Review Article

Prognostic Significance of Sarcomatoid Renal Carcinoma

Pramod Singh Khatri*, Chukwunonso Livinus Udeh 1

*Head of Department and Program Coordinator, Dept of Clinical Research, 
Amity Medical School, Amity University, Gurgaon. 
1 MSc Clinical Research, Amity Medical School, Amity University, Gurgaon.

ARTICLE INFO

<table>
<thead>
<tr>
<th>Article History:</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received on 07th August, 2016</td>
<td>Sarcomatoid renal cancer is an advanced type of renal cancer. It occurs at stage IV of any category of renal cancer, be it papillary, clear cell or chromophobe. Renal carcinomas with Sarcomatoid differentiation are not of a distinct subtype. They are only defined based on their histology. SCRR is known to have high level of proliferation with poor prognosis. The major type of immunohistochemical staining used to different SCRR from other renal cancers is the PAX8. Sarcomatoid renal cancer cells showed to have occurrence of multiple structural forms in it immunohistochemistry. There is becoming an increase rate of sarcomatoid differentiation in renal cancers. Symptoms of SCRR are the same with symptoms of kidney cancers. These symptoms include; hematuria, high body temperature and pressure, anemia, prolonged back pain, weight loss, fatigue, loss of appetite and lump on the kidney region. Therapeutic agents like sorafenib, everolimus, temsirolimus, cytokines, anti-VEGF have been tried systematically for treatment of SCRR but none gave a convincing result. The only hopeful treatment for SCRR is the anti-VEGF agent.</td>
</tr>
<tr>
<td>Revised on 28th August, 2016</td>
<td></td>
</tr>
<tr>
<td>Accepted on 23rd September, 2016</td>
<td></td>
</tr>
</tbody>
</table>

Keywords: 
Sarcomatoid Renal Cancer, Cell, Metastasis, Carcinoma, Prognosis, Therapeutic agents.
INTRODUCTION
Renal cell carcinoma (RCC) is a histological heterogeneous disease. Clear cell carcinoma is the most common type which is approximately 70%-80% found in all cases. Other less common histologies include the papillary (10%-15%), medullary and unclassified (4%-6%) and chromophobe (3%-5%). Each type of histology originates from different parts of the nephron and comprises of distinct genetic profile, clinical characteristics and prognosis. Sarcomas are groups of cancers that develop from tissues like muscles and bones.\textsuperscript{31} The term Sarcomatoid can be defined as the morphologic changes within a Renal Cell Carcinoma tumour alike to sarcomas; like spindle-shaped cells, elongated, increased cellularity and cellular atypia. It can be recognized in relation to every histological type of RCC. The World Health Organization 2004 classification of renal tumors stated that, Renal Cell Carcinomas with sarcomatoid differentiation are not considered to be a prominent subtype, instead they are grouped based on the originating histology; when no epithelial elements can be recognized, those tumors are categorized as unclassified.\textsuperscript{1}
World Health Organization in 2004 also defined Sarcomatoid Renal Carcinoma under the classes of renal tumors to be any histological type of RCC which is made up of foci of high-grade malignant spindle cells. A certain number of evidences collected depicts an elevated risk in accordance with a sarcomatoid components consisting 5-10% of total tumor volume. These evidences imply that even a low level of sarcomatoid differentiation can be clinically relevant and should be included in reports of pathology.\textsuperscript{10} The first persons to describe Sarcomatoid renal carcinoma is Farrow \textit{et al} in 1968.\textsuperscript{28} Origination of SCRR is still difficult to understand.\textsuperscript{22} In the past twenty years, there have been many changes in the understanding and maintenance of RCC.\textsuperscript{27}
Sarcomatoid Renal Cell Carcinoma is a tumor that grows rapidly. It is eruptive and aggressive. It is a form of differentiated carcinoma with high incidence of metastases to the lungs.\textsuperscript{2, 14} Sarcomatoid renal cell carcinoma is not a common type of kidney (renal) cancer. 15 out of 100 results of kidney cancers are Sarcomatoid Renal Carcinomas. This type of cancer is associated with poor prognosis.\textsuperscript{26}
Majority of kidney cancers originate from clear cells. Some can start in kidney cells too. Any type of kidney cancer can be sarcomatoid. In other words, sarcoma cells have similarities with cells of any kidney cancer. This is why they are termed sarcomatoid. Sarcomatoid Renal Cancer is prone to growing faster than any type of cancer. They also spread easily to other parts of the human body. This is the main reason why they are not easy to treat.\textsuperscript{3}
Initially, SRCCs were considered as Adrenal Sarcoma. Now, Sarcomatoid Renal Cell Carcinoma (SRCC) is distinguished as the transfiguration of conventional RCC to a higher histologic grade. Sarcomatoid RCCs are characterized by spindle cell morphology, but the tumours characteristically show both epithelial and mesenchymal differentiation on ultrastructural and immunohistochemical analyses. Sarcomatoid differentiation can occur in papillary, clear cell, chromophobe tumors and all other types/subtypes of Renal Cell Carcinoma. Sarcomatoid RCCs are hostile and invasive. Out of all renal cancers, patients with sarcomatoid RCC have the worst prognosis. The presence of sarcomatoid RCC is an autonomous predictor of reduced survival with increasing amounts of sarcomatoid RCC associated with an increase prognosis.\textsuperscript{4}

IMMUNOHISTOCHEMISTRY
Sarcoma features include, high cellularity, cellular atypia and spindle-like cells. These features are similar to SRCCs. Divisions of sarcomatoid changes without pronounced epithelial components (wavy or rhabdoid parts without epithelial features) are not considered sarcomatoid. Sarcomatoid changes can be uniform or varying. Resemblance of these uniform patterns can be seen as malignant fibrous histiocytoma or fibrosarcoma. There is also osteoid or chondroid differentiation which has been described. This uniformity doesn’t have any effect on the clinical behavior. SRCCs have characteristics such as microvascular invasion and necrosis which are seen in high-risk tumors (30% and 90% cases each).\textsuperscript{1}
Immunohistochemical staining done on primary lesions and metastatic lesions (21 and 51, respectively) of Renal Cell carcinoma showed that staining for CD10 and EMA were positive. 50% positive cases were reported for Renal Cell Carcinoma Marker (RCCMa), Pan-cytokeratin (CK), vimentin (VT) and PAX2. Cytokeratin 20 (CK20) result was negative in all the tumors and Cytokeratin 7 (CK7) result was positive only in one case.\textsuperscript{17}
Tissue samples for Clear Cell Carcinoma and SCRR showed positive antibodies stain for AE1/AE3, cytokeratin 8, 18,19 and EMA. AE1/AE3 is a marker of epithelial origin. They are not always seen in spindle cells.\textsuperscript{21}

Other sensitive markers for Renal Cell Carcinomas are the PAX8 and GATA3 markers. There is a limited data for PAX8 and GATA3 on SRCC. They both mark positive in sarcomatoid for renal carcinoma in 14 out of 45 cases. PAX8 can be used to understand the difference between SRCC, primary renal or retroperitoneal sarcomas and atypical epithelioid angiomyolipomas (AMLs).\textsuperscript{18}

**Figure 1:** (a and b) shows the result from the histopathological examination of growth of SCRR. This imaged showed that the fascicles of spindle-shaped cells interspersed with epithelioid cells in SRCC. The cells exhibited pleomorphism, had high nucleus/cytoplasm ratio, vesicular nuclei, eminent nucleoli and moderate to abundant clear cytoplasm (H and E, ×40). The tumor cells did not react for cytokeratin (c) and immunonegative for HMB-45 (d).\textsuperscript{19}

**EPIDEMIOLOGY OF SRCC**

Reports show that Sarcomatoid differentiation found in Renal Cell Carcinomas are 4-32% in overall. According to RCC histological subtypes, the incidence rates for clear cell renal cell carcinoma (CCRCC), papillary RCC, chromophobe RCC and unclassified RCC are 5-13%, 2-7%, 9-13% and 11-26% respectively. In the renal conducting duct of the nephron, 29% of sarcomatoid differentiation occurs.

Sources of Sarcomatoid Renal cell cancer histologically are:

- CCRCC, 79-87%
- Chromophobe RCC, 7-7.5%
- Papillary RCC, 4-8%

Unclassified RCC, 2-4%
Collecting (Bellini) duct carcinoma, 2%.\textsuperscript{11}

**MOLECULAR CHARACTERIZATION**

There is a limitation to the molecular characterization of SRCC. This is attributed to a lot of reasons. One of them has been that studies done on tumors with sarcomatoid differentiation were done using the whole tumor instead of the sarcomatoid part alone. To confirm the aggressiveness of SRCC transformation, the differentiated cancer component alone has to be assessed. The fast progression and advancement of the disease make available samples from patients for assessment less. Studies combining multiple histologies are difficult to interpret because SRCC emerge from all subtypes of renal epithelial. Focusing on one particular subtype can be beneficial for the fact that there may be varying molecular activities in each histology.\textsuperscript{1}

**SYMPTOMS AND DIAGNOSIS**

Symptoms of sarcomatoid kidney cancer are the same as the symptoms of kidney cancer. They include;

- Hematuria
- Weight loss
  - Increase in body temperature with high level of sweating
  - Prolonged lower back pain
- Tiredness
- Loss of appetite
- Feeling of poor health in general
- A protruded kidney area

Increased blood pressure and anemia also can be symptoms of kidney cancer. All these symptoms are associated with the hormones that the kidneys produce.\textsuperscript{3}

**RECENT FINDINGS**

Few patients with early stages of SCRR (I and II) show extended survival. It’s been reported that after diagnosis, many of the patients have median survival period of only 4-9 months. Patients with SRCC still have worse prognosis compared to those with high-grade renal cancers. Sarcomatoid components alone in renal carcinomas may be one of the most influential determinant of patient outcomes. As the amount increases, the prognosis becomes worst. There is no harmonized cut-point for risk stratification yet.\textsuperscript{1}
Sarcomatoid differentiation is attributed to poor outcomes in renal cell carcinoma (RCC). It is also a determinant of an elevated mortality risk across all stages of the disease. Sarcomatoid differentiation is an independent make-up of prognosis for patients with grade 4 Renal Cell Carcinoma (RCC) with or without distant metastases. The 2009 primary tumor classifications, regional lymph node status, coagulative tumor necrosis, the presence of distant metastases classifications and the amount of sarcomatoid differentiation are independent pinpoints of survival for patients with sarcomatoid RCC. Early stage Renal Carcinoma is cured in more than 50% of the patients, but the outcome for stage IV of the disease is poor.

Genes like AT-rich interaction domain 1A, BRCA1 associated protein and Tumor protein P53 are known to be intertwined with sarcomatoid degeneration. Currently, 71 months is known to be the longest period a patient with metastatic SCRR can survive. Combination of radical surgery, cytokine therapy, molecular-targeting therapy, radiotherapy and bone-modifying agent therapy, are effective for this long-term survival. The sarcomatoid variant of Renal Cell Carcinoma (RCC) features a spindle-shaped phenotype and has been reported to have a poor prognosis compared with other histological types of RCC. Even with the treatment of tyrosine kinase inhibitor, prognosis of patients with SRCC is still poor. Tyrosine kinase inhibitors are widely used as anticancer drugs.

Targeted therapy was adopted lately and it showed to improve progression-free trial (P.F.S) and overall survival (O.S) for patients with metastatic renal cell carcinoma in more fold phase III clinical trials. Nevertheless, the effectiveness of these new drugs is limited for patients with Sarcomatoid Renal Cell Carcinoma. Doxorubicin and gemcitabine added with chemotherapy has antitumor activity against Sarcomatoid Renal Cell Carcinoma. This was noted from small clinical trials. Currently, ongoing investigations are carried out on the use of combined chemotherapy, anti-angiogenic therapy and post-nephrectomy adjuvant therapy for these patients. A few studies have tried to stratify the risk of patients with SRCC based on clinical and pathological characteristics. Most of the studies were executed in the pre-targeted therapy era. There is no usual accepted prognostic system currently existing for this subset of patients. Also, the relevance of the amount of sarcomatoid differentiation of the prognosis is still unclear. Pure sarcomatoid carcinoma or sarcomatoid carcinoma associated with epithelial elements that do not conform to usual renal carcinoma cell types are considered as unclassified renal cell carcinoma. Sarcomatoid Renal Cell Carcinomas are commonly associated with presence of peritumour neovascularity, exhibits large tumor size and larger peritumoural vessels than clear cell RCCs. Also SRCCs by texture analysis are more heterogeneous than CCRCCs.

**ACTIVE CLINICAL TRIALS**

Majority of the targeted agents approved recently has been tested mainly on patients with CCRCC. More organized studies on the less common types of renal carcinoma will enable better treatment approach to different types of renal cell cancers. Various centers in the United States are currently enrolling patients into sarcomatoid tumor studies.

Beth Israel Deaconess Medical Center and Dana Farber Cancer Institute is undergoing a phase II clinical trial, investigating the effect of combined therapy with Sunitinib and Gemcitabine in patients with sarcomatoid or poor-risk characteristics. This is done using the Motzer criteria. This trial circulates around a 3-week cycle in which patients are administered sunitinib for the first 2 weeks and gemcitabine is administered on the first and eight day respectively. Michaelson and his colleagues at the 2015 American Society of Clinical Oncology Genitourinary Cancer Symposium reported the versal experience garnered using the regimen. Only 3 out of the first 9 patients with SRCC showed partial response. They also reported that the midpoint period to progression was only 4.6 months.

**TREATMENT**

Sarcomatoid renal cell carcinoma responds poorly to cancer drugs and chemotherapy. Despite all the therapy and treatment methods used, the efficacy remains poor. In 2008, a patient started his treatment with sorafenib. He was evaluated using CT every 3 months. The disease remained stable till 2010. The treatment was changed to everolimus which gave a positive effect. Everolimus is a type of treatment used till today. A therapeutic agent known as Temsirolimus is considered an agent likely to be used as first line
therapy treatment for metastatic renal cell carcinomas with sarcomatoid components. The use of Temsirolimus is based on the Physician’s level of experience and discretion.  

A treatment study conducted in 2015 reported that anti-VEGF (anti vascular endothelial growth factor) agents, cytokines, targeted therapies or systemic treatments are not effective towards the treatment of Sarcomatoid Renal Cell Carcinomas. Although anti-VEGF agents remains the reasonable prospective treatment for SRCC. These treatment efficacies are unknown. Most common agents used in this systemic chemotherapy were doxorubicin in combination with gemcitabine or ifosfamide.  

DISCUSSION

This literature review work is aimed at understanding the causes, components, advancements and any possible treatment of Sarcomatoid Renal Carcinomas. It’s still a standing definition that SRCC is a histologic type of renal cell cancers that is made up of high-grade malignant spindle cells. They are known for their poor prognosis. The origination is difficult to understand. This tumour grows rapidly and has high level of proliferation. Ultrastructural and immunohistochemical analyses showed that SRCCs are characterized by spindle cell morphology and show both epithelial and mesenchymal differentiation. Many makers have been used to differentiate SCRR from other types of cancers. They include renal cell carcinoma marker (RCCM), Cytokeratins (8, 18, 19, 20), Vimentin, PAX (2 and 8), AE1/AE3 and GATA3. Only PAX8 can be used to differentiate SCRR from retroperitoneal sarcomas and atypical epitheloid angiomyolipomas (AMLs). Symptoms of SCRRs are the same with symptoms of kidney carcinomas. No therapy or treatment is yet 100% effective on SCRR but the most reasonable agent against this cancer is the anti-VEGF agents.  

CONCLUSION

Sarcomatoid Renal Cell Carcinoma is confirmed to be an advanced form of renal cell cancer in stage IV. It grows rapidly with poor prognosis. It has a high rate of metastasis to the lungs. Many studies have been conducted using different therapeutic agents for treatment of SRCC but none gave a good result. This review work shows that patients with this type of cancer don’t have a long period to live. A standardized treatment or therapy for this cancer is not yet established. Sarcomatoid components may portray a terminally similar identity originating from any histological type of renal cell carcinoma. It may also originate from a completely different identity. The standard of care is surgery but consideration should be put into assisted trial participations because of high risk of re-occurrence. A randomized fashion of cytoreductive nephrectomy has not been studied and it is not yet believed to be beneficial in treatment of this disease because of its swift progression. It is still difficult to detect the histology of SRCC preoperatively. The greatest possible improvement against SRCC is from determination of better molecular and genetic characterization and specific therapy designs.

CONFLICT OF INTEREST-Nil

REFERENCES