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【 CASE REPORT 】

IgA Nephropathy that Developed as an Immune-related Adverse Event of Pembrolizumab Complicated with Interstitial Nephritis

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Abstract:
A 70-year-old man received pembrolizumab as a second-line treatment for squamous cell lung cancer of the lower right lobe. After three courses, proteinuria and hematuria were observed, which worsened after seven courses. He was diagnosed with a combination of IgA nephropathy and active interstitial nephritis. Steroid pulse therapy was started, and the dose of prednisolone was gradually reduced from 60 mg/day. Renal dysfunction as an immune-related adverse event of pembrolizumab monotherapy for non-small cell lung cancer has been reported previously. Therefore, establishing a system for the early detection and treatment that distinguishes immune-related glomerular diseases is essential.

Key words: pembrolizumab, immune-related adverse events (irAEs), IgA nephropathy

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Introduction

With the advent of many key drugs in the treatment of lung cancer, a long-term survival has become possible. It is important to prevent deterioration of the renal function to continue treatment. Currently, immune checkpoint inhibitors (ICIs) are widely used in the treatment of lung cancer. Acute kidney injury occurs in approximately 10-29% of immune-related adverse events (irAEs) due to ICI treatment, with acute interstitial nephritis the most common (1).

We herein report a case in which ICI was administered to treat primary lung cancer, and steroid treatment was used to treat IgA nephropathy that developed as an irAE.

Case Report

A 70-year-old man was diagnosed with right lower lobe squamous cell lung cancer (brain metastasis/pleural dissemination stage IVB, programmed death-ligand 1 tumor protection score 1-24%). He received cisplatin/gemcitabine as the first-line treatment in the same year. However, the treatment was discontinued after only one course owing to febrile neutropenia. Pembrolizumab (Pembro) was started as the second-line treatment. No abnormal urinalysis and no obvious renal dysfunction findings were observed before the introduction of Pembro, but urinary protein and urinary occult blood (1+) were observed after the completion of three courses. The tumor had shrunk in size (Fig. 1), but after the completion of seven courses, urinary protein and urinary occult blood (3+) were observed; therefore, the administration of Pembro was discontinued. The renal dysfunction and abnormal urinalysis findings did not improve even after the discontinuation of Pembro, so the patient was hospitalized for an examination, and a renal biopsy was performed.

An additional urinalysis showed elevated urinary β2-microglobulin (β2-MG) and NAG. As a noteworthy blood test finding, the serum IgE was high at 650 IU/mL. Histopathology showed glomerular collapse, paramesangial cell proliferation and matrix expansion (Fig. 2A), and fibrocellular

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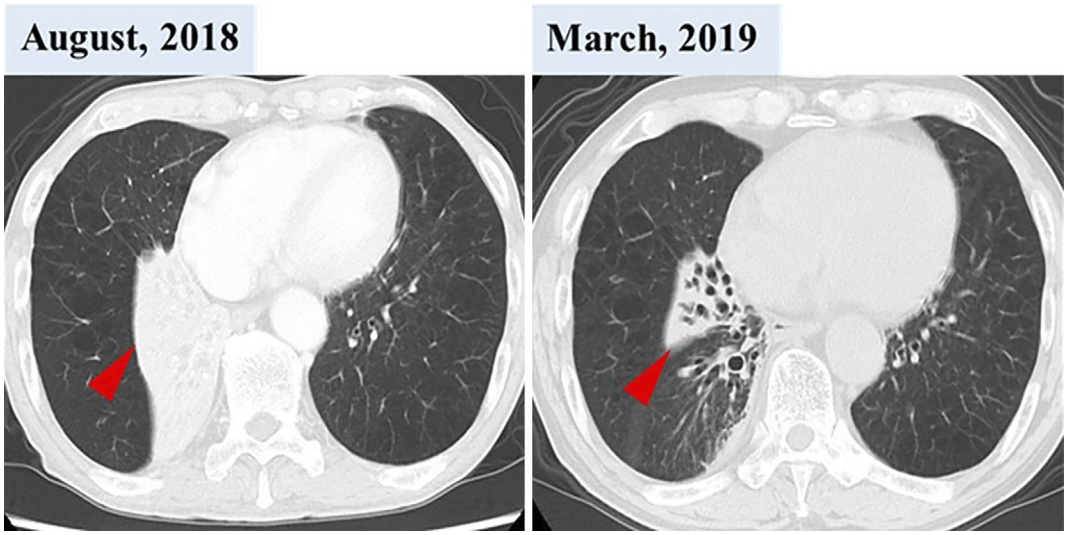

Figure 1. **Image findings. After seven courses of pembrolizumab, the primary tumor size was reduced.**

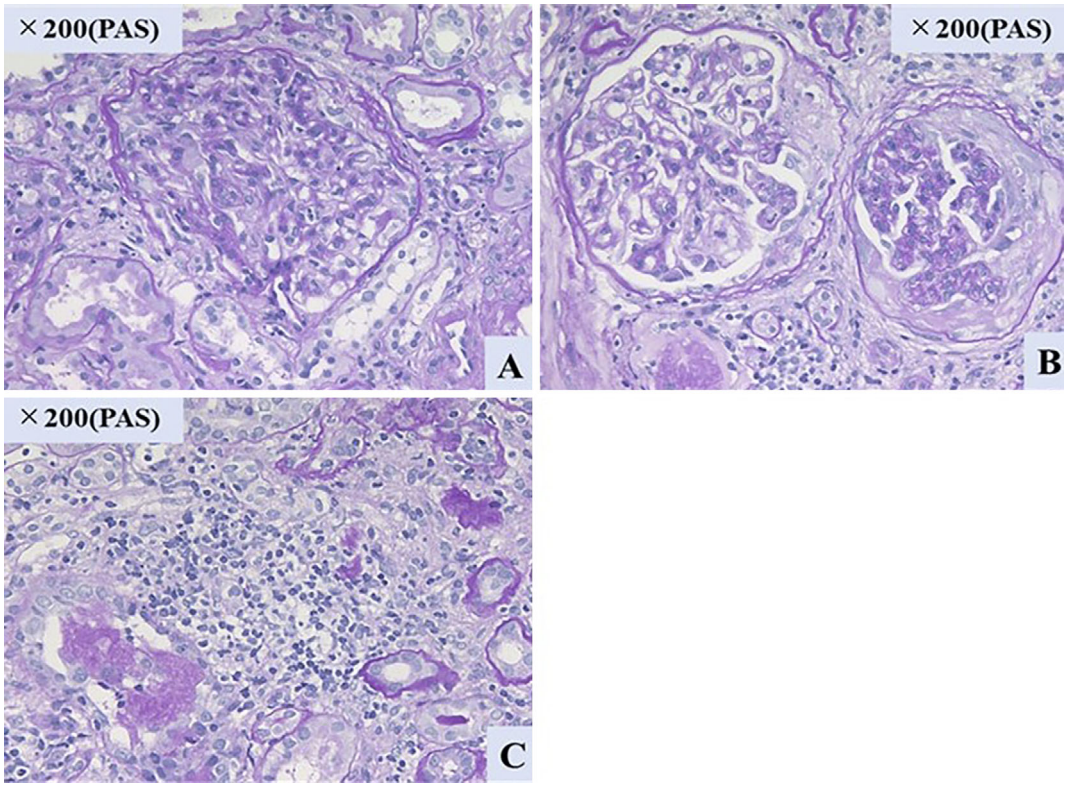

Figure 2. **Histopathological findings. Glomerular collapse, paramesangial cell proliferation and matrix expansion (A), fibrocellular crescent formation (B), and the proximal tubule interstitium showed mononuclear cell infiltration (C).**

crescent formation (Fig. 2B), and the proximal tubule interstitium showed mononuclear cell infiltration (Fig. 2C). In addition, Azan staining showed clear fibrosis of the renal interstitium (Fig. 3). The fluorescent antibody method showed granular deposition of IgA and C3 in mesangial regions. In contrast, only slight deposition of C1q was observed. Other immunostaining methods did not show any significant glomerular deposition of IgG or IgM (Fig. 4A). Electron microscopy revealed the accumulation of electron-dense deposits in the mesangial region (Fig. 4B). Based on these findings, we diagnosed the patient with renal dysfunction of IgA nephropathy with interstitial nephritis.

