

Spindle Cell Carcinoma of the Kidney and Its Variant

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Published Date: January 30, 2016

ABSTRACT

Sarcomatoid Renal Cell Carcinoma (**SRCC**) is also known as spindle-cell carcinoma, anaplastic carcinoma, and carcinosarcoma. It is an aggressive tumor variant thought to arise predominantly from differentiation of clear cell carcinoma. A few reports of SRCC associated with non-clear cell tumors led to the presumption that SRCC may arise from any renal cell carcinoma, although direct evidence of this is lacking. We report a case of a 70-year-old male patient, who presented with acute left upper quadrant abdominal pain and was diagnosed to have SRCC after pathological examination. The patient was given high dose interleukin (IL-2)-based immunotherapy and is apparently free of disease 2 years after surgery.

Another variant is Mucinous Tubular and Spindle Cell Carcinoma (**MTSCC**), which is a low-grade renal epithelial neoplasm and is a recent entity introduced in World Health Organization Classification 2004. We report a case of 57 year old male presenting as loin pain and dragging sensation. Imaging revealed a large mass arising from left kidney. Radical nephrectomy was performed and a diagnosis of MTSCC along with high grade areas consistent with sarcomatoid differentiation was made on histopathology.

Keywords: Spindle cell carcinomas, Kidney, Immunohistochemistry

INTRODUCTION

Sarcomatoid Renal Cell Carcinoma (**SRCC**) is also known as spindle-cell carcinoma, anaplastic carcinoma, and carcinosarcoma. It is an uncommon but particularly aggressive variant of renal cell carcinoma, accounting for 1-5% of all renal malignant neoplasms [1-3]. Until recently, SRCC was thought to represent a primary renal sarcoma, [4-6] but since these tumors co-express both epithelial and stromal markers, they are now believed to represent a form of dedifferentiated carcinoma [4,5]. Most sarcomatoid carcinomas are found in association with conventional (clear cell) renal carcinoma, but there are occasional descriptions of Sarcomatoid transformation of chromophobe carcinoma, collecting duct carcinoma and papillary carcinoma [4,6]. These are largely composed of spindle and/or pleomorphic tumor giant cells, and their appearance may simulate malignant fibrous histiocytoma, fibrosarcoma, rhabdomyosarcoma, or angiosarcoma. The sarcomatoid component may also differentiate in the direction of cartilage and bone, and it may contain osteoclast-like multinucleated giant cells [3,4].

Another novel entity has recently been identified under the denomination of “Mucinous Tubular and Spindle Cell Carcinoma” (**MTSCC**), which was first recognized as a specific entity in the World Health Organization consensus conference on the classification of renal neoplasms in December 2002 [5]. To date, approximately 100 cases of MTSCC have been reported in series, with metastases occurring in rare cases; however, no tumor-related death has been reported [7-8]. The histological profile of this tumor is well established. MTSCC has a less malignant potential than other subtypes of RCC, and so it is of prognostic and therapeutic important to distinguish it from the others, to avoid unnecessary adjuvant immunotherapy with interferon- α and interleukin-2 [7,8].

Histologically, the tumor consists of anastomosing tubules of cuboidal and spindle cells with low grade nuclei [9]. Staining with alcian blue reveals lakes of mucin. Immunohistochemical studies shows that MTSCC is positive for the markers of epithelial cells and distal nephron, and negative for proximal nephron [10]. Sarcomatoid change is seen in many Renal Cell Carcinomas (**RCC**), which is usually associated with a poorer outcome. Tumors containing Sarcomatoid Differentiation (**SD**) have a decreased 5 year survival rate from 79% to 22% in stage-matched patient cohorts; tumors containing >50% SD have an even worse prognosis [7,8]. We report the clinical, histological and immunohistochemical study of sarcomatoid renal cell carcinoma and MTSCC with sarcomatoid differentiation, which have a worse prognosis.

CASE SUMMARY

Case 1

A 70-year-old male patient presented to the emergency room with acute left upper quadrant abdominal pain. A pelvic Computed Tomographic (**CT**) scan showed a large heterogenous mass measuring 8 × 5 cm without any calcification, in the center of the left kidney. The medical history was non-contributory, and the patient underwent radical nephrectomy.

Gross examination revealed a solid firm, yellowish white, well-circumscribed mass measuring 8×6 cm, in the center of the kidney involving the pelvis (Figure 1). Five micrometer sections were cut from the paraffin blocks of the tumor and stained with hematoxylin and eosin for light microscopy. For immunohistochemical analysis, the Avidin- Biotin Complex (ABC) method was applied on 3μ paraffin sections with primary antiserum Vimentin (1/100, vimentin, Dakopatts). Histological examination of the renal mass revealed anaplastic spindle cells with a high mitotic rate, including atypical mitosis. The neoplastic matrix was intermingled with poorly differentiated pleomorphic tumor cells (Figure 2). Immunohistochemically, the mesenchymal marker vimentin was diffusely positive in the tumor cells (Figure 3). The patient was given high dose interleukin (IL-2)- based therapy and is apparently free of disease 2 years after surgery.

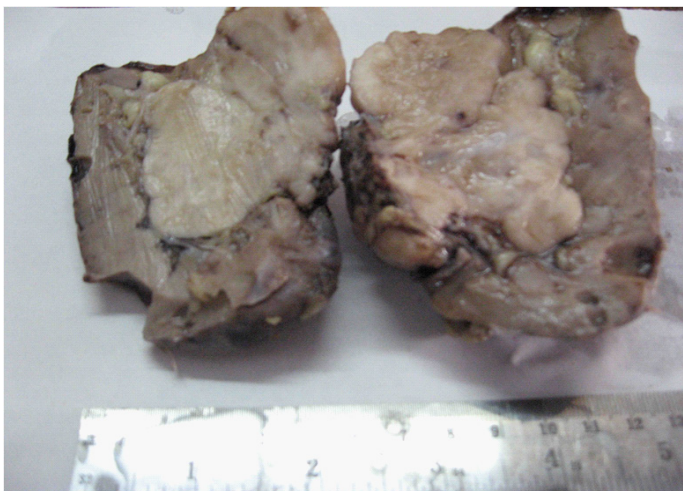


Figure 1: Sarcomatoid Renal Cell Carcinoma (SRCC): Gross examination showing a solid firm, well-circumscribed, yellowish white mass involving the renal pelvis.

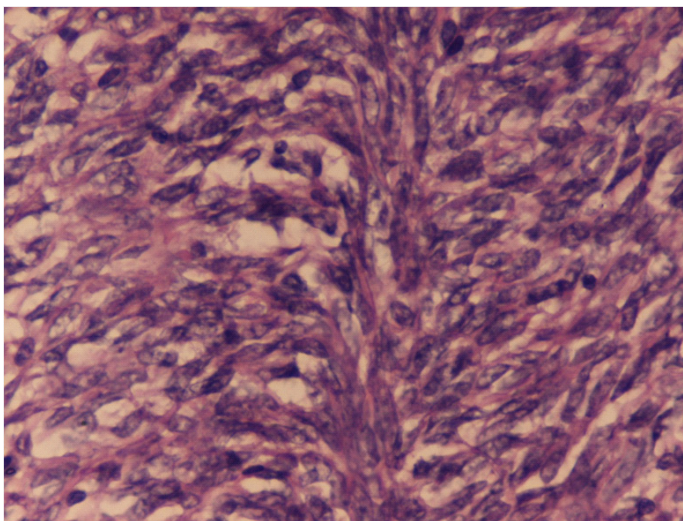


Figure 2: SRCC: Tissue section showing anaplastic spindle cells with a high mitotic rate intermingled with poorly-differentiated pleomorphic tumor cells. Hematoxylin & Eosin $\times 40X$.

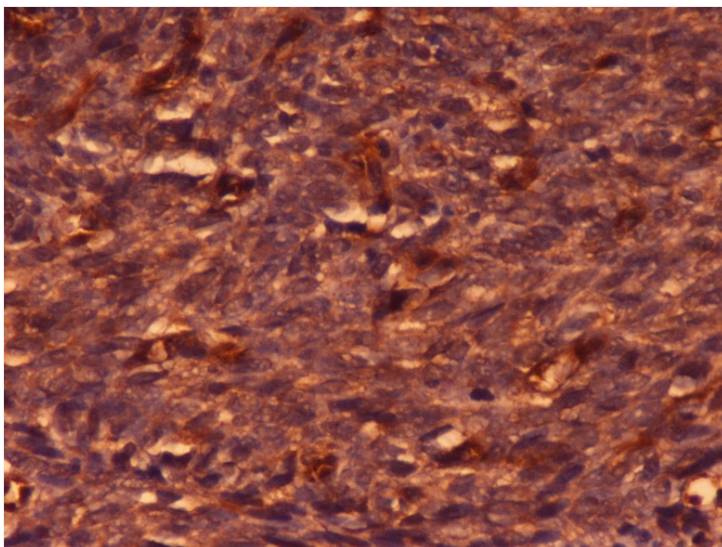


Figure 3: SRCC: Immunohistochemistry showing diffuse positivity for vimentin in the tumor cells. IHC Vimentin ×40X.

Case 2

A 57 years old male patient presented with pain and dragging sensation in left loin along with weight loss. On CECT examination of abdomen, a large cystic mass of size 17 x 11 x 24.6 cm arising from middle and upper pole of left kidney was seen. No abdominal lymphadenopathy was appreciated. USG scrotum and Colonoscopy findings were unremarkable. Beta- HCG, S. LDH, CEA and AFP values were within normal limits. Left radical nephrectomy was performed.

The operated specimen was encapsulated, beige yellow color with foci of hemorrhage and necrosis, solid to cystic with visible areas of capsular breach, of size 21 x 18 x 7 cm and encased upper pole and mid of the kidney. Perirenal fat and Gerota's fascia was not involved. Microscopically, the tumor consisted of elongated, anastomosing tubules separated by lakes of mucin from a prominent spindle cell area. Tubules were composed of low cuboidal cells with amphophilic to eosinophilic cytoplasm with mild anisonucleosis. A focus of sarcomatoid differentiation was seen with pleomorphic low grade nuclei, without any evidence of vascular invasion. (Figures 4 and 5) Alcian Blue stain showed the typical blue coloured mucin in the stroma between the tubules and cords. (Figure 6) The tumor cells were diffusely positive for Cytokeratin 7 (Figure 7), Epithelial Membrane Antigen (**EMA**) and vimentin; but negative for CD15 or CD10. Six cycles of Cisplatin based adjuvant chemotherapy was given to the patient and he is doing well after 12 months of follow up period.

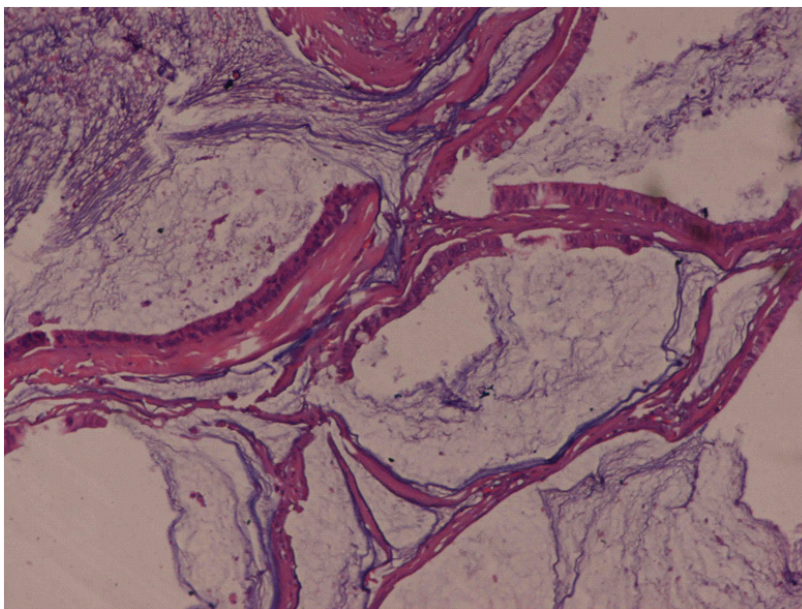


Figure 4: Mucinous Tubular And Spindle Cell Carcinoma (**MTSCC**): Microscopically, the tumor consisted of elongated, anastomosing tubules separated by lakes of mucin from a prominent spindle cell area. Tubules were composed of low cuboidal cells with an amphophilic to eosinophilic cytoplasm with a low grade nucleus. Hematoxylin and Eosin x 10X.

