CLINICAL VIGNETTE

Acute Kidney Injury with Pembrozulimab

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Introduction

Over the past decade, immunotherapy, especially immune check point inhibitors have been increasingly used in the treatment of solid and hematological malignancies and have substantially improved the prognosis of patients with advanced malignancy. Acute Kidney Injury (AKI) is very common in patients receiving chemotherapy due to multiple etiology. Immune check point inhibitor- associated acute kidney injury (ICPI-AKI) is an increasingly frequent cause of acute kidney injury (AKI). We present 2 cases of presumed ICPI-AKI related to the commonly used programmed cell death receptor 1 (PD-1) inhibitor Pembrozulimab.

Case Discussion

Case 1 - A 77-year-old man with malignant melanoma to lymph nodes, diagnosed by left parotid biopsy was started on Pembrozulimab single agent chemotherapy. After Cycle 2 he underwent neck dissection with continued monthly Pembrozulimab infusions. He received 11 cycles dosed at 200 mg, every 4 weeks. After the 11th cycle his serum creatinine increased from a baseline of 0.8 mg/dL to peak creatinine of 6.8 mg/dL. He was hospitalized and additional tests included BUN 80 mg/dL, creatinine 6.8, potassium 3.8, and total CO_2 of 19, chloride 106. WBC count was 11.09, hemoglobin 11.6, platelet count 524. Urinalysis showed 14 RBC per microL, 276 WBC per microL. Serum protein electrophoresis, RPR, hepatitis-B surface antigen, HIV were negative and C3 and C4 were normal. Urine albumin creatinine ratio was 42.1 mg, urine eosinophils less than equal to 5%. He was diagnosed with Allergic Interstitial Nephritis (AIN) presumed due to Pembrozulimab and was started on oral Prednisone dosed at 60 mg per day. His serum creatinine gradually improved over the next 4 weeks to 1.49. Given an improvement in his renal function a kidney biopsy was not performed. He was tapered off Prednisone over three months and his serum creatinine remained around 1.4. He was on Pantoprazole 40 mg daily which was continued during his treatment with prednisone. He did not resume treatment with Pembrozulimab.

Case 2 - A 79-year-old female with history of non-small cell lung carcinoma was maintained on Erlotinib, but had progression of disease and switched to Osimertinib. She had further progression and was switched to a combination of Carboplatin, Pemetrexed and Pembrozulimab. Her baseline serum creatinine was 1.0 mg/dL. After her first cycle she developed significant gastrointestinal symptoms and subsequent treatment was Pembrozulimab for 5 cycles, dose 200 mg, every 3 weeks. After the 5th cycle her serum creatinine increased to 4.99 mg/dL. Initial urinalysis showed 50-100 WBC/HPF. The remainder of the AKI testing was unremarkable. Her AKI was presumed to be related to Pembrozulimab based on timeline of rise in creatinine and she was started on Prednisone 40 mg daily (dosed at 1 mg/kg body weight). She responded well to the prednisone with creatinine improving to 1.1 within 6 weeks of starting prednisone which was gradually tapered off. Again, in this case a kidney biopsy was not performed due to significant early response to prednisone. This patient was also prescribed Pantoprazole 40 mg daily for gastrointestinal protection. She continues to be off Pembrozulimab at this time.

Discussion

AKI is common in patients with cancer due to multiple causes including ischemic/nephrotoxic tubular injury, drug-induced allergic interstitial nephritis (AIN), various glomerular injuries, and urinary obstruction. Patients with cancer and AKI should be carefully evaluated for potential causes. Immune checkpoint inhibitors (ICPIs) which are part of targeted immune therapies are increasingly used in Oncology. ICPIs are monoclonal antibodies that target inhibitory receptors expressed on T cells, other immune cells, and tumor cells. These receptors include cytotoxic T lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-ligand 1 (PD-L1). By inhibiting these receptors, ICPIs "remove the brakes" on the immune system, allowing T cells to become activated and exert antitumor activity.[1] ICPIs have been demonstrated to prolong overall- and progression-free survival in patients with melanoma, non-small-cell lung cancer, urothelial cancer, renal cell cancer and many other malignancies and are becoming first-line therapies for many types of cancer.[2] Pembrolizumab is a highly selective monoclonal IGg4-kappa (immunoglogulin G4-Kappa) isotype antibody that selectively binds to PD-1 blocking the receptor's negative impact on lymphocyte function.

ICPIs can cause a unique spectrum of autoimmune phenomena known as immune-related adverse events (irAEs). The most common tissues involved are the skin, gastrointestinal tract, and endocrine system.[3] AKI is less commonly seen but poses unique diagnostic and management challenges. The incidence of ICPI- AKI is estimated to be around 2 to 3 percent based on a recent meta-analysis of 48 clinical trials that involved 11,482 patients.[4] The precise mechanisms of AKI related to ICPIs are

poorly understood. Patients usually present with sterile pyuria or sub-nephrotic proteinuria. Only a minority of patients exhibit eosinophilia. If found it may be helpful in the diagnosis. Another important finding is the latency period between initiation of ICPI and development of AKI is much longer than commonly reported irAEs. In one multicenter study[1] the median time from ICPI initiation to AKI onset was 14 weeks. Our first case the time period for AKI was after 11 cycles (around 33-34 weeks) and our second case time period was around 15 weeks of therapy.

Some risk factors for the development of ICPI-AKI include concomitant use of Proton Pump Inhibitor (PPIs), combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents, and lower baseline eGFR.[1] PPIs, along with other drugs known to cause ATIN such as nonsteroidal anti-inflammatory drugs, should be used with caution in patients receiving ICPIs, and should be discontinued in those who develop ICPI-AKI. Both our patients were on PPI Pantoprazole which was continued due to ongoing gastrointestinal distress especially with steroid therapy.

In a single-center large case series observational cohort by Izzedine et al,[2] 676 patients who received Pembrozulimab who were referred for AKI and/or proteinuria following pembrolizumab therapy were analyzed. All underwent kidney biopsy (KB). Twelve patients (7 men) out of 676 pembrolizumab-treated patients in this center were included in the study. Pembrolizumab was used at standard dosage (2 mg/kg intravenously every 3 weeks). Kidney involvement occurred at a median time of 9 months (range 1–24 months) after the beginning of treatment, characterized by AKI (11 patients, 91.5%), proteinuria (2 patients, 16.6%, with proteinuria >3 g/day), microscopic hematuria (3 patients, 25%) and/or aseptic leukocyturia (4 patients, 33.3%). Kidney biopsies identified three distinct types of renal damage associated with Pembrolizumab therapy: acute interstitial nephritis (AIN), acute tubular and minimal change disease. Patients with AIN also had tubulitis- flattening of the tubular epithelium (4 patients) and interstitial fibrosis. No significant glomerular deposit was found by immunofluorescence analysis. There have been few reports of glomerulopathies, mainly podocytopathy- like minimal change nephropathy/focal segmental glomerulosclerosis (MCN/FSGS), immune complex glomerulonephritis or proteinase 3 anti-neutrophil cytoplasmic auto-antibodies (PR3 ANCA) vasculitis. Suggested mechanisms include direct lymphocytic cellular infiltration of renal interstitium, immune complex-mediated kidney injury, lupus nephritis, IgA, microangiopathic hemolytic anemia (TMA), or release of cytokines leading to podocyte foot process effacement.[5]

Treatment involves discontinuation of ICPIs, usually held for 6 weeks and initiation of corticosteroids, typically Prednisone which is tapered off over 4 to 24 weeks based on kidney biopsy findings, response to therapy and recurrence of renal disease. Both of our patients received prednisone with good response and in Case 1 AKI partially resolved with serum creatinine stabilizing at 1.4. In Case 2, there was good response to prednisone and creatinine returned to baseline in 4-6 weeks.

Conclusion

With the increasing use of ICPIs as a part of chemotherapy AKI has been more commonly seen. Kidney function should be judiciously monitored in patients receiving these medications. If AKI develops a kidney biopsy should be obtained. The implicated medication should be held and when applicable steroids should be initiated with close monitoring of the renal function. ICPIs are usually held for 6 weeks and resumed depending on recovery of renal function.

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