We started with 1,000 mg methylprednisolone (mPSL) for 3 days and then continued administering prednisolone (PSL) (1 mg/kg). We gradually reduced the PSL at a rate of 5-10 mg every 2 weeks; the current dose of PSL is 40 mg. Re-

garding the renal function, the urinary protein in spot urine tests showed a quantitatively clear decrease, but the estimated glomerular filtration rate (eGFR) did not recover in response to steroid therapy (Fig. 5A). We also found that the urinary N-acetyl-β-D-glucosaminidase (NAG) and β2-MG levels decreased after steroid therapy (Fig. 5B).

Discussion

IgA nephropathy occurs when IgA in the blood forms immune complexes that are deposited in the mesangial region; however, the cause of this immune complex formation is not clear. Among the IgA isoforms present in humans, IgA1 has five O-linked sugar chains added to the hinge portion. IgA1 in patients with IgA nephropathy lack O-linked glycan. The IgA1 and IgG-type autoantibodies causing the glycan deficiency target the N-acetylgalactosamine (GalNAc) exposed on the surface of IgA1. This results in the formation of immune complexes (2). The activation of the immune system following Pembro treatment can induce an autoantibody specific to the sugar chain-deficient IgA1, leading to IgA nephropathy. The Oxford classification for IgA nephropathy in the present case was M0S0E1T2. According to the risk classification in the 3rd edition of the IgA Nephropathy Treatment Guideline in Japan, the clinical severity was C grade III, the histological severity was H-Grade II, and the risk of introducing dialysis was high (3).

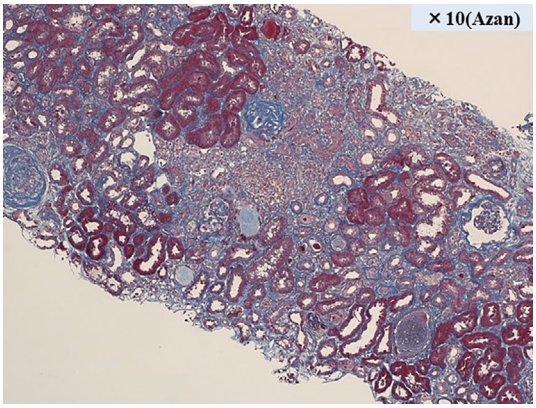

Figure 3. **Kidney tissue image by azan staining. Azan staining showed clear fibrosis of the renal interstitium.**

There have been two reports of IgA nephropathy as an irAE caused by ICIs (4, 5). Oki et al. reported a case of non-small-cell lung cancer treated with Pembro; they discontinued Pembro when the eGFR decreased by approximately 10 mL/min/1.73 m^2, and the renal function was restored (4). However, Kishi et al. reported a case of squamous cell carcinoma treated with nivolumab. They discontinued treatment when the eGFR decreased by approximately 30 mL/min/1.73 m^2; however, the renal function did not recover completely (5).

According to Japan's IgA nephropathy guideline 2017, when urinary protein is ≥1.0 g/day, a steroid pulse of 1 g/day is administered 3 times for 3 days+PSL 0.5 mg/kg/day for 6 months. In addition, the case investigated here was Grade 2 (6). The treatise states that steroids should be used at 0.5-1 mg/kg. There is no evidence of IgA nephropathy being induced by an ICI. However, there was early inflammation; this case involved highly active IgA nephropathy that formed a crescent, and the infiltration of inflammatory cells in the stroma was high. Therefore, we decided to administer a steroid pulse of 1 g/day×3, followed by oral steroids at 1 mg/kg. Other reports corroborate the use of steroids as a better choice for the long-term maintenance of the renal function than not using steroids (7).

