

[CASE REPORT]

Renal Effects after Pembrolizumab Treatment for Non-small Cell Lung Carcinoma

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Abstract:

Immune checkpoint inhibitors (CPIs), including pembrolizumab, are becoming common oncological treatments. CPIs have been associated with a significant risk of developing immune-related adverse events (irAEs), such as nephritis and interstitial nephritis. However, the occurrence of glomerulonephritis has only rarely been reported. We herein present the case of a 75-year-old woman with non-small cell lung carcinoma (NSCLC) who developed proteinuria and microscopic hematuria during treatment with pembrolizumab. Renal biopsy revealed tubulointerstitial nephritis and IgA nephropathy. Considering that a urinalysis showed no abnormality before treatment, the condition might have been induced by pembrolizumab. In this report, we focus on the correct diagnosis and management of renal irAEs, which remain controversial.

Key words: onconeurology, immune checkpoint inhibitors (CPI), pembrolizumab, immune-related adverse events (irAEs), IgA nephropathy, acute tubulointerstitial nephritis

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Introduction

Immune checkpoint inhibitors (CPIs) have shown great promise as cancer therapeutics. Among the immune checkpoint inhibitors, programmed cell death (PD)-1/PD-ligand (L)1 and T-lymphocyte-associated antigen (CTLA)-4 inhibitors have been attracting the attention of researchers focused on developing novel cancer treatments (1). Pembrolizumab is a humanized monoclonal IgG4 antibody directed against human cell surface receptor PD-1.

CPI treatment has been associated with a significant risk of developing immune-related adverse events (irAEs). Common irAEs include colitis, hepatitis, and interstitial pneumonia, as well as endocrinopathies, including hypophysitis, thyroiditis, and pancreatitis, with various degrees of severity, ranging from mild to fatal. Renal irAEs have been reported in 2-4.5% of patients treated with CPIs (2). In most cases, renal irAEs are characterized by acute tubulointerstitial nephritis (2). Several reports have recently shown other types of renal pathologies in patients treated with CPIs, including

lupus nephropathy, thrombotic microangiopathy, focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, pauci-immune glomerulonephritis, and IgA nephropathy (2). However, the diagnosis, treatment, and management of renal irAEs remain unclear. Another problem is that most reports do not include a urinalysis before the use of CPI, which makes it difficult to ascertain whether CPI triggers nephritis. We herein report a case of acute tubulointerstitial nephritis and mesangial proliferative glomerulonephritis (IgA nephropathy) in a patient treated with pembrolizumab for non-small cell lung carcinoma (NSCLC).

Case Report

The patient was a 75-year-old woman with no previous history of kidney disease who had been diagnosed with stage IIIB unresectable NSCLC of the right lower lobe lung 2 years previously. She had a more than 10-year history of hypertension. Her blood pressure was controlled to approximately 130/70 mmHg using azilsartan and amlodipine. She had never used non-steroidal anti-inflammatory drugs or

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Table. Laboratory Findings on Admission.

Peripheral blood	
White Blood Cells (μL)	5,700
Neu(%)	73.6
Lym(%)	21.5
Eo(%)	0.4
Baso(%)	0.4
Red Blood Cells ($\times 10^4/\mu\text{L}$)	402
Hemoglobin (g/dL)	13.3
Platelets ($\times 10^4/\mu\text{L}$)	20
Blood chemistry	
AST (U/L)	20
ALT (U/L)	18
LDH (U/L)	234
TP (g/dL)	7.4
Alb (g/dL)	4.3
BUN (mg/dL)	12.6
Cre (mg/dL)	0.79
Na (mmol/L)	140
K (mmol/L)	4.1
Cl (mmol/L)	103
Ca (mg/dL)	10.2
IP (mg/dL)	2.7
Serological tests	
CRP (mg/dL)	0.04
IgG (mg/dL)	1,290
IgA (mg/dL)	275
IgM (mg/dL)	54
C3 (mg/dL)	95
C4 (mg/dL)	26
CH50 (U/mL)	44.7
PR3-ANCA (U/mL)	Not detected
MPO-ANCA (U/mL)	Not detected
Anti-GBM-antibody (U/mL)	<2.0
Antinuclear antibody	<40
Urinalysis	
Occult blood	2+
Proteinuria (g/gCr)	1.7
Sediment RBC	10-19/HPF
Sediment WBC	1-4/HPF
NAG	15.2 IU/gCr
$\alpha 1$ -microglobulin	10.2 mg/gCr

