

• Clinical Research •

Clinicopathologic analysis of 4 cases of primary renal synovial sarcoma

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[Abstract] Background and Objective: Primary renal synovial sarcoma is rare and might be misdiagnosed as another renal tumor. This study demonstrates the clinicopathologic and immunohistochemical features, differential diagnosis, and prognosis of such tumors. **Methods:** Histologic slides and clinical data were reviewed for 4 patients with primary renal synovial sarcoma and immunohistochemical staining was performed. Molecular analysis was performed on 2 cases to demonstrate the presence of the SYT-SSX gene fusion transcripts by reverse transcriptase polymerase chain reaction (RT-PCR). **Results:** The patients were 2 women and 2 men aged from 32 to 48 years. The tumors were 10.0–15.0 cm in diameter, grey-white and solid, and hemorrhage or necrosis was observed. Microscopically, the tumors consisted of mitotically active, monomorphic plump spindle cells with indistinct cell borders growing in short, intersecting fascicles. Hypocellular myxoid areas and a prominent hemangiopericytomatous pattern were present in all cases. The average mitotic rate was 5–8 mitoses/10 high-power fields. Hemorrhage and tumor necrosis were easily found. Scattered small cysts lined with flat, cuboidal, or hobnailed epithelia were found in 3 cases. Tumor cells are immunoreactive for Vimentin (4/4), Bcl-2 (4/4), CD99 (4/4), and CD56 (3/4), and focally for EMA (3/4) and Cytokeratin (3/4). SYT-SSX1 gene fusion was detected in the 2 cases in which RT-PCR analysis was performed. One patient had tumor metastasis to the lung 6 months after surgery and died 5 months later. Multiple metastasis to the liver occurred in one patient and the patient died 13 months after the initial surgery. The other 2 patients had tumors recur at 8 and 15 months and died at 18 and 21 months, respectively, after the initial operation. **Conclusion:** Primary renal synovial sarcoma is rare, with poor prognosis, characterized by SYT-SSX gene fusion, and needs to be differentiated from other renal sarcomas.

Key words: Kidney; synovial sarcoma; pathology; prognosis

Synovial sarcoma is the fourth most common soft-tissue sarcoma, which mainly develops in the limbs of young people¹. Besides soft tissue, synovial sarcoma also occurs in organs without synovial components as reported in the research, such as head and neck, third ventricle², duodenum³, heart⁴, pericardium⁵, pleura⁶, lung⁷, fallopian tubes⁸, mediastinum⁹, abdominal wall¹⁰, abdominal cavity¹¹, thyroid¹², vulva¹³ and prostate¹⁴. Primary renal sarcomas are relatively rare, and of those tumors, leiomyosarcoma, liposarcoma, and fibrosarcoma¹⁵ are more common, and malignant fibrous histiocytoma, osteosarcoma, rhabdomyosarcoma, hemangiopericytoma, hemangiosarcoma, and malignant peripheral nerve sheath tumors have also been

reported. Nevertheless, primary renal synovial sarcoma is rare¹⁶⁻¹⁸.

Diagnosing primary renal synovial sarcoma needs to exclude renal sarcomatoid carcinoma, metastatic sarcoma, and retroperitoneal sarcoma involving the kidney. The SYT-SSX gene fusion caused by t(X; 18) (p11.2; q11.2) translocation is the specific molecular biology of synovial sarcoma¹⁹. SSX has 5 subtypes: SSX1, SSX2, SSX3, SSX4, SSX5²⁰. In synovial sarcoma, SSX1 and SSX2 are the most common subtypes that fuse with the SYT gene of chromosome 18^{19,21}. In recent years, SYT-SSX4 gene fusion has also been reported. In this study, clinicopathologic analysis of 4 patients with primary renal synovial sarcoma was carried out to investigate the morphologic features, immunohistochemical features, differential diagnosis, and prognosis of this rare tumor.