Why C1q is deposited is unclear due to the small number of cases. In IgA nephropathy, C1q deposition is present in about 2% to 8.1% of cases, and a previous report noted that

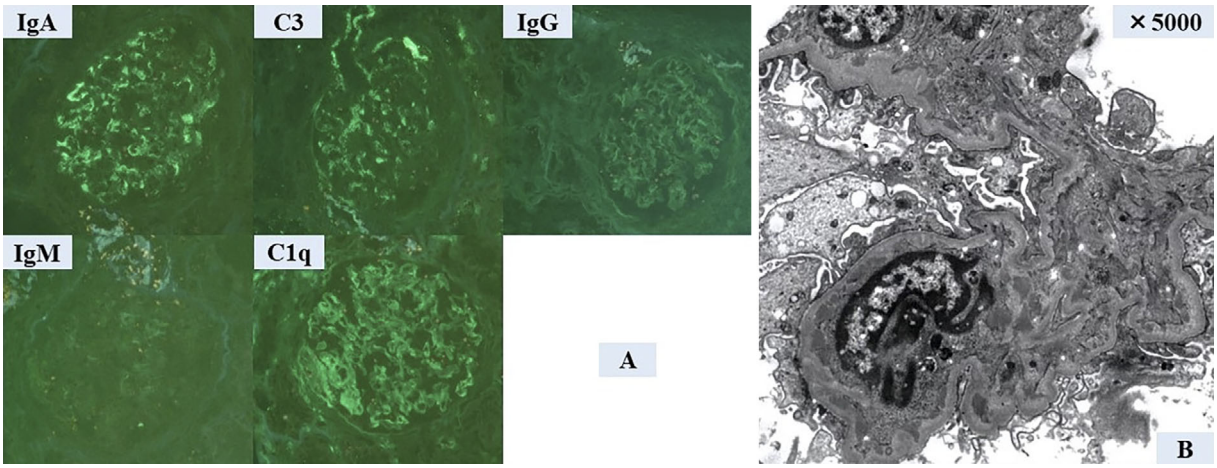

Figure 4. **Findings by immunofluorescence and electron microscopy. The fluorescent antibody method showed granular deposition of IgA and C3 in mesangial regions. In contrast, only slight deposition of C1q was observed, and other immunostaining methods did not show any significant glomerular deposition of IgG or IgM (A). Electron microscopy revealed deposits in the mesangial matrix, with mild mesangial cell hyperplasia and substrate increase (B).**

