Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors

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Immune checkpoint inhibitors (CPIs), monoclonal antibodies that target inhibitory receptors expressed on T cells, represent an emerging class of immunotherapy used in treating solid organ and hematologic malignancies. We describe the clinical and histologic features of 13 patients with CPI-induced acute kidney injury (AKI) who underwent kidney biopsy. Median time from initiation of a CPI to AKI was 91 (range, 21 to 245) days. Pyuria was present in 8 patients, and the median urine protein to creatinine ratio was 0.48 (range, 0.12 to 0.98) g/g. An extrarenal immune-related adverse event occurred prior to the onset of AKI in 7 patients. Median peak serum creatinine was 4.5 (interquartile range, 3.6–7.3) mg/dl with 4 patients requiring hemodialysis. The prevalent pathologic lesion was acute tubulointerstitial nephritis in 12 patients, with 3 having granulomatous features, and 1 thrombotic microangiopathy. Among the 12 patients with acute tubulointerstitial nephritis, 10 received treatment with glucocorticoids, resulting in complete or partial improvement in renal function in 2 and 7 patients, respectively. However, the 2 patients with acute tubulointerstitial nephritis not given glucocorticoids had no improvement in renal function. Thus, CPI-induced AKI is a new entity that presents with clinical and histologic features similar to other causes of drug-induced acute tubulointerstitial nephritis, though with a longer latency period. Glucocorticoids appear to be a potentially effective treatment strategy. Hence, AKI due to CPIs may be caused by a unique mechanism of action linked to reprogramming of the immune system, leading to loss of tolerance.

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The recent emergence of immune checkpoint inhibitors (CPIs), a novel type of immunotherapy, represents a substantial advance in oncology. CPIs are monoclonal antibodies that target inhibitory receptors expressed on T cells, other immune cells, and tumor cells. These receptors include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 protein (PD-1), and programmed death–ligand 1 (PD-L1).[1] CTLA-4 prevents T cell activation by outcompeting CD28 for its ligand, B7, thereby inhibiting T cell costimulation,[2] whereas PD-1 down-regulates effector T cell function by engaging its 2 ligands, PD-L1 and PD-L2.[3] Thus, by inhibiting CTLA-4 and PD-1/PD-L1, CPIs enhance tumor-directed immune responses and have been leveraged as novel therapeutic agents for solid and hematologic malignancies.[1]

The efficacy of 1 CTLA-4 antagonist, ipilimumab, and 2 PD-1 antagonists, nivolumab and pembrolizumab, has been well established in the treatment of advanced melanoma[4–6] and non–small cell lung cancer,[7,8] and more recent data support their efficacy in patients with renal-cell carcinoma,[9] Hodgkin lymphoma,[10] and many other malignancies. CPIs are known to cause a unique spectrum of side effects termed immune-related adverse events (IRAEs). The most common IRAEs include rash, colitis, hepatitis, and hypophysitis.[1] Sparse case reports have described acute kidney injury (AKI) related to CPIs.[11–13] Here, we present the largest series to date of CPI-induced AKI, with a focus on clinical features, pathology, and response to treatment.

RESULTS

Baseline characteristics

We identified 13 patients from 7 academic medical centers across the United States with CPI-induced AKI who

Table 1 | Baseline characteristics

Pt	Age/sex	Malignancy	SCr/eGFR	Proteinuria (dipstick)	Comorbidities	Checkpoint inhibitor regimen	Cumulative dose
1	70/M	Melanoma	0.9/86	NA	Asthma, osteoarthritis, basal cell carcinoma, and squamous cell carcinoma	Ipi 3 mg/kg × 1	Ipi 3 mg/kg
2	64/M	Melanoma	1.3/58	Neg	CKD, hypertension, and BPH	Ipi 3 mg/kg + Nivo 1 mg/kg q 6 wks × 2	Ipi 6 mg/kg Nivo 2 mg/kg
3	74/M	Melanoma	1.1/66	Neg	Hypertension	Ipi 3 mg/kg + Nivo 0.3 mg/kg q 3 wks × 2, followed by Ipi 3 mg/kg × 1 (7.5 wks later)	Ipi 9 mg/kg Nivo 0.6 mg/kg
4	62/F	Melanoma	0.7/92	Trace	CHF and atrial fibrillation	Ipi 10 mg/kg q 3 wks × 3	Ipi 30 mg/kg
5	71/F	NSCLC	0.6/92	NA	Hypothyroidism and history of pulmonary embolism	Ipi 3 mg/kg q 12 wks × 3 + Nivo 3 mg/kg q 2 wks × 14	Ipi 9 mg/kg Nivo 42 mg/kg
6	64/M	Pancreatic cancer	0.8/78	Neg	Adrenal insufficiency and hypothyroidism	Ipi 10 mg/kg q 3 wks × 4, followed by Ipi 10 mg/kg × 1 (12 wks later)	Ipi 50 mg/kg
7	71/M	Melanoma	1.0/57	Neg	CKD and hypothyroidism	Nivo 0.1 mg/kg q 2 wks × 4, followed by Nivo 1 mg/kg q 2 wks × 12	Nivo 12.4 mg/kg
8	58/M	Melanoma	0.5/107	NA	Hypertension	Ipi 3 mg/kg q 3 wks × 8	Ipi 24 mg/kg
9	75/M	Melanoma	0.9/63	NA	BPH	Ipi 3 mg/kg + Nivo 1 mg/kg q 3 wks × 2	Ipi 6 mg/kg Nivo 2 mg/kg
10	32/F	Hodgkin lymphoma	1.0/74	Neg	BMT for Hodgkin lymphoma	Ipi 10 mg/kg q 3 wks × 4	Ipi 40 mg/kg
11	73/F	Melanoma	1.0/56	Neg	Hypertension	Ipi 3 mg/kg q 3 wks × 3	Ipi 9 mg/kg
12	66/M	Bladder carcinoma	1.5/48	1+	CKD, hypertension, and hay fever	Pembro 2 mg/kg × 1	Pembro 2 mg/kg
13	41/F	Melanoma	0.9/80	Neg	Asthma and migraine headaches	Pembro 2 mg/kg q 3 wks × 10	Pembro 20 mg/kg

