

CASE REPORT

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Primary Monophasic Synovial Sarcoma of the Kidney: A Case Report and Review of Literature

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Abstract: Primary synovial sarcoma (SS) of the kidney is a rare neoplasm and its presenting features are similar to other common renal tumors, making early diagnosis difficult. To date, few cases have been reported in the literature. Primary renal SSs can exist in either a monophasic or a biphasic pattern, the former being more common and tending to have a better prognosis than the biphasic variant. Herein we describe a case of primary renal SS that was diagnosed based on histopathology and immunohistochemistry after radical nephrectomy. Fusion gene product analysis was also done by FISH and RT-PCR. Patient follow-up and literature review are presented, focused on systemic therapy. We highlight that these tumors should be correctly diagnosed as clinical results and specific treatment are distinct from primary epithelial renal cell carcinoma. Adjuvant chemotherapy should be tailored for each patient in the management of disease, although its role still remains unclear.

Keywords: synovial sarcoma, kidney neoplasms, SYT-SSX fusion protein, chemotherapy

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Introduction

Soft tissue sarcomas (STSs) have remained as a therapeutic challenge over the last decades, due in large part to their diverse biological behavior and the lack of consistent literature data concerning treatment of individual histologies.

Synovial sarcoma (SS) is a STS of uncertain histogenesis and most commonly affects the proximal lower limb of young adults. However, SS has also been identified in a range of less common locations, such as head and neck, heart, lungs, and prostate.¹⁻⁵ The first reported case of primary SS of the kidney was described in 1999 and published in 2000 by Argani et al.⁶ To date, there are fewer than fifty cases described in the literature.⁷

This case reports an uncommon presentation of SS, originating in the kidney in a 19-year-old man. Patient follow-up and literature review are also presented.

Case Report

A 19-year-old male was referred to our hospital with a four-month history of left lumbar pain associated with gross hematuria. Abdominal CT scan revealed an expansive mass in the middle and lower third of the left kidney, confined to the renal capsule (Figs. 1 and 2). The CT series also showed tumor thrombus in the left renal vein extending up to 5 mm into the inferior vena cava. Staging chest CT scan showed only a small residual calcified granuloma and no evidence

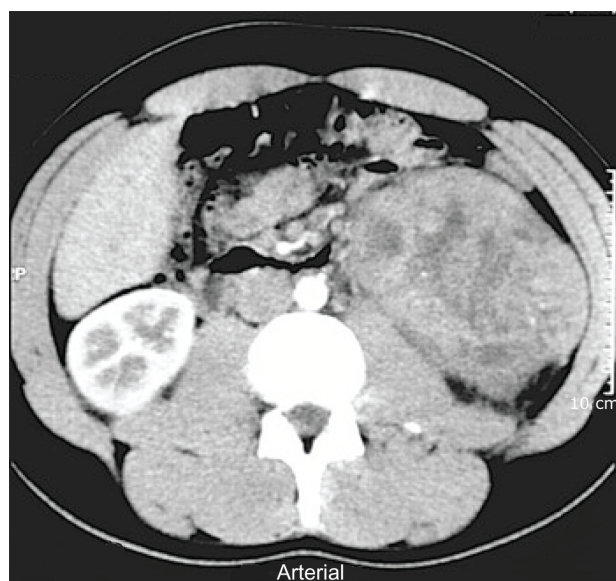


Figure 1. Abdominal CT scan shows lower left renal mass (arterial phase).



Figure 2. Abdominal CT scan shows lower left renal mass (portal phase).

of metastasis. The patient subsequently underwent left nephrectomy and left renal vein thrombectomy with no complications. Per-operative observation describes a large renal mass in the left flank and the presence of loose adhesions and neo-vascularization.

Pathological evaluation revealed a 678 g left kidney with fat coat revealed a tumor measuring $9.0 \times 8.2 \times 7.2$ cm in the renal inferior pole, associated with vascular thrombus and infiltration of the renal sinus. Renal capsule was easily detachable, but there were loose adhesions overlying the tumor. Ureteral border, para-aortic lymph node, and adrenal gland showed no evidence of cancer. Histological evaluation by high power magnification field of tumoral tissue revealed monomorphic atypical spindle cells, sometimes showing active mitotic figures, diffusely arranged (Fig. 3A). Immunohistochemistry analysis, using the streptavidin biotin peroxidase method, stained positive for P53, vimentin, CD99, and focally positive for AE1/AE3 and EMA (Fig. 3B–D). There was no uptake for low molecular weight cytokeratin, CEA, desmin, cromogranine, synaptophysin, enolase, S-100, CD 10, CD 117, bcl-2, β -catenin, FLI-1, and WT-1.

The final pathological diagnosis on this case was based on morphological and immunohistochemistry features, which depicted a pattern typical of SS, due to the presence of epithelial and mesenchymal markers.^{3,4,6}

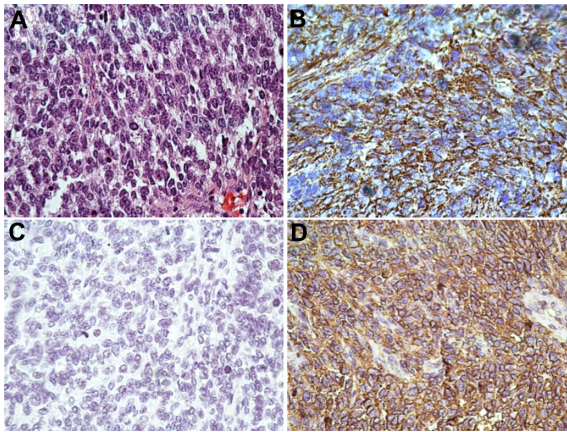


Figure 3. (A) Monomorphic neoplastic spindle cells mitotic activity (H & E, $\times 400$). (B) Vimentin immunopositive cells ($\times 400$). (C) AE1/AE3 focal immunopositive cells ($\times 400$). (D) CD99 immunopositive cells ($\times 400$).

According to these findings, a diagnosis of primary monophasic SS of the kidney was defined. On medical oncology appraisal, it was decided for serial follow up and no adjuvant treatment was given. At ten months of follow up, the patient remained asymptomatic. However, chest CT scan detected lung metastasis with basal predominance, measuring up to 1.1 cm. Following these findings, the patient was referred to be included in a clinical trial with anthracycline-based chemotherapy.

Molecular studies have demonstrated the presence of the chromosomal translocation $t(X;18)(p11;q11)$ in over 90% of cases of SS. This anomaly leads to a hybrid product which involves gene SYT on 18p11 and one gene of SSX family on chromosome X, mostly SSX-1, less frequently SSX-2, and seldom SSX-4.^{8–11} This finding led the attending team to attempt a confirmation of the pathology diagnosis and immunohistochemistry (both typical and conclusive of SS) using molecular biology techniques. The analysis of the rearrangement $t(X, 18)$ by FISH method, following previously detailed procedures,^{12,13} was performed and the presence of multiple fluorescence signals posed difficulties in the interpretation of the results. Hence, they were inconclusive. This is a finding which could represent polyploidy or multiple copies of a region of variable length of the SS-18 gene.¹³ In a second moment, we performed real-time polymerase chain reaction (RT-PCR), in order to detect the mutation reported in literature. There was difficulty in amplification of DNA for analysis requiring the test to be repeated more than once. However, the test results were negative.

Despite any doubts or difficulties to confirm the initial diagnosis, the patient presented a typical natural history of SS, with systemic spread to the lungs in a few months following surgery. He was treated with five cycles of doxorubicin 75 mg/m^2 on the first day and an investigational product 150 mg/m^2 over 3 days every three weeks. Due to grade 3 neutropenic fever during the third cycle, doses were reduced to 80% on the fourth cycle and further reduced to 60% on the fifth cycle due to grade 2 neutropenia. Persistence of grade 2 neutropenia after the fifth cycle precluded a planned sixth cycle and, following protocol procedures, first line palliative chemotherapy was terminated. Other than hematologic toxicity, other toxicities were mild, with grade 2 nausea, alopecia, and weight loss. His response to systemic chemotherapy was favorable, with shrinkage of the pulmonary nodules. No radiotherapy or surgery was offered. At present the patient remains in ambulatory care, with a good performance status, in clinical follow-up and without disease progression more than one year after the last chemotherapy dose.

Discussion

Primary SS of the kidney constitutes a subtype of the cases identified as embryonal sarcoma of the kidney and can clinically mimic an advanced renal cell carcinoma (RCC), making the correct diagnosis challenging. In addition to the rarity of these tumors, primary SS of the kidney is also difficult to differentiate pathologically from other spindle cell histologies of the kidney such as adult Wilms tumors, primary PNET/Ewing,⁸ sarcomatoid RCC, and undifferentiated carcinoma.

SS is considered to be an aggressive form of STS, with a high probability of systemic spread, and it is considered to be more sensitive to anthracycline-based chemotherapy than usual (up to 53% of response rate).¹⁴ This disease very rarely develops in solid organs, like the kidney. The limited number of cases reported has shown a gender ratio close to one, a mean age at diagnosis of 37 years (ranging between 13 and 67), and mean tumor largest diameter of 11 cm, ranging from 3 to 21 cm. The rate of metastasis on admission seems to be low.⁷ Firstly managed through surgery, there is no consensus about the role of chemotherapy on these cases, either as neoadjuvant or adjuvant therapy.



Table 1. Differential diagnosis of synovial sarcoma (SS) of the kidney. Modified from references 3 and 28.

