


Case Report

Successful pembrolizumab treatment in a patient with metastatic urothelial carcinoma and underlying overlap syndrome involving systemic sclerosis and systemic lupus erythematosus

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Abbreviations & Acronyms

AE = adverse event
 AID = autoimmune diseases
 CT = computed tomography
 GC = gemcitabine plus cisplatin therapy
 irAE = immune-related adverse event
 MVAC = methotrexate, vinblastine, adriamycin and cisplatin therapy
 NSCLC = non-small-cell lung carcinoma
 PD = programmed death
 PD-L1 = programmed death-ligand 1
 SLE = systemic lupus erythematosus
 SSc = systemic sclerosis

Introduction: The safety and efficacy of pembrolizumab administration in patients with urothelial carcinoma and underlying autoimmune disease (including overlap syndrome) is unknown.

Case presentation: We present the case of a 67-year-old woman with cT3N2M0 metastatic renal pelvic cancer who had been treated with prednisolone for overlap syndrome involving systemic sclerosis and systemic lupus erythematosus for 20 years. She had a remarkable response to pembrolizumab as a third-line systemic therapy, wherein the tumor reduced in size and all regional lymph node and pulmonary metastases disappeared. She did not develop any immune-related adverse events or autoimmune disease flare-ups during the treatment.

Conclusion: This case report suggests that pembrolizumab could be beneficial to patients with urothelial carcinoma and underlying well-controlled overlap syndrome.

Key words: autoimmune disease, metastatic urothelial carcinoma, overlap syndrome, pembrolizumab, renal pelvic cancer.

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Keynote message

The safety and efficacy of using PD-1 inhibitors in patients with underlying AID is unknown. We present the case of a 67-year-old woman with metastatic urothelial carcinoma and pre-existing well-controlled overlap syndrome involving SSc and SLE. This case report suggests that pembrolizumab could be beneficial to patients with urothelial carcinoma and underlying well-controlled overlap syndrome.

Case presentation

A 67-year-old woman was admitted with suspicion of a right renal tumor at a general checkup ultrasound examination. CT showed a right renal tumor of 10 cm with invasion into the peripelvic fat and two para-aortic lymph node metastases. Retrograde pyelography revealed a filling defect in the lower calyx but urine cytology was suspicious. To make a definite diagnosis, percutaneous renal tumor biopsy was performed under ultrasound guidance. Renal tumor pathology revealed urothelial carcinoma. Finally, she was diagnosed with cT3N2M0 renal pelvic carcinoma. She had been diagnosed with overlap syndrome involving SSc and SLE 20 years ago because of malar rash, photosensitivity, Raynaud's phenomenon, swollen fingers, a high anti-centromere antibody titer (index: 152.0, normal range <10), and a high anti-nuclear antibody titer (1:640). She had been treated for overlap syndrome with a maintenance dose of prednisolone 2.5–5 mg; overlap syndrome had been well-controlled and asymptomatic for several years. Induction systemic treatment was initiated with gemcitabine (1000 mg/m²), which was administered on days 1, 8, and 15, and cisplatin (70 mg/m²) on day 1 of a 28-day cycle (GC). She experienced grade 3 neutropenia and thrombocytopenia during GC treatment. However, the para-aortic lymph node metastases progressed after three cycles. Therefore, we continued the second-line systemic therapy comprising methotrexate