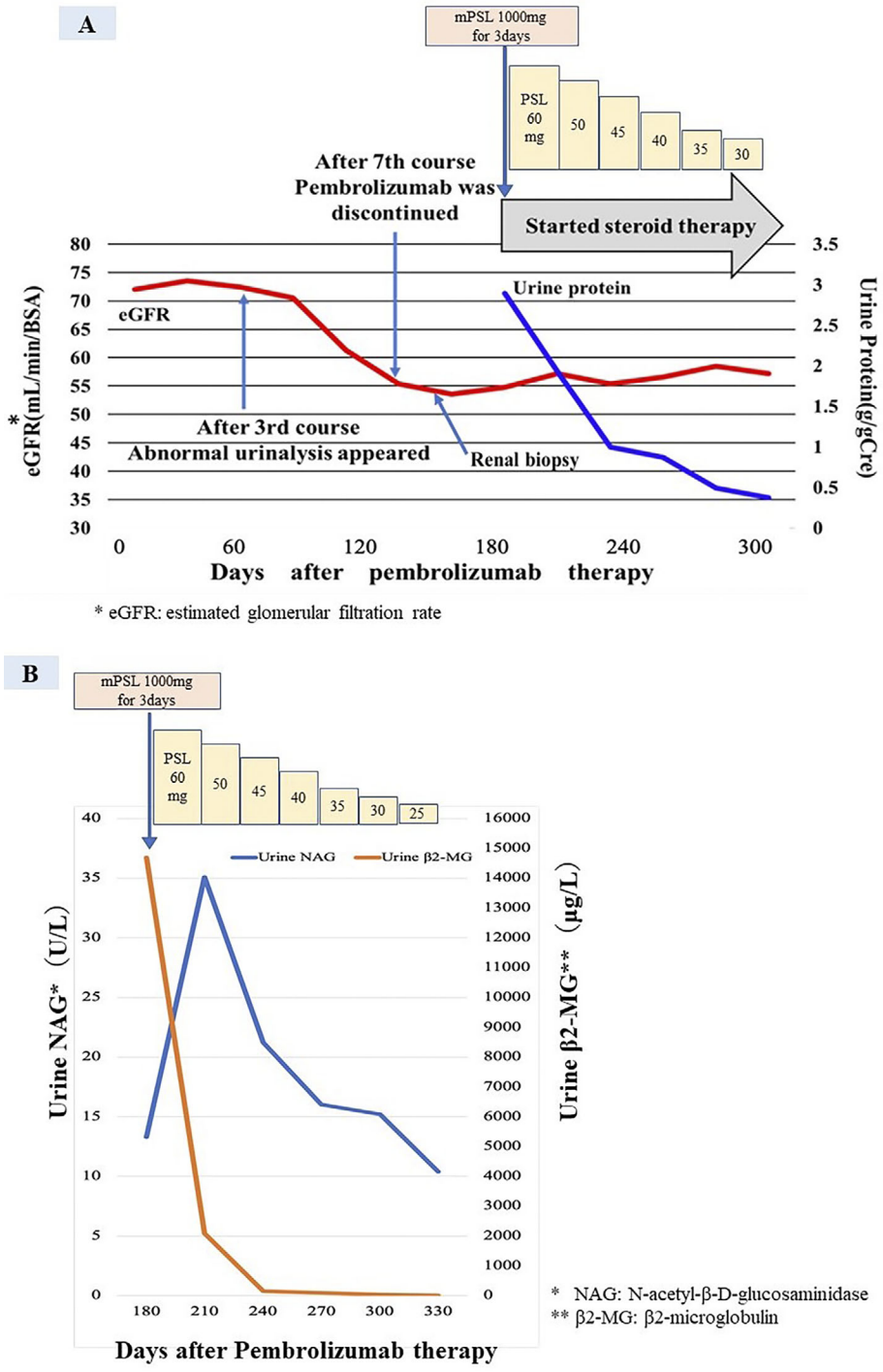

Figure 5. **Progress after the introduction of pembrolizumab. After three courses of pembrolizumab, the renal function began to decline. Discontinuation of pembrolizumab after the completion of seven courses and the start of steroid therapy after a renal biopsy led to a decrease in both urinary protein and urinary occult blood but did not completely restore the renal function (A). We also found that urinary N-acetyl-β-D-glucosaminidase (NAG) and β2-microglobulin (β2-MG) had decreased after steroid therapy (B).**

the renal function was significantly deteriorated and the prognosis poor in cases with C1q deposition (8, 9). In our case, we discontinued Pembro and started steroid therapy when the eGFR dropped by 20 mL/min/1.73 m^2 from the baseline; as a result, proteinuria decreased, but the eGFR did not recover. Pathological findings showed a cellular crescent, indicating irreversible glomerular damage. We predicted that steroids would improve the inflammation in interstitial nephritis. However, in tissues collected by renal biopsy, 5 out of 42 glomeruli had total nodal sclerosis, 6 had fibrous crescents, 2 had fibrous crescents, and 4 had cellular crescents. The observed cellular crescents resulted in a high disease

activity, and steroid pulse therapy failed to prevent structural destruction of the glomerular and tubular interstitium, leading to the resolution of inflammation over time. This is the main reason we considered that the renal function did not recover, even if the patient was given high dose steroids. Furthermore, as mentioned above, the positive C1q findings on immunofluorescence staining may also have contributed to the deterioration of the renal function.

Current guidelines recommend that serum creatinine (SCr) be used as a criterion for ICI-induced renal impairment (10). However, when the renal function is evaluated using SCr alone, irreversible renal damage develop, as in the present case, and it may not be possible to adequately protect the renal function. During ICI administration, early detection, examinations, and intervention for renal impairment are necessary, in addition to being alert for abnormal urinalysis findings.

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

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