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# Immune Check Point Inhibitor–Associated Glomerulonephritis



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## INTRODUCTION

Immune check point inhibitors (CPIs) are a relatively new class of drug used to treat a variety of malignancies by releasing the immune system from specific inhibitory "check points" that have been built in to allow for self-tolerance and prevent an excessive inflammatory response. Some tumors can exploit these inhibitory signals to evade the immune system, resulting in proliferation and metastasis of tumor cells. Cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1 (PD-1) are both examples of "check point" receptors that negatively regulate T-cell activation and blunt T-cell function. CPIs are antibodies designed to block these negative regulators and help stimulate the immune system to control and kill tumor cells.[1] Unleashing the immune system from negative regulation comes with the obvious potential for side effects, such as loss of self-tolerance and excessive inflammatory activity. With respect to the nephrotoxic potential of these agents, there is a clear link between CPIs and the development of acute kidney injury (AKI) due to acute interstitial nephritis.[2–4] The link between CPIs and glomerulonephritis (GN) is much less clear, although we know of 2 reported cases of immune complex–mediated GN developing in the setting of CPI use.[5,6] We report a case of immune complex–mediated GN that developed following therapy with PD-1 inhibitor pembrolizumab, responded to discontinuation of the CPI along with initiation of corticosteroids, and then recurred after rechallenge with nivolumab, a different PD-1 inhibitor. The response to discontinuation of CPI therapy and biopsy-proven recurrence after rechallenge with a different agent in the same class supports a link between CPI treatment and development of immune complex–mediated GN.

## CASE PRESENTATION

The patient is a 68-year-old man with a malignant melanoma originally located over the right lower back. Surgical excision was complicated by the development of in-transit metastases that were deemed unresectable. He was started on Talimogene laherparepvec local injections, but given the high risk of progressing to stage IV, he was also treated with pembrolizumab, an immune CPI targeting PD-1. After receiving 3 doses of pembrolizumab over 1.5 months, the patient reported an episode of macroscopic hematuria and was treated empirically for presumed urinary tract infection. Urine cultures were negative. Three weeks later, he reported another episode of macroscopic hematuria. Additional workup revealed AKI with serum creatinine of 3.72 mg/dl from his baseline of 0.91 mg/dl.

The patient was admitted to the hospital for further workup of AKI. On further questioning, he reported a skin rash on his chest of 2 days' duration. His past medical history was otherwise relevant for chronic obstructive pulmonary disease secondary to a long history of smoking. His medications included omeprazole 40 mg, atorvastatin 20 mg, citalopram 20 mg, montelukast 10 mg, and ipratropium-albuterol inhaler. His physical examination was notable for the presence of a macular rash with dry crusts extending over the chest area. The rest of his examination was unremarkable. On admission, his blood pressure was 184/79 mm Hg, his pulse and temperature were 61 beats per minute and 36.9 °C. Detailed laboratory values are presented in Table 1. A kidney biopsy was performed and showed a diffuse endocapillary proliferative GN with cellular crescents in 3 of 20 glomeruli. Immunofluorescence showed deposits that stained 2 to 3+ for C3 and 1+ IgG, kappa, lambda, and C1q (scale 0–3+).