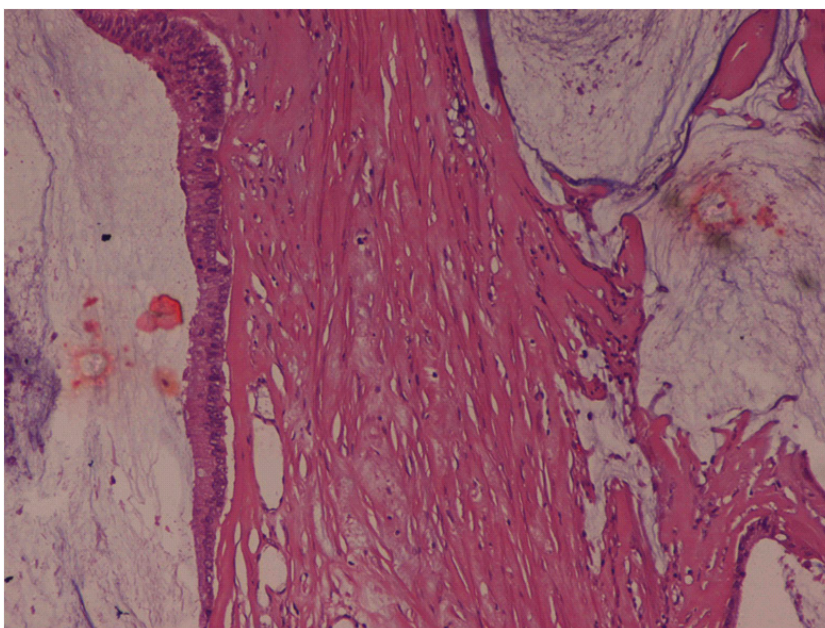


Figure 5: MTSCC: Foci of sarcomatoid differentiation was seen with pleomorphic high grade nuclei without any evidence of vascular invasion. Hematoxylin and Eosin x 10X.

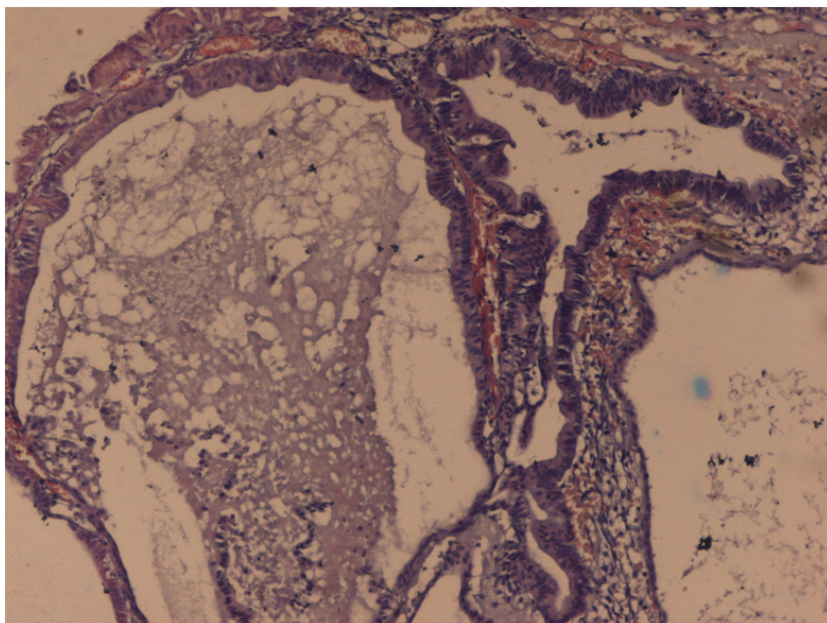


Figure 6: MTSCC: The typical blue coloured mucin in the stroma between the tubules and cords. Alcian Blue stains x 40X.

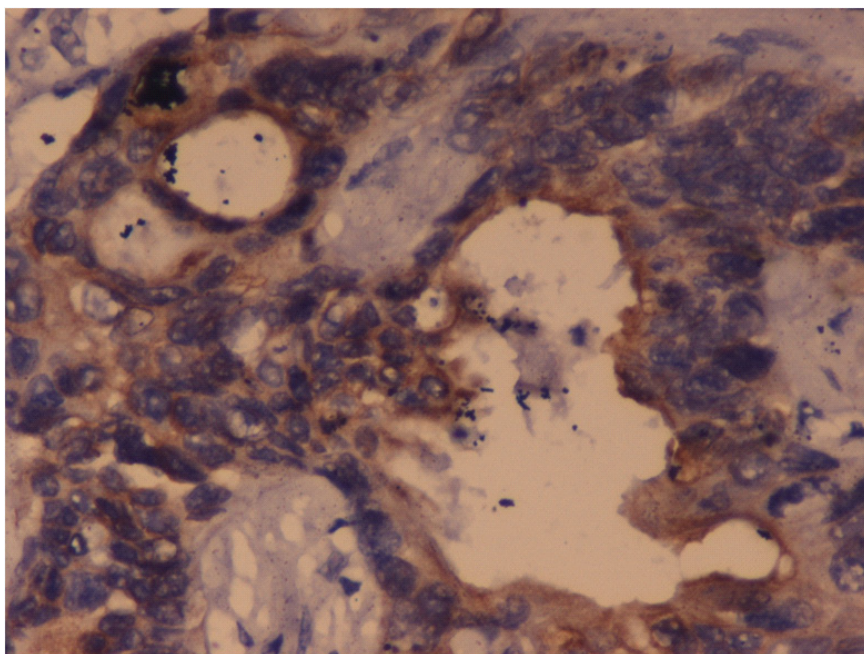


Figure 7: MTSCC: Immunohistochemistry showing diffuse positivity for Cytokeratin in the tumor cells. IHC Cytokeratin x40X.

DISCUSSION

SRCC is considered a late and almost invariably fatal cancer, with a mean survival time of less than six months [2]. Our patient remains well and apparently free of disease six months after surgery. It usually evolves from conventional (clear cell) renal cell carcinoma [3,4]. Although it is acknowledged that SRCC may be associated with multiple renal tumor subtypes of differing biological behavior, direct evolution from non-clear cell tumors has not previously been proven and SRCC remains classified as a single pathological entity with a uniformly poor prognosis [6]. Similarly, Congiano et al., have reported improved survival of 1-2 years in 48 and 37% cases, respectively, in their study on 31 cases of SRCC treated with a combination of surgical resection and immunotherapy [1]. Surgical resection and high dose interleukin (IL-2)-based immunotherapy may play a role in the treatment of SRCCs. Mucinous Tubular And Spindle Cell Carcinoma (**MTSCC**) is a low grade tumor with a good prognosis [7]. It is preferentially observed in adults, aged 21 to 81 years, with a mean age of 56 years [8,9]. The right kidney is more commonly involved with a mean tumor diameter of 6 cm [7]. It has a preponderance in females with a male to female ratio of 1:3 [7,8].

The tumor is usually present as an asymptomatic mass, often found on ultrasound. Occasionally, the patients may present with flank pain or hematuria, as was seen in our patient [10,11]. The tumors were generally confined (pT1 or pT2) in more than 80% of the cases with foci of hemorrhage and necrosis [7,10,11]. Histologically, the tumor has tubular and solid growth patterns with tightly packed, small elongated tubules, separated by pale myxomatous stroma [11]. Cells are small, round to oval in shape, with eosinophilic cytoplasm and low-grade nuclear features. The tubules are associated with proliferation of spindle cells forming cords and fascicles [10-12].

Since the recognition of MTSCC as an individual entity by WHO, several variants of the tumor have been described, like mucin poor and MTSCC with neuroendocrine differentiation [13,14]. Fine et al., recognized two different variants of MTSCC, “a classic” variant (60% of cases) owing to the presence of characteristic abundant extracellular blue gray mucinous/myxoid matrix (>50%) accompanying the typical tubular and spindle cell epithelial components. The second variant was designated “mucin-poor” with lack of appreciable extracellular mucin on H & E staining [15]. The majority of the cases showed scant (<10%) mucin in cellular areas on Alcian blue. Histochemically, the myxomatous stroma exhibits a positive reaction for Alcian blue at pH 2.5 [12]. Sarcomatoid differentiation has been recognized in all types of renal cell carcinoma since the Heidelberg classification of renal cell tumors was published in 1997 [16]. Sarcomatoid component can have fibrosarcoma like appearance, which is reported in 14-65% of cases [6]. 3-24% tumors have no pattern of appearance, while hemangiopericytoma like pattern and malignant fibrosarcoma like appearance has also been documented [3-5,12]. Ours is an unusual case of MTSCC with Sarcomatoid Differentiation (**SD**) in a 57 year old male; only a few of which have been described yet. Features like interconnecting tubules of low grade cuboidal cells in a mucinous matrix with

areas of benign spindle cells were diagnostic of MTSCC in our case. A distinct focus of low grade morphology, consistent with sarcomatoid differentiation was seen. Diagnosis of MTSCC with sarcomatoid differentiation was assisted by immunohistological findings.

The differentials of Mucinous Tubular And Spindle Cell Carcinoma (**MTSCC**) includes papillary RCC, collecting duct carcinoma, and metanephric adenoma. Papillary RCC lacks a spindle cell component and rarely shows lakes of mucin. Collecting duct carcinoma shows high-grade histological features and lacks mucin. Metanephric adenoma shows tubulo-papillary architecture, but stromal and spindle cell components are lacking [16,17]. The use of has so far been more pivotal in difficult cases, especially when cytogenetic studies are not feasible [18]. MTSCC with sarcomatoid differentiation has a poor prognosis. Thus it is essential to search for areas of sarcomatoid differentiation in a case of MTSCC followed by regular clinical and radiological follow up.

MTSCC tumors have a complex immunoprofile. Shen et al demonstrated the expression of differentiation markers of proximal tubules, which were renal cell carcinoma marker antigen (RCC Ma) (92%), a-Methylacyl-CoA racemase (AMACR) (92%), CD15 (Leu M1) (67%) as well as CK7, which is known to stain the distal tubules (92%). Positive staining was seen with markers that were found in the collecting duct epithelium, including EMA and peanut agglutinin (PNA) [14]. The remaining markers, which are more specific to the proximal tubules, are CD10, the collecting duct (aquaporin 3) and the kidney-specific cadherin expressed in only a few cases [14,18]. The vimentin positivity was infrequent, observed in 14-40% of the cases [10,18]. The proliferative rate (MIB-1) was low, suggesting a low proliferation activity, a finding that may in part explain the low malignancy of this tumor type [19]. The immunohistochemical profile diversity (positivity for markers of the proximal tubules as well as for markers for the distal part of the nephron) suggests tumor cells being pluripotent and differentiates in different directions based on sequentially acquired genomic abnormalities [14,18].

Ultrastructurally, the spindle cells show features like tight junctions, desmosomes, microvillous borders, luminal borders and occasional microfilaments [17,19]. Using comparative genomic hybridization (CGH), Rzymkowska et al., first demonstrated that MTSCC showed consistent multiple chromosomal loss (-1, -4, -6, -8, -9, -13, -14, -15 and -22). Similar results have been reported in subsequent studies. In addition, gains of chromosomes (+7, +16, +17, +20) have also been reported [10,17]. The association with other renal abnormality as a simple renal cyst, a synchronous renal cell carcinoma, a papillary adenoma or angiomyolipoma have been reported [20].

The treatment of MTSCC is surgical, and it consists of a widened nephrectomy. A partial nephrectomy may be indicated in a small tumor [20,21]. The prognosis is generally favorable with only lymph node metastases have been reported [20,21]. There has been no reported case of distant organ metastasis or cancer specific deaths due to MTSCC [19,20]. Further investigations

are required to determine the frequency and true prognosis of these tumors [20]. Our reports are beneficial supplement for better understanding the clinicopathological features of spindle cell carcinoma of the kidney and its variant. Meanwhile, the CT findings, treatment and follow-up data are valuable information for guiding future clinical practice.

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