HPF: high power field

proton pump inhibitors. She received definitive chemoradiotherapy, including cisplatin. Although it was initially effective, a relapse of NSCLC was detected. As such, pembrolizumab (200 mg, every 3 weeks) treatment was initiated one year prior to her current presentation. After treatment, her creatinine levels remained normal (0.65-0.69 mg/dL) and no urinary abnormalities were detected before pembrolizumab treatment. She continued pembrolizumab for 7 cycles in the span of 9 months, including a period in which the treatment was discontinued due to the development of radiation recall pneumonitis (RRP). Steroid therapy had not been used to treat her RRP. Nine months after the initiation of pembrolizumab treatment, the patient exhibited proteinuria and mi-

croscopic hematuria. She was referred to the nephrology department of our hospital for further examination. There were no signs of purpura or peripheral edema on a physical examination. Her serum creatinine level was 0.79 mg/dL, which was slightly higher than the baseline level. A urinalysis revealed that her urinary protein content was 1.0 g/gCr and her urinary sediment contained 10-19 red blood cells (RBCs) per high power field. Thus, we judged, with reference to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, that creatinine elevation (grade 1) and proteinuria (grade 2) had occurred as adverse events related to pembrolizumab. Pembrolizumab was resumed. However, proteinuria and hematuria continued. As such, we performed a renal biopsy. The laboratory findings are summarized in Table.

The total number of glomeruli was 49, with 19 glomeruli in a state of advanced obsolescence. There were no glomerular crescents. Approximately 50% of the tubulointerstitial lesion was detected in the cortical area. The region of acute tubulointerstitial nephritis occupied more than 80% of the whole tubulointerstitial region. Light microscopy revealed tubular atrophy and interstitial inflammation, with infiltration of mononuclear as well as polymorphonuclear leukocytes and plasma cells (Fig. 1a). Tubulitis was not found, but tubular basement membranes were occasionally broken (Fig. 1a). Diffuse mesangial matrix expansion and endocapillary cell proliferation were seen in several glomeruli (Fig. 1b). As for arterial and arteriolar changes, medial thickening was present, reflecting aging and hypertension. Immunofluorescence microscopy revealed granular deposition of IgA, IgM, and C3 in the mesangial area (Fig. 2). Electron microscopy showed the presence of paramesangial dense deposits (Fig. 3). The patient was therefore diagnosed with tubulointerstitial nephritis and IgA nephropathy. In this case, the patient's glomerulosclerosis may have resulted from nephrosclerosis or damage from past chemotherapy, including cisplatin. Pembrolizumab was not restarted after the kidney biopsy, according to the guidelines for the management of irAEs published by the American Society of Clinical Oncology (ASCO). We did not initiate any treatment, including steroid therapy. The patient's proteinuria and hematuria persisted for 6 months, and then subsequently began to decrease. At 6 months after disconnection of pembrolizumab, the patient's urinary protein decreased to 0.7 g/gCr with the amelioration of tubulointerstitial biomarkers such as urine $\alpha 1$ MG and N-acetyl-beta-D-glucosaminidase (NAG), and her creatinine level remained stable (Fig. 4). The patient's serum IgA decreased slightly from 275 mg/dL to 247 mg/dL. Before pembrolizumab was started, her serum IgA level was 176 mg/dL, which was much lower. However, a relapse of NSCLC was detected at the same time as the decrease in her urinary protein level. Thus, chemotherapy including carboplatin and pemetrexed was initiated to treat relapsed NSCLC.

