**Acute interstitial nephritis, a potential predictor of response to immune checkpoint inhibitors in renal cell carcinoma**

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**ABSTRACT**

Immune checkpoint inhibitors (ICIs) such as nivolumab and ipilimumab have improved outcomes in metastatic renal cell carcinoma (mRCC) patients, but they are also associated with immune-related adverse events (irAEs). As observed in melanoma, we hypothesized that patients experiencing an autoimmune reaction directed against the tissue of origin may be more likely to benefit from ICI. Specifically, we asked whether patients with immune-related acute interstitial nephritis (irAIN) exhibited improved outcomes. Using Kidney Cancer Explorer (KCE), a data portal and i2b2-based central database for clinical, pathological and experimental genetic data, we systematically identified all patients with mRCC at UT Southwestern Medical Center (UTSW) from 2014–2018 who received at least one dose of ICI. More recent cases were identified through a provider query. We extracted creatinine (Cr) values at baseline and over the entirety of each patient ICI treatment course using KCE. Patients with ≥1.5-fold Cr increase over baseline were investigated. The likelihood of irAIN was determined based on the work-up (biopsy, if available), or by clinical criteria (timing of kidney injury, exclusion of other etiologies, treatment with immunosuppressants and response). We identified 177 mRCC patients who received at least one dose of ICI, 36 of whom had ≥1.5-fold increase in Cr over baseline while on treatment. Of those, two had biopsy-proven irAIN and one was clinically diagnosed, resulting in an incidence of 1.7%. One additional biopsy-proven case past 2018 was identified through a provider query, for a total of four patients. Two received combination nivolumab and ipilimumab in the first line, whereas the remaining received nivolumab after first line therapy. irAIN onset ranged from 1.5 to 12 months. All four patients stopped ICI with recovery of renal function, at least partially, three after receiving systemic steroids. Notably, all four patients had a deep response. In conclusion, irAIN is a rare event, but it may portend a higher likelihood of response. One possible explanation is antigenic overlap between normal renal tubular cells and tumor cells.

**INTRODUCTION**

Renal cell carcinoma (RCC) is the ninth leading cause of cancer in the USA, with an estimated 73,750 new cases and 14,830 deaths in 2020.1 The overall 5-year survival for all stages of RCC is 74.8%; however, this number drops to 12% when the cancer has metastasized.1 Fortunately, outcomes for metastatic renal cell carcinoma (mRCC) are improving with the adoption of new therapies including immune checkpoint inhibitor (ICIs) and ICI/tyrosine kinase inhibitor combinations.2–5 ICIs used in the treatment of RCC target the PD1/PD-L1 and CTLA-4 immune checkpoints, and they are associated with improved outcomes in several observational studies, although the data are mixed and prospective studies are lacking.7 The mechanisms underlying irAEs are not yet entirely understood; however, studies suggest that disinhibition of autoregulatory T-cells and recognition of shared antigens may play a role.6–8 Consistent with the latter, several observational studies9–10 and a prospective clinical trial11 have linked the development of vitiligo with particularly good outcomes in patients with ICI-treated melanoma. Given the origin of RCC from renal epithelium, we hypothesized that immune-related acute interstitial nephritis (irAIN) may predict treatment efficacy in ICI-treated mRCC.

Here, we present the clinical outcomes of four cases of ICI-treated mRCC that developed irAIN at UT Southwestern Medical Center (UTSW).
METHODS

