Introduction
For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the main text of this article (Mark A. Perazella and Michael Choi, comoderators).

Patient History
A 70-year-old man with autosomal dominant polycystic kidney disease received a kidney transplant with alemtuzumab induction followed by steroid avoidance immunosuppression with tacrolimus and mycophenolic acid. Seven years later, the patient noticed a pruritic, nonbleeding, nonhealing sore over his left temple. On examination, he had diffuse actinic lesions over exposed skin and a 2-cm lesion with heaped up edges and surrounding erythema. Biopsy showed squamous cell carcinoma.

Question 1
Which statement about dermal squamous cell cancer after transplant is correct?

A. Dermal squamous cell cancer is less common than basal cell cancer.
B. Conversion to mammalian target of rapamycin (mTOR) inhibitor therapy increases cancer risk.
C. Risk factors for squamous cell cancer include older age and prolonged immunosuppressive drug exposure.
D. Preventive strategies are less effective than immunosuppression reduction.

Discussion of Question 1
The correct answer is C. Cancer risk increases significantly following organ transplant. Unlike in the general population, squamous cell cancer is more common than basal cell cancer. Conversion to mTOR inhibitor–based therapy may modestly reduce subsequent squamous cell cancer. Prolonged immunosuppression and increased age increase risk. Preventive strategies and minimization of immunosuppression are both important in promoting better outcomes.

Clinical Course
Following surgery, the patient received external beam radiation. Six months later, a positron emission tomography scan showed enhanced activity in the right clavicle treated with excision and radiation therapy. One year later, a third lesion was detected in the right axilla with palpable axillary lymph nodes. Positron emission tomography scan was positive, and lymph node biopsy confirmed metastatic squamous cell cancer. Treatment with an immune checkpoint inhibitor (nivolumab) was recommended.

Question 2
Which of the following is associated with immune checkpoint inhibitor therapy?

A. AKI is the most common complication.
B. Immune-complex GN is more common than acute interstitial nephritis.
C. An allograft biopsy is usually indicated in the workup if a patient treated with an immune checkpoint inhibitor develops AKI.
D. Graft loss may occur in 40%–50% of patients treated with immune checkpoint inhibitors.

Discussion of Question 2: Immune Checkpoint Inhibitors and Adverse Events
The correct answer is D. To understand why this is correct, it is necessary to appreciate how immune checkpoint inhibitors exercise their antitumor effect. Briefly, malignant cells evade tumor immune surveillance mechanisms by activating immune checkpoint pathways that suppress antitumor activity. The immune checkpoint inhibitors suppress these negative costimulatory pathways that mitigate T cell activity and support recognition of the tumor with
T cell activation, resulting in the elimination of malignant cells (1). The immune checkpoint pathways are responsible for self-tolerance and polymorphisms in cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death-1 ligand (PD-L1) genes that are linked to autoimmune disease.

Immune checkpoint inhibitors (ICIs) have been approved by the Food and Drug Administration since 2011 under the accelerated approval program. The first agent approved was ipilimumab (an antibody to CTLA-4), a downregulatory costimulatory molecule in T cells. Nivolumab and pembrolizumab belong to another class of immune checkpoint inhibitors and are antibodies to the PD-1 receptor on activated T cells, blocking the interaction with PD-L1, which is overexpressed on tumor cells. Finally, a third class consists of atezolizumab, durvalumab, and avelumab, monoclonal antibodies to PD-L1. Immune checkpoint inhibitors have been used for treatment of many cancers, including B cell lymphoma, cervical cancer, gastric cancer, hepatocellular cancer, Hodgkin lymphoma, melanoma, non-small cell lung cancer, and urothelial carcinoma. Although a combination of targeting both CTLA-4 and PD-1/PD-L1 interactions is under study, the latter approach may be more effective (reviewed in ref. 2).

Immune checkpoint inhibitor therapy is associated with immune-related adverse events in 70%–90% of patients (1). These events are mediated by disrupting the T cell tolerance or anergy typically induced by tumor cells, resulting in autoimmunity. The most common immune-related adverse events are skin disorders (seen in 50%–70% of patients), and they include vitiligo, rash, and erythema. Gastrointestinal disorders, occurring in 30%–40% of patients, include diarrhea from enteritis or colitis. Hepatotoxicity occurs in 5%–10% of treated patients. Endocrinopathies, including diabetes, thyroiditis with hypothyroidism, and hypophysitis, occur in 10% of patients.

Immune checkpoint inhibitor–associated AKI was once believed to be uncommon. However, in part because of differences between the definition of AKI used by the National Cancer Institute Common Criteria for Adverse IIs, it may have been under-recognized and under-reported (2). The clinical features of immune checkpoint inhibitor–associated AKI are not specific (3), although as first reported in a patient series of 13 patients, the characteristic pathology findings are of interstitial nephritis seen in 12 of 13 patients, with 1 patient with thrombotic microangiopathy (4). A more comprehensive single-center series of immune checkpoint inhibitor–treated patients demonstrated an overall AKI incidence of 17%, but only 3% of all patients were thought to have immune checkpoint inhibitor–related AKI (5). The severity of AKI in these patients was variable; four patients required hemodialysis. The median time from immune checkpoint inhibitor therapy was 91 days (interquartile range, 21–245 days). Proteinuria ranged from 0.12 to 0.98 g/g. Of 12 patients with acute interstitial nephritis, 10 received corticosteroid treatment, resulting in full or partial improvement in 9 patients. Two untreated patients did not improve. Further results from a multicenter study of 138 patients with immune checkpoint inhibitor–associated AKI echoed the findings of earlier patient series, noting a variable timing of onset with findings of subnephrotic proteinuria in the majority of patients and about 50% having pyuria (6). In those patients with a kidney biopsy, tubulointerstitial nephritis was the dominant lesion seen in 93% of patients. Most patients received steroid treatment, and although most had a complete or partial recovery, 15% did not recover kidney function. Combination therapy with a CTLA-4 antibody and anti–PD-1/PD-L1 antibodies, concomitant proton pump inhibitor use, and a lower baseline eGFR independently increased risk of AKI. Interestingly, some patients with AKI were rechallenged with an immune checkpoint inhibitor, the majority with the same agent, and only 23% had recurrent AKI.

Kidney immune-related adverse events have been classified by the American Society of Clinical Oncology into four grades of severity (7). Grade 1 toxicity, an increase in creatinine by 0.3 mg/dl or 1.5–2.0 times above baseline, should prompt temporary cessation of immune checkpoint inhibitor treatment and review of other potential causes of AKI. The guidelines suggest discontinuation of immune checkpoint inhibitor therapy and using prednisone 0.5–1 mg/kg per day for grade 2 toxicity (increase in creatinine from two to three times baseline) and increasing this to 1–2 mg/kg per day if there is no improvement or for grade 3 (increase in creatinine above three times baseline or >4.0 mg/dl) or grade 4 toxicity (requirement for dialysis or life-threatening complications). Steroids should be slowly tapered over several weeks. Addition of immunosuppression can be considered for high-grade toxicity not responsive to therapy. A nephrology consult is recommended for grade 2 immune checkpoint inhibitor–associated AKI and above. Surprisingly, these guidelines do not recommend a kidney biopsy when other causes of AKI can be excluded on clinical grounds. However, given the nonspecific clinical presentation of immune-related adverse events in the kidney, a biopsy may shed light on diagnosis and prognosis, and it may avoid unnecessary steroid exposure (6).

**Immune Checkpoint Inhibitors in Cancer Treatment of Kidney Transplant Recipients**

Clinical trials have excluded organ transplant recipients due to concerns for potential rejection mediated by T cell activation. The lack of treatment options for advanced cancer has led to cautious use of immune checkpoint inhibitors in this population. To date, there are patient reports and series with variable rejection rates and allograft outcomes (8–11). Of 44 kidney transplant recipients treated with immune checkpoint inhibitors in one “systematic” review, 18 developed rejection (11); 33% of these rejections were classified as acute cellular rejection, 17% were mixed cellular and antibody mediated, and 50% were unspecified. Of those with rejection, 83% ultimately developed graft failure, and 44% died, with only modest tumor response. A report from the MD Anderson Cancer Hospital identified 23 patients with kidney transplants treated with checkpoint inhibitors, with rejection seen in 48% of patients with similar frequency between anti–CTLA-4 or anti–PD-1 inhibitors (8). Similar rates of rejection were reported by De Bruyn et al. (9).

Questions remain regarding the use of these agents in transplant recipients. These include the risk of rejection with different immune checkpoint inhibitors. Although combination
therapy is associated with higher rates of native allergic interstitial nephritis, can we presume that transplant rejection rates will similarly be higher (6)? Can adverse events, including rejection, be mitigated by judicious adjustment of immunosuppression? Current clinical practice is to reduce immunosuppression to a minimum, often to corticosteroid monotherapy, but approaches that include mTOR inhibitors may be useful. When faced with death by cancer or allograft loss, a frank discussion must be held between the patient, transplant physician, and oncologist to balance expected survival with quality of life. In this reported case, the patient succumbed to his cancer after one course of treatment.

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