Supplementary Material

[BACKGROUND]

Since their first approval in 2011, immune checkpoint inhibitors (ICPIs) became the most widely prescribed anticancer therapies because of their remarkable efficacy against advanced tumors. Durvalumab, a PD-L1 inhibitor, is a high-affinity-human immunoglobulin G1 monoclonal antibody that blocks PD-L1 from binding to PD-1 or CD80. It was approved by the Food and Drug Association in March 2020 for patients with unresectable stage III non-small-cell lung cancer (NSCLC) whose disease has not progressed following concurrent chemotherapy and radiation therapy [S1].

While ICPIs have shown effective therapeutic effects, immune-related adverse effects (irAEs) have been reported in organs throughout the body due to reactivation of the patient's immune response. Renal complications of irAEs are relatively rare, occurring in 2% to 5% of patients treated with ICPIs. Although most cases of renal irAEs have presented with interstitial nephritis, rare cases of glomerulopathy and nephrotic syndrome have also been reported [S2]. Since durvalumab is a novel drug, the characteristics and epidemiology of its adverse events remain unclear. Also, If ICPIs-induced MCD achieved complete remission (CR), acceptance of rechallenge ICPIs is still not clear.

[CASE PRESENTATION]

A 75-year-old Asian man presented with a history of proteinuria. He was diagnosed with locally advanced NSCLC stage IIIB and received concurrent chemoradiotherapy: three cycles of paclitaxel/carboplatin and radiotherapy (60 Gy in 30 fractions). As NSCLC did not progress following chemoradiotherapy, he was treated with four cycles of durvalumab monotherapy. Proteinuria was negative before the administration of durvalumab; however, urinary protein was detected after the third administration of durvalumab, on the 59th day of the first administration. The administration of durvalumab was discontinued, and the patient was admitted to our hospital. He had no history of renal disease and did not take any other medications since the start of durvalumab. Upon admission, his blood pressure was 126/84 mmHg, with moderate pitting edema observed bilaterally in the lower limbs. Laboratory tests revealed an increased and nonselective urinary protein excretion (9.99 g/day, selectivity index 1.08), hypoalbuminemia (1.7 g/dL), a normal serum creatinine level (0.88 mg/dL), and an elevated total serum cholesterol level (377 mmol/L). Renal biopsy showed minor glomerular abnormalities. Immunofluorescence staining showed no immunoglobulin or complement deposition. Electron microscopy showed no electron-dense deposits, while podocyte foot process effacement was observed (Figure S1).

Because he had planned to receive the coronavirus disease 2019 vaccination,

immunosuppressive treatment was not initiated, and he was followed up conservatively with salt restriction and the use of angiotensin II receptor blocker (ARB). Although the proteinuria improved to 3.99 g/day, this recovery was not sufficient. He was admitted to the hospital again and treated with methylprednisolone (mPSL) 500 mg/day for three consecutive days followed by 0.8 mg/kg/day (50 mg) of prednisolone. One week after the administration of steroids, proteinuria decreased to 0.06 g/day and serum albumin level increased to 2.3 g/dL; thus, CR was achieved. The dosage of prednisolone was tapered to 40 mg/day, followed by 35 mg/day one week later. He was discharged three weeks after starting steroids, his serum albumin level had improved to 3.5 g/dL (Figure S2), and relapse of nephrotic syndrome has not been noticed since.

[DISCUSSION]

This is a case of drug induced MCD caused by durvalumab, which responded well to steroid therapy, resulting in CR. In the present case, it was necessary to differentiate between MCD secondary to NSCLC and drug induced MCD caused by durvalumab. Among tumor-induced MCD, Hodgkin's lymphoma is the most common underlying cause, but some cases of NSCLC have also been reported. NSCLC-induced MCD has been characterized by a relative correlation between disease activity and the amount of proteinuria [S3]. In the present

case, proteinuria was negative before the administration of durvalumab, and a large amount of proteinuria was observed soon after four cycles of durvalumab, while the tumor was shrinking. Furthermore, in the present case, the administration of steroids improved MCD dramatically, whereas NSCLC-induced MCD often improved with successful treatment of the tumor [S3]. Based on these facts, MCD, in this case, was induced by durvalumab.

