Brief Report

Unclassified renal-cell carcinoma with significant response to nivolumab

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Running head: Adra et al

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BRIEF REPORT

A 56 year-old man presented in fall of 2015 with left flank pain and hematuria. He was evaluated by his primary care physician and CT scan showed nephrolithiasis, a left renal mass, significant lymphadenopathy in the left hilar region, small indeterminate pulmonary nodules, and a small sclerotic lesions in the left femur and left humerus. He underwent left radical nephrectomy with excision of retrocrural lymph nodes and retroperitoneal lymph node dissection. Pathology revealed a 9cm unclassified renal cell carcinoma with 40% sarcomatoid features and invasion into renal vein, perirenal fat, and hilar fat (Figure 1A). Tumor was graded as Fuhrman grade 4. Adrenal gland was involved by tumor. Three retrocrural and 5 interaortocaval lymph nodes were involved with carcinoma. Repeat CT scans post operatively showed enlarging right retrocrural lymph node that was not resected during surgery and new lung nodules. Surgical pathology was sent for further immunohistochemistry and next-generation sequencing. No actionable deoxyribonucleic acid (DNA) mutations, copy number variants, or gene fusions were found. Messenger ribonucleic acid (RNA) expression analysis showed high expression of the kidney-specific biomarker CA IX (CA9) at 35.3 fold of normal. Immunohistochemistry review revealed programmed death-ligand 1 (PD-L1) expression on 90% of tumor cells with 3+ intensity (Figure 1B). Moreover, PD-L1 tumor infiltrating lymphocytes (TILs) were present in 10% of the tumor sample with 2+ intensity. Given the presence of metastatic disease, patient was started on treatment with sunitinib 50mg orally daily for 4 weeks on and 2 weeks off schedule. Two months after initiating treatment of sunitinib, he experienced growing supraclavicular lymph nodes causing local pain. Repeat CT scans showed enlarging left supraclavicular (4cm),

paraesophageal (2.5cm), right paraspinal (2cm), bilateral retrocrural (2cm), and retroperitoneal (2cm) lymphadenopathy. In addition there were growing pulmonary nodules, and new liver metastatic disease. Figure 2 shows CT scans of the chest, abdomen, and pelvis at the time of progression. Second-line treatment with the programmed death-1 (PD-1) inhibitor nivolumab 3mg/kg intravenously every 2 weeks was initiated. After 1 dose of nivolumab, patient's supraclavicular lymphadenopathy was no longer palpable and the associated pain subsided. Repeat CT scans after treatment with nivolumab showed partial response with marked improvement in lymphadenopathy and lung nodules (Figure 3). Some of the previously noted lymph nodes were completely resolved and others much smaller in size. In addition there was decrease in size of pulmonary and liver metastasis.

Patient is now 10 months into treatment with nivolumab for his unclassified renal cell carcinoma and continues to have a significant response. He has received palliative radiotherapy to metastatic disease in the left femoral head and left humerus at a dose of 20Gy divided over 5 fractions. He has an excellent quality of life and is able to function at the level prior to being diagnosed with metastatic unclassified kidney cancer.

DISCUSSION

Renal cell carcinoma (RCC) is histologically classified as clear cell RCC, papillary RCC, chromophobe RCC, collecting duct RCC, or unclassified RCC.[1,2]Several reports have indicated significant differences in pathologic features and clinical outcomes among patients with different RCC histologic subtypes.[3,4] Unclassified RCC is comprised of a renal cortical epithelial neoplasms that could not be assigned to any of the other RCC subtypes based on histologic evaluation and it constitutes 3-5% of cases of RCC.[1]

Unclassified RCC is a category that encompasses a wide range of genetic alterations and histologic findings that might contain elements of other histologic subtypes of RCC or sarcomatoid features. Tumors with pure sarcomatoid or mixed sarcomatous and anaplastic features are also designated as unclassified RCC. These unclassified tumors are generally high grade and have unrecognizable cell types. Studies evaluating unclassified RCC indicate that these neoplasms are associated with highly aggressive biological behavior and poor clinical outcomes.[5-12] Patients tend to present with larger tumors, have increased risk of invasion to adjacent organs, increased risk for regional and non-regional lymph node metastasis, and increased risk for bone metastasis.[9] In addition, several studies have indicated that patients with unclassified RCC are more likely to present with higher grade and stage that are associated with shorter cancer-specific and overall survival compared to patients with clear-cell RCC.[7,8]

In this report, a patient with unclassified RCC developed progressive metastatic disease shortly after nephrectomy and retroperitoneal and retrocrural lymph node dissection. Next-generation sequencing did not reveal actionable mutations. Further immunohistochemistry testing showed 3+ PD-L1 expression on 90% of tumor cells and 10% of the tumor sample contained TILs with 2+ intensity. Patient rapidly progressed after first-line sunitinib with worsening symptoms and progressive disease on imaging. Treatment with the PD-1 inhibitor nivolumab was instituted and patient had a clinical and anatomic response with resolution of symptoms and regression or resolution of metastatic lesions on CT imaging. This response was durable and is currently ongoing after 10 months of therapy.

To our knowledge, there is limited data of treating patients with unclassified RCC with immune checkpoint inhibitor based therapy. Here we report a case of metastatic unclassified RCC with high PD-L1 tumor expression and a significant response to nivolumab. PD-L1 expression appears to predict response to PD-1/PDL-1 inhibitors in lung cancer and melanoma but not in metastatic clear-cell RCC.[13-15]It is unclear whether PD-L1 expression may be a predictive marker of response to immune checkpoint inhibitors in non-clear cell RCC, and particularly in the unclassified histotype. The findings in this report suggest that further investigation is warranted for utilizing checkpoint inhibitors upfront in this subgroup of RCC patients who have limited therapeutic options, especially in case of high PD-L1 expression.

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FIGURE LEGENDS

- Fig 1:

Fig 1A: Hematoxylin and eosin (H&E) staining with 10x power of left kidney sample showing unclassified renal cell carcinoma with 40% sarcomatoid features.

Fig 1B: Immunohistochemistry of renal tumor showing programmed death-ligand 1 (PD-L1) expression on 90% of tumor cells with 3+ intensity at 10x power

- Fig 2: CT scan at the time of progression on sunitinib showing left supraclavicular lymph node measuring 2.9 x 4.1 cm (Fig 2A), paraesophageal lymph node measuring 2.3 x 2.4 cm (Fig 2B), and right lower lobe lung nodule measuring 1.4 x 1.7 cm (Fig 2C).

- **Fig 3:** CT scan after treatment with Nivolumab showing left supraclavicular lymph node measuring 1.6 x 1.2 cm (Fig 3A), paraesophageal lymph node measuring 1.3 x 1.0 cm (Fig 3B), and right lower lobe lung nodule measuring 0.5 x 0.5 cm (Fig 3C).

Fig 1.