Materials and Methods

Clinical data and gross observation

Four patients (2 men and 2 women aged 48–32 years) had

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primary renal synovial sarcomas dissected at Tumor Hospital of Linyi City, Shandong. Ultrasound and computed tomography (CT) showed kidney masses in all 4 patients, and 3 were on the left, 1 was on the right. Clinical symptoms included lower back pain and hematuria. The tumors were large with an average diameter of 12 cm (10–15 cm), gray cross-section, tenacious texture, hemorrhage, and necrosis. Small cysts with smooth inner walls were found in 3 tumors, which was different in number and unlike the pseudocyst of tumor necrosis. One patient had renal hilum.

Methods

The tumors were fixed by 10% neutral buffered formalin and conventionally treated for histologic examination. Clinical data and all histopathologic sections were reviewed, of which the representative ones were prepared for immunohistochemical staining. The EnVision two-step method was performed for immunohistochemical staining, and antibodies included: cytokeratin (CK) (AE1/AE3, Dako, 1:80), EMA (E29, Dako, 1:100), Vimentin (V9, Dako, 1:100), CD34 (Dako, 1:20), S100 (Dako, 1:800), SMA (1A4, SigmaChemical, 1:1600), Desmin (D33, Dako, 1:100), CD99 (12E7, Dako, 1:50), Bcl-2 (Dako, 1:20), CD117 (KIT, Dako, 1:300), CD56 (novocastra, 1:50), progesterone receptor (PR) (Biogenex, 1:40), and estrogen receptor (ER) (Biogenex, 1:50). Molecular analysis was

performed in 2 cases by reverse transcriptase polymerase chain reaction (RT-PCR) to detect SYT-SSX gene fusion according to ref. 22.

All patients underwent radical surgery and were followed up by telephone.

Results

Microscopic appearance

The tumor border was relatively clear, and no capsule was detected. Under high-powered microscopy, the tumor comprised fusiform, round or oval cells as solid sheets or fascicular arrangements, which was characteristic of fusiform, round or oval nuclei, light-stained chromatin, and less cytoplasm (Figure 1A). The mitotic phase was 5–10 mitoses/10 high-power fields (HPF). In some regions, rich and rarefied areas of cells were mixed, and the stroma of the rarefied area showed as mucus (Figure 1B). Focal hemorrhage and necrosis were detected, as well as hemangiopericytoma-shaped structures in all 4 cases (Figure 1C). Multiple small cysts of different sizes were scattered in 3 cases, whose inner walls were covered with flat, cube, or spike-shaped cells (Figure 1D). Occasionally, the renal tubule and fatty tissue were wrapped around the tumor.