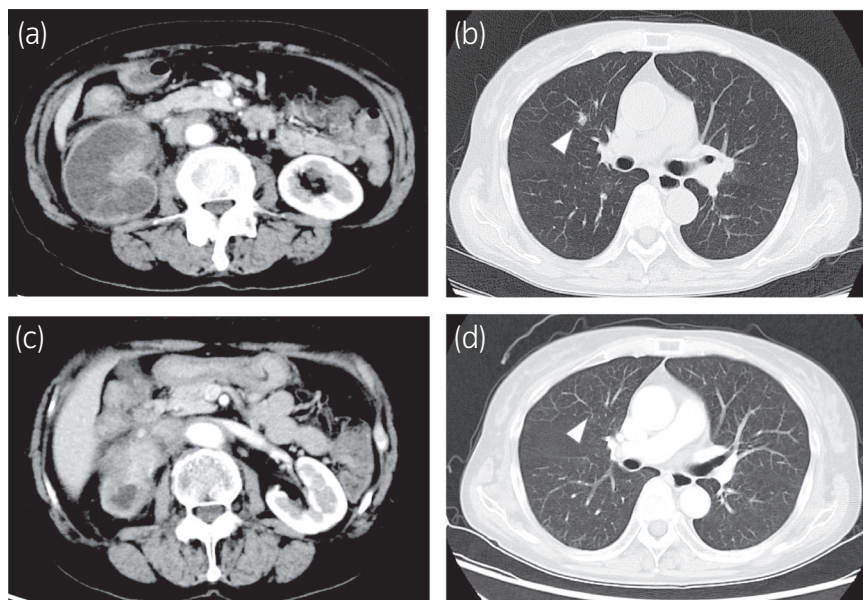


Fig. 1 (a) CT scan shows a right renal pelvic mass and para-aortic lymph node swelling at the time of pembrolizumab initiation. (b) CT scan shows a lung metastasis (arrowhead) at the time of pembrolizumab initiation. (c) CT scan shows a primary right renal pelvic tumor shrinkage after 6 months from pembrolizumab initiation. (d) CT scan shows disappearance of lung metastasis (arrowhead) after 6 months from pembrolizumab initiation.

(30 mg/m²) on days 1 and 15, along with vinblastine (3 mg/m²), doxorubicin (30 mg/m²), and cisplatin (70 mg/m²) on day 2 for a 28-day cycle (MVAC). She experienced grade 2 anorexia, grade 3 thrombocytopenia, and grade 4 neutropenia. After three cycles of MVAC therapy, she developed multiple lung metastases (Fig. 1a,b). Pembrolizumab was administered as a third-line systemic therapy every 3 weeks. The primary tumor reduced in size and all lymph nodes and pulmonary metastases disappeared (Fig. 1c,d). The response continued until the latest follow-up date, which was 6 months from the initiation of pembrolizumab. Daily administration of prednisolone (2.5 mg) was continued throughout pembrolizumab therapy, and she did not develop any AEs including irAEs or overlap syndrome flares. Anti-nuclear antibody (1:640–1:1280) and centromere antibody titer (index: 142–152) did not change significantly during treatment and were associated with neither treatment response nor AEs.

Discussion

Pembrolizumab is an immune-oncologic drug that acts to inhibit PD-1, a cell surface receptor that regulates T-cell activation. It is recommended in the guidelines from the National Comprehensive Cancer Network¹ and the European Urological Association² for patients with platinum-based chemotherapy-resistant urothelial carcinoma. Clinical trials with PD-1 inhibitors exclude patients with pre-existing AID because of concerns associated with an increased risk for developing serious irAEs.³ In addition, corticosteroids are commonly used to treat AID, and they potentially have an immunosuppressive effect.⁴ Therefore, the safety and efficacy of PD-1 inhibitors in such patients is unclear. Our patient had a remarkable response to pembrolizumab with no AEs.

SSc may overlap with SLE.⁵ It is important to regularly monitor serious SSc complications, such as pulmonary arterial hypertension, pulmonary fibrosis, malignant hypertension and acute renal failure.⁵ SSc-SLE overlap syndrome patients

are typically female, Asian, tend to be younger than pure SSc patients at diagnosis, and more frequently have pulmonary fibrosis than those with pure SSc.⁶ Throughout the course of pembrolizumab treatment, our case did not develop any skin lesions, renal crises, or interstitial lung disease.

