previously administered. For those patients deemed unresectable or not candidates for local therapy, systemic treatment with doublet or single-agent chemotherapy is feasible, with response rates up to 25%[11]. Upon recurrence, the patient in the vignette underwent a ventriculoplasty with incomplete resection due to technical difficulties. Due to the limited residual LVEF we were not able to offer any systemic treatment after resection. To date, after six-month follow-up from the ventriculoplasty, the patient remains free of recurrence and with little limitation to his daily living, which is similar to the outcomes reported by other authors.

The five-year survival rate for patients with extremity synovial sarcoma can reach up to 65%[12]. In cardiac synovial sarcoma, the survival varies substantially from that reported for extremity synovial sarcoma. In a report by Yokouchi, et al. they found five of 10 patients alive for more than one year[13], and the longest survival reported for cardiac synovial sarcoma is 14 years in a 26-year old man with pericardial invasion reported by Van der Mieren, et al.[14] who underwent multiple surgical resections combined with systemic treatment and radiotherapy. In our case scenario, we have planned second-line treatment with ifosfamide only when the patient develops clinical signs of disease progression in order to limit cardiac morbidity.

CONCLUSION

Cardiac synovial sarcoma is a rare disease that presents in various clinical scenarios encompassing the spectrum of heart disease. As with other rare disorders, it is usually not taken into account in the differential diagnosis in the initial approach. A high index of suspicion must be present in order to correctly diagnose cardiac synovial sarcoma, often done after the surgical specimen has been evaluated by a specialized pathologist. Of particular importance is the availability of the correct tools to facilitate the differential diagnosis such as an extended immunohistochemistry panel and a cytogenetics laboratory.

The contribution of this case report to the medical literature highlights the importance of early referral to a specialized oncology center and the necessity of a multidisciplinary team to plan treatment of this complex disorder in order to obtain the best outcomes possible.

REFERENCES

1. Mullen JR, Zagars GK. Synovial sarcoma outcome following conservation surgery and radiotherapy. Radiother Oncol. 1994;33:23-30.
2. Goldblum JR, Folpe AL, Weiss SW, Enzinger FM, Weiss SW. Enzinger and Weiss's Soft Tissue Tumors. 2014.
3. Wolters Kluwer-DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.
4. Haldar M, Randall RL, Capecchi MR. Synovial sarcoma: From genetics to genetic-based animal modeling. Clin Orthop. 2008;466:2156-67.
5. Lewis TB, Coffin CM, Bernard PS. Differentiating Ewing's sarcoma from other round blue cell tumors using a RT-PCR translocation panel on formalin-fixed paraffin-embedded tissues. Mod Pathol. 2007;20:397-404.
6. Kottu R, Prayaga AK. Synovial sarcoma with relevant immunocytochemistry and special emphasis on the monophasic fibrous variant. J Cytol. 2010;27:47-50.
7. Dal Cin P, Rao U, Jani-Sait S, Karakousis C, Sandberg AA. Chromosomes in the diagnosis of soft tissue tumors. I. Synovial sarcoma. Mod Pathol. 1992;5:357-62.
8. Zhang L, Qian J, Li Z, Jing H. Primary synovial sarcoma of the heart. Cardiol J. 2011;18:128-33.
9. Sarcoma Meta-analysis Collaboration (SMAC). Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Cochrane Database Syst Rev. 2000:CD001419.

10. DeLaney TF, Spiro IJ, Suit HD, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys. 2003;56:1117-27.
11. van Oosterom AT, Mouridsen HT, Nielsen OS, et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer. 2002;38: 2397-406.
12. Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. Cancer Med. 2014;3:1404-15.
13. Yokouchi Y, Hiruta N, Oharaseki T, et al. Primary cardiac synovial sarcoma: a case report and literature review. Pathol Int. 2011;61:150-5.
14. Van der Mieren G, Willems S, Sciot R, et al. Pericardial synovial sarcoma: 14-year survival with multimodality therapy. Ann Thorac Surg. 2004;78:e41-2.
15. Koletsa T, Kotoula V, Hytiroglou P, Spanos P, Papadimitriou CS. Synovial sarcoma of the heart. Virchows Arch. 2004;444:477-9.
16. Miller DV, Deb A, Edwards WD, Zehr KJ, Oliveira AM. Primary synovial sarcoma of the mitral valve. Cardiovasc Pathol. 2005;14:331-3.
17. Provenzano SC, Con R, Jones OD, Grant PW. Synovial sarcoma of the heart. Heart Lung Circ. 2006;15:278-9.
18. Boulmay B, Cooper G, Reith JD, Marsh R. Primary cardiac synovial sarcoma: a case report and brief review of the literature. Sarcoma. 2007;2007: 94797.
19. Khan H, Chaubey S, Edlin J, Wendler O. Primary cardiac synovial sarcoma. A rare tumor with poor prognosis. Asian Cardiovasc Thorac Ann. 2014;22:835-8.
20. Yin L, Chen M, Ye F, et al. A poorly differentiated synovial sarcoma arising from the pulmonary valve. Cardiovasc Pathol. 2013;22:501-2.
21. Huo Z, Lu H, Mao Q, et al. Primary synovial sarcoma of the right heart involving the tricuspid valve in an elderly Chinese woman: a case report. Diagn Pathol. 2015;10:80.
22. Sharma A, Dixit S, Sharma M, Sharma N, Sharma O. Primary synovial cell sarcoma of the heart: A rare case. Heart Views. 2015;16:62-4.