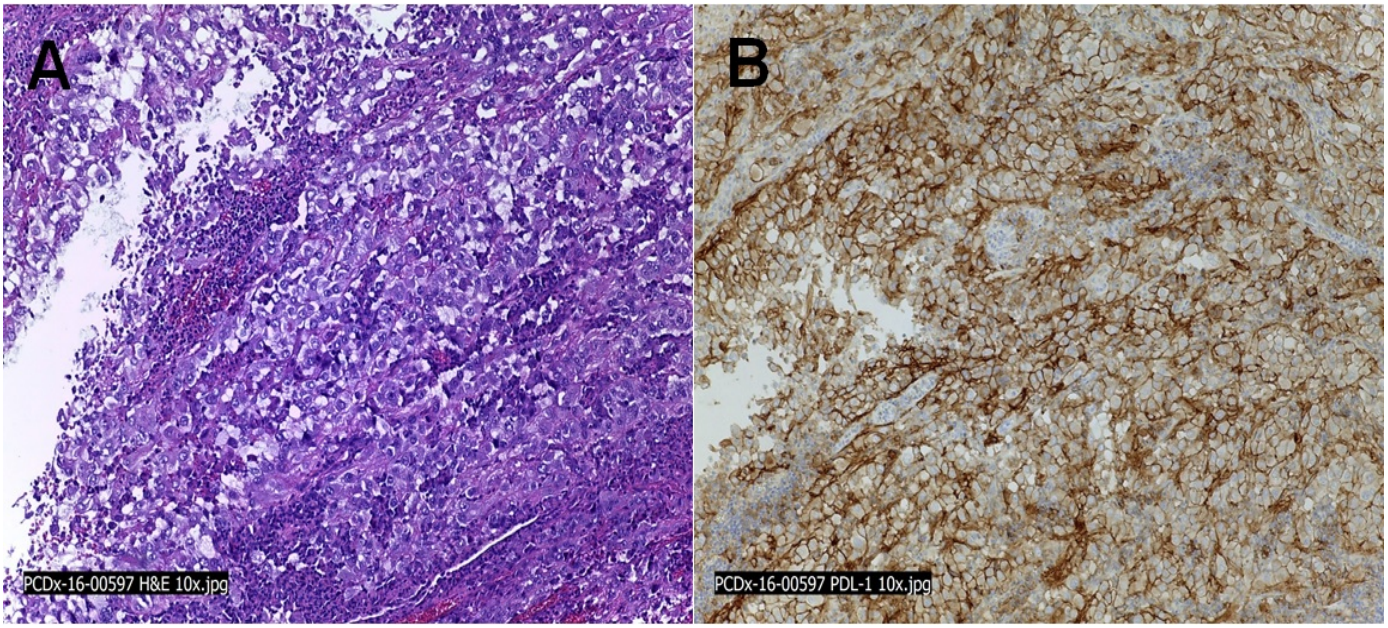

Fig 2.

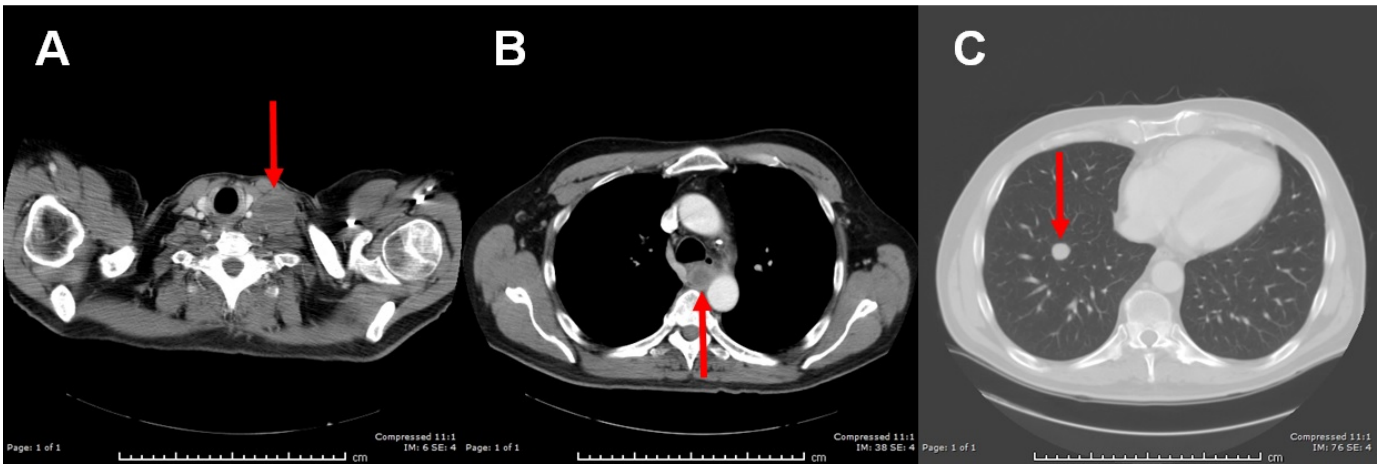

Fig 3.