We used Kidney Cancer Explorer (KCE), an Institutional Review Board-approved, i2b2-based queryable database that integrates clinicopathologic data automatically extracted from the electronic medical record (EMR) sponsored by the UTSW Kidney Cancer Program and the Lyda Hill Department of Bioinformatics Core Facility (manuscript in preparation). We collected comprehensive clinical and pathology data from patients with mRCC at UTSW who received at least one dose of ICI from January 1, 2014 until December 31, 2018. Creatinine (Cr) values prior to treatment initiation (baseline) and on treatment were automatically extracted, and patients with one or more Cr values demonstrating a $\geq 1.5$-fold increase over baseline during ICI therapy were investigated. More recent cases, diagnosed after the most recent KCE update (January 2019–February 2020), were identified by querying genitourinary oncology faculty at our institution. The diagnosis of irAIN was determined by renal biopsy, when available, or clinically if a biopsy was not available. Clinical inclusion criteria were defined as: (i) Cr rise after administration of ICI; (ii) exclusion of other causes of acute kidney injury (AKI), including prerenal, postrenal, or other intrinsic causes (including ischemia, sepsis, vasculitis, and nephrotoxin-induced AKI); and (iii) improvement following systemic steroid administration. Medical records for index patients were reviewed by at least two independent physicians (VP, RE) and a nephrologist (MV). Baseline characteristics were reported at the time of ICI initiation. Renal biopsies were reviewed by a qualified genitourinary pathologist (PK) and a nephrologist (MV). Response was assessed retrospectively using RECIST V.1.1 criterion by a qualified radiologist (IP).

RESULTS

A total of 177 patients with mRCC treated with at least one dose of ICI were identified from 2014 through 2018. Of these, 36 (20.3%) patients had at least one Cr value that was $\geq 1.5$-fold over baseline while receiving ICI therapy. A total of 33 (18.6%) patients were found to have non-irAIN etiologies of AKI including: 24 patients with prerenal injury resulting from poor fluid intake and/or gastrointestinal losses; 7 patients who developed AKI in the context of a systemic illness (i.e., sepsis or acute heart failure); and 2 patients with postobstructive AKI (figure 1). irAIN was suspected in 3 (1.7%) cases identified through the KCE search. One additional case diagnosed in 2019 was identified through a provider query. Three patients had renal biopsies confirming the irAIN diagnosis. The clinical characteristics of the four patients included in the study are summarized in table 1.

CASE PRESENTATIONS

Case 1

The patient is a 71-year-old man with a medical history of hypertension (HTN), who initially presented in 2013 with a locally advanced tumor and a level II tumor thrombus. Radical nephrectomy and thrombectomy revealed clear cell (cc)RCC, nuclear grade (NG) 4 with 10% sarcomatoid features. Three months following resection, the patient was diagnosed with an isolated biopsy-proven iliac bone metastasis which was treated with stereotactic body radiotherapy (SBRT). Over a period of 2 years, he developed four brain lesions amenable to focal therapy with resection of the largest (1.8 cm) metastasis and stereotactic radiosurgery (SRS) to the remaining subcentimeter lesions. Despite the...
| Case | Age | Sex | IMDC | Subtype | NG | Sarcomatoid features | ICI | Prior Tx | Time to iRAIN (months) | Biopsy proven AIN? | CR [mg/dL] (eGFR [mL/min/1.73 m²]) | iRAIN Tx duration (months) | BR | DOR (months) |
|------|-----|-----|------|---------|----|----------------------|-----|----------|----------------------|------------------|----------------------------|------------------|-----|-------------|
| 1    | 71  | M   | Int. | ccRCC  | 4  | 10%                  | N   | Pazoo     | 12.8                 | Yes              | 1.3 (55)                  | 2.25 (35)                  | 1.48 (50)       | None         | CR  | 52§        |
| 2    | 70  | M   | Poor | ccRCC  | 2**| Absent               | N   | Pazoo PT2385 Axi | 10.8                 | Yes              | 1.5 (42)                  | 10 (5)                      | 1.85 (36)       | Mpred 500 mg | 3  | 14         |
| 3    | 48  | M   | Int. | ccRCC  | 3**| Absent               | N+i | None      | 1.4                  | No               | 1.2 (>60)                 | 2.45 (28)                  | 1.28 (60)       | Pred 1 mg/kg daily††‡ | 4  | CR 29†     |
| 4    | 58  | M   | Poor | pRCC   | 3  | Absent               | N+i | None      | 2.1                  | Yes              | 0.8 (>60)                 | 2.65 (37)                  | 1.74 (49)       | Pred 1 mg/kg daily | 3  | PR 8       |

