Oncology

Metastatic Renal Cell Carcinoma to Jejunum: An Unusual Case Presentation

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A B S T R A C T
The small intestine is a very uncommon and peculiar site for metastasis from renal cell carcinoma (RCC). We present a clinical presentation of insidious and unusual development of a jejunal metastasis while having stable disease in a remainder of metastatic sites, in a patient undergoing immunotherapy with nivolumab. Due to the extreme rarity of metastatic renal cell carcinoma to the lumen of the small bowel, it is easy to overlook and misdiagnose symptoms of this pathologic entity, particularly when the remainder of metastatic disease responds well to ongoing therapy.

Introduction
Recently, advances in the molecular and cellular understanding of antitumor immune response have led to the development of multiple single-agent cancer immunotherapies. An example of this is nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, recently approved by the FDA for second-line treatment in patients with metastatic renal clear-cell carcinoma. Despite immunotherapy showing encouraging results and durable responses, we still have to be cognizant of the possibility of a mixed response, particularly at the sites deemed extremely rare for RCC metastasis. Furthermore, this new category of therapy offers rare toxicities, and differentiating between toxicity and disease progression will be of paramount importance in the care of patients with metastatic RCC. Here, we present a case that demonstrates this point.

Case presentation
We present the case of a 64-year-old female patient, who presented with elevated calcium on routine laboratory studies. She underwent the appropriate workup, and computerized tomography (CT) scan revealed multiple bilateral pulmonary nodules, and a 10.2 cm mass arising from the lower pole of the right kidney. She underwent radical right sided nephrectomy with resection of the primary tumor with negative surgical margins. Pathology review showed grade 3 clear cell renal cell carcinoma. She had an LDH of 163, and hemoglobin of 12.6. She had an excellent performance status, and had a favorable prognosis per Memorial Sloan-Kettering Cancer Center Score for Metastatic RCC. Biopsy of a lung nodule revealed metastatic RCC. Though offered high-dose IL2 therapy, she opted for watchful waiting, and was shown to have stable metastatic pulmonary disease for 2 years. Eventually, upon progression in lung disease, she was started on therapy with pazopanib. After 1 month of treatment, due to intolerance, she was ultimately switched to immunotherapy with nivolumab. After 5 months of treatment with nivolumab, her metastatic lung findings were stable, but she started experiencing vague epigastric abdominal pain as her only symptom. It was thought not to be related to therapy or malignancy, and she was treated with proton pump inhibitors, laxatives, and gas relievers. After 10 months of treatment with nivolumab, her metastatic lung findings were stable, but she started experiencing vague epigastric abdominal pain as her only symptom. It was thought not to be related to therapy or malignancy, and she was treated with proton pump inhibitors, laxatives, and gas relievers. After 10 months of therapy with nivolumab, due to further development of nausea and frequent vomiting, she underwent restaging studies consisting of a CT of the chest and abdomen which revealed a near obstructing 5 cm jejunal mass (Fig. 1), and stable disease in the lung.

Patient underwent laparoscopic resection of jejunal mass, small bowel resection, and enterostomy. Per operative report,
there was no evidence of metastatic disease in the liver, or carcinomatosis. Pathologic examination revealed a 2.5 cm nodule involving the luminal surface of the small bowel. Histologically, the tumor exhibited the characteristic morphology of clear cell renal carcinoma, and was composed of nests of cells with variably prominent nucleoli and abundant clear cytoplasm (Fig. 2A). The tumor primarily involved the small bowel mucosa, with exophytic growth into the luminal space. Immunohistochemical stains were performed and showed that the tumor was positive for PAX8 and PAX2, consistent with renal origin (Fig. 2B).

Two weeks post-operatively, the patient’s symptoms completely resolved, and she recovered fully after surgery. Due to the development of jejunal metastasis while on nivolumab, the patient was started on third-line combination therapy with everolimus and lenvatinib. She still has optimal performance status, 4 years post original diagnosis of metastatic RCC.

Discussion

Metastatic RCC represents the spread of a primary renal cell carcinoma from the kidney to other organs. Approximately 25–30% of patients have metastatic disease by the time they are diagnosed with RCC. This high rate is explained by occult clinical signs that are generally mild until the disease progresses to a more severe state. Most common sites for metastasis are lymph nodes, lung, bones, liver, and brain. Occurrences of metastatic disease from RCC to the small intestine are exceedingly rare, with just a few cases reported in the literature. Cancers most commonly metastasizing to the small bowel include malignant melanoma and tumors arising from the breast, lung, esophagus, and head and neck. The prognosis of metastatic RCC compared to other cancers, has historically been low, with average survival time almost decade ago under a year. However, average survival times have increased over the last decade due to treatment advances including tyrosine kinase inhibitors, MTOR inhibitors and antiangiogenics. Immunotherapy such as nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, was recently approved by the FDA for patients with metastatic clear cell RCC, previously treated with anti-angiogenic therapy, based on results from the phase III CheckMate 025 study, which showed significantly longer median overall survival for Nivolumab versus Everolimus (25.0 vs 19.6 months). To our knowledge, we report a novel first case of RCC metastasizing to the...
small intestine in a patient undergoing immunotherapy with nivolumab.

**Conclusion**

As immunotherapy gains more traction in the treatment of malignant disorders, one needs to be cognizant of the unique toxicities patients can present with, that may include colitis. Upper gastrointestinal symptoms in a patient with known metastatic RCC whom has had a long disease interval, should trigger more detailed gastrointestinal work-up, with CT imaging, upper endoscopy, and if necessary video capsule endoscopy. The old adage in medicine of “when you hear hoof beats think horse and not zebra” may no longer apply in this modern era of immunotherapy.

**Conflict of interest**

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None.

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