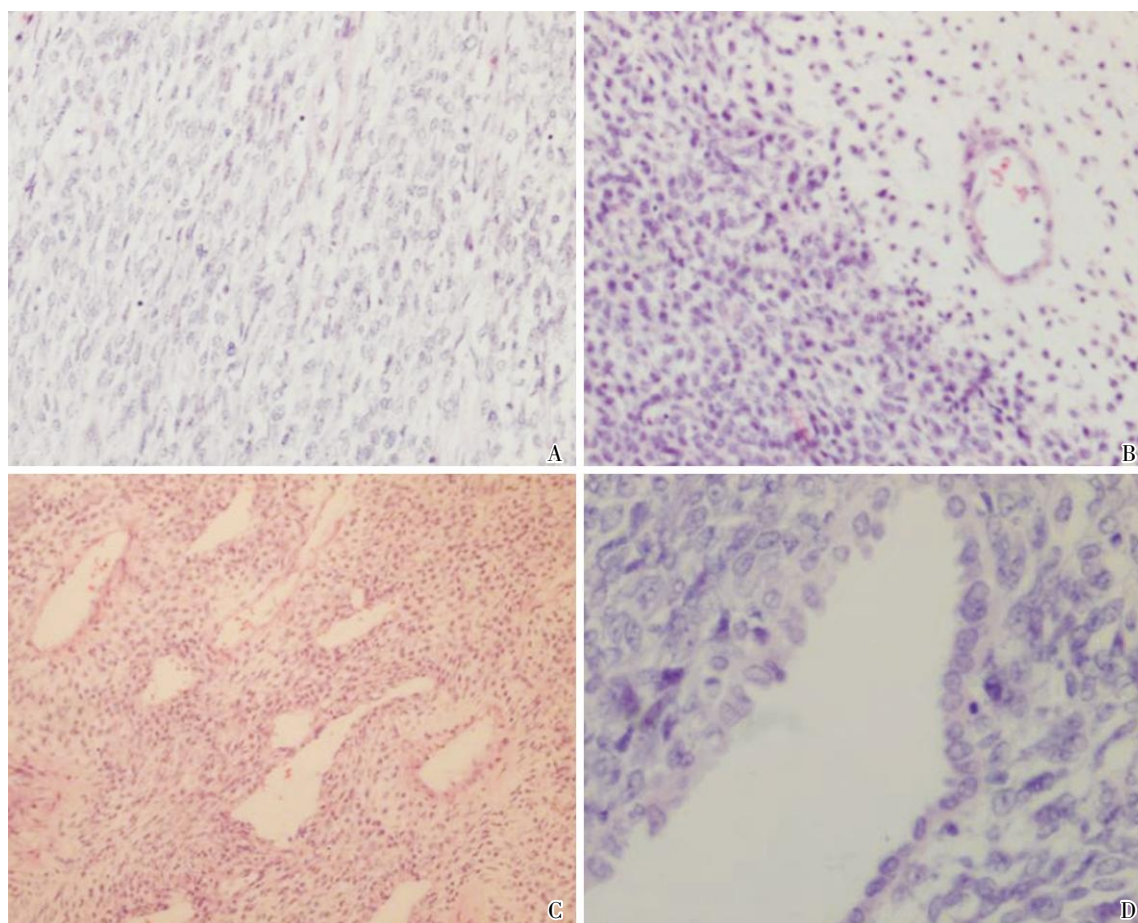


Figure 1 Morphology of primary renal synovial sarcoma

A, tumors consist of spindle-shaped, round, or oval cells, arranging in a solid or fascicle pattern (HE ×100). B, hypocellular myxoid and hypercellular areas are mixed in the tumor (HE ×100). C, a hemangiopericytoma-like pattern is present (HE ×100). D, the cyst is lined with flat, cuboidal, or hobnail epithelia (HE ×200).

Immunohistochemical staining

In immunohistochemical staining, diffuse expression of Vimentin, CD99, and Bcl-2 (Figure 2A, 2B) were detected in the tumor cells. Moreover, 3 cases showed focal expressions of CD56, CK, and EMA. The epithelial lining of the cysts expressed EMA and CK (Figure 2C). S-100, CD34, Desmin, Actin, PR, ER,

and CD117 were not expressed in the tumor cells.

RT-PCR analysis

Molecular analysis of SSX-SYT gene fusion was performed in 2 cases, and the result showed SYT-SSX1 gene fusion in both cases (Figure 3).