*From start of ICI therapy.
†Maximal immunosuppressive therapy, tapered over treatment duration.
‡Following pseudoprogression.
§At 36 months post-ICI initiation, patient developed an asymptomatic brain lesion which was irradiated.
¶Ongoing.
**Diagnosis via biopsy of primary tumor.
††Tapered over 7 weeks.
Axi, axitinib; BID, twice daily; BR, best response; ccRCC, clear cell RCC; CR, complete response; DOR, duration of response; I, Iplimumab; IMDC, international metastatic RCC database risk group score at the time of starting ICI; Int, intermediate risk; Mpred, methylprednisolone; Myco, mycophenolate; N, Nivolumab; NG, nuclear grade; Pazo, Pazopanib; PR, partial response; pRCC, papillary RCC; Pred, Prednisone; PT2385, experimental HIF-2α inhibitor; Tx, treatment.

The patient is a 70-year-old man with a history of stage II chronic kidney disease, type 2 diabetes (T2DM), and HN. He was initially treated with pazopanib and had a partial response. He was then started on nivolumab (240 mg every 2 weeks) due to mild progression. Two months later, his Cr increased from a baseline of 1.5 to 2.25 mg/dL (eGFR of 52 mL/min/1.73 m²), and a normal urine protein to Cr ratio (>0.2). The patient remained off therapy and free of systemic disease 3 years after starting nivolumab initially, nivolumab was reinitiated (240 mg every 2 weeks). At this time, the patient developed grade II pneumonitis which was treated with steroids and the patient transitioned to active surveillance. Unfortunately, the patient developed grade II pneumonitis which was treated with steroids.

**Case 2**

The patient is a 70-year-old man with a history of stage II chronic kidney disease, type 2 diabetes (T2DM), and HN. He was initially treated with pazopanib and had a partial response. He was then started on nivolumab (240 mg every 2 weeks) due to mild progression. Two months later, his Cr increased from a baseline of 1.5 to 2.25 mg/dL (eGFR of 52 mL/min/1.73 m²), and a normal urine protein to Cr ratio (>0.2). The patient remained off therapy and free of systemic disease 3 years after starting nivolumab initially, nivolumab was reinitiated (240 mg every 2 weeks). At this time, the patient developed grade II pneumonitis which was treated with steroids. The patient's Cr gradually decreased to 1.7 mg/dL (eGFR 25 mL/min/1.73 m²) over the course of 2 years. Presently, 4 years following the development of iRAIN, the patient remains in remission of therapy and free of systemic disease. The patient's clinical condition has significantly improved with the exception of a single subcentimeter brain lesion that was stable. The patient's Cr gradually decreased to 1.3 mg/dL (eGFR 35 mL/min/1.73 m²). At this time, the patient developed grade II pneumonitis which was treated with steroids. The patient's Cr gradually decreased to 1.7 mg/dL (eGFR 35 mL/min/1.73 m²) over the course of 2 years. Presently, 4 years following the development of iRAIN, the patient remains in remission of therapy and free of systemic disease. The patient's clinical condition has significantly improved with the exception of a single subcentimeter brain lesion that was stable. The patient's Cr gradually decreased to 1.3 mg/dL (eGFR 35 mL/min/1.73 m²). At this time, the patient developed grade II pneumonitis which was treated with steroids.
Figure 2  ICI-associated tumor changes. Case 1: Red arrows highlight representative lesions at baseline including a paraesophageal lymph node, which was biopsied (A1) and pulmonary nodule (A2). Post-ICI imaging (B1 and B2) demonstrate resolution of these lesions. Case 2: Red arrows show representative pulmonary (C1) and hepatic lesions (C2); red asterisk highlights left lower lobe consolidation/atelectasis secondary to metastatic lesion and pleural effusion (C1). Post-ICI imaging demonstrates substantial improvement of pulmonary disease (D1) and the liver lesion (D2). Case 3: Red arrows show large liver masses (E1) and tumor thrombus (E2) with mass-like enlargement of tumor thrombus at the confluence with the inferior vena cava (arrowhead). Post-ICI imaging shows significant shrinkage of liver metastases (F1) and tumor thrombus (F2). Case 4: Baseline imaging with peritoneal deposits (orange arrowheads), malignant ascites (red asterisk) (G1), and omental caking (red arrows) (G2). Post-ICI imaging demonstrates resolution of ascites and omental caking, as well as significant reduction in peritoneal deposits (orange arrowheads). ICI, immune checkpoint inhibitor.