Some retrospective studies have reported that immune-oncologic treatment for patients with underlying AID is generally manageable. In a study comprising 52 melanoma patients with pre-existing AID treated with PD-1 inhibitor, 38% of patients had flare-ups and 20% developed irAEs, of which 10% were grade 3 with no grade 4 or 5 events.⁷ In another study comprising 56 patients with AID and NSCLC, who were treated with PD-1/PD-L1 inhibitor, 23% developed flare-ups and 38% developed irAEs, of which 26% were grade 3 or 4 with no grade 5 events.⁸ These rates of AEs were similar to the trials, wherein patients with AID were excluded.^{7,8} In addition, 50% of the patients with NSCLC and symptomatic AID at the time of PD-1/PD-L1 inhibitor initiation developed flare-ups. On the other hand, only 18% of the other patients who were initially asymptomatic developed flare-ups.⁸ In our case, the overlap syndrome had been well-controlled for several years and the patient was asymptomatic at the time of pembrolizumab initiation. Thus, the possibility of a flare-up was considered to be low.

Corticosteroids are commonly used in patients with AID. Those drugs suppress the immune system by inhibiting lymphocyte activation and inducing apoptosis in lymphocytes.⁹ The immunosuppressive effect of corticosteroids can theoretically reduce the efficacy of PD-1 inhibitors. In a retrospective study of patients with NSCLC treated with PD-1/PD-L1 inhibitors, baseline corticosteroid use of more than 10 mg of prednisone-equivalent was correlated with worse clinical outcome compared with those who administered <10 mg of prednisone-equivalent.¹⁰ Generally, stable SLE or SSc patients are maintained on low-dose glucocorticoids (2.5–7.5 mg/day).^{11,12} Three cases with SSc or SLE treated with PD-1 inhibitors were reported in the NSCLC study, but

detailed information on the treatments and efficacy was not described in the report.⁸ In an NSCLC and SLE case treated with pembrolizumab, who had been well controlled with prednisolone 5 mg and tacrolimus 1 mg, complete remission was attained.¹³ Our patient also had been treated with 2.5–5 mg prednisolone for 20 years and we speculate that those low-dose corticosteroid (in the range of physiologic adrenal secretion) might not affect the response to pembrolizumab.

Further studies are required to clarify the safety and efficacy of pembrolizumab and optimal maintenance dose of immunosuppressants in patients with AID.

Conclusions

This case report suggests that pembrolizumab could be beneficial to patients with urothelial carcinoma and pre-existing well-controlled AID.

Conflict of interest

The authors declare no conflict of interest.

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Editorial Comment

Editorial Comment to Successful pembrolizumab treatment in a patient with metastatic urothelial carcinoma and underlying overlap syndrome involving systemic sclerosis and systemic lupus erythematosus

Pembrolizumab is a standard therapy for patients with platinum-based chemotherapy-resistant urothelial carcinoma.¹ Although pembrolizumab administration for patients with pre-existing autoimmune disease (AID) needs careful considerations, Kurokawa *et al.* reported a fortunate case of advanced renal pelvic cancer who was successfully treated with third-line pembrolizumab.² They also reported the potential role of monitoring of AID titer (anti-nuclear antibody and centromere antibody) during treatment for management. However, an indication of immunotherapy needs to be careful consideration because 23–38% of patients with preexisting AID experienced flares in other cancers, especially in patients with symptomatic AID (up to 50%).^{2,3} Furthermore, the optimal dose of maintenance corticosteroids during immune-oncologic therapy remains unclear. Although the previous study

suggested that low-dose corticosteroids (<10 mg) were not associated with worse outcomes in patients with non-small-cell lung carcinoma treated with programmed death-1/programmed death-ligand 1 inhibitors,⁴ the precise mechanism is not yet elucidated. Therefore, the safety and efficacy of pembrolizumab in patients with preexisting AID need further studies. Currently, the indication of immune-oncologic therapy might be limited to the selected patients with asymptomatic and stable AID.

The negative aspect of corticosteroids uses for immune-oncologic therapy needs attention. A previous study suggested the reduced antitumor effect of immune-oncologic therapy in the early use of corticosteroids.⁵ They suggested the role of memory CD8⁺ T cells for the antitumor response. Their experimental model showed that simultaneous administration of corticosteroids impaired immune-oncologic responses mediated by the CD8⁺ T cell proliferation reduction. Also, early administration (≤ 7 weeks) of corticosteroids due to the severe immune-related adverse events decreased low-affinity memory T cells and resulted in shorter overall survival in melanoma patients. Therefore, we need to be aware both

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