

Primary renal synovial sarcoma – a diagnostic dilemma

Amulya Yellala MD,^a Prashant Mukesh Jani, MD,^b Ariel Sandhu, MD,^b Naga Sai Krishna Patibandla, MD,^a Larisa Greenberg, MD,^b Suzanne Schiffman, MD,^c and Dulabh Kaur Monga, MD^b

Departments of ^aInternal Medicine, ^bHematology/Oncology, and ^cSurgical Oncology, Allegheny Health Network, Pittsburgh, Pennsylvania

Soft tissue sarcomas are rare mesenchymal tumors that comprise 1% of all malignancies. Synovial sarcoma accounts for 5% to 10% of adult soft tissue sarcomas and usually occurs in close association with joint capsules, tendon sheaths, and bursa in the extremities of young and middle-aged adults.¹ Synovial sarcomas have been reported in other unusual sites, including the head and neck, thoracic and abdominal wall, retroperitoneum, bone, pleura, and visceral organs such as the lung, prostate, or kidney.² Primary renal synovial sarcoma is an extremely rare tumor accounting for <2% of all

malignant renal tumors.³ To the best of our knowledge, fewer than 50 cases of primary renal synovial sarcoma have been described in the English literature.⁴ It presents as a diagnostic dilemma because of the dearth of specific clinical and imaging findings and is often confused with benign and malignant tumors. The differential diagnosis includes angiolipoma, renal cell carcinoma with sarcomatoid differentiation, metastatic sarcoma, hemangiopericytoma, malignant solitary fibrous tumor, Wilms tumor, and malignant peripheral nerve sheath tumor. Hence, a combination of histomorphologic, immunohistochemical, cytogenetic, and molecular studies that show a unique chromosomal translocation t(X;18) (p11;q11) is imperative in the diagnosis of primary renal synovial sarcoma.⁴ In the present report, we present the case of a 38-year-old man who was diagnosed with primary renal synovial sarcoma.

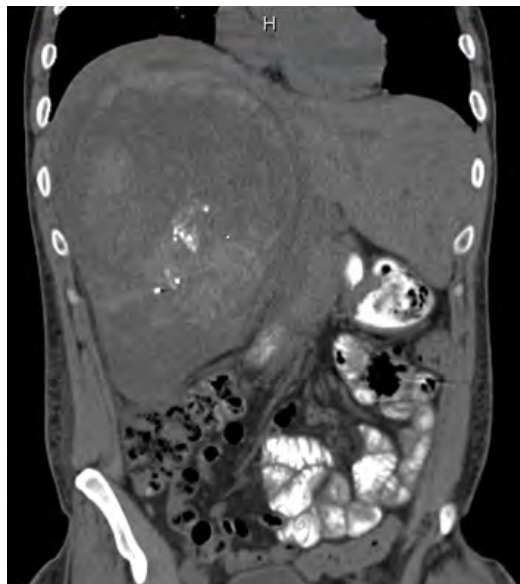


FIGURE 1 Coronal section of a computed-tomographic scan of the abdomen and pelvis, showing large right retroperitoneal hematoma with indwelling punctate calcifications, raising concern for underlying retroperitoneal or renal neoplasia and mass. Right kidney is displaced antero-inferiorly.

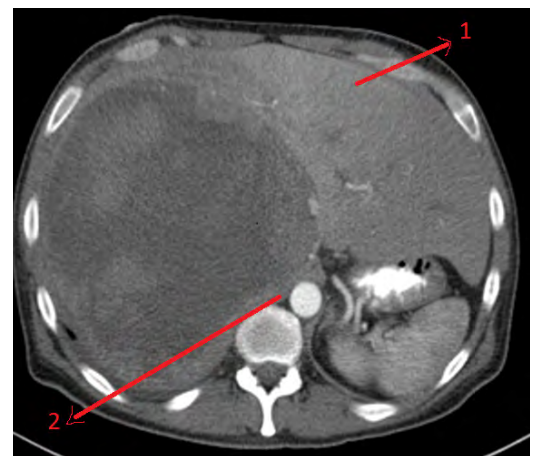


FIGURE 2 Cross-section of the abdomen and pelvis with contrast, showing the liver displaced to the left (1) and the inferior vena cava displaced anteriorly and to the left (2).

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Case presentation and summary

A 38-year-old man with a medical history of gastroesophageal reflux disease and Barrett's esophagus presented to our hospital for the first time with persistent and progressive right-sided flank and abdominal pain that was aggravated after a minor trauma to the back. There was no associated hematuria or dysuria.

Of note is that he had experienced intermittent flank pain for 2 years before this transfer. He had initially been diagnosed at his local hospital close to his home by ultrasound with an angiomyolipoma of 2 × 3 cm arising from the upper pole of his right kidney, which remained stable on repeat sonograms. About 22 months after his initial presentation at his local hospital, the flank pain increased, and a computed-tomographic (CT) scan revealed a perinephric hematoma that was thought to originate from a ruptured angiomyolipoma. He subsequently underwent embolization, but his symptoms recurred soon after. He presented again to his local hospital where CT imaging revealed a significant increase in the size of the retroperitoneal mass, and findings were suggestive of a hematoma. Subsequent angiogram did not reveal active extravasation, so a biopsy was performed.

Before confirmatory pathologic evaluation could be completed, the patient presented to his local hospital again in excruciating pain. A CT scan of his abdomen and pelvis demonstrated a massive subacute on chronic hematoma in the right retroperitoneum measuring 22 × 19 × 18 cm, with calcifications originating from an upper pole right renal neoplasm. The right kidney was displaced antero-inferiorly, and the inferior vena cava was displaced anteriorly and to the left. The preliminary pathology returned with findings suggestive of sarcoma (Figures 1 and 2).

The patient was then transferred to our institution, where he was evaluated by medical and surgical oncology. A CT scan of the chest and magnetic-resonance imaging (MRI) of the brain did not reveal metastatic disease. He underwent exploratory laparotomy that involved the resection of a 22-cm retroperitoneal mass, right nephrectomy, right adrenalectomy, partial right hepatectomy, and a full thickness resection of the right postero-inferior diaphragm followed by mesh repair because of involvement by the tumor.

In its entirety, the specimen was a mass of 26 × 24 × 14 cm. It was sectioned to show extensively necrotic and hemorrhagic variegated white to tan-red parenchyma (Figure 3). Histology revealed a poorly differentiated malignant neoplasm composed of round cells with scant amphophilic cytoplasm arranged in solid, variably sized nests separated by prominent thin-walled branching vascular channels (Figure 4). The mitotic rate was high. It was determined to be a histologically ungraded sarcoma according to the French Federation of Comprehensive Cancer Centers system of grading soft tissue sarcomas; the margins were indeterminate. Immunohistochemistry was positive for EMA, TLE1, and negative for AE1/AE3, S100, STAT6, and

Nkx2.2. Molecular pathology fluorescent in situ hybridization (FISH) analysis demonstrated positivity for *SS18* gene rearrangement (*SS18-SSX1* fusion).

After recovering from surgery, the patient received adjuvant chemotherapy with doxorubicin and ifosfamide. It has been almost 16 months since we first saw this patient. He was started on doxorubicin 20 mg/m² on days 1 to 4, ifosfamide 2,500 mg on days 1 to 4, and mesna 800 mg on days 1 to 4, for a total of 6 cycles. He did well for the first 5 months, after which he developed disease recurrence in the postoperative nephrectomy bed (a biopsy showed it to be recurrent synovial sarcoma) as well as pulmonary nodules, for which he was started on trabectedin 1.5 mg/m² every 3 weeks. Two months later, a CT scan showed an increase in the size of his retroperitoneal mass, and the treatment was changed to pazopanib 400 mg daily orally, on which he remained at the time of publication.

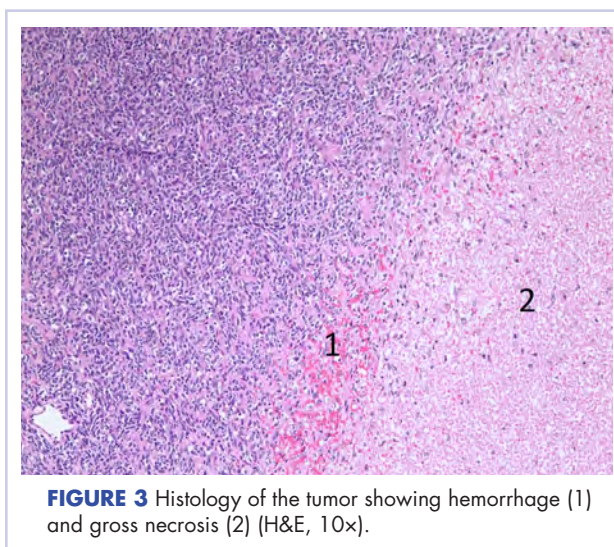


FIGURE 3 Histology of the tumor showing hemorrhage (1) and gross necrosis (2) (H&E, 10x).

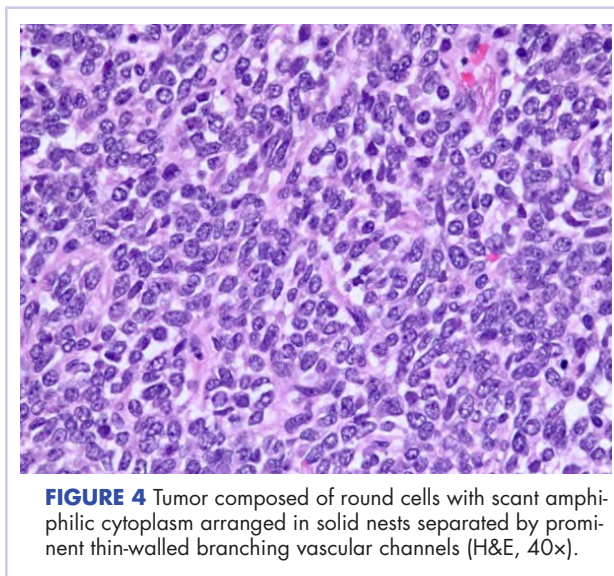


FIGURE 4 Tumor composed of round cells with scant amphiphilic cytoplasm arranged in solid nests separated by prominent thin-walled branching vascular channels (H&E, 40x).

Discussion

Synovial sarcoma is the fourth most common type of soft tissue sarcoma, accounting for 2.5% to 10.5% of all primary soft tissue malignancies worldwide. It occurs most frequently in adolescents and young adults, with most patients presenting between the ages of 15 and 40 years. Median age of presentation is 36 years. Despite the nomenclature, synovial sarcoma does not arise in intra-articular locations but typically occurs in proximity to joints in the extremities. Synovial sarcomas are less commonly described in other sites, including the head and neck, mediastinum, intraperitoneum, retroperitoneum, lung, pleura, and kidney.^{4,5} Renal synovial sarcoma was first described in a published article by Argani and colleagues in 2000.⁵

Adult renal mesenchymal tumors are classified into benign and malignant tumors on the basis of the histologic features and clinicobiologic behavior.^{6,7} The benign mesenchymal renal tumors include angiomyolipoma, leiomyoma, hemangioma, lymphangioma, juxtaglomerular cell tumor, renomedullary interstitial cell tumor (medullary fibroma), lipoma, solitary fibrous tumor, and schwannoma. Malignant renal tumors of mesenchymal origin include leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, solitary fibrous tumor, and synovial sarcoma.

Most of these tumor types cause the same nonspecific symptoms in patients – abdominal pain, flank pain, abdominal fullness, a palpable mass, and hematuria – although they can be clinically silent. The average duration of symptoms in synovial sarcoma is 2 to 4 years.⁸ The long duration of symptoms and initial slow growth of synovial sarcomas may give a false impression of a benign process.

A preoperative radiological diagnosis of primary renal synovial sarcoma may be suspected by analyzing the tumor's growth patterns on CT scans.⁹ Renal synovial sarcomas often appear as large, well-defined soft tissue masses that can extend into the renal pelvis or into the perinephric region.⁹ A CT scan may identify soft tissue calcifications, especially subtle ones in areas where the tumor anatomy is complex. A CT scan may also reveal areas of hemorrhage, necrosis, or cyst formation within the tumor, and can easily confirm bone involvement. Intravenous contrast may help in differentiating the mass from adjacent muscle and neurovascular complex.^{9,10} On MRI, renal synovial sarcomas are often described as nonspecific heterogeneous masses, although they may also exhibit heterogeneous enhancement of hemorrhagic areas, calcifications, and air-fluid levels (known as “triple sign”) as well as septae. The triple sign may be identified as areas of low, intermediate, and high signal intensity, correlating with areas of hemorrhage, calcification, and air-fluid level.^{9,10} Signal intensity is about equal to that of skeletal muscle on T1-weighted MRI and higher than that of subcutaneous fat on T2-weighted MRI.

In the present case, the tumor was initially misdiagnosed

as an angiomyolipoma, the most common benign tumor of the kidney. Angiomyolipomas are usually solid triphasic tumors arising from the renal cortex and are composed of 3 major elements: dysmorphic blood vessels, smooth muscle components, and adipose tissue. When angiomyolipomas are large enough, they are readily recognized by the identification of macroscopic fat within the tumor, either by CT scan or MRI.¹¹ When they are small, they may be difficult to distinguish from a small cyst on CT because of volume averaging.

On pathology, synovial sarcoma has dual epithelial and mesenchymal differentiation. They are frequently multilobulated, and areas of necrosis, hemorrhage, and cyst formation are also common. There are 3 main histologic subtypes of synovial sarcoma: biphasic (20%-30%), monophasic (50%-60%), and poorly differentiated (15%-25%). Poorly differentiated synovial sarcomas are generally epithelioid in morphology, have high mitotic activity (usually 10-20 mitoses/10 high-power field; range is <5 for well differentiated, low-grade tumors), and can be confused with round cell tumors such as Ewing sarcoma. Poorly differentiated synovial sarcomas are high-grade tumors.

Immunohistochemical studies can confirm the pathological diagnosis. Synovial sarcomas usually stain positive for Bcl2, CD99/Mic2, CD56, Vim, and focally for EMA but negatively for desmin, actin, WT1, S-100, CD34, and CD31.⁵ Currently, the gold standard for diagnosis and hallmark for synovial sarcomas are the t (X;18) translocation and *SYT-SSX* gene fusion products (*SYT-SSX1* in 67% and *SYT-SSX2* in 33% of cases). These can be detected either by FISH or reverse-transcription polymerase chain reaction. This genetic alteration is identified in more than 90% of synovial sarcomas and is highly specific.

The role of *SYT-SSX* gene fusion in the pathogenesis of synovial sarcoma is an active area of investigation. The fusion of SYT with SSX translates into a fusion protein that binds to the transcription activator SMARCA4 that is involved in chromatin remodeling, thus displacing both the wildtype SYT and the tumor suppressor gene *SMARCB1*. The modified protein complex then binds at several super-enhancer loci, unlocking suppressed genes such as *Sox2*, which is known to be necessary for synovial sarcoma proliferation. Alterations in *SMARCB1* are involved in several cancer types, implicating this event as a driver of these malignancies.¹² This results in a global alteration in chromatin remodeling that needs to be better understood to design targeted therapies.

The clinical course of synovial sarcoma, regardless of the tissue of origin, is typically poor. Multiple clinical and pathologic factors, including tumor size, location, patient age, and presence of poorly differentiated areas, are thought to have prognostic significance. A tumor size of more than 5 cm at presentation has the greatest impact on prognosis, with studies showing 5-year survival rates of 64%

for patients with tumors smaller than 5 cm and 26% for patients with masses greater than 5 cm.^{13,14} High-grade synovial sarcoma is favored in tumors that have cystic components, hemorrhage, and fluid levels and the triple sign.

Patients with tumors in the extremities have a more favorable prognosis than those with lesions in the head and neck area or axially, a feature that likely reflects better surgical control available for extremity lesions. Patient age of less than 15 to 20 years is also associated with a better long-term prognosis.^{15,16} Varela-Duran and Enzinger¹⁷ reported that the presence of extensive calcifications suggests improved long-term survival, with 5-year survival rates of 82% and decreased rates of local recurrence (32%) and metastatic disease (29%). The poorly differentiated subtype is associated with a worsened prognosis, with a 5-year survival rate of 20% through 30%.^{18,19} Other pathologic factors associated with worsened prognosis include presence of rhabdoid cells, extensive tumor necrosis, high nuclear grade, *p53* mutations, and high mitotic rate (>10 mitoses/10 high-power field). More recently, the gene fusion type *SYT-SSX2* (more common in monophasic lesions) has been associated with an improved prognosis, compared with that for *SYT-SSX1*, and an 89% metastasis-free survival.²⁰

Although there are no guidelines for the treatment of primary renal synovial sarcoma because of the limited

number of cases reported, surgery is considered the first choice. Adjuvant chemotherapy with an anthracycline (doxorubicin or epirubicin) combined with ifosfamide has been the most frequently used regimen in published cases, especially in those in which patients have poor prognostic factors as mentioned above.

Overall, the 5-year survival rate ranges from 36% to 76%.¹⁴ The clinical course of synovial sarcoma is characterized by a high rate of local recurrence (30%-50%) and metastatic disease (41%). Most metastases occur within the first 2 to 5 years after treatment cessation. Metastases are present in 16% to 25% of patients at their initial presentation, with the most frequent metastatic site being the lung, followed by the lymph nodes (4%-18%) and bone (8%-11%).

Conclusion

Primary renal synovial sarcoma is extremely rare, and preoperative diagnosis is difficult in the absence of specific clinical or imaging findings. A high index of suspicion combined with pathologic, immunohistochemical, cytogenetic, and molecular studies is essential for accurate diagnosis and subsequent treatment planning. The differential diagnosis of renal synovial sarcoma can be extensive, and our experience with this patient illustrates the diagnostic dilemma associated with renal synovial sarcoma.

References

- Majumder A, Dey S, Khandakar B, Medda S, Chandra Paul P. Primary renal synovial sarcoma: a rare tumor with an atypical presentation. *Arch Iran Med*. 2014;17(10):726-728.
- Fetsch JF, Meis JM. Synovial sarcoma of the abdominal wall. *Cancer*. 1993;72(2):469-477.
- Wang Z, Zhong Z, Zhu L, et al. Primary synovial sarcoma of the kidney: a case report. *Oncol Lett*. 2015;10(6):3542-3544.
- Abbas M, Dämmrich ME, Braubach P, et al. Synovial sarcoma of the kidney in a young patient with a review of the literature. *Rare tumors*. 2014;6(2):5393
- Argani P, Faria PA, Epstein JI, et al. Primary renal synovial sarcoma: molecular and morphologic delineation of an entity previously included among embryonal sarcomas of the kidney. *Am J Surg Pathol*. 2000;24(8):1087-1096.
- Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization classification of tumours: pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: IARC; 2004.
- Tamboli P, Ro JY, Amin MB, Ligato S, Ayala AG. Benign tumors and tumor-like lesions of the adult kidney. Part II: benign mesenchymal and mixed neoplasms, and tumor-like lesions. *Adv Anat Pathol*. 2000;7(1):47-66. 8. Weiss SW, Goldblum JR. Malignant soft tissue tumors of uncertain type. In: Weiss SW, Goldblum JR, eds. *Enzinger and Weiss's soft tissue tumors*. 4th ed. St. Louis, MO: Mosby, 2001; 1483-1565.
- Lacovelli R, Altavilla A, Ciardi A, et al. Clinical and pathological features of primary renal synovial sarcoma: analysis of 64 cases from 11 years of medical literature. *BJU Int*. 2012;110(10):1449-1454.
- Alhazzani AR, El-Sharkawy MS, Hassan H. Primary retroperitoneal synovial sarcoma in CT and MRI. *Urol Ann*. 2010;2(1):39-41.
- Katabathina VS, Vikram R, Nagar AM, Tamboli P, Menias CO, Prasad SR. Mesenchymal neoplasms of the kidney in adults: imaging spectrum with radiologic-pathologic correlation. *Radiographics*. 2010;30(6):1525-1540.
- Sápi Z, Papp G, Szendrői M, et al. Epigenetic regulation of SMARCB1 by miR-206, -381 and -671-5p is evident in a variety of SMARCB1 immunonegative soft tissue sarcomas, while miR-765 appears specific for epithelioid sarcoma. A miRNA study of 223 soft tissue sarcomas. *Genes Chromosomes Cancer*. 2016;55(10):786-802.
- Ferrari A, Gronchi A, Casanova M, et al. Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. *Cancer*. 2004;101(3):627-634.
- Rangheard AS, Vanel D, Viala J, Schwaab G, Casiraghi O, Sigal R. Synovial sarcomas of the head and neck: CT and MR imaging findings of eight patients. *Am J Neuroradiol*. 2001;22(5):851-857.
- Oda Y, Hashimoto H, Tsuneyoshi M, Takeshita S. Survival in synovial sarcoma: a multivariate study of prognostic factors with special emphasis on the comparison between early death and long-term survival. *Am J Surg Pathol*. 1993;17(1):35-44.
- Raney RB. Synovial sarcoma in young people: background, prognostic factors and therapeutic questions. *J Pediatr Hematol Oncol*. 2005;27(4):207-211.
- Varela-Duran J, Enzinger FM. Calcifying synovial sarcoma. *Cancer*. 1982;50(2):345-352.
- Cagle LA, Mirra JM, Storm FK, Roe DJ, Eilber FR. Histologic features relating to prognosis in synovial sarcoma. *Cancer*. 1987;59(10):1810-1814.
- Skytting B, Meis-Kindblom JM, Larsson O, et al. Synovial sarcoma – identification of favorable and unfavorable histologic types: a Scandinavian sarcoma group study of 104 cases. *Acta Orthop Scand*. 1999;70(6):543-554.
- Murphey MD, Gibson MS, Jennings BT, Crespo-Rodríguez AM, Fanburg-Smith J, Gajewski DA. Imaging of synovial sarcoma with radiologic-pathologic correlation. *Radiographics*. 2006;26(5):1543-1565.