A case of renal cell carcinoma with abundant smooth muscle (leiomyomatous) stroma and the differential diagnosis

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Abstract
Renal cell carcinoma with smooth muscle stroma (RCCSMS) is a rare and controversial renal cancer type with indolent behavior. This separation of this entity from other types of renal cell carcinoma is supported by recent published studies but not yet recognized by the World Health Organization. We present a case of a 72 years old female, with incidental finding on abdominal ultrasound of a renal nodule with 1.5cm. The patient underwent partial nephrectomy and the pathological evaluation showed an epithelial tumor composed of nests and trabeculae of polygonal cells with clear cytoplasm and low grade nuclear features, surrounded by an abundant stroma composed by fascicles of spindle cells without significant pleomorphism or mitoses. Immunohistochemically, the epithelial cells showed strong and diffuse positivity for CK7, CD10, vimentin and EMA; staining for RCC was focal. The stromal cells were positive for vimentin, smooth muscle actin, HHF35, desmin and caldesmon; ER and PR were negative. The staining for HMB45 and Melan-A was negative in both components. So the final diagnosis of RCCSMS was made. It’s important to be aware of this entity in order to differentiate RCCSMS from renal cancers with less favorable prognosis and higher degree of malignancy, like clear cell renal cell carcinoma, especially with sarcomatoid change.

Keywords: Kidney, renal cell carcinoma, clear cells, leiomyomatous stroma

Virtual Slides: http://www.diagnosticpathology.eu/vs/2015_1_28/
Introduction

Kidney cancer is the 13th most common cancer in the world, where around 338,000 new cases were diagnosed in 2012 (2% of the total). It’s a cancer with many morphological and molecular variants. There has been some discussion about the classification of renal carcinomas with abundant smooth muscle stroma, with several publications describing tumors of this kind utilizing different names, such as: benign renal angiomyoadenomatous tumor, variant of renal cell carcinoma with prominent angioleiomyoma-like proliferation of the stroma, leiomyomatous renal cell carcinoma, renal angiomyoadenomatous tumor (RAT), clear cell renal cell carcinoma with smooth muscle stroma (RCCSMS) and renal cell carcinoma with leiomyomatous stroma. These multiple designations provided pathologists with a challenge for diagnosing this tumor, given the lack of uniform and reproducible denomination. The 2004 World Health Organization (WHO) Classification of Renal Tumours did not discriminate carcinomas with abundant smooth muscle stroma into any specific category. The recent update, with the publication of the International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia, recognized five new distinct epithelial tumors, one of them a clear cell (tubulo) papillary renal cell carcinoma (CCPRCC), which included the tumors previously known as RATs. So it must be stated that the designation RCCSMS used in this report refers to a new recognized entity, which excludes RATs.

Despite the absence of RCCSMS in the latest update of renal neoplasia classification, even more recent articles considered the likely possibility that this tumor is indeed different from other renal neoplasms, despite some similarities in morphology, immunohistochemistry and molecular alterations, namely with some clear cell renal cell carcinomas (CCRCC) with abundant smooth muscle stroma, RAT/CCPRCC and epithelioid angiomyolipomas (EAMP).

In this report we describe a case of a RCCSMS diagnosed at our institution and its clinical and histopathological characteristics.

Case Report

Clinical data

A 72 years old female patient was referred for Urological evaluation in our institution for having an incidental finding of a right renal nodule with 1.5cm on a routine abdominal ultrasound. The patient was asymptomatic and had no relevant past medical history.

Physical examination and routine blood and serum analysis were unremarkable.
Computerized tomography (CT)-scan showed a 1.5cm nodular lesion of the middle third of the right kidney, with enhancement after contrast administration. The right kidney also had two simple cysts with less than 1cm in diameter. There were no lesions suspects of metastasis.

The patient underwent laparoscopic partial right nephrectomy, which didn’t have any intercurrence. During the post-operative, there was a drop in the hemoglobin values associated with a 15x2cm peri-renal hematoma. The patient progressively recovered the hemoglobin values and was discharged on the 9th day after surgery.

**Macrosopy**

We received a partial nephrectomy specimen with 7g and 3cm, with a brownish capsular surface. Serial sections showed a solid nodular lesion with 1.2cm, well defined and composed by a white fasciculated tissue (Fig. 1A), with a distance to the renal surgical marginal of 0.1cm.

**Microscopy**

Examination was performed on Haematoxylin and Eosin (HE) stained slides, observed under a light microscope – Nikon Eclipse 50i and images were obtained using a Nikon-Digital Sight DS-Fi1 camera.

The lesion corresponded to an expansive malignant epithelial tumor, composed by nests and trabeculae of polygonal cells with clear cytoplasm, well defined cell membranes and regular round nuclei with nucleolus occasionally evident on 200x amplification – Furhman Grade 2.

The stroma was abundant and composed by fascicles of spindle cells, with eosinophilic cytoplasm, elongated nuclei showing smooth contours without significant pleomorphism or atypia and without mitoses. Such morphology resembled benign smooth muscle tissue (Fig. 1B – 1D).
Fig. 1 – Morphological aspects of renal cell carcinoma with smooth muscle stroma (RCCSMS). A – Macroscopic picture showing a solid nodular lesion with 1.2cm, well defined and composed by a white fasciculated tissue, surrounded by brownish renal parenchyma; B – The tumor (right) is well demarcated from the normal renal parenchyma (left) (HE stain, 20x); C – The tumor is composed by nests and trabeculae of neoplastic epithelial cells embedded in an abundant fasciculated stroma (HE stain, 100x); D – Polygonal epithelial cells with clear cytoplasm, well defined cell membranes and regular round nuclei, surrounded by stromal spindle cells with eosinophilic cytoplasm and elongated nuclei showing smooth contours, without significant pleomorphism or atypia and without mitoses (HE stain, 400x).

