The Role of Kidney Biopsy in Immune Checkpoint Inhibitor-Associated AKI

Arash Rashidi,1 Chintan Shah,2 and Miroslav Sekulic3

Key Points
- AKI in the setting of immune checkpoint inhibitors.
- Need for kidney biopsy for diagnosis of immune checkpoint inhibitors.
- Importance of pathology in diagnosis of immune checkpoint inhibitor–induced AKI.

Introduction
Immune checkpoint inhibitors (ICPIs) are widely used to treat various types of malignancies. They function by over-activating the immune system to stimulate antitumor immunity. However, this response is not only selective to the tumor cells, but also toward different organ systems, resulting in collateral adverse events, more commonly known as immune-related adverse events (irAEs). The most common irAEs involve organ systems, such as the skin, liver, and gastrointestinal tract. Recent studies have shown ICPIs can result in AKI, with the most common manifestation on biopsy being acute interstitial nephritis (AIN) (1–3). Because ICPIs are becoming more widely used, various etiologies of AKI have been reported besides AIN, such as IgA nephropathy (4), FSGS (5), minimal change disease (6,7), vasculitis (8,9), and thrombotic microangiopathy (2). Usually, AKI related to an ICPI is diagnosed clinically by the oncologist or involved nephrologist, and treatment includes corticosteroids along with consideration for stopping the implicated ICPI(s). On the basis of expert opinion, kidney biopsy is suggested when there are high clinical suspicions of ICPI-induced AKI, along with nephrotic range proteinuria (>3 g/day), oliguria, dysmorphic red blood cells (RBC) in the urine, or when there is an incomplete response to empirically administered corticosteroids (7).

In this study, we present a case series of patients with high clinical suspicion of ICPI-induced AKI, in which a kidney biopsy revealed acute tubular injury/necrosis (ATI), as opposed to the expectant AIN. Accurate diagnosis guided by biopsy findings allows for the continuation of immunotherapy and avoids potentially toxic use of high-dose corticosteroids.

Patient 1
A 57-year-old Black man with a medical history of adenocarcinoma of the lung (stage 3) and hypertension. Throughout, the lung cancer treatment regimen included cisplatin, pemetrexed, and nivolumab. His baseline kidney function before initiation of the treatment regimen was normal, with a serum creatinine of 0.9 mg/dl increased to 2.6 mg/dl 2 months after he was put on nivolumab. At this point, his nivolumab was stopped with the diagnosis of ICPI-related AKI, and he was referred to the onconephrology clinic. Before a kidney biopsy was performed, other notable laboratory findings included a urine protein to creatinine ratio of 0.8 g/g, urinalysis showed 5–20 RBC/high-power field (HPF), and 20 white blood cells (WBC)/HPF, and urine culture was negative. A kidney biopsy was subsequently performed and evaluated, which showed ATI superimposed on mild background chronic changes of the kidney parenchyma (minimal global glomerulosclerosis, mild tubular atrophy, interstitial fibrosis, and no vascular sclerosis). His nivolumab, part of neoadjuvant treatment before surgery, was stopped after AKI and was not resumed later. In follow-up, kidney function did not recover, and serum creatinine level stayed stable at 3 mg/dl 4 months after discontinuation of the ICPI. The clinicopathologic correlation could not determine an etiologic etiology for the ATI.

Patient 2
A 68-year-old Black woman was referred for onconephrology consultation with AKI and a medical history of surgically unresectable poorly differentiated metastatic adenocarcinoma of the gallbladder, hypertension, and diabetes mellitus. The patient was initially treated with gemcitabine and capcitabine for 6 months, which was later switched to a combination of nivolumab and ipilimumab, which was continued for 1 year before presentation. Throughout her treatment with combination ICPI, the patient was also diagnosed with secondary adrenal insufficiency, which

1Division of Nephrology and Hypertension, University Hospitals Cleveland Medical Center, Cleveland, Ohio
2Division of Nephrology, Hypertension and Renal Transplant, University of Florida, Gainesville, Florida
3Department of Pathology, Columbia University Medical Center, New York, New York

Correspondence: Dr. Arash Rashidi, University Hospitals Cleveland Medical Center, 11100 Euclid Ave., Cleveland, OH. Email: arash.rashidi@uhhospitals.org

