Immune Check Point Inhibitor–Associated Endothelialitis

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Shane A. Bobart[1], Itunu Owoyemi[1], Joseph Grande[2], Nelson Leung[1] and
Sandra M. Herrmann[1]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; and [2]Division of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence: Sandra M. Herrmann, 200 First Street SW, Rochester, Minnesota 55901, USA. E-mail: herrmann.sandra@mayo.edu

INTRODUCTION

Immune checkpoint inhibitors (ICPis) are humanized monoclonal antibodies that are now commonly used to harness the immune system's ability to fight hematological and solid organ malignancies.[1,2] However, when overactivation of the immune system occurs, multiple organs can be affected, particularly with the immune phenomenon termed immune-related adverse events (irAEs).[3] Acute kidney injury (AKI), specifically, acute interstitial nephritis (AIN), is the most common renal irAEs reported.[4,5] As a result, some current practice guidelines suggest empiric treatment with corticosteroids if the urinalysis and clinical course is consistent with ICPi-AKI. When there is worsening renal dysfunction or evidence of glomerulonephritis on urine sediment, biopsy is indicated.[2,6]

Noninvasive testing is not specific in diagnosing the potential renal lesion from ICPi-AKI, and several other renal lesions are being discovered as the population of patients treated with ICPis expands. Recently, a case series reported 3 cases of renal vasculitis and 1 case of pauci-immune crescentic glomerulonephritis (GN).[1] In addition, a multicenter cohort of patients treated with ICPi therapy demonstrated renal biopsy findings of minimal change disease with acute tubular injury, anti-neutrophil cytoplasmic antibody–negative pauci-immune crescentic GN, anti–glomerular basement membrane disease, and C3GN. We report a case of renal endothelialitis in the setting of treatment with cemiplimab, an intravenous programmed cell death–1 receptor monoclonal antibody recently approved for treatment of programmed cell death–1 receptor advanced invasive squamous cell carcinoma.[7]

CASE PRESENTATION

An 87-year-old Caucasian man with a history of congestive heart failure with preserved ejection fraction, coronary artery disease status after coronary artery bypass grafting, type 2 diabetes mellitus, chronic kidney disease stage 3b, baseline serum creatinine (SCr) 1.6 mg/dl, polycythemia vera (JAK2617F mutation positive on aspirin and hydroxyurea), and prostate and bladder carcinoma status postresection was diagnosed with metastatic squamous cell carcinoma. He underwent Mohs surgery and radiation and in the setting of positron emission tomography scan findings of residual left preauricular metabolically active disease, subsequently started treatment with i.v. cemiplimab 350 mg, a programmed cell death protein 1 (PD-1) inhibitor. At the time of cemiplimab initiation, SCr was 1.67 mg/dl.