Immunohistochemistry

The characteristics of the antigens used are summarized in table 1. Studies were performed on one representative block of the lesion, resorting to the avidin-biotin-peroxidase complex detection system and performed on a Ventana Marker Platform Bench Mark ULTRA IHC/ISH.

Immunohistochemically, the neoplastic epithelial cells showed strong and diffuse positivity for cytokeratin (CK)7, cluster of differentiation (CD)10, vimentin and epithelial membrane antigen (EMA) (Fig. 2A – 2D); the staining for renal cell carcinoma (RCC) was focal.
Fig. 2 – Immunostaining profile of the neoplastic epithelial component seen in this case of RCCSMS. **A** – Strong and diffuse membrane and cytoplasm staining for CK7; **B** – Positive membrane staining for CD10; **C** – Strong and diffuse membrane and cytoplasm staining for vimentin (also stains the stromal component); **D** – Strong and diffuse membrane and cytoplasm staining for EMA. All images were captured using 200x magnifications.

The stromal cells were positive for vimentin, smooth muscle actin, muscle actin (HHF35), desmin and caldesmon (Fig. 3A – 3C); estrogen and progesterone receptor (ER and PR) were negative. The staining for human melanin black 45 (HMB45) and Melan-A was negative in both components (Fig. 3D).
Fig. 3 – Immunostaining profile of the stromal component and staining for HMB45 in both components. A – Strong and diffuse cytoplasm staining for smooth muscle actin (200x); B – Positive cytoplasm staining for caldesmon (40x); C – Positive cytoplasm staining for HHF35 (200x); D – Negative staining in both components for HMB45 (200x).

**Diagnosis and Pathological Staging**

The tumor was diagnosed as RCCSMS and staged as pT1aNxMx (TNM 7th edition); AJCC/UICC – Stage I (cN0 and cM0).

**Discussion**

RCCSMS is a rare renal tumor, with a very limited number of reports in the literature, occurring at an age range from 33 to 78 years\(^1\). It’s found incidentally in a majority of cases during routine imagiological studies, with only 25% of the patients presenting with hematuria\(^2\).

Grossly, RCCSMS is usually a small tumor, with a variegated cut surface appearance (mahogany brown, yellow or white), possibly with cystic changes, calcification and foci of necrosis. Histologically it is characterized by nests or trabeculae of epithelial cells with optically clear...
cytoplasm, embedded in an abundant stroma rich in smooth muscle cells, showing no significant pleomorphism or atypia and without mitotic activity².

Immunohistochemically the epithelial component is positive for pancytokeratin, CK7, EMA, CD10 and RCC. The stromal component is positive for smooth muscle actin, HHF35 and desmin, being negative for ER and PR. Both components are negative for HMB45²,14,15.

Recent studies have attempted characterization of RCCSMS at a molecular level. RCCSMS should not show alterations more characteristic of CCRCC, such as Von-Hippel Lindau (VHL) gene mutation or hypermethilation and loss of heterozygosity of chromosome 3p, although the role of genetics for this diagnosis is still widely discussed¹⁴,¹⁵,¹⁶.

Regarding its origin, some authors believe that the prominent leiomyomatous stromal component is an exaggerated mesenchymal reaction⁷. Supporting this theory, a recent study analyzing the clonality of the smooth muscle component in 14 selected cases of renal epithelial neoplasms, rich in this type of stroma, found them to be polyclonal in all analyzable cases (8 of 14)⁶.

The major differential diagnosis of RCCSMS are other renal tumors with similar morphology, including clear cell renal cell carcinoma (CCRCC), especially with abundant smooth muscle stroma or sarcomatoid change, CCTPRCC/RAT, EAMP, and mixed epithelial and stromal tumor (MEST). The following characteristics are useful for the distinction between the mentioned entities:

- CCRCC usually has no conspicuous smooth muscle stroma and is CK7 negative. Sarcomatoid change usually shows conspicuous cellular pleomorphism, nuclear atypia and mitotic activity. Alterations of VHL gene or chromosome 3p are absent in RCCSMS;
- CCCPRCC/RAT is also formed by low nuclear grade clear cells and the immunoprofile is similar to RCCSMS, however, both the characteristic linear arrangement of nuclei away from the basal aspect of the cell and the negativity for CD10 seen in the former are useful for the differential diagnosis;
- EAMP has epithelioid cells with hyperchromatic and irregular nuclei, being positive for HMB45 and Melan-A;
- MEST predominantly affects perimenopausal female patients, not having a predominant clear cell component and the tumor stroma resembles the ovary, with positivity for ER and PR.

It’s important for pathologists to have knowledge of this entity to avoid misdiagnosis, especially with higher malignant renal cancers like renal cell carcinoma with sarcomatoid change.

The biological behavior of RCCSMS is still an open question. To this date, no local recurrences or metastasis have been described¹⁴, with surgical resection being curative and the treatment of
choice. In our case, the patient is alive and has no signs of recurrent disease, with a follow-up time of 6 months in the Urologic department.

References


