Primary Cardiac Synovial Sarcoma

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Primary cardiac synovial sarcoma is an uncommon malignant neoplasm, with only a handful of cases reported in the English literature to date. Synovial sarcomas have also been described at other unusual sites, such as the heart, pleuropulmonary region, kidney, prostate, liver, mediastinum, retroperitoneum, gastrointestinal tract, and peripheral nerve. For synovial sarcomas that arise at these unusual locations, definitive diagnosis is challenging and requires use of ancillary diagnostic procedures, such as immunohistochemistry, electron microscopy, and molecular genetic techniques, for confirmation of diagnosis. The nonrandom occurrence of t(X;18) has been found consistently in synovial sarcomas. It has also been found as a sole cytogenetic abnormality in some cases, suggesting it as a key molecular event in tumor development. This review highlights salient features of primary cardiac synovial sarcoma and the associated diagnostic challenges. (Arch Pathol Lab Med. 2012;136:454–458; doi: 10.5858/arpa.2011-0008-RS)

Synovial sarcoma (SS) is a clinically and histomorphologically well-defined soft tissue tumor that is extremely uncommon in joint cavities and has no apparent relation to synovial structures. Between 5% and 10% of all soft tissue sarcomas are synovial sarcomas, with about 90% occurring on the extremities. Although the term synovial sarcoma continues to be the designation of choice to date, it is a misnomer. This tumor is considered to be a tumor of unknown histogenesis, as it has no precise normal tissue counterpart. The tumor’s positive staining pattern for both epithelial and mesenchymal markers negate its origin from synovium, since immunohistochemical staining for epithelial markers such as cytokeratin is not found in normal synovium. Synovial sarcoma arising primarily from heart is an uncommon tumor and it is usually identified at a late stage because of its nonspecific presentation and difficulty in obtaining a biopsy from this site. In addition, the spindle cell morphology brings into consideration a vast range of differential diagnoses, which poses a diagnostic dilemma for the pathologist. Ancillary diagnostic methods like cytogenetics and fluorescence in situ hybridization help in identifying specific and variant genetic mutations that suggest a clonal evolution of this tumor. This is particularly true in recurrent or metastatic tumors and is in accord with the accepted view that tumor progression may be accompanied by new genetic abnormalities in the neoplastic cells.

CLINICAL FEATURES

The clinical presentations of cardiac SS are nonspecific, and the tumor may not be detected until it has reached an advanced stage. The patients usually present with symptoms and signs related to the tumor’s local space-occupying effects. In reported cases, most of the patients have presented with more than 1 complaint, shortness of breath and dyspnea being the most common, followed by chest pain and weight loss. One patient presented with strokelike symptoms of arm weakness and aphasia (resulting from probable tumor emboli). One patient presented with facial edema and neck vein congestion due to mass effect.

LOCATION

Synovial sarcoma arising primarily in the heart is a rare occurrence, with only 26 previously reported cases. In the heart, SSs tend to arise from the heart but may also arise from the pericardium. Cases that arise from the heart locate predominantly to the right side—particularly the right atrium, with a right to left ratio of 2:1. Of the 26 cases (with information available) reported, 21 have originated in the heart (14 in the right atrium, 5 in left atrium, and 2 in left ventricle). This is similar to the 2:1 ratio (right to left ratio) reported by Kim et al in their 10-year single-institution report of 24 primary cardiac sarcomas. In that series, 16 of 24 cases were right-sided lesions, with the atrium being the most commonly involved chamber (14 of 24 cases). Like other cardiac sarcomas, which are usually diagnosed at advanced stage, most synovial sarcomas tend to involve more than 1 anatomic compartment within the heart by the time they are discovered. This may be explained by direct extension due to close proximity of the 4 chambers.

DEMOGRAPHICS

The mean age of the patient with cardiac synovial sarcoma is 32.5 years, with a range of 13 to 66 years, and a clear-cut male preponderance (male to female ratio of 3:5:1). This is in contrast to the soft tissue SS, which is more prevalent in adolescents and young adults (15–35 years of age) and in females. Of the total cases reported in the English literature so far, only a few mentioned the race and ethnicity of patients. Since there are only a handful of cases reported so far, the prevalence of synovial sarcoma in 1 ethnic group compared to other groups cannot be established with...
certainty. Also in soft tissue SS, there appears to be no ethnic or racial predilection.\textsuperscript{1,2,23}

**PATHOLOGIC FEATURES**

**Macroscopic Features**

The size of the tumors is variable and ranges from 2.9 to 15 cm\textsuperscript{7,12} (Figures 1 and 2). Left-sided lesions are of comparatively smaller size because they tend to present early owing to their mass effect and obstruction of pulmonary veins. Synovial sarcomas of heart frequently involve more than 1 anatomic site within the heart, with right-sided lesions extending more frequently to the same or contralateral side (Table 1). Only 1 previously reported left-sided tumor extended beyond 1 anatomic compartment.\textsuperscript{20} The reason is not apparent but may be due to the left ventricle being more muscular, thus providing more room for tumor growth before it extends to adjacent chambers.