**Table 1.** Detailed laboratory values at time of first and second renal biopsies

| Date | October 27, 2016 | November 16, 2017 |
|---|---|---|
| Laboratory variable | Results | Results |
| WBCs (3.70–11.00 k/μl) | 7.61 K/μl | 6.49 K/μl |
| Hb (13.0–17.0 g/dl) | 12.2 g/dl | 10.1 g/dl |
| Platelets (150 – 400) k/μl | 262 K/μl | 300 K/μl |
| Sodium (136–144 mmol/l) | 144 mmol/l | 145 mmol/l |
| Potassium (3.7–5.1 mmol/l) | 4.1 mmol/l | 4.7 mmol/l |
| BUN (9–24 mg/dl) | 34 mg/dl | 51 mg/dl |
| Creatinine (0.73–1.22 mg/dl) | 3.72 mg/dl | 2.62 mg/dl |
| Chloride (97–105 mmol/l) | 106 mmol/l | 108 mmol/l |
| Bicarbonate (22–30 mmol/l) | 25 mmol/l | 21 mmol/l |
| Urinalysis | Positive at 100 mg/dl for protein and 3+ for hemoglobin. | Positive at >300 mg/dl for protein and 3+ for hemoglobin. |
| Urine microscopy | Too-numerous-to-count red blood cells (no acanthocytes), 0–5 WBCs, and no cellular casts were identified under high-power magnification | Too-numerous-to-count red blood cells (positive for acanthocytes), 6–10 WBCs, and no cellular casts were identified under high-power magnification |
| Serology workup: | | |
| ANA, ANCA, Anti-GBM Ab, HBsAg, and HCV Ab | Negative | |
| C3 (86–166 mg/dl) | 97 mg/dl | 79 mg/dl (low) |
| C4 (13–46 mg/dl) | 39 mg/dl | 29 mg/dl |

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; anti-GBM, anti–glomerular basement membrane; BUN, blood urea nitrogen; C3, complement 3; C4, complement 4; Hb, hemoglobin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; WBC, white blood cells.

Electron microscopy confirmed the presence of electron-dense deposits in mesangial and subendothelial areas as well as occasional subepithelial hump-shaped deposits (Figure 1). Given the hump-shaped deposits and C3 dominance by immunofluorescence, infection-related GN was high in the morphologic differential diagnosis. Clinically, the patient had no clinical signs suggestive of an active infection. He had no fevers or leukocyturia and blood and urine cultures were both negative. Transthoracic ECHO was negative for vegetations and antistreptolysin antibody was negative. Given the absence of detectible ongoing or recent infection and given his recent exposure to pembrolizumab, the possibility that the immune CPI was the cause of the immune complex–mediated GN increased. Serum creatinine continued to worsen and peaked at 5.51 mg/dl but he did not require dialysis. Immunotherapy was held and he was started on a high dose of prednisone (2 mg/kg per day). His creatinine had decreased to 4.13 mg/dl on discharge and continued to improve, reaching a nadir of 2 mg/dl. In total, he received prednisone for just more than 2 months.

Off of pembrolizumab, the patient's melanoma progressed and he was found to have a hypermetabolic right inguinal lymphadenopathy on positron emission tomography scan in June of 2017. It was decided to rechallenge him with a different PD-1 inhibitor, so he was started on nivolumab and received a total of 3 doses. His serum creatinine worsened from his new baseline of 2 mg/dl to 2.62 mg/dl 2 weeks after his last dose of nivolumab. His urinalysis showed hematuria/pyuria and review of his urine sediment revealed dysmorphic red blood cells. Urine culture was negative. Urine protein/creatinine showed 2 g of proteinuria. Further laboratory findings are displayed in Table 1. He underwent a repeat kidney biopsy. It showed recurrence of the findings that characterized the first biopsy, including endocapillary proliferation, immune complex deposition, and subepithelial deposits. CPI therapy was withdrawn permanently and the patient was restarted on prednisone 60 mg once daily. His serum creatinine improved to 1.93 over the next 10 weeks.

## DISCUSSION

Immune CPIs have shown promise in the treatment of a variety of malignancies, including advanced forms of melanoma, non–small-cell lung cancer, urothelial carcinomas, head and neck squamous cell tumors, and Hodgkin lymphoma. The balance between preserving self-tolerance and effective cancer surveillance is a delicate one and depends in part on appropriate T-cell regulation at key negative regulatory check points. Tumor cells can exploit these regulatory points to prevent detection by the immune system, allowing them to proliferate and metastasize.[7] CPIs are monoclonal antibodies that target inhibitory receptors expressed on T cells, other immune cells, and tumor cells, including PD-1 and cytotoxic T-lymphocyte antigen 4. When bound by ligands expressed by antigen-presenting cells, PD-1 and cytotoxic T-lymphocyte antigen 4 downregulate costimulatory signals, which consequently suppress T-cell activation and an unwanted inflammation. Although check point blockade

