Case Report

A case of pseudoprogression in avelumab maintenance therapy for metastatic bladder cancer

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Abbreviations & Acronyms
CT = computed tomography
GC = gemcitabine and cisplatin
ICIs = immune checkpoint inhibitors
irAE = immune-related adverse effect
UC = urothelial carcinoma

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Introduction: A unique phenomenon of immune therapy is pseudoprogression; however, a definite mechanism and predictive factors remain unclear. We herein report a case of pseudoprogression with avelumab maintenance therapy.

Case presentation: A 67-year-old male diagnosed with muscle-invasive bladder cancer with lung metastasis was treated with four cycles of gemcitabine and cisplatin chemotherapy immediately after cystectomy and ileal conduit urinary diversion. The response to cisplatin-based chemotherapy was a stable disease. Avelumab maintenance therapy was started after first-line chemotherapy but was interrupted due to his general fatigue after the third administration of avelumab. At that time, computed tomography (CT) revealed an increased size of lung metastases. Two months after the interruption, avelumab maintenance therapy was restarted. At the end of the seventh dose of avelumab administration, CT showed a dramatic reduction of lung metastatic tumors.

Conclusion: Pseudoprogression may also occur with avelumab maintenance therapy in metastatic bladder cancer.

Key words: avelumab, bladder cancer, maintenance, metastasis, pseudoprogression.

Keynote message

Pseudoprogression is a unique and rare phenomenon. One of the issues in cancer immune checkpoint therapy is distinguishing pseudoprogression from true progression. Herein, we describe a case of pseudoprogression in a metastatic bladder cancer patient receiving avelumab maintenance therapy.

Introduction

Avelumab is an anti-programmed death-ligand 1 antibody, a type of immune checkpoint inhibitor (ICI). It is the first drug to be approved for maintenance therapy for unresectable and/or metastatic urothelial carcinoma (UC) in the post-platinum chemotherapy setting.

One unique and rare phenomenon of immune therapy is pseudoprogression, which is an atypical response of solid tumors under treatment with ICIs and is defined as an increase in the tumor size and number followed by tumor regression. The incidence of pseudoprogression in patients treated with ICIs has been reported to be 2–12% in previous clinical trials for various cancers.[1] However, so far there have been no reports on pseudoprogression with avelumab therapy, especially in the maintenance setting in advanced UC patients.

Herein, we describe a case of pseudoprogression in a patient treated with avelumab maintenance therapy for metastatