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Case Report

Rare Case of Sarcomatoid Renal Cell Carcinoma Metastasis to the Duodenum: Report of a Case and Review of the Literature

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Abstract

Metastatic Sarcomatoid Renal Cell Carcinoma has been shown to be a diagnosis that holds a median survival time of under a year. Top metastases locations have been reported to be the lung, retroperitoneal lymph nodes, and axial skeleton. Tutor markers vary widely, making the histological understanding of this disease particularly important. Whether higher percentage of sarcomatoid histopathology corresponds with a worse prognosis or not is also highly debated in the literature. Here we present a case of Sarcomatoid Renal Cell Carcinoma that has metastasized to the Duodenum, which to the best of our knowledge, is the first reported case. We hope to raise awareness of the potential duodenum metastasis and corresponding tumor markers of Sarcomatoid Renal Cell Carcinoma to aid in the treatment of future patients.

Keywords: Sarcomatoid renal cell carcinoma; Immunohistochemistry; Metastasis

Abbreviations

RCC: Renal Cell Carcinoma; **SRCC:** Sarcomatoid Renal Cell Carcinoma; **NF2:** Neurofibromatosis 2; **VHL:** Von Hippel–Lindau; **EGD**: Subsequent Esophagogastroduodenoscopy; **CT**: Computed Tomography; **OS:** Overall Survival

Introduction

Renal Cell Carcinoma (RCC) is the third most common genitourinary cancer after bladder and prostate cancer, encompassing 21% of tumors [1]. A histologically unique type of RCC, Sarcomatoid Renal Cell Carcinoma (SRCC), was first discovered by Farrow et al. in 1968 and was classified as a different subtype due to its aggressive nature [2]. Since then it has been reported that approximately 1-5% of RCC tumors have a sarcomatoid component [3] and around 3% of renal carcinomas are purely sarcomatoid [4]. SRCC are more commonly reported in metastatic and advanced disease, with numbers as high as 15% [5] and 20% [5,6], respectively. On immunohistochemically analysis, SRCC commonly expresses cytokeratin (91%), epithelial membrane antigen (EMA, 87%), vimentin (100%) [3], PAX8 64% [7], and TP53 42.3% [8]. Neurofibromatosis 2 (NF2) mutations were found to be mutually exclusive with TP53 but not with Von Hippel–Lindau (VHL) mutations. This essentially divides sRCC into two groups on the basis of harboring either TP53 or NF2 mutations, which may aid in treatment selection [8].

The majority of series reports of metastatic (SRCC) show a median survival time of only 3 –10 months after diagnosis [9,10]. A recent study identifying 562 patients with metastatic RCC treated between 1989 and 2018 showed that lung (20.4%), retroperitoneal nodes (11.2%), and axial skeleton (7.65%) were the top metastasis locations [11]. The median age for metastatic SRCC was shown to be lower than non-metastatic SCC, at 59 years of age [11]. Metastatic SRCC most commonly spreads to the lung, retroperitoneal nodes and axial skeleton [11,12[, with the median diameter of the tumor reported to be 10.5 cm [3]. We are reporting a rare case of SRCC that has metastasized to the duodenum, followed by a review of the current literature, including current treatment paradigms.

Case Presentation

A 60-year-old female with a past medical history of hypothyroidism and depression presented with three weeks of weakness, shortness of breath, and melena. She was taking 2-3 tablets of Ibuprofen three times a day for leg cramps. On admission her vital signs were 133/64 mm Hg, 84 bpm, 100% saturation on pulse oximetry, respiratory rate 13 on supplemental oxygen via nasal cannula at 2L/min with no other significant findings on physical exam. At the time of admission she had iron deficiency anemia with Hemoglobin of 5.5 g/dL (normal 12-16 g/dL), Hematocrit of 19.5% (normal 38-47%), Leukocyte count 17.16 k/mm^3 (normal 4.50 – 11.00 k/mm^3), as well as transaminases ALT of 37 U/L (normal 7 – 40U/L), AST of 40 U/L (normal 13-

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40 U/L), alkaline phosphatase of 144 U/L (normal 46 – 116U/L). The patient was started on antibiotics and intravenous fluids and received multiple blood transfusions during her hospital stay.

The patient was found to have a non-occlusive left popliteal deep vein thrombosis. Subsequent esophagogastroduodenoscopy (EGD) and colonoscopy were performed and were significant for a circumferential easily friable duodenal mass with exudates. Multiple biopsies were obtained from the mass that showed poorly differentiated and diffuse high grade anaplastic neoplasm involving the submucosa consistent with renal origin neoplasm suggestive of sarcomatoid renal cell carcinoma. Immunohistochemistry was strongly positive for CK-7, Vimentin and PAX-8, and was weakly positive for CDX-2. Computed Tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed irregular thickening of the duodenum at the junction of its 2nd and 3rd segments and periduodenal adenopathy. Perforation of the posterior wall of the duodenum into an approximately 5.8 x 3.5 cm ill-defined irregular thick-walled interaortocaval fluid collection was also noted that was concerning for a necrotic mass, causing right hydronephrosis and probable compression of the inferior vena cava. The CT scan was also significant for multiple hepatic lesions accompanied by a small-volume ascites suggestive of metastatic neoplasm. She was later transferred to an outside hospital for further interventions including a gastrointestinal stent placement.

Discussion

The proportion of men and women diagnosed with SRCC was found to be identical [13], though more aggressive and larger tumors were found in men compared to women [14]. Whether higher percentage of sarcomatoid histopathology corresponds with a worse prognosis or not is highly debated in the literature. Recently Wang et al. found that patients with a proportion of sarcoma components ≥ 50% exhibited a significantly shorter survival time compared with the < 50% group. The mortality risk in the ≥ 50% group was 4.6 times higher compared with those in the < 50% group [15]. A 5-month increase in overall survival (OS) in patients with metastatic sRCC who underwent cytoreductive nephrectomy has been observed [16]. Bhindi et al. demonstrated that patients with metastatic RCC receiving an upfront cytoreductive nephrectomy are more likely to ultimately receive targeted therapy plus surgery, which furthered improved OS [17].

A recent retrospective study encompassing 2286 participants (sRCC: n = 230 and non-sRCC: n = 2056) showed that 93% received Vascular Endothelial Growth Factor (VEGF) inhibitors as first-line therapy, making it the most used in metastatic RCC [18]. The utility of VEGF-targeted therapy on metastatic SRCC showed that 53% of patients who were treated achieved some degree of tumor shrinkage while on therapy [12]. Bevacizumab, an angiogenesis inhibitor, is used in novel combination regimens such as IFN-a for the treatment of metastatic RCC [19,20]. Median OS was 23.3 months with bevacizumab plus IFN-a and 21.3 months with IFN plus placebo. Post protocol therapy including bevacizumab plus IFN-a was 38.6 months and IFN-a plus placebo arm was 33.6 months [20]. Two recent studies, both from 2018, found the greatest therapeutic benefit for SRCC patients when using the combination of atezolizumab plus bevacizumab, versus sunitinib monotherapy [21,22]. Molina, A. M. et al contradicts this with the study evaluated patients with metastatic sRCC, of whom 29 out of 63 were treated with sunitinib. Moderate improvement

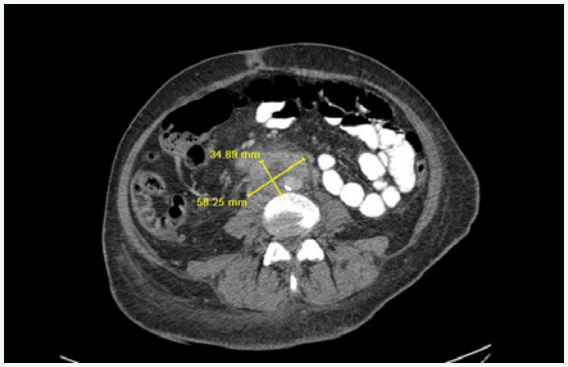

Figure 1 CT scan abdomen/pelvis with contrast: Perforation of the posterior wall of the duodenum into an approximately 5.8 x 3.5 cm ill-defined irregular thick-walled interaortocaval fluid collection consistent with a necrotic mass.

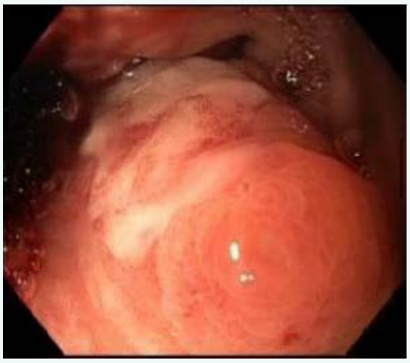

Figure 2 Esophageal Duodenoscopy (2nd portion of duodenum): A circumferential easily friable duodenal mass was noted with exudates and multiple biopsies were obtained via cold biopsy forceps and sent for histopathological analysis.

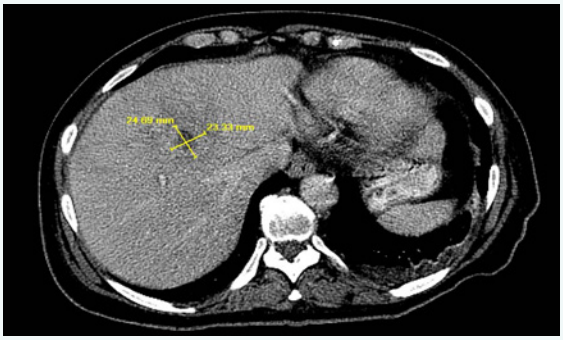

Figure 3 CT scan abdomen/pelvis with contrast: 2.4 x 2.3 cm ill-defined hypodense rim enhancing liver lesion with subtle adjacent satellite lesions/finger-like projections.

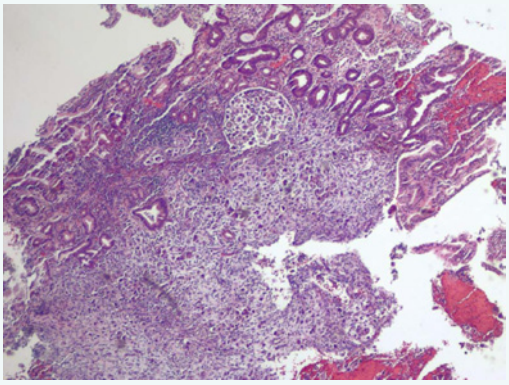

Figure 4 Stomach biopsy shows clusters of neoplastic cells within lamina propria. The surface appears normal and inflamed gastric epithelium.

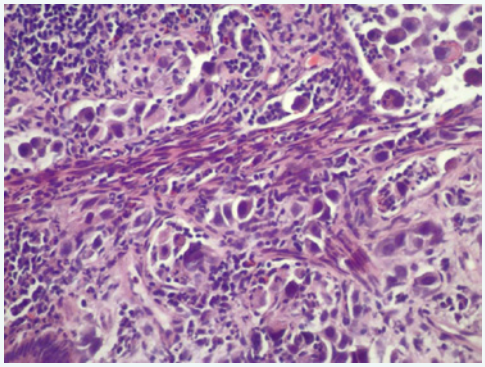

Figure 5 Histology shows atypical appearing neoplastic cells, with prominent nuclear in desmoplastic background.

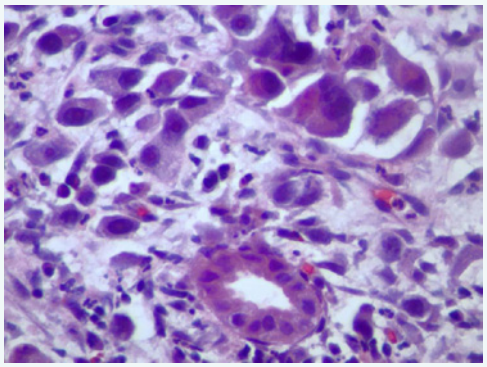

Figure 6 Histology shows atypical appearing neoplastic cells under a high power field view (400X).

in progression-free survival (PFS) was noted for the sunitinib group compared with those who were treated with other therapies [9]. It has also been shown that when bevacizumab was added later for patients initially receiving chemotherapy alone there was an incremental benefit [19].

Immune checkpoint inhibitors used in metastatic sRCC patients seemed logical because sRCC tumors have greater expression of PD-1 and PD-L1 receptor expression in tumors with sarcomatoid dedifferentiation [24,25]. A more recent study has shown that PD-L1, PD-1 and CD8 positive cell density were expressed at a higher density in metastatic RCC compared to grade 4 clear RCC [25]. Preliminary results of clinical trials in patients with sarcomatoid RCC showed encouraging survival data with objective response being as high as 62% and complete response rates up to 18% [26]. These results suggest SRCC tumors could be more sensitive to immunotherapy PD-1/PD-L1 blockade

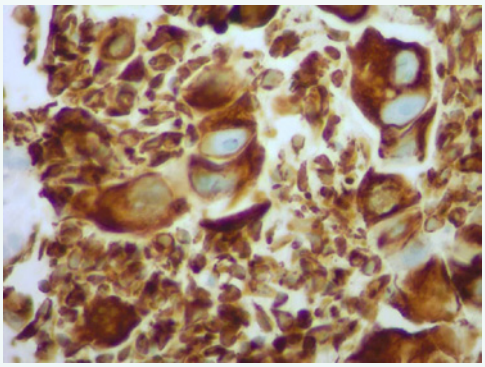

Figure 7 The Immunostain of Vimentin is positive in tumor cells.

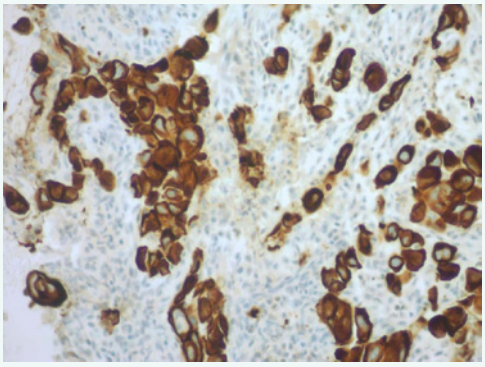

Figure 8 The Immunostain of CK7 is positive in tumor cells.

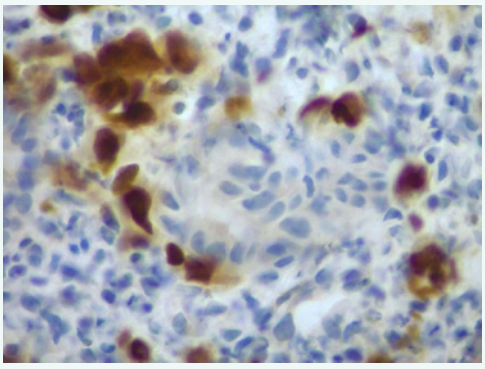

Figure 9 The Immunostain of PAX-8 is positive in tumor cells.

Antibody	
CK-7	Positive (Strong)
Vimentin	Positive (Strong)
PAX-8	Positive (Strong)
CDX-2	Positive (Weak and Patchy)
CD45	Negative
B-HCG	Negative
CK-20	Negative
S-100	Negative

Table 1 Immunohistochemistry results for our patient.

therapy than non-sarcomatoid RCC, warranting further research. Raychaudhuri et al. reported two cases that showed significant clinical response to the PD-1 inhibitor Nivolumab. This response was hypothesized to have resulted due to high PD-L1 expression on tumor cells, increased mutational burden within the tumor, and the presence of tumor-infiltrating lymphocytes [27].

Hyper-progressors in MDM2 amplification have been reported after immunotherapy with single-agent checkpoint PD-1/PD-L1 inhibitors. Results showed worse clinical outcomes and significantly increased rates of tumor growth. Suster et al. evaluated 49 sarcomatoid renal cell carcinoma cases by fluorescence with 10% testing positive for MDM2 gene amplification [28]. This suggests possible elevated expression of MDM2 in SRCC patients, stressing the need for testing for gene amplification prior to treatment [28]. Furthermore, MDM2 antagonists have previously resulted in apoptosis of RCC cells [29], though it's effectiveness on metastatic SRCC has yet to be proven.

Conclusion

It is difficult to provide the correct treatment to SRCC patients given the paucity of information regarding all aspects of identification and metastatic potential. One interesting case showed the efficiency of the combination of gemcitabine and doxorubicin, resulting in a 20% reduction of tumor. Grade 3 neutropenia forced treatment of the combination to cease, which was followed by temsirolimus. Maintenance of disease was obtained for 19 months with no major adverse events, with the exception of grade 2 nausea, with the patient succumbing to their disease at 30 months following the initiation of treatment [23]. This suggests that systemic chemotherapy followed by temsirolimus maintenance is a potential treatment option for patients with metastatic SRCC [23]. Only small clinical trials have shown the combined chemotherapy consisting of gemcitabine and doxorubicin to be effective in patients with sRCC [30,31], but this combination has not yet been tested in metastatic SRCC. Our case highlights both the rare and heterogeneous nature of SRCC. Our aim is to raise awareness and bring attention to this highly aggressive malignancy when assessing gastrointestinal tumors.

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