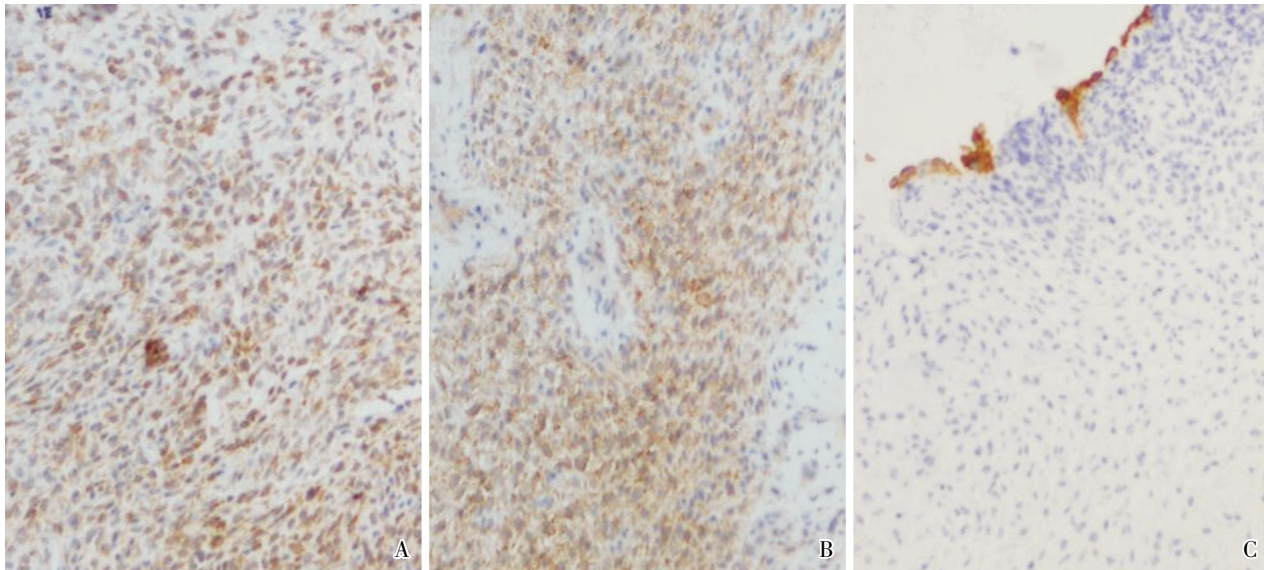


Figure 2. Immunohistochemical staining of primary renal synovial sarcoma (SP $\times 100$)

The tumor cells are diffusely positive for CD99 (A), and Bcl-2 (B); the epithelium lining the cysts are positive for CK (C).

Follow-up results

Of these 4 patients with primary renal synovial sarcoma, 1 patient reported multiple hepatic metastases postoperatively, and died 13 months after surgery. Lung metastasis was found in 1 patient 6 months after surgery, who died 5 months later. The other 2 patients had disease recurrence 8 and 15 months after surgery, and died at 18 and 21 months, respectively.

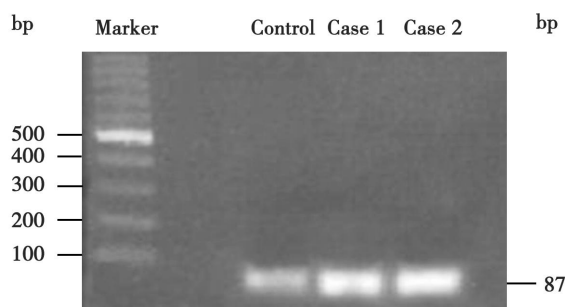


Figure 3 Expression of SYT-SSX1 fusion gene in primary renal synovial sarcoma detected by RT-PCR

Discussion

Although the origin is unknown, synovial sarcoma is a

well-defined clinical and pathologic tumor type that mainly develops in juxtaarticular soft tissue or in the limbs of young people and adults¹. Synovial sarcoma has 3 histologic subtypes: unidirectional, bidirectional, and poorly differentiated. Because of epithelial- and spindle-cell components, bidirectional differentiated synovial sarcoma is easy to diagnose; but sometimes it is difficult to distinguish unidirectional synovial sarcoma from other spindle-cell sarcomas.

Primary renal synovial sarcoma needs to be differentially diagnosed from leiomyosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumors, primitive neuroectodermal tumors, solitary fibrous tumors, hemangiopericytoma, mixed epithelial and mesenchymal tumors, Wilm's tumors, and renal sarcomatoid carcinoma. Leiomyosarcoma and fibrosarcoma are also rare in the kidney, and are solid, have no small cysts with a spike-shaped cell lining, and few hemangiopericytoma-shaped structures, often express SMA, but do not express BCL-2, CD99, and CD56.

Hemangiopericytoma and solitary fibrous tumors occasionally occur in the kidney, and only a few cases have been reported^{23, 24}. Synovial sarcoma has hemangiopericytoma-shaped structures, and sometimes it is difficult to discriminate it from hemangiopericytoma and solitary fibrous tumors. However, in synovial sarcoma cells, pleomorphism and heteromorphism are obvious and cells in the mitotic phase are more common. Moreover, lacunules with a spike-shaped cell lining can be observed, while for hemangiopericytoma, the irregular

antler-shaped blood vessels are more visible, the cells have no obvious heteromorphism, and no small cysts with cube or spike-shaped cell linings exists. Also the immunohistochemistry is different. The expression of CD34 is diffuse and strongly positive in hemangiopericytoma and solitary fibrous tumors, and no epithelial markers are detected.