Most cases of renal irAEs present with acute kidney injury (AKI) due to interstitial nephritis. However, rare cases of glomerulopathy or nephrotic syndrome have also been reported, which are summarized in Table 1. The ICPIs used were pembrolizumab (6 cases), ipilimumab (2 cases), nivolumab, and investigational drug (1 case each). The present case is the first report of MCD caused by a PD-L1 inhibitor, including durvalumab.

The mechanism of MCD caused by ICPIs, especially PD-L1 inhibitors, is not well understood. In the pathophysiology of MCD, T-cell-derived humoral factors, such as vascular permeability factors and hemopexin, damage the glomerular filtration barrier [S4]. Therefore, T-cell activation by ICPIs is thought to be the main cause of MCD, which leads to an imbalance in T-cell regulation and enhances the effect of these humoral factors [S2]. CD80 activation in podocytes has recently been investigated as another pathway for MCD pathogenesis. CD80 immunostaining of podocytes was found in more than 50% of kidney biopsy specimens collected randomly from patients with proteinuria [S5]. Lipopolysaccharide

sensing by TLR-4 induces CD80 in podocytes, leading to foot process effacement and proteinuria, but this response does not occur in CD80-deficient mice [S6]. These findings suggest that the induction of CD80 in podocytes by various stimuli leads to impairment of the glomerular filtration barrier [S6]. PD-L1 binds to CD80, which competitively inhibits the binding of CD80 to CD28. Thus, durvalumab promotes the binding of CD80 to CD28 [S1]. Therefore, durvalumab may directly impair the glomerular filtration barrier via CD80 activation in podocytes as a direct effect of the PD-L1 inhibitor on podocytes [S7].

The irAEs management guidelines from the American Society of Clinical Oncology recommend discontinuing ICPIs and administering oral corticosteroids (0.5 to 2 mg/kg/day) to patients who develop grade 2 or higher renal complications. If the patient improves to grade 1, the corticosteroids are tapered off over at least 4 to 6 weeks [S8]. According to Table 1, most of the patients were treated with PSL 1 to 2 mg/kg/day and tapered off over 6 to 26 weeks. The mean urine protein excretion improved markedly from 12.52 g/day to 0.73 g/day after treatment. If renal complications are grade 2 or lower, ICPIs may be resumed as long as the tumor responds to them and the renal function is maintained within the normal range [S8].

Finally, the present case will be considered the rechallenge of durvalumab in the future, because the tumor was not resected surgically. Gupta et al. reported that 31 patients

were rechallenged after ICPI-induced AKI, and only seven experienced recurrent AKI, six of whom had complete or partial renal recovery [S9]. As shown in Table 1, three of the six patients with CR were re-treated with ICPIs, and two of these patients relapsed. The two patients who relapsed did not receive maintenance therapy, while the patient who did not relapse received maintenance therapy with PSL 10 mg/day (Table 1). In the present case, a maintenance dose of PSL might be required when the rechallenge with durvalumab for worsening NSCLC is considered.

[DISCLOSURE]

All the authors declared no competing interests.

[PATIENT CONSENT]

The authors declare that they have obtained consent from the patient discussed in the report.

Supplementary References

S1. Gray JE, Villegas A, Daniel D*, et al.* Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *J Thorac Oncol* 2020; **15:** 288-293.

S2. Vaughan E, Connolly E, Hui M*, et al.* Minimal change disease in a patient receiving checkpoint inhibition: Another possible manifestation of kidney autoimmunity? *Cancer Rep (Hoboken)* 2020; **3:** e1250.

S3. Ohara G, Satoh H, Kurishima K*, et al.* Paraneoplastic nephrotic syndrome in patients with lung cancer. *Intern Med* 2009; **48:** 1817-1820.

S4. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; **5:** 2115-2121.

S5. Larsen CP, Messias NC, Walker PD. B7-1 immunostaining in proteinuric kidney disease. *Am J Kidney Dis* 2014; **64:** 1001-1003.

S6. Reiser J, von Gersdorff G, Loos M*, et al.* Induction of B7-1 in podocytes is associated with nephrotic syndrome. *J Clin Invest* 2004; **113:** 1390-1397.

S7. Kitchlu A, Fingrut W, Avila-Casado C*, et al.* Nephrotic Syndrome With Cancer Immunotherapies: A Report of 2 Cases. *Am J Kidney Dis* 2017; **70:** 581-585.

S8. Brahmer JR, Lacchetti C, Schneider BJ*, et al.* Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; **36:** 1714-1768.

S9. Gupta S, Cortazar FB, Riella LV*, et al.* Immune Checkpoint Inhibitor Nephrotoxicity: Update 2020. *Kidney360* 2020; **1:** 130-140.

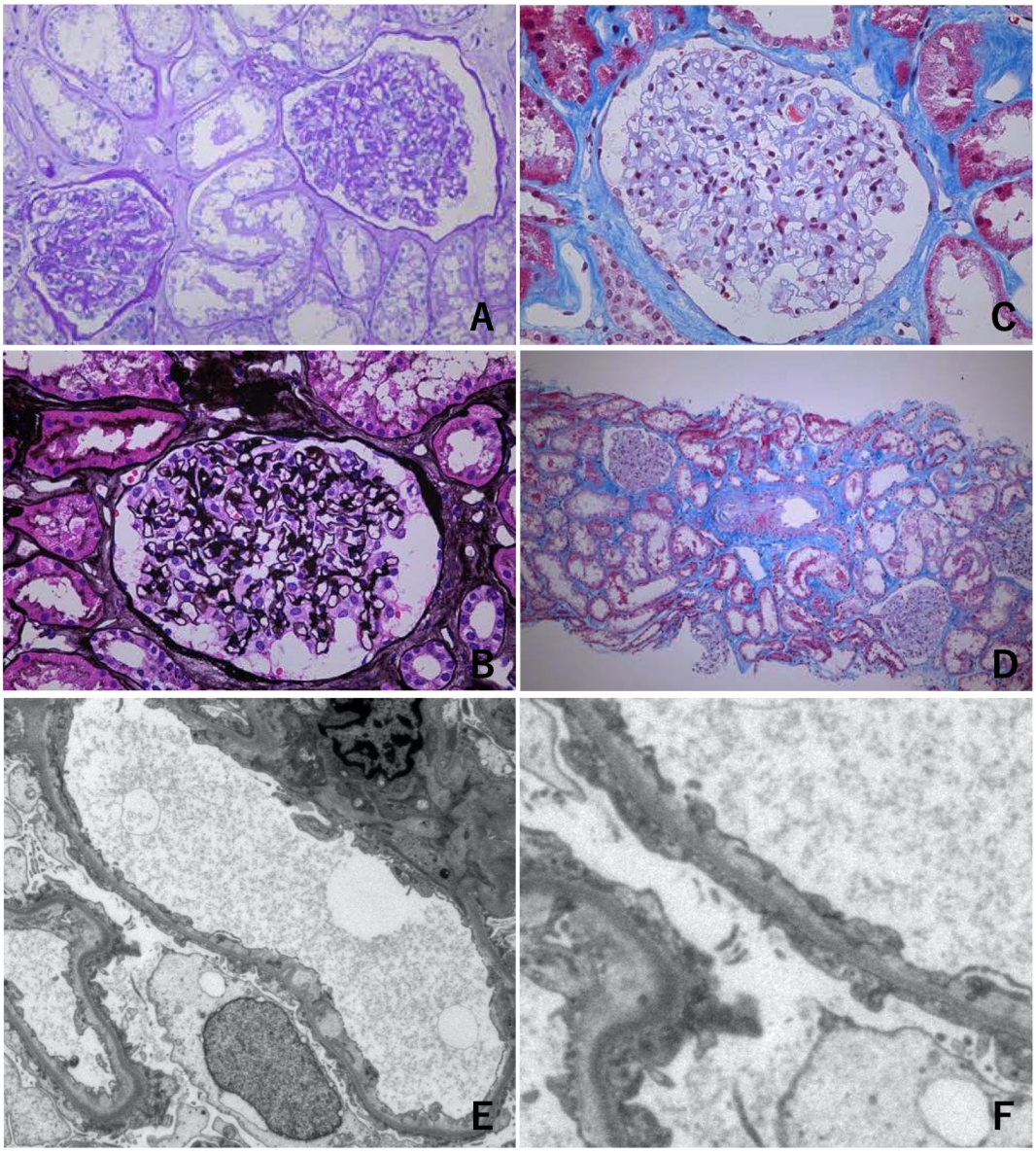

Figure S1. Representative images of kidney biopsy

A-D: Light microscopy of kidney biopsy. Periodic acid-Schiff (A), Periodic acid methenamine silver (B), and Masson's trichrome (C, D) staining showed minor glomerular abnormalities. E, F: Electron microscopy of the kidney biopsy. Extensive, diffuse foot process effacement with subendothelial widening. No electron-dense deposits are observed. Normal thickness of the glomerular basement membrane

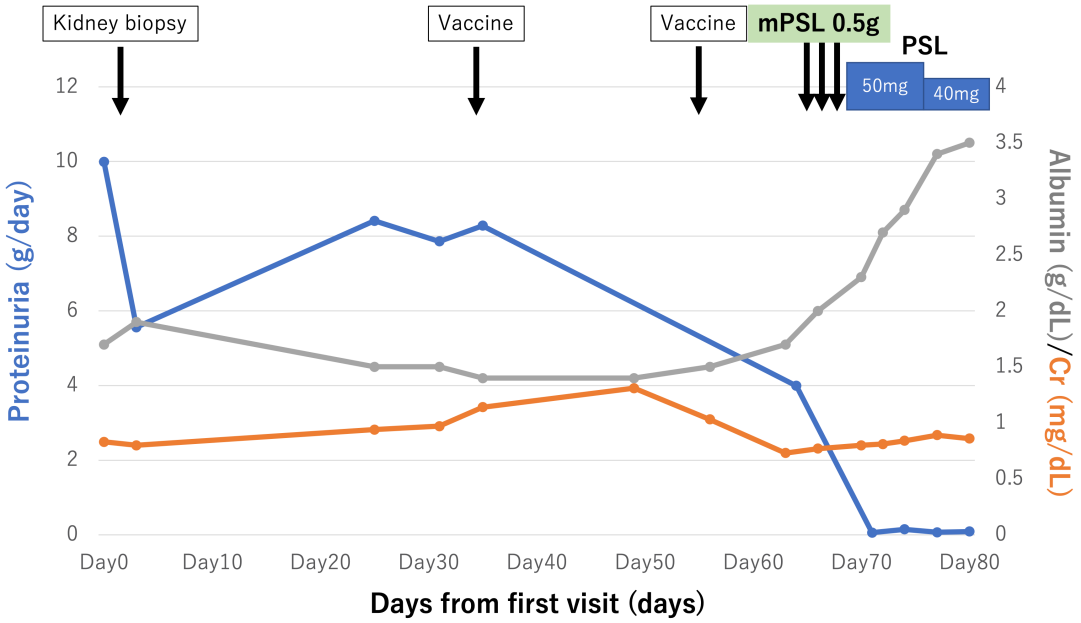

Figure S2. Proteinuria, albumin, and creatinine longitudinally from the first visit to complete remission

Urinary protein excretion (g/day) is indicated by the primary y-axis in the blue line. Serum albumin (g/dL) and creatinine (mg/dL) are shown by the secondary y-axis in gray and orange lines, respectively. On the first visit day, laboratory tests revealed increased urinary protein excretion (9.99 g/day), hypoalbuminemia (1.7 g/dL), and a normal serum creatinine level (0.88 mg/dL). Proteinuria improved to 3.99 g/day with conservative treatment by salt restriction and oral ARB, but the albumin level did not change. The patient was admitted to the hospital again and treated with methylprednisolone (mPSL) 500 mg/day for three consecutive days, followed by 0.8 mg/kg/day (50 mg) of prednisolone. One week after the

administration of steroids, urine protein excretion decreased to 0.06 g/day and the albumin level improved to 2.3 g/dL; thus, complete remission was achieved.

ARB; angiotensin II receptor blocker, mPSL; methylprednisolone, PSL; prednisolone