Three weeks later, he presented for follow-up prior to his second dose of cemiplimab. At that visit, blood pressure was 125/48 mm Hg, with laboratory test results notable for hemoglobin 13.0 g/dl, SCr 2.45 mg/dl, mildly elevated liver function test results, and urinalysis showing 1 to 3 white blood cells per high-power field (WBC/hpf), granular casts, renal epithelial cells, no hematuria, with 1.5 g estimated 24-hour proteinuria. He was started on empiric prednisone 80 mg daily for suspected renal irAE and referred to onco-nephrology with the addition of prophylactic famotidine and trimethoprim–sulfamethoxazole. Cemiplimab treatment was resumed on resolution of AKI while the patient remained on prednisone, tapered by 10 mg per week, and there was no extrarenal irAE identified. Approximately 4 weeks later, the patient presented for follow up in the onco-nephrology clinic, at which time his SCr was back to baseline of 1.67 mg/dl on 40 mg of
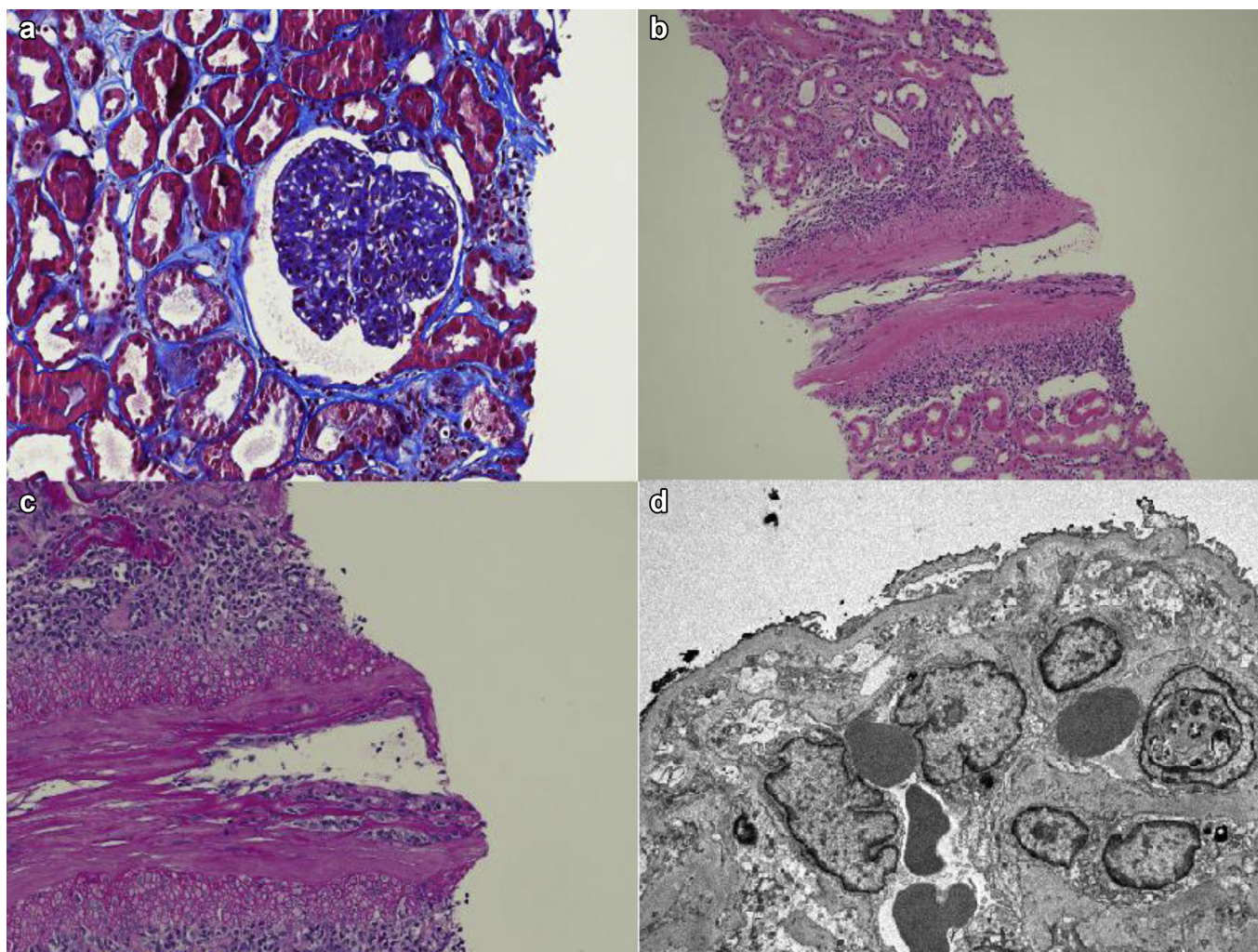
Figure 1. (a) Masson trichrome stain showing diffuse mesangial matrix expansion compatible with diabetic glomerulosclerosis. (b) Hematoxylin and eosin stain of an arcuate size artery showing moderate endothelialitis without mural necrosis (original magnification ×100). (c) Hematoxylin and eosin stain showing endothelialitis of an arcuate-sized artery (original magnification ×200). There is associated interstitial inflammation adjacent to the artery. (d) Electron microscopic image showing segmental double contouring of the glomerular capillary basement membrane.

prednisone. At that time, he received his third dose of cemiplimab.