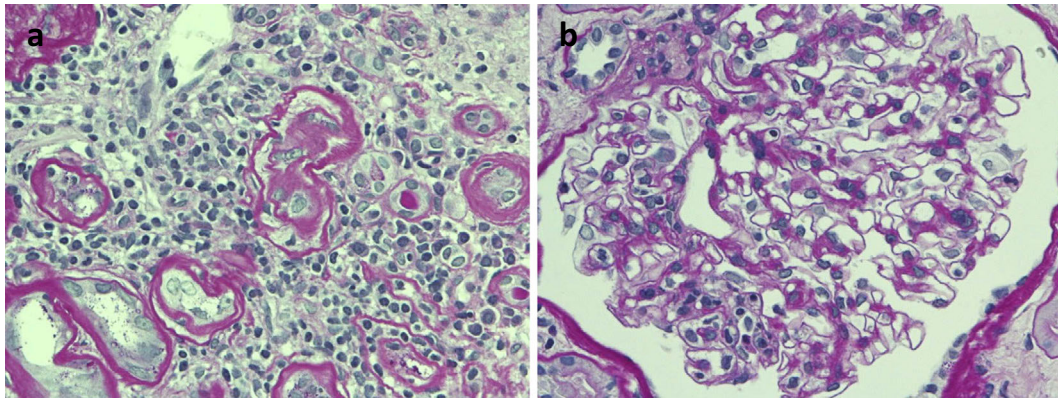


Figure 1. (a) Tubular atrophy and interstitial inflammation (PAS staining×400). (b) Mesangial matrix expansion and endocapillary cell proliferation (PAS staining×400).

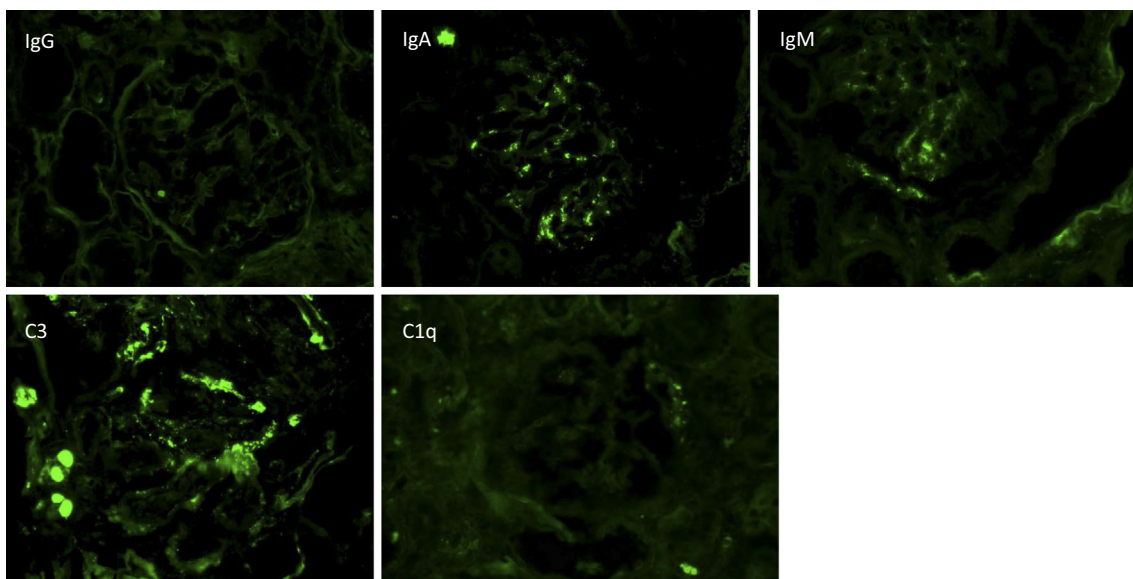


Figure 2. Immunofluorescence revealed IgA, IgM and C3 deposition in the mesangial area.

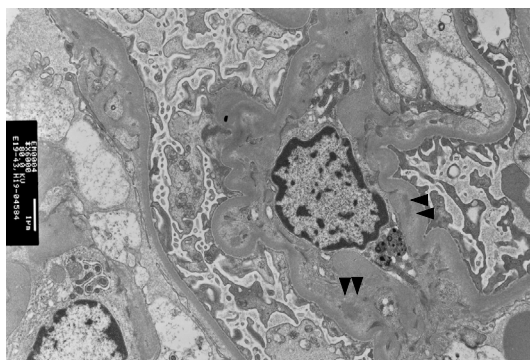


Figure 3. Electron microscopy findings. Electron microscopy revealed paramesangial dense deposits shown (arrowheads).