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was well controlled with oral hydrocortisone, allowing the continuation of ICPI therapy. Follow-up imaging confirmed continued partial response to malignancy. However, ICPI was withheld due to AKI with a rise in serum creatinine from 0.6 mg/dl to 2.2 mg/dl over a period of 2 weeks. The patient had intermittent diarrhea, and initially, there was concern the AKI was related. Kidney function failed to improve with outpatient isotonic intravenous fluid resuscitation, but resulted in significant anasarca, so the patient was referred to onconephrology for further evaluation, with a presumed diagnosis of ICPI-related AKI. Other notable laboratory findings before a kidney biopsy being performed included a urine dipstick negative for proteinuria, and urinalysis was negative for the presence of RBCs or WBCs. A kidney biopsy was subsequently performed and evaluated, showing severe vascular sclerosis and associated mild chronic changes, including minimal global glomerulosclerosis, mild tubular atrophy, and interstitial fibrosis. ICPI therapy was resumed within 2 weeks after the kidney biopsy, and kidney function returned to baseline within 1 month after the kidney biopsy.

**Patient 3**

A 48-year-old Asian man with a medical history of metastatic clear cell kidney cell carcinoma (with sarcomatoid and rhabdoid features), diabetes mellitus, hypertension, hyperlipidemia, and obesity presented with increasing creatinine. The patient was post a radical nephrectomy, and 4 months after resection, he presented with malignant ascites (which was drained). The patient was started on dual therapy with ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) and received four cycles, and there was evidence of shrinkage of most metastatic lesions. Then 8 months after resection, monotherapy with nivolumab was continued at 3 mg/kg every 4 weeks. Over 4 months from the start of monotherapy with nivolumab, kidney function was noted to decrease with serum creatinine increasing from a baseline of 1.6 mg/dl to 3.13 at the time of the kidney biopsy. Before a kidney biopsy was performed, other notable laboratory findings included BUN of 21 mg/dl, serum albumin of 3.9 g/dl, urine protein to creatinine ratio of 0.15 g/g, and urinalysis showed six RBCs/HPF and one WBC/HPF. The kidney biopsy revealed ATI superimposed on diffuse secondary/adaptive glomerulosclerosis, severe tubular atrophy, interstitial fibrosis, and moderate vascular sclerosis (Figure 1, C and D). The clinicopathologic correlation could not determine a definitive etiology for the ATI. Subsequent to the biopsy findings, monotherapy with nivolumab was continued. The clinical course has not significantly changed, and 4 months after the kidney biopsy, the serum creatinine had minimally decreased to 2.52 mg/dl.

There were three more patients with AKI and clinical diagnosis of ICPI-related AKI who were empirically treated.
Discussion

With the more readily available and widespread use of ICPI in treating different types of malignancies, it is now well described that these medications affect the kidneys as potential irAEs. Although the most common type of kidney-related irAEs associated with these medications is AIN, other etiologies, such as renal tubular acidosis, minimal change disease, glomerulonephritis, and even vasculitis, have been reported (10–12).

Current guidelines do not necessarily include performing a kidney biopsy for the diagnosis of ICPI-related AKI. The American Society of Clinical Oncology (ASCO) guidelines on the management of irAEs in patients treated with ICPI suggest a nephrology consult for stage ≥2 AKI. This guideline does not support a kidney biopsy if other causes of AKI can be excluded clinically on clinical grounds (13). It also recommends withholding Immune Check Point Inhibitor (ICPI) and oral corticosteroids for patients whose symptoms persist for >1 week. For those developing grade 3 and 4 complications, CPI is discontinued, and a more intensive corticosteroid regimen is suggested. Gürgarts et al. reported kidney biopsy should be considered only when there is a high clinical suspicion for ICPI-related AKI along with nephrotic range proteinuria (>3 g/day proteinuria), oliguria, or dysmorphic RBC in the urine, or when there is an incomplete response to empirical treatment with corticosteroids (10). In two other experts’ opinions, Perazella (11) and Herrmann (12) also suggest kidney biopsy in the setting of high-grade proteinuria, hematuria, WBC/RBC granular cast, and renal tubular acidosis and AKI stage 2/3.