Neoplasm	Gross appearance	Pathology	Immunohistochemistry	Cytogenetics
Adult Wilms tumor	Solitary masses mostly sharply demarcated from renal parenchyma	Undifferentiated blastemal cells Epithelial component in the vast majority Stromal patterns may vary and make diagnosis difficult May contain heterogeneous differentiation	Blastemal cells: regular expression of vimentin, also focal neuron specific enolase, desmin, cyokeratin WT-1: frequent in blastemal areas with nuclear staining Expression of vimentin and CD99 or HBA-71	Ten per cent of cases associated with dysmorphic syndromes—deletion 11p13 involving WT-1 gene or point mutations WT-1 role in sporadic cases limited
Primary PNET/Ewing	Large masses, may measure over 10 cm Greyish-tan to white lobulated surface Areas of haemorrhage and necrosis	Monotonous polygonal cells with hyperchromatic, rounded nucleus		t(11;22)(q24;q12) translocation creates fusion transcript between the EWS gene (22q12) and the ETS-related oncogene FLI1
Sarcomatoid RCC	Fleshy, gray-white, infiltrative margins Mean size 9 cm	Atypical spindle cells admixed with epithelial cells typical of a specific RCC Considered as a manifestation of high grade carcinoma of the type from which it arose Sarcomatoid elements No recognizable epithelial elements or cell types which permit classification into a category of RCC		
Undifferentiated carcinoma	None specified			
Synovial sarcoma of the kidney	Most tumor are solid Areas of hemorrhage, necrosis and cyst formation	Monophasic: monomorphous spindle cells, scant to moderate cytoplasm Biphasic: spindle-shaped cells admixed with plump epithelioid cells	Positive for cytokeratin, vimentin, bcl-2, epithelial membrane antigen Negative for actin, desmin, S-100 or CD-34	Translocation SSX-SYT in more than 90% of cases, mostly SYT-SSX2



With the development of specific clinical treatment, great effort has been made to better understand the clinical course of the disease, investigate treatment response (predictive), and prognostic factors in SS.^{15,16} Lately, molecular research has contributed even more, including the identification of the aforementioned translocation in SS,^{9,11} though much has yet to be done to provide better tools to assess risk. Cytogenetic studies have shown a characteristic t(X;18)(p11;q11) chromosomal translocation as a diagnostic indicator of SS⁹ as well as cytogenetic or molecular methods have been used in order to detect it.

One possible explanation for the negative results in FISH and RT-PCR tests in this patient lies in the difficulty to amplify DNA, possibly due to the quality of the sample material. Another possibility is that we may be dealing with a novel splicing or fusion protein, such as SYT-SSX-4, that could not be detected through current means.^{13,17–19} Any of them can be present at this moment, although we cannot establish nor distinguish which role each of them played in this case.

Controversy still revolves on the clinical benefit of adjuvant chemotherapy on sarcoma. Initial studies, mostly based on anthracycline-only chemotherapy, when analyzed together, did not show improvement on overall survival, despite a small gain on recurrence-free survival.²⁰ Later studies, including anthracycline and ifosfamide-based chemotherapy, revealed a small gain on survival,²¹ which could not be reproduced in another large trial.²² Thus, no consensus has been achieved and debate is still ongoing, with management varying between institutions and countries. There is no compelling evidence of benefit on survival, which may be due to the mixing inclusion of different histological subtypes in studies as well as the evolution in the quality of treatment and differing criteria for selecting patients for adjuvant systemic therapy.²³ Shared decision-making, discussing benefits, and risks of systemic treatment has been the most commonly recommended approach.^{24,25} Because of this uncertainty about benefit, there is a higher possibility for adjuvant chemotherapy to be used in younger patients and larger tumors, especially in more chemosensitive histologies, such as SS, in which a net benefit of treatment could be achieved.^{26,27}

Our option on this case was for follow-up, with no adjuvant therapy being offered (whether chemotherapy or radiotherapy), considering rarity and no established

benefit on literature. Nevertheless, incorporating new management standards into routine clinical care is a process in evolution as new questions are answered, such as the appropriate timing of each therapeutic intervention. We emphasize the importance of an adequate pathological diagnosis for better clinical decision, to ensure optimized treatment and results in patient care, no matter the type of cancer. We conclude that SS, even in unusual presentations, is a disease that can be treated with a multidisciplinary approach and that radical surgery for the primary tumor and chemotherapy with additional surgery for pulmonary nodules, if possible, remains the standard of care up-to-date.

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Author Contributions

Conceived and designed the case report: HL, CADP, LERZ, SVS, FMC. Analyzed the data: HL, FMC, CADP, SRMS, MLC. Wrote the first draft of the manuscript: HL. Contributed to the writing of the manuscript: HL, FMC, CADP. Agreed with manuscript results and conclusions: HL, CADP, LERZ, SVS, SRMS, MLC, FMC. Jointly developed the structure and arguments for the paper: HL, CADP, FMC. Made critical revisions and approved final version: HL, CADP, FMC. All authors reviewed and approved of the final manuscript.

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consent has been obtained from the patient or representatives for the reproduction of images. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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