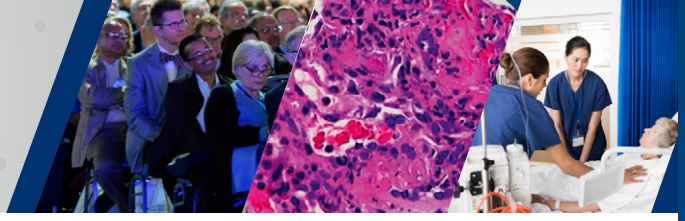

AKI in Patients Receiving Immune Checkpoint Inhibitors

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Introduction

A patient with nonsmall cell lung cancer treated with nivolumab for the past 5 months developed an increase in serum creatinine (1.2–3.6 mg/dl). Urinalysis/urine microscopy demonstrated 1+ protein with sterile pyuria but no casts. The oncologist discontinued nivolumab and wants to administer corticosteroids. Nephrology is consulted to provide recommendations.

Tumor Microenvironment and Immune Checkpoints

Cancer cells within the tumor microenvironment resist host immune system eradication primarily by evading detection and destruction by tumor-infiltrating lymphocytes. They survive by using the normal host immune system regulatory pathways by expressing inhibitory ligands, such as programmed cell death protein ligand-1, that suppress T cell activation (1,2). The immune checkpoint inhibitors resist cancer-evasive mechanisms by allowing host immune cells to identify and eliminate malignant cells (3,4). Immune checkpoint inhibition of negative costimulatory signaling through cytotoxic T lymphocyte–associated protein-4 (CTLA-4) or programmed cell death protein-1 (PD-1)/programmed cell death protein ligand-1 on T cells restores tumor-directed T cell responses and anticancer effects. Food and Drug Administration–approved drugs include CTLA-4–blocking antibodies (ipilimumab/tremelimumab) and PD-1–blocking antibodies (nivolumab/pembrolizumab). Increasing use of immune checkpoint inhibitors with unrestrained T cell activation has seen the emergence of immune-related adverse events, including AKI (3,4).

Immune-Related Adverse Effects

Immune-related adverse events occur in >50% of patients treated with these drugs; grade 3 (severe)/4 (life-threatening) toxicities develop in approximately 20% of patients. Various organs are affected; however, skin, gastrointestinal tract, and endocrine are most commonly involved (5). Immune-related adverse events affecting the kidney are less common: 1%–2% with monotherapy and 4.9% with combined immune checkpoint inhibitors (6), although this is likely an underestimate. Various types of kidney injury have been described in the literature with these drugs; AKI due to acute interstitial nephritis (AIN) is most common (3,4). A smaller number of glomerular lesions and electrolyte abnormalities are also described (3,4).

Immune Checkpoint Inhibitor–Associated AKI

Four patient series best illustrate the nephrotoxicity of the immune checkpoint inhibitors. Six cases of biopsy-proven AIN from either nivolumab or pembrolizumab ($n=1$, combination therapy) were described by Shirali *et al.* (7) in patients developing AKI approximately 3–16 months after drug exposure. All patients were previously on either an non-steroidal anti-inflammatory drug or a proton pump inhibitor, drugs commonly associated with the development of AIN. Other organ immune-related adverse events were seen in only two of six patients, and four of six had pyuria. Drug was discontinued in five patient, and corticosteroids were administered to five patients. Five had full kidney recovery, and one had partial kidney recovery. Rechallenge in one patient was associated with recurrent AKI.

Cortazar *et al.* (6) reported 13 patients with nephrotoxicity at approximately 1–6 months after immune checkpoint inhibitor monotherapy (ipilimumab, nivolumab, or pembrolizumab) or combination therapy (ipilimumab/nivolumab) exposure. Eight were receiving other drugs potentially associated with AIN before immune checkpoint inhibitor exposure. Eight patients had other organ immune-related adverse events before AKI, and nine had pyuria on urinalysis. Twelve patients had AIN, whereas one had thrombotic microangiopathy on kidney biopsy. Immune checkpoint inhibitors were discontinued in 12 patients, and 11 received corticosteroids. Kidney recovery in ten patients with AIN who were treated with corticosteroids was complete in two and partial in seven (two untreated patients with AIN did not recover kidney function, and one was dialysis dependent). Drug rechallenge in two patients was not associated with AKI.

Izzedine *et al.* (8) reported kidney biopsy findings in 12 patients treated with pembrolizumab who developed AKI and/or proteinuria after 1–24 months. Urine studies revealed pyuria and hematuria in four

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and three patients, respectively. Acute tubular injury was observed in five of the biopsies and AIN was observed in four of the biopsies for AKI, whereas minimal change disease was noted in two patients with proteinuria (one had acute tubular injury/minimal change disease). Pembrolizumab was discontinued in ten of 12 patients, and seven received corticosteroids. Partial kidney recovery occurred in most but not all patients. Reintroduction of pembrolizumab in a patient with AIN was associated with recurrence of AKI.