One week after this visit, the patient developed acute blood loss anemia, and famotidine was switched to a proton pump inhibitor for suspected gastrointestinal bleeding with occult positive stools. When prednisone was at 10 mg daily, the patient was seen again for follow-up; he had decided to stop steroids because of their side effects of fluid retention and poor sleep, and his SCr was 1.94 mg/dl. A positron emission tomography–computed tomography scan at that time showed no evidence of metastatic squamous cell carcinoma. He was requested to return the following week for follow-up; he presented with volume overload and AKI with SCr 2.24 mg/dl, prompting admission, and cemiplimab was held.

Workup was pertinent for urinalysis with 4 to 10 WBCs/hpf, 3-10 RBCs/hpf, nondysmorphic, 1 to 3 renal epithelial casts, and protein/Cr ratio of 0.3. Anti-

neutrophil cytoplasmic antibody panel and anti–glomerular basement membrane test results were negative. C3 was low at 56 (75–175 mg/dl) and C4 normal at 22 (14–40 mg/dl). A renal biopsy was performed, which revealed diffuse diabetic mesangial sclerosis (Figure 1a) with a lymphocytic interstitial infiltrate (Figure 1b and c). An arcuate-sized artery showed moderate endothelialitis, without fibrinoid necrosis (Figure 1b and c). Immunofluorescence was positive for 1+ GBM IgG and 2+ mesangial IgM. Double contouring of the capillary loop basement membrane was noted on electron microscopy (Figure 1d). A diagnosis of interstitial nephritis with endothelialitis on a background of diabetic nephropathy was made. Steroid therapy was reintroduced at a pulse dose of 500 mg methylprednisone for 3 days with a planned taper to 60 mg of oral prednisone. Hemodialysis was initiated because of anuria and a progressive rise in creatinine. Due to concern for irAE refractory to

Table 1. Glomerular/non-AIN lesions seen with checkpoint inhibitors

Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Lupus nephritis
IgA nephropathy
C3 glomerulopathy
Pauci-immune clomerulonephritis
Thrombotic microangiopathy
Anti–glomerular basement membrane disease
Renal vasculitis
Endothelialitis
Teaching point: Although AIN remains the most common biopsy finding in ICPi-AKI, several other lesions can be found. Kidney biopsy remains a useful tool in this setting.

AIN, acute interstitial nephritis; ICPi-AKI, immune checkpoint inhibitor–acute kidney injury.

pulse steroids and concern about an ongoing T cell–driven process, the patient received 2 doses of anakinra. In the setting of worsening comorbidities and quality of life, the patient declined further dialysis and immunosuppression, opted for comfort measures, and subsequently died under hospice care.

DISCUSSION

The most common renal lesion found in the setting of ICPi-AKI is AIN. However, as ICPi use has increased, a wide variety of lesions are being reported. We demonstrate that vascular lesions such as endothelialitis can occur as a result of ICPi use in a native kidney, highlighting the importance of renal biopsy in this setting. From a renal perspective, endothelialitis (intimal arteritis/endarteritis) is commonly a lesion of the renal allograft, with acute cellular rejection being the most common etiology, However, it can be seen in the native kidney in cases of thrombotic microangiopathy and even artheroembolic disease.[8] However, we are unaware of any prior reports of endothelialitis occurring in the setting of ICPi use.