Figure 3  Histological features of irAIN. H&E stained sections from three biopsied cases showing a diffuse interstitial inflammatory infiltrate with prominent lymphocytes, a few plasma cells and occasional eosinophils. Focal lymphocytic tubulitis (yellow arrows) and focal tubular epithelial cell injury with mild interstitial edema was observed. Case 1 shows background focal segmental glomerulosclerosis likely unrelated to the acute presentation. Case 2 shows diffuse diabetic glomerulopathy with global and segmental glomerulosclerosis, consistent with the patient’s history of T2DM and CKD. CKD, chronic kidney disease; H&E, hematoxylin and eosin; irAIN, immune-related acute interstitial nephritis; T2DM, type II diabetes.
10 mg/dL (eGFR decreased from 42 to 5 mL/min/1.73 m³). This was accompanied by the development of proteinuria, with a urine P/C ratio of 2.6 (previously <0.2). The patient was not oliguric or symptomatic. Ultrasound-guided biopsy of the kidney confirmed irAIN (figure 3). Nivolumab was stopped, methylprednisolone 500 mg daily was administered intravenously for 3 days, and subsequently he received a prednisone taper starting at 120 mg PO daily over 3 months. His renal function improved with a decrease in Cr to 1.85 mg/dL (eGFR, 36 mL/min/1.73 m³) and urine P/C of 2.3 with eventual decrease to 1.6. The patient was followed with active surveillance for an additional 3 months. Imaging at this time demonstrated progressive disease with new lung nodules and enlargement of liver lesions. He received a combination of lenvatinib and everolimus, on which he had stable disease lasting an additional year, and ultimately passed away due to complications of pneumonia.

**Case 3**

The patient is a 58-year-old otherwise healthy man who was initially diagnosed with RCC and a level II thrombus with bulky retroperitoneal lymphadenopathy and synchronous metastases to the liver. Biopsy of the primary tumor revealed ccRCC. NG on the biopsy was 3 and no sarcomatoid or rhabdoid features were appreciated. The patient was initially started on combination ipilimumab and nivolumab, with SBRT to the primary tumor through the RADVAX trial (NCT03065179). Following the second infusion of ipilimumab/nivolumab (1 mg/kg and 3 mg/kg, respectively), an elevation in Cr to 2.45 mg/dL from a baseline of 1.2 mg/dL (eGFR from >60 to 28 mL/min/1.73 m³) was noted on routine labs. Additional ICI infusions were held, and the patient was started on 1 mg/kg prednisone twice daily, with initial improvement in Cr. After 1 week, the prednisone dose was reduced to 1 mg/kg once daily, but this resulted in a gradual rise in Cr, prompting the addition of mycophenolate 1.5 mg/kg once daily while the prednisone was gradually reduced over a period of 6 weeks. Four months later, immunosuppressive therapy was stopped, methylprednisolone 500 mg/dL, up from a baseline of 0.8 mg/dL (eGFR from >60 to 37 mL/min/1.73 m³). Urinalysis at this time did not demonstrate proteinuria. Renal biopsy demonstrated inflammatory changes consistent with irAIN (figure 3), as well as IgA nephropathy with diffuse, global, granular mesangial positive staining by IgA (not shown). The patient was started on 1 mg/kg of prednisone which was tapered down over a period of 3 months. The patient’s Cr gradually down trended to 1.74 mg/dL (eGFR, 49 mL/min/1.73 m³). Imaging 4 months following ICI demonstrated a remarkable improvement in the peritoneal carcinomatosis (figure 2, compare G and H), and resolution of ascites.