Mamlouk *et al.* (9) identified immune checkpoint inhibitor–induced AKI in 16 patients over a 10-year period. Median time from drug to AKI was 14 weeks; it was longer with PD-1 inhibitors and shorter with CTLA-4 inhibitors. Nonkidney immune-related adverse events were noted in eight patients. Pyuria and hematuria were present in 12 and eight patients, respectively. Tubular proteinuria was observed in ten of 16 patients, whereas three patients with glomerular lesions had nephrotic proteinuria. AIN was noted on 14 of 16 biopsies as either the predominant finding ($n=5$) or interstitial inflammation associated with concomitant glomerular pathology ($n=9$). One patient had acute tubular injury, and the other had chronic tubulointerstitial fibrosis. Immune checkpoint inhibitors were discontinued in 15 of 16 patients, and corticosteroids (with or without other immunosuppression) were used in 14 of 16 patients. Three of five patients with AIN achieved partial kidney recovery, and eight of nine patients with AIN-GN had complete or partial recovery; three patients died.

AKI is common in patients with cancer due to ischemic/nephrotoxic tubular injury, drug-induced AIN, various glomerular injuries, crystalline nephropathy, and urinary obstruction. Patients with cancer and AKI should undergo a careful evaluation for potential causes; sometimes, kidney biopsy is required. Along the same line, AIN is only one of the possible causes of AKI in patients with cancer receiving immune checkpoint inhibitors. These patient series stress the importance of performing a careful clinical evaluation, which includes kidney biopsy to establish the correct diagnosis. The slower development of AKI with immune checkpoint inhibitors may sometimes be a clinical clue, but it may be missed in the outpatient setting. The presence or absence of other immune-related adverse events does not always predict what the underlying kidney lesion will be. The same is true for urinalysis/urine sediment findings, although the presence of sterile pyuria/leukocyte casts along with other immune-related adverse events may represent AIN.

Our experience with patients developing immune checkpoint inhibitor–associated AKI is similar—many have causes other than AIN. No clinical or laboratory features reliably differentiate AIN from acute tubular injury in these patients. Yet, on the basis of American Society of Clinical Oncology guidelines (10), oncologists commonly discontinue the immune checkpoint inhibitor and administer corticosteroids when AKI develops without pursuing an appropriate evaluation or tissue diagnosis. In our opinion, this is not the proper approach in these patients and represents suboptimal clinical practice. For example, patients with acute tubular injury will lose the benefit of continued immune checkpoint inhibitor treatment and inappropriately receive corticosteroids. One might also predict that immune checkpoint inhibitor retreatment will be less likely to cause recurrent AKI in patients with acute tubular injury unless these drugs are shown to be directly nephrotoxic. Thus, obtaining the correct diagnosis will change patient management, and kidney biopsy should be performed as long as it can be done safely.

Approach to Immune Checkpoint Inhibitor–Associated AKI

Patients with stage 1 AKI can be monitored and evaluated for causes, such as volume depletion and contrast/non-steroidal anti-inflammatory drug–related kidney injury. Those with higher AKI stages should have a nephrology consultation to evaluate for the cause of AKI and consideration for kidney biopsy. As seen in the published literature, absence of immune-related adverse events does not exclude AIN. Although sterile pyuria and/or leukocyte casts suggest an inflammatory kidney lesion, these findings lack both sensitivity and specificity for AIN. Thus, severe AKI without an obvious cause would benefit from kidney biopsy to define the underlying lesion. This information will help guide therapy, because immune checkpoint inhibitor–induced AIN is generally corticosteroid responsive, whereas other lesions are not.

In the patient described, nephrology recommended kidney biopsy to define the patient's cause of AKI. Acute tubular injury was noted with no glomerular or interstitial pathology. Kidney function recovered without corticosteroids over the next 10 days, and nivolumab was restarted.

Finding non-AIN lesions, as in our patient, reduces unnecessary and potentially harmful corticosteroid exposure in patients with cancer and may permit continued use of immune checkpoint inhibitors. In addition to corticosteroids, patients with biopsy-proven AIN should have any other drugs known to be associated with AIN removed. We recommend intravenous pulse-dose corticosteroids in patients with stage 3 AKI (without contraindications) followed by 1 mg/kg prednisone and only oral prednisone (1 mg/kg) for less severe AKI. Corticosteroid may need to be continued for longer periods, such as up to 6 months, with regular monitoring on corticosteroid taper/discontinuation. In patients with stage 2/3 AKI from AIN, the immune checkpoint inhibitor should probably be discontinued. Re-exposure to immune checkpoint inhibitors in patients who developed AKI is an unresolved issue. It may be reasonable to reinitiate immune checkpoint inhibitors if AIN responded well to corticosteroids or if acute tubular injury was found on biopsy, particularly in patients with limited options. However, discussion with oncology/nephrology is required to assess the risks and benefits of restarting immunotherapy. Reinitiating immune checkpoint inhibitors with low-dose corticosteroids may be an option but has not been studied.