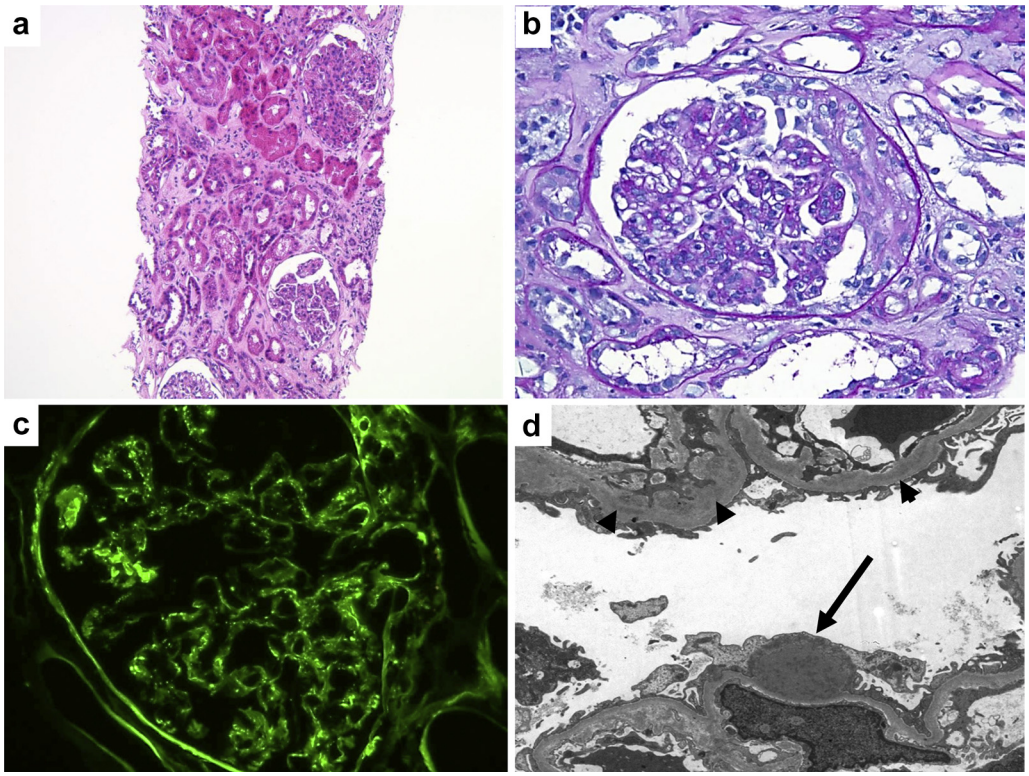


**Figure 1.** Representative images from the patient's first biopsy. At low power (a, original magnification ×100, hematoxylin-eosin) the glomeruli appear hypercellular. There is a mild increase in interstitial fibrosis and some mild chronic scaring but no substantial tubulointerstitial inflammation was seen. Several glomeruli displayed cellular crescent formation, in addition to endocapillary proliferation (b, original magnification ×200, periodic acid–Schiff). Immunofluorescence revealed dominant staining for C3 (c, original magnification ×400) with lesser degrees of staining for IgG, kappa, lambda, and C1q. Electron microscopy (d, original magnification ×4800) showed electron-dense deposits in the subendothelial distribution (arrowheads), as well as occasional subepithelial hump-shaped deposits (arrow). The repeat biopsy 1 year later after rechallenge with a different PD-1 inhibitor showed very similar findings.

can result in substantial antitumor benefits, it also comes with the risk of side effects due to excessive and nonspecific immunologic activity. These adverse effects have been termed immune-related adverse events, and include a spectrum of autoimmune diseases, such as rash, colitis, hepatitis, and hypophysitis.[1] AKI is generally considered to be among the less common immune-related adverse events caused by CPIs. In a combined analysis of 3695 patients treated with CPIs, the overall incidence of AKI was 2.2%, and the incidence of grade III or IV AKI was 0.6%.[3] As experience with these agents has broadened, it has been proposed that renal toxicities may be more common than previously thought, with some studies showing incidence rates ranging from approximately 10% to 30%.[4] A recent comprehensive meta-analysis examining renal toxicity of CPIs looked at 48 clinical trials that included more than 11,000 patients receiving PD-1 inhibitors. This meta-analysis showed a 2.2% incidence rate of AKI.[8]

The vast majority of renal toxicity due to CPIs is due to acute interstitial nephritis.[2,3,9] A recent review of the nephrotoxic potential of CPIs highlights that glomerular toxicity also has been reported, primarily as podocyte injury, manifesting as minimal change disease or focal segmental glomerulosclerosis, and occasionally as immune complex–mediated GN.[9] The first case of immune complex–mediated GN was reported by Fadel and colleagues[5] in 2009 and detailed the case of a 64-year-old man with metastatic melanoma who developed nephrotic syndrome in the setting of cytotoxic T-lymphocyte antigen 4 inhibitor ipilimumab, which was an investigational agent at the time. This patient developed positive antinuclear antibodies and anti–double-stranded DNA antibodies and kidney biopsy showed immune deposits that stained with IgG, IgM, C3, and C1q, suggestive of lupus nephritis. After discontinuing ipilimumab, the autoantibodies resolved after 3 months and at last reported follow-up 12 months after diagnosis, proteinuria had decreased from 7.5 g per day at diagnosis to 1 g per day.[5] The other reported case of immune complex–mediated GN was reported by Jung and colleagues[6] in the setting of PD-1 inhibitor use. The patient was a 70-year-old man with metastatic clear cell renal cell carcinoma who was treated with nivolumab. His tumors responded well to therapy, but

**Table 2.** Proposed CPI nephrotoxicity management, National Comprehensive Cancer Network guidelines[10]

| Grade | Acute kidney injury | Intervention |
|---|---|---|
| Grade 1 (mild) | Creatinine 1.5–2 x above baseline; increase of ≥ 0.3 mg/dl | - Consider holding immunotherapy<br>- Follow creatinine and urine protein every 3–7 d |
| Grade 2 (moderate) | Creatinine 2–3 x above baseline | - Hold immunotherapy<br>- Nephrology consultation<br>- Follow creatinine and urine protein every 3–7 d<br>- Start prednisone 0.5–1.0 mg/kg per d if other causes are ruled out; treat until symptoms improve to <Grade 1 then taper over 4–6 wk<br>- If no improvement in 1 wk, prednisone/methylprednisolone to 1–2 mg/kg per d |
| Grade 3 (severe) | Creatinine>3 x baseline or >4.0 mg/dl | - Stop immunotherapy permanently<br>- Nephrology consultation<br>- Consider inpatient care<br>- Consider renal biopsy<br>- Prednisone/methylprednisolone 1–2 mg/kg per d<br>- If > Grade 2 after 1 wk of steroids, consider:<br>■ Azathioprine<br>■ Cyclophosphamide<br>■ Infliximab<br>■ Mycophenolate |
| Grade 4 (life-threatening) | Creatinine>6 x baseline; dialysis indicated | Same as Grade 3 |

approximately 10 months after initiating therapy he presented with AKI and a serum creatinine of 10 mg/dl. Renal biopsy showed a proliferative GN with cellular crescents that stained for IgA, C3, kappa, and lambda. Similar to the case reported here, electron microscopy was notable for subepithelial hump-shaped deposits and initially IgA-dominant acute postinfectious GN was diagnosed. Similar to our case, no evidence of recent or active infection was found at the time and the PD-1 inhibitor was discontinued over the concern that it could be the source of the GN and corticosteroid therapy was initiated. Over a 6-month period, the patient's creatinine improved back to baseline of 1.8 mg/dl.[6] Our case is notable in that we show development of a biopsy-proven immune complex–mediated GN, which developed first after therapy with pembrolizumab and then again approximately 1 year later after rechallenge with nivolumab, a different PD-1 inhibitor. The temporal association with PD-1 inhibitor therapy and more importantly recurrence after rechallenge with a similar agent serve to strengthen the assertion that immune CPIs can cause immune complex–mediated GN.

The mechanism by which CPIs can cause GN is unclear. We could reasonably speculate that given the reduced self-tolerance and increase in T-cell activity caused by CPIs, the formation of autoantibodies, deposition of antibody-antigen complexes in the kidney, and an ensuing inflammatory response would provide one possible explanation. Another potential explanation would be the development of an antibody directed against the CPI itself, which is a monoclonal antibody. Our case showed development of a similar GN after exposure to 2 different PD-1 inhibitors, suggesting that the more likely mechanism is a generalized increase in autoimmunity rather than an immune response directed at a specific monoclonal antibody or a specific hypersensitivity response.

Given the increasing use of CPIs, nephrologists should be familiar with the diagnosis and management of their associated nephrotoxic side effects. Perazella and Shirali[9] proposed a surveillance plan in patients receiving CPIs that includes checking serum creatinine and urinalysis at baseline, after 3 months, after 12 months, and then once yearly. The National Comprehensive Cancer Network guidelines for the management of CPI nephrotoxicity are based on the severity of the kidney injury (Table 2). For grade 1 renal toxicity (creatinine 1.5–2.0 times above baseline; or increase of ≥0.3 mg/dl), recommendations are to consider holding immunotherapy and follow creatinine and urine protein every 3 to 7 days. In cases of grade 2 toxicity (creatinine 2–3 times above baseline), immunotherapy should be held. If no other obvious source for AKI is present, they recommend starting prednisone 0.5 to 1.0 mg/kg per day and if no improvement in 1 week, increasing prednisone to 1 to 2 mg/kg per day. In cases of grade 3 (creatinine >3 times baseline of >4.0 mg/dl) or grade 4 (creatinine >6 times baseline; dialysis

**Table 3.** Summary of key points regarding renal complications of check point inhibitor therapy

| Key teaching points |
|---|
| - Check point inhibitor (CPI)-related acute kidney injury (AKI) occurred in 2.2% of patients in phase 2/3 clinical trials, but may be more common than previously recognized and is a potentially severe condition that nephrologists caring for patients with cancer should be aware of. |
| - Acute interstitial nephritis is the most common histologic finding in CPI-related AKI, but as this case illustrates, there is increasing evidence that immune complex–mediated glomerulonephritis and other forms of glomerular injury can also occur in the setting of CPI therapy. |
| - Early recognition of kidney injury and withdrawal of CPI therapy, often along with systemic corticosteroid treatment, are essential, as many patients can achieve partial to complete recovery of renal function. |

indicated) toxicity, immunotherapy should be stopped permanently, corticosteroid therapy with prednisone 1 to 2 mg/kg per day should be started, and renal biopsy should be considered.[10]

## CONCLUSION

In conclusion, our case helps to expand the spectrum of nephrotoxic effects that can be associated with CPI therapy and highlights the importance of recognizing the renal complications of CPI therapy (Table 3). Although acute interstitial nephritis is the most common cause of AKI attributed to CPI use, immune complex–mediated GN also can be seen. As in this case, the GN initially may be attributed to another cause, such as postinfectious GN. The presence of a second renal biopsy documenting the redevelopment of the GN on rechallenge with CPI therapy makes a strong argument that GN should be considered to be a lesion in the spectrum of CPI nephrotoxicity.

## DISCLOSURE

All of the authors declared no competing interests.

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