Discussion

CPIs have demonstrated remarkable clinical success in the treatment of various cancers. The PD-1-blocking antibody

pembrolizumab has been approved by the Food and Drug Administration for the treatment of melanoma, non-small cell lung cancer, and classical Hodgkin's lymphoma.

However, it is well known that CPIs are associated with irAEs. According to clinical trials, renal irAEs are rare in comparison to irAEs affecting other organs. Elevated creatinine was reported in 1.4% (any grade) and 0.2% (grade 3 or 4) of patients undergoing pembrolizumab monotherapy (2). On the other hand, the rate of urinary abnormalities related to irAEs is still unclear. As previously reported, pathological findings of renal irAEs include acute tubulointerstitial nephritis (ATIN) and glomerulonephritis. Mamlouk et al. reported that ATIN was the most common pathologic finding, being identified in 14 out of 16 cases (2). Moreover, ATIN was shown to be associated with glomerulonephritis in 9 out of 16 cases (2). Notably, a few reports identified IgA nephropathy as an irAE. Kishi et al. reported a case of nivolumab-associated IgA nephropathy (3). The patient was a 72-year-old man who was treated with nivolumab for lung squamous cell carcinoma. In that case,

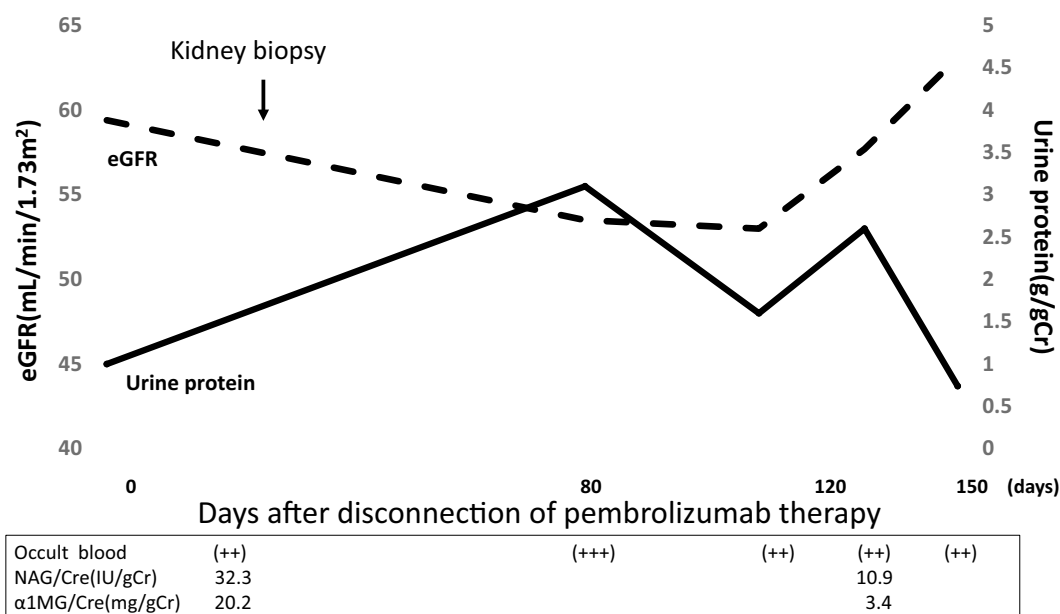


Figure 4. The clinical course. The estimated glomerular filtration rate (mL/min/1.73 m²) and urinary protein level (g/gCr) are shown in a dotted and solid lines, respectively. The course of occult blood, urine NAG, and urine α 1MG are also shown under the chart.

elevated serum creatinine levels (1.35 mg/dL) and proteinuria were observed ten months after the initiation of nivolumab therapy. Renal biopsy revealed IgA nephropathy, after which nivolumab treatment was stopped. Subsequently, the proteinuria was ameliorated and his creatinine levels stabilized. Likewise, we identified a patient with pembrolizumab-associated IgA nephropathy, suggesting that the PD-1 blocking antibodies may cause IgA nephropathy.