Malignant peripheral nerve sheath tumor (MPNST) is histologically similar to synovial sarcoma, especially when MPNST is accompanied by an adenoid structure (so-called adenoid MPNST). About 50%–70% of MPNST express S-100 and synovial sarcoma is usually negative²⁵. Although a few MPNSTs express EMA and CD56, they rarely express CK and CD99. In contrast, synovial sarcoma is often CK- and CD99-positive and NF-negative. Primitive neuroectodermal tumor (PNET) comprises more primitive small cells, and sometimes a rosette structure can be observed. Immunohistochemically, the expressions of CD99 and CD56 are positive, while the expressions of EMA and CK are negative. In this study, the 4 cases all expressed BCL-2, Vimentin, EMA, CK, CD99, and CD56, which could exclude MPNST and PNET.

Mixed epithelial and mesenchymal tumor (MEMT), and cystic nephroma (CN) are composed of the spindle cell areas, ovarian stroma, and cysts with epithelial linings, which also need to be identified with synovial sarcoma. And the spindle cell of synovial sarcoma, which is characteristic of obvious heteromorphism and the mitotic phase, is different from the benign mesenchymal components of MEMT and CN. Moreover, the ovarian stroma of MEMT and CN can express Inhibin, PR, and ER²⁶.

Wilm's tumor occasionally occurs in adults, but the tumor can develop a primordial composition and an immaturely differentiated renal tubule, which is absent in synovial sarcoma. At the same time, Wilm's tumor can express WT-1, which is negative in synovial sarcoma.

Sometimes it is difficult to differentiate renal sarcomatoid carcinoma and synovial sarcoma, for sarcomatoid carcinoma also expresses epithelial markers and Vimentin²⁷. Via multiple sampling, typical cancer areas of sarcomatoid carcinoma is often found, such as clear-cell carcinoma components, nipple-shaped structures, or carcinous cryptae of obvious heteromorphisms, and the malignant cryptae are different from the remnants of the small-tube or cystic structures of synovial sarcoma, which is not cell atypia. In addition, the sarcomatoid region of sarcomatoid carcinoma does not express CD99 and CD56.

In this study, the carcinogenic ingredient was not found in the 4 cases by extensive sampling. Cysts with cuboidal epithelium or a spike-shaped cell lining are important histologic features of renal synovial sarcoma, and these cystic structures are rarely found in other primary renal sarcomas, such as smooth muscle sarcoma, fibrosarcoma, MPNST, PNET, or sarcomatoid carcinoma. Argani *et al.*²⁸ reported on 15 patients with renal primary synovial sarcoma, where the majority of the tumors had small visible cavities with smooth inner walls, which were different from the pseudocavities of tumor necrosis. Since 1987, when t (X; 18) translocation was found, this abnormality has been considered as the genomic character of synovial sarcoma, which can be detected in approximately 90% of synovial sarcomas²⁹⁻³¹.

Crew *et al.*¹⁹ noted that the t (X; 18) (p11.2; q11.2) translocation of synovial sarcomas resulted in the fusion of the SYT gene and one of the homologous genes (SSX1, SSX2) on chromosome 18. This genetic abnormality was found in all synovial sarcoma subtypes, including the bidirectional, the unidirectional, and the poorly differentiated subtypes.

By fluorescence in situ hybridization, Birdsall *et al.*³² found that specific t (X; 18) translocation of synovial sarcoma was detected in both epithelial cells and spindle-cell components of 3 bi-directionally differentiated synovial sarcomas, and the results showed that whether bidirectional or unidirectional differentiated synovial sarcoma, tumor cells were monoclonal hyperplasia. In this study, SYT-SSX1 gene fusion was detected in both cases where RT-PCR was used and the diagnoses were confirmed.

Conclusion

Renal synovial sarcoma is rare and its prognosis is poor. Most patients die within 1–2 years of tumor recurrence or metastasis. In this study, the longest survival time after surgery was 21 months. Its morphologic and immunohistochemical characteristics may be related to other spindle-cell tumors of the kidney. Therefore, diagnosis of primary renal synovial sarcoma needs to exclude other similar diseases and confirm the SYT-SSX gene fusion by molecular analysis.

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