BMT, bone marrow transplant; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; Ipi, ipilimumab; NA, not available; Nivo, nivolumab; NSCLC, non–small cell lung carcinoma; Pembro, pembrolizumab; Pt, patient; q, every; SCr, serum creatinine (mg/dl). Estimated glomerular filtration rate (ml/min) was calculated using the CKD-EPI equation.[33]

underwent a kidney biopsy. Baseline characteristics are summarized in Table 1. All patients were Caucasian except for patient 10, who was Hispanic. Chronic kidney disease, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2, was present in 4 patients. Dipstick proteinuria was negative in 7 patients, trace in 1 patient, and not available in 5 patients.

The most common malignancy in our cohort was melanoma (9 of 13 patients). Other malignancies included non–small cell lung cancer ($n = 1$), pancreatic cancer ($n = 1$), Hodgkin lymphoma ($n = 1$), and bladder carcinoma ($n = 1$). The treatment regimen varied widely across the cohort. Patients received ipilimumab alone ($n = 6$), ipilimumab in combination with nivolumab ($n = 4$), nivolumab alone ($n = 1$), and pembrolizumab alone ($n = 2$).

Concomitant medications

Concomitant medications are shown in Supplementary Table S1. In 3 cases, a medication associated with acute tubulointerstitial nephritis (AIN) was introduced within 4 weeks prior to AKI onset: patient 1 began pantoprazole 24 days prior to AKI; patient 8 began ibuprofen 19 days prior to AKI; and patient 12 began taking a 3-day course of ciprofloxacin 20 days prior to AKI.

Clinical features of CPI-induced AKI

The clinical features of AKI following treatment with a CPI are summarized in Table 2. The interval from initiation of a CPI to AKI ranged from 21 to 245 days (median [interquartile range (IQR)]: 91 [60, 183]), and the interval from the last CPI dose to AKI ranged from 7 to 63 days (median [IQR]: 21 [18, 49]). Pyuria, defined as >5 white blood cells per high power field, was present in 8 of 13 patients. Hematuria, defined as >2 red blood cells per high power field, was present in 3 of 13 patients. Eosinophilia occurred in 1 patient. Complement levels (C3 and C4) were normal in all 8 patients who were tested.

New or worsened hypertension occurred in 2 patients. Patient 6, who had a baseline blood pressure (BP) of 115/70, had a BP of 170/95 when he first developed AKI. By the following day, his BP had fallen to 140/90 spontaneously. Patient 9, who had a baseline BP of 145/80, had an initial BP of 218/95 when he first developed AKI. He required triple antihypertensive therapy with amlodipine, furosemide, and labetalol to control his BP.

The median (IQR) peak serum creatinine (SCr) during AKI was 4.5 (3.6, 7.3) mg/dl. Two patients had oliguric AKI. Among the 8 patients whose proteinuria was quantified, the urine protein–creatinine ratio ranged from 0.12 to 0.98 g/g. At least 1 extrarenal IRAE was documented prior to AKI onset in 7 patients and concurrently with AKI in 1 additional patient. The most common IRAEs were hypophysitis and colitis ($n = 3$ each). Two patients developed AKI while on a glucocorticoid taper for an extrarenal IRAE.

Pathology

Representative renal pathology images are shown in Figure 1 (larger versions are available in Supplementary Figure S1A–F)