Figure 1 outlines our approach to AKI that develops in patients with cancer receiving immune checkpoint inhibitors.

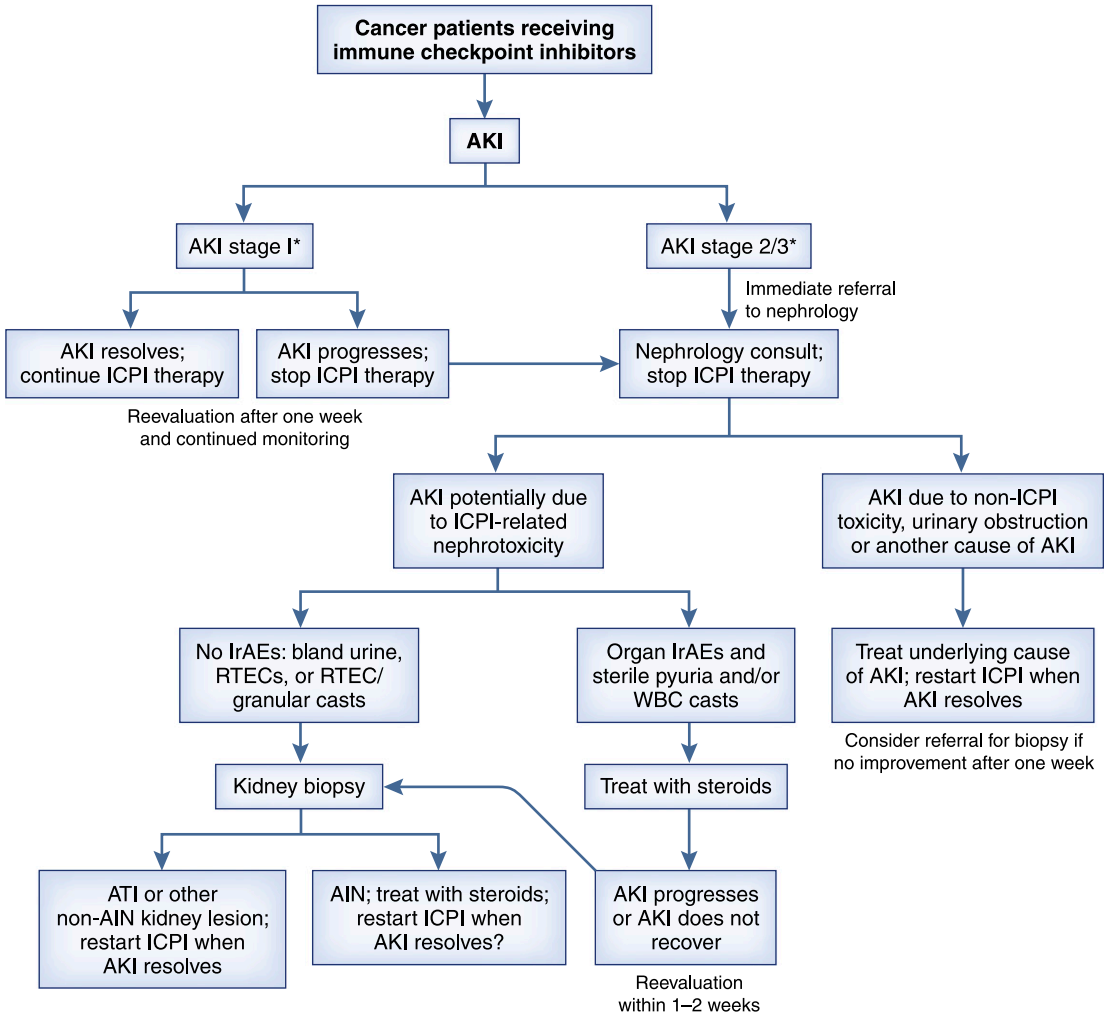

Figure 1. | **Algorithm for management of patients with cancer and AKI in the setting of immune checkpoint inhibitor therapy.** AIN, acute interstitial nephritis; ATI, acute tubular injury; ICPI, immune checkpoint inhibitor; IrAE, immune-related adverse effect; RTEC, renal tubular epithelial cell; WBC, white blood cell. *Kidney Disease Improving Global Outcomes AKI staging definition.

Disclosures

None.

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