Cemiplimab, is an intravenous PD-1 inhibitor that is dosed at 350 mg every 3 weeks currently approved for the treatment of metastatic cutaneous squamous cell carcinoma.[7] From a pharmacokinetic perspective, it has a fairly small volume of distribution (5.3 L), a half-life of 19 days, and takes 16 weeks to achieve steady-state pharmacodynamics. Of note, cemiplimab, and other PD-1 inhibitors are not cleared by the liver or kidney but rather by proteolytic degradation, which appears to be related to the extent of tumor burden.[2] As a result, even after discontinuation, the active drug is still present, highlighting the delay of development of AKI weeks to months after treatment in our case and that found in a recent multicenter study.[5]

Recently, a study with the largest known cohort of patients with ICPi-AKI was published, outlining clinical features and outcomes of these 138 patients. A total of 60 of 138 patients (43%) underwent renal biopsy, for which 56 of 60 (93%) showed the expected findings of acute tubulointersitial nephritis.[5] However, 4 patients had other diagnoses, including minimal change disease with acute tubular injury, anti–glomerular basement membrane disease, anti-neutrophilic cytoplasmic autoantibody–negative pauci-immune crescentic GN and C3GN. To further support the widening spectrum of renal pathology, a recent case series noting 4 cases of renal vasculitis and pauci-immune GN were described.[1] Our case adds to the already growing number of additional renal consequences of ICPi use (Table 1), and importantly, these lesions, together with our case of endothelialitis, would potentially present the clinician with a different management strategy other than just corticosteroid therapy.

As data emerge, several risk factors for ICPi-AKI have been identified, including lower eGFR at initiation, concomitant proton pump inhibitor use and combination ICPi therapy.[5,9] It has been suggested that there ICPi treatment can result in loss of tolerance via activation or reactivation of drug-specific T cells in some patients, which may explain the lower threshold of occurrence of AIN with medications such as PPIs.[5] There have also been reports of statin therapy associated with AIN in very few cases, making it noteworthy to highlight that our patient was also initiated on pravastatin therapy for heart failure exacerbation during hospitalization.

When managing iRAEs, several inflammatory pathways can be targeted, such as tumor necrosis factor–α, interleukin (IL)-6, IL-17, IL-12, IL-23, mTOR, CD-20, and complement. The vast majority of agents that can target these pathways are long acting. If possible, the goal of treatment should be directed toward the underlying mechanism of injury. In our case, this lesion was pauci-immune and lymphocyte predominant. We considered interleukin inhibition as a reasonable target in this case. Tocilizumab has been associated in lower gastrointestinal tract perforation, and our patient already had had a previous episode of guaiac-positive stools. Given the patient's age, comorbidities, and ongoing discussions of goals of care, we opted to treat with an IL-1 inhibitor, anakinira, given its favorable side effect profile and short half-life, in the event that the patient considered comfort measures. Indeed, our patient opted for comfort measures shortly after initiation, precluding further follow-up.

From an outcomes standpoint, the patient initially responded well to treatment with corticosteroids, with SCr returning back to baseline, but then when

re-challenged with cemiplimab, he developed recurrence of ICPi-AKI and subsequently required renal replacement therapy. Concomitant extrarenal irAEs have been shown to be associated with a lower likelihood of renal recovery.[5] Although our patient was not specifically diagnosed with any other irAE, he developed worsening heart failure, fluid overload and atrial fibrillation during his hospitalization. It is possible he may have had additional irAEs; however, no further workup was performed, in keeping with the patient's wishes.

Immune checkpoint inhibitor use is becoming more prevalent, with a variety of agents available for approved indications. As a result, a plethora of lesions other than AIN are being described. We demonstrate that endothelialitis can be added to the spectrum of ICPi-AKI and emphasize the importance of serological workup and kidney biopsy in this growing patient population.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

SAB, IO, JG, NL, and SMH contributed to the design of the study, the analysis of the results, and the writing of the manuscript. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE, AND CONSENT FOR PUBLICATION

The patient's surrogate decision-maker has provided written informed consent for publication.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available to protect individuals' privacy but are available from the corresponding author on reasonable requests.

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