As opposed to expectant ICPI-associated AIN being seen in the biopsy, two of the presented patients revealed a primary diagnosis of ATI, and one patient showed primarily prominent vascular sclerosis. Overall, the background chronic changes of the kidney parenchyma in the described patients were generally mild in severity as characterized by the degree of globally sclerosed glomeruli, tubular atrophy, and interstitial fibrosis, and vascular sclerosis (except for Patient 2, with respect to vascular sclerosis). For all three patients by light, immunofluorescence, and electron microscopy, there was no evidence of interstitial nephritis, paraprotein deposition, immune complex deposition, an active arteriolitis, or a primary podocytopathy. A definitive etiology for the three patients with biopsies showing ATI could not be determined: in general toxic and/or ischemic etiologies need to be considered when encountering ATI. However, in these complex patients with comorbidities, facing numerous medications/therapies, and occasionally bearing significant tumor burden, the development of ATI and AKI is likely multifactorial.

Accurate diagnosis of ICPI-associated AKI is imperative because the empirical discontinuation of the ICPI and administration of potentially harmful corticosteroids on the basis of the assumption of an underlying AIN could be deleterious to a patient. Although AIN is the most common kidney lesion associated with ICPI, patients with cancer could potentially develop AKI because of a wide variety of etiologies, such as exposure to multiple nephrotoxic medications, paraneoplastic kidney damage, and hemodynamic instability. Although some clinical and laboratory findings might provide clues for the clinical diagnosis of AIN in the setting of ICPI, they may not be reliable. Tubular-range proteinuria and an inflammatory urine sediment (pyuria and/or leukocyte casts and hematuria) occur in only approximately one half and two thirds of patients, respectively. Besides, the patient might have proteinuria and pyuria because of reasons other than ICPI-related AKI.

In this study, we presented three patients with AKI in detail and three other patients in brief, who were clinically diagnosed with ICPI-related AIN, but a subsequent kidney biopsy proved otherwise. Not all of them fulfilled the

Table 1. Patients with clinical diagnosis of immune checkpoint inhibitor–related AKI who were started on systemic steroid and later a kidney biopsy showed acute tubular necrosis

| Age, yr | Sex | Type of Malignancy | Immune Checkpoint Inhibitors | Other Treatments | Biopsy Result | Baseline Creatinine, mg/dl | Creatinine Level before Biopsy, mg/dl | Steroid before Biopsy (Number of Doses before Biopsy) |
|---------|-----|-------------------|-----------------------------|-----------------|--------------|--------------------------|-----------------------------------|--------------------------------------|
| 64      | M   | Lung adenocarcinoma | Pembrolizumab               | Carboptin/pemetrexed/SGN-B6A          | ATI          | 1.1                        | 14.2                              | Methylprednisone 1 g (two doses)       |
| 63      | M   | Non-small cell lung cancer | Pembrolizumab/pemetrexed/atezolizumab | Carboptin/pemetrexed/bevacizumab | ATI          | 0.9                        | 2.4                               | Prednisone 60 mg (10 doses)          |
| 63      | M   | Melanoma          | Nivolumab/Ipilimumab        | None             | ATI          | 0.9                        | 6.7                               | Methylprednisone 160 mg (two doses)  |

M, male; ATI, acute tubular injury/necrosis.
\( ^{a} \)SGN-B6A is an antibody-drug conjugate that targets integrin beta-6.
\( ^{b} \)There was no improvement in kidney function after 10 days of prednisone and after that, the patient was referred to the nephrologist.
suggested expert opinion criteria for a kidney biopsy. Kidney biopsy not only helped achieve an accurate diagnosis, but helped to prevent unnecessary interruption of immunotherapy and avoided potentially toxic corticosteroid therapy. Given the lack of specific clinical features for ICPI-related AKI and the importance of the correct diagnosis, kidney biopsy should be strongly considered when feasible, particularly when a plausible alternative etiology for AKI exists. We suggest a kidney biopsy when clinical work-up does not reveal any definite explanation for AKI in the setting of ICPI, even in the absence of the suggested expert opinion criteria for a kidney biopsy, such as heavy proteinuria, hematuria, pyuria, or WBC/RBC cast. Accurate diagnosis of AKI can guide therapy and potentially improve the overall outcome in these patients.

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A. Rashidi reports receiving speakers bureau from Otsuka Pharmaceutical. All remaining authors have nothing to disclose.

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Author Contributions
A. Rashidi was responsible for the data curation, provided supervision, and wrote the original draft; A. Rashidi, M. Sekulic, and C. Shah were responsible for the investigation, and reviewed and edited the manuscript.

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