Although the pathogenesis of CPI-related ATIN and glomerulonephritis remains unclear, there some possible mechanisms have been suggested. A previous report showed that PD-1 knockout mice developed immune complex glomerulonephritis, suggesting the importance of PD-1 signaling in the minimization of T cell-mediated renal inflammation (4). Moreover, PD-L1- and PD-1-deficient animals also developed autoimmune disease (2). Blocking the PD-1 pathway may enhance antigen recognition, not only for tumor antigens but also for self-antigens, leading to cytotoxic T cell activation against both the tumor and normal tissues. One possible explanation for the development of IgA nephropathy, in this case, may be the alteration of the gut microbiota and gut mucosal defense system. PD-1 knockout mice displayed qualitative changes in gut IgA and dysbiosis (5). Considering that gut dysbiosis was reported to be related to the development of IgA nephropathy (6), changes in the gut microbiota and immune system-even in patients who did not develop colitis as irAEs-can be one of the causes of the development of IgA nephropathy. We also diagnosed acute tubulointerstitial nephritis as a complication in this patient. It is known that tubulointerstitial injuries can occur secondary to various conditions, other than those induced by pembrolizumab, including IgA nephropathy and arteriolosclerosis. We identified both these conditions in this patient. However,

the inflammatory phase and expansion of tubulointerstitial nephritis in this case were disproportionate to the glomerular damage and the chronicity of the vascular lesions. Furthermore, urinary indices, such as α 1MG and NAG, improved after the cessation of pembrolizumab. These findings suggest that the tubulointerstitial lesions observed in the current case could be attributed to pembrolizumab-associated ATIN.

According to the pharmaceutical reference of pembrolizumab (KEYTRUDA), if creatinine levels become elevated to grade 2 (serum creatinine 1.5-3.0 \times baseline), the medication should be withheld. If creatinine levels are elevated to grade 3 (serum creatinine >3.0 \times baseline), treatment with systemic steroids, such as prednisolone (1-2 mg/kg), is recommended. Meanwhile, there is no clear consensus on the effectiveness of steroid therapy for ATIN, due to the fact that there have been no randomized, controlled studies (7). According to the analysis of the outcomes of patients with advanced NSCLC treated with nivolumab, the use of steroids was shown to be significantly associated with lower progression-free survival [heart rate (HR)= 3.27, 95% confidence interval (CI) 1.39-7.69, p = 0.006] (8). Thus, we did not use steroids, considering the effect of immunosuppression on the progression of NSCLC.

It is controversial whether CPI therapy should be discontinued. It was previously reported that patients with metastatic melanoma can achieve a durable complete remission after the discontinuation of pembrolizumab (9). The 24-month disease-free survival rate from the time of complete response (CR) was 90.9% in all 105 patients with CR (9). However, that of the 67 patients who discontinued pembrolizumab after achieving a CR was 89.9% (9). This report suggests that patients can have persistent clinical benefits, even after the discontinuation of CPI therapy in order to mitigate

irAEs. This also explains why proteinuria and hematuria lasted for 6 months in the present case. The fact that the patient's proteinuria decreased 6 months after the discontinuation of pembrolizumab supports that the effect of the medicine may continue for as long as 6 months. It is interesting to note that the effect of pembrolizumab on the kidneys may persisted for a certain period after drug withdrawal. Moreover, the use of systemic steroids for the management of renal irAEs is also highly disputed. This necessitates an analysis of the risks and benefits in relation to the original disease. Thus, the early correct diagnosis of renal irAEs is important. Close monitoring of the kidney function and urinary findings, as well as appropriately timed kidney biopsy, may play a role in successful treatment. The accumulation of similar cases is needed to establish evidence to determine the best strategy for the management of renal irAEs.

The authors state that they have no Conflict of Interest (COI).

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