**DISCUSSION**

Through a systematic database search, we identified three patients with mRCC who developed irAIN following ICI therapy for an incidence rate of 1.7%. We also identified a fourth patient, diagnosed after the latest database update, through a query of oncologists at UT Southwestern. ICI was held for all four patients and immunosuppressive therapy was started in three of four patients. All patients demonstrated at least a partial recovery of renal function, and none required renal replacement therapy. The presence of proteinuria was variable, with one patient (case 1) developing nephrotic range proteinuria and another with more modest impairment of renal function without detectable urine protein (case 4).

Both the prevalence and clinical spectrum of irAIN in this series is consistent with studies of irAIN of pooled tumor types. Interestingly, the time to irAIN onset was quite variable. The two patients treated with nivolumab monotherapy developed irAIN as a late complication and only after reintroduction of nivolumab. Late onset irAEs may be attributable to antigenic spread following a successful antitumor response, possibly resulting in the immune recognition of shared tumor and normal epitopes. Conversely, the two patients treated with combination ipilimumab/nivolumab developed irAIN within 3 months of starting therapy. This may be attributable to the increased rate of irAEs observed with dual ICI therapy relative to single agent therapy.

IgA nephropathy was observed on the renal biopsy of Case 4. IgA nephropathy following PD-L1 inhibitor therapy has been reported; however, IgA nephropathy is also a recognized paraneoplastic syndrome of RCC, thus, causality is difficult to establish. Case 3 received concurrent SBRT to the primary renal lesion with combination ipilimumab-nivolumab; however, it is unlikely that the kidney injury sustained was induced by radiation toxicity since renal toxicity following SBRT is uncommon and usually of late onset.

All four patients demonstrated a deep response to therapy, with two patients demonstrating long term disease control.
off systemic therapy, one of which has had an ongoing response lasting 4 years. Importantly, our cohort includes patients with pathologic and imaging findings associated with poor prognosis such as bone metastases (patient 2); large hepatic metastases (patient 3); and high grade pRCC with diffuse peritoneal carcinomatosis (patient 4). As a reference, responses rates with single agent nivolumab are 25%, and 40% with combination therapy. Our data raises the possibility that irAIN may be correlated with improved outcomes in ICI-treated RCC, although the conclusions are obviously limited by the small sample size and retrospective nature of this report. While irAIN can develop following ICI therapy of different tumor types, we are unaware of any literature suggesting irAIN specifically correlates with improved oncologic outcomes in non-RCC tumors. Conversely, we have identified two case reports in which patients with RCC demonstrated a prolonged response to ICI treatment following the development of irAIN. These data support the notion of antigenic overlap. We propose that oncological benefit following irAIN may be unique to RCC, and possibly due to shared epitopes between normal renal epithelium and RCC that drive a robust and sustained immune response. Finally, by identifying a second tumor type (besides melanoma) in which improved responses are associated with irAEs directed towards the tissue of origin, our data suggest that this phenomenon might be generalizable to other tumor types; that is, immune mediated adverse events of the tissue of origin might portend improved oncological outcomes, though further studies are needed to evaluate this notion.

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**Conclusions**

**Conception and design:** VP, RE, JB. **Development of methodology:** AC, VM, VP, RE, JB. **Acquisition of data:** VP, RE, JF, WS, AC, VM, PK, RM, IP, HH, JB. **Analysis and interpretation of data:** VP, RE, JF, QC, PK, MV, IP, RH, JB. **Writing, review, and/or revision of manuscript:** VP, RE, WS, PK, MV, RM, IP, RH, HH, JB.

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