**Microscopic Features**

Cardiac synovial sarcomas have the same morphologic spectrum as their soft tissue counterparts and therefore may be biphasic or monophasic. The classic biphasic SS has epithelial and spindle cell components admixed in varying proportions. The classic monophasic variant contains only the spindle cell component arranged in similar patterns as seen in fibrosarcomas. No epithelial component is detected even with thorough sampling of the tumor. However, with the help of immunohistochemistry (IHC), some of the cells may stain positively for epithelial markers such as cytokeratin and epithelial membrane antigen. Ancillary cytogenetic studies may be necessary for the confirmation of diagnosis in these cases. Of the reported cases, 14 were biphasic type and the remaining 12 were monophasic.

**Monophasic.**—Similar to their soft tissue counterparts, the reported monophasic synovial sarcomas of the heart consist of monomorphous spindle-shaped cells with scant to moderate cytoplasm and nuclei with fine chromatin and an apparent or single, small nucleolus. Various patterns of arrangement of tumor cells have been described, with most having interlacing fascicles of spindle cells with indistinct cell margins. However, 2 cases have been reported with the presence of hemangiopericytoma-like vascular structures, a histomorphologic pattern that is rarely seen even in the soft tissue SS (Figure 3).\textsuperscript{14,18} The presence of long perpendicularly bisecting fascicles in the soft tissue synovial sarcomas is uncommon and so is the presence of herringbone-like arrangement, which is more typical of fibrosarcomas.\textsuperscript{2,14} So far, only 1 case of cardiac sarcomas has been reported with presence of herringbone arrangement of spindle-shaped cells.\textsuperscript{14} The stroma is usually unremarkable but may show myxoid change.\textsuperscript{20}

**Biphasic.**—The biphasic cases showed the presence of spindle-shaped cells arranged in any of the aforementioned patterns, admixed with plump epithelioid-appearing cells commonly arranged in the form of glands or diffusely intermixed with spindle-shaped cells. One of the previously reported cardiac SSs had diffusely intermixed spindle and epithelioid cells with no glandular formations. In that case, the presence of epithelial differentiation was confirmed by electron microscopy, which showed cell adhesion molecules as desmosomes.\textsuperscript{18} Cases with glandular arrangement are more common and may show the presence of eosinophilic secretions within the lumen (Figure 4).\textsuperscript{5,9}

Both the spindle-shaped and the epithelial components are usually intricately admixed (Figure 5). Evidence of stromal calcification has not been reported in cardiac synovial sarcomas in contrast to their soft tissue counterparts, which may show stromal calcification in as many as 20% of the cases.\textsuperscript{7} Cellular pleomorphism may be present with or without brisk mitotic activity. Between 2 to 6 mitoses per high-power field have been reported in cases with a high mitotic count.\textsuperscript{7,12} Tumor necrosis is not a prominent feature but may be seen in high-grade tumors.

**ANCILLARY TESTS**

**Immunohistochemistry**

The advent of IHC, with its enhancement by antigen retrieval techniques, and the ability to demonstrate cellular proteins such as vimentin, cytokeratin, and epithelial membrane antigen have revolutionized the histopathologic diagnosis of SS with formalin-fixed, paraffin-embedded tissue sections.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Synovial sarcoma arising from the left atrium.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Cut section showing fleshy, homogenous appearance and knoblike site of attachment.}
\end{figure}
Expression of both cytokeratin and vimentin is seen in most cases of SS with biphasic histology, with cytokeratin and vimentin in the epithelial and mesenchymal components, respectively (Figure 6). Epithelial membrane antigen may also be expressed by the tumor cells, but to a lesser extent (Figure 7). Synovial sarcomas almost always express at least 1 epithelial cell marker, although expression may be focal. In poorly differentiated tumors, the proportions expressing epithelial markers may be as low as 30%.

In monophasic SS, tumor cells stain diffusely positive for vimentin and variably positive for epithelial proteins in cells that do not appear epithelial on hematoxylin-eosin staining. Presence of epithelial cells on hematoxylin-eosin staining, even in a spindle cell–predominant SS, qualifies such a tumor for classification as a biphasic SS with overwhelming spindle cell component.1

For 23 previously reported primary SSs of the heart, expression of cytokeratin was documented in 13 biphasic tumors and epithelial membrane antigen was expressed in 8 tumors.14 The positivity for cytokeratin ranged from diffuse to focal and may be seen in both gland-forming microvilli and cells with abundant rough endoplasmic reticulum and indistinct basal lamina.1,5,6,13,18 Molecular genetic studies have shown a balanced reciprocal translocation, t(X;18)(p11.2;q11.2), between SYT gene on chromosome 18 and SSX1 or SSX2 gene on chromosome X (Figure 8). This translocation is a specific cytogenetic abnormality that occurs consistently in SS (monophasic and biphasic). Its detection by fluorescence in situ hybridization or real-time polymerase chain reaction has therefore become the gold standard for confirming the diagnosis of SS.

Complex karyotypes have also been reported and may have prognostic significance. Three cases have demonstrated the presence of chromosomal abnormalities, which include t(X;18)(p11.2;q11.2), der(1)t(1;8)(q10;q10), der(4), −13, −14, −16, +17, −18, +4, +7, +8, and der(13;15)(q10;q10).1,4,19,20 Cases of synovial sarcoma with complex karyotype have a greater tendency to metastasize, as evidenced by the fact that 2 of 3 cases with complex karyotypes also had clinical and histologic evidence of metastasis.3

### Differential Diagnosis
Currently, there is growing evidence that many tumors in the mediastinum, which could represent potential SS in this location, are not systematically examined with adequate representative sectioning and use of molecular markers. Many previously diagnosed spindle cell tumors such as mesothelioma, fibrosarcoma, hemangiopericytoma, and even malignant peripheral nerve sheath tumor (MPNST) and undifferentiated sarcoma could well represent underdiagnosed SS in this location.16 Thorough sampling from representative areas and biphasic histology, if present, are the key features that should prompt

**MOLECULAR PATHOLOGY**

The cases reported earlier in the literature used electron microscopy to ascertain the lineage of cells and reported the presence of desmosomes, endothelial-like cells with microvilli and cells with abundant rough endoplasmic reticulum and indistinct basal lamina.1,5,6,13,18

**Table 1. Primary Cardiac Synovial Sarcoma**

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Age, y/Sex</th>
<th>Location</th>
<th>Histology</th>
<th>Molecular Test/CG</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAllister &amp; Fenoglio, 1978</td>
<td>30/M</td>
<td>RV/pericardium</td>
<td>Biphasic</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Sheffield et al, 1988</td>
<td>53/M</td>
<td>RA/RV</td>
<td>Biphasic</td>
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<tr>
<td>Siebenmann et al, 1990</td>
<td>31/F</td>
<td>RA/RV</td>
<td>Biphasic</td>
<td>NA</td>
<td>None</td>
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<tr>
<td>Burke &amp; Virmani, 1996</td>
<td>46/F</td>
<td>RV</td>
<td>Biphasic</td>
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<td>NA</td>
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<tr>
<td>Korn et al, 1994</td>
<td>35/M</td>
<td>RA</td>
<td>Monophasic</td>
<td>t(X;18), karyotype</td>
<td>Asbestosis</td>
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<td>Iyengar et al, 1995</td>
<td>38/M</td>
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<td>t(X;18), karyotype</td>
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<td>RA</td>
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<td>Donsbeck et al, 1999</td>
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<td>RA</td>
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<tr>
<td>Ozümü et al, 1999</td>
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<td>Cassellmann et al, 1999</td>
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<tr>
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<td>Pericardium</td>
<td>Biphasic</td>
<td>SYT-SSX, RT-PCR</td>
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<td>Bittina et al, 2000</td>
<td>47/M</td>
<td>RA</td>
<td>Biphasic</td>
<td>NA</td>
<td>Metastasis/PFO</td>
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<tr>
<td>Zhao et al, 2007</td>
<td>36/M</td>
<td>RA and LA</td>
<td>Monophasic</td>
<td>SYT-SSX1, RT-PCR</td>
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<tr>
<td>McGilbray &amp; Schulz, 2003</td>
<td>37/M</td>
<td>LV</td>
<td>Biphasic</td>
<td>Complex karyotype</td>
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<tr>
<td>Hazelbag et al, 2004</td>
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<td>LA/LV</td>
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<td>Complex karyotype</td>
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<td>Koletsa et al, 2004</td>
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<td>RA</td>
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<tr>
<td>Hannachi Sassi et al, 2004</td>
<td>45/M</td>
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<td>Miller et al, 2005</td>
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<tr>
<td>Bégueret et al, 2005</td>
<td>26/M</td>
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<tr>
<td>Zhang et al, 2008</td>
<td>29/M</td>
<td>Pericardium</td>
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<tr>
<td>Kim et al, 2008</td>
<td>66/M</td>
<td>RA</td>
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<td>t(X;18)/FISH</td>
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<tr>
<td>Present case, 2009</td>
<td>47/M</td>
<td>LA/LV</td>
<td>Biphasic</td>
<td>t(X;18)/FISH</td>
<td>None</td>
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</tbody>
</table>

Abbreviations: CG, cytogenetics; FISH, fluorescence in situ hybridization; LA, left atrium; LV, left ventricle; NA, not available; PFO, patent foramen ovale; RA, right atrium; RT-PCR, real-time polymerase chain reaction; RV, right ventricle; SYT-SSX, fusion gene resulting from t(X;18)(p11.2;q11.2).
Figure 3. Hemangiopericytoma-like areas in biphasic synovial sarcoma with staghorn type of vasculature (hematoxylin-eosin, original magnification ×100).

Figure 4. Epithelial elements forming glands filled with eosinophilic secretions (hematoxylin-eosin, original magnification ×400).

Figure 5. Intricately admixed epithelial and spindle-shaped cells in biphasic synovial sarcoma (hematoxylin-eosin, original magnification ×200).

Figure 6. Diffuse vimentin positivity in spindle-shaped cells and scattered epithelial cells (original magnification ×100).

Figure 7. Epithelial membrane antigen positivity in cells arranged in glandular fashion in biphasic synovial sarcoma (original magnification ×100).

Figure 8. Fluorescence in situ hybridization showing classic translocation with a break-apart probe involving chromosomes X and 18 (original magnification ×100).
immunohistochemical staining for both mesenchymal and epithelial markers. Molecular testing for the specific mutation is the gold standard for correct diagnosis and excludes all other possibilities.

The differential diagnosis of cardiac SS includes carcinosarcoma, malignant mesothelioma, leiomyosarcoma, hemangiopericytoma, and MNPS. Unlike these malignant tumors, SS usually has a low-grade histologic appearance, with little or no cytologic atypia and cellular pleomorphism. In addition, a list of IHC markers listed in Table 2 may help resolve problems posed by these differential diagnoses. Finally, molecular genetic studies for t(X;18) does provide a definite solution, as the abnormality is unique to SS.

### PROGNOSIS

The survival of persons with primary cardiac sarcomas is poor, with most patients dying within a few months after diagnosis and surgery. The longest reported survival after surgery and chemotherapy is 5 years. However, the molecular diagnosis was not confirmed in that case, and it is the only case in which survival is reported in years. Two other patients who were disease-free at 13 months and 12 months posttherapy had tumors that were pericardial in origin. Since cardiac SSs are rare, prognostic factors are hard to ascertain, but younger age at diagnosis, absence of complex chromosomal abnormalities, and origin of tumor from the pericardium seem to be favorable factors.

### CONCLUSION

Primary cardiac synovial sarcoma is a rare entity and has a broad list of differential diagnoses that may include mesothelioma, fibrosarcoma, leiomyosarcoma, undifferentiated sarcoma, and myxoma. During surgical resection of this tumor, tissue sample may be sent for intraoperative surgical pathology consultation (frozen-section analysis). In such situations, whenever tumors with spindle cell populations are observed in this location, synovial sarcoma should be considered in the differential diagnosis. By virtue of its rarity and unusual location, synovial sarcoma of heart continues to present a diagnostic dilemma to pathologists, even on permanent sections. Careful and generous sectioning of representative areas, along with the use of ancillary diagnostic techniques such as immunohistochemistry and molecular genetic studies, are the key tools for making the correct diagnosis, an essential prerequisite for correct therapeutic decisions and good treatment outcome.

### References


### Table 2. Differential Diagnoses Based on Immunohistochemistry

<table>
<thead>
<tr>
<th>Tumor</th>
<th>CK(AE1/3)</th>
<th>EMA</th>
<th>CK7</th>
<th>CK19</th>
<th>CD31</th>
<th>CD34</th>
<th>S100</th>
<th>SMA</th>
<th>Desmin</th>
<th>Calretinin</th>
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<tr>
<td>SS</td>
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<td>+/-</td>
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<td>-/+</td>
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<td>-/+</td>
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<td>MNPS</td>
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<td>-</td>
<td>-/+</td>
<td>-/+</td>
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<td>-/4</td>
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</table>

Abbreviations: ANGS, angiosarcoma; CK, cytokeratin; CS, carcinosarcoma; EMA, epithelial membrane antigen; HEMP, hemangiopericytoma; LEIOS, leiomyosarcoma; MERO, mesothelioma; MNPS, malignant peripheral nerve sheath tumor; SMA, smooth muscle actin; SS, synovial sarcoma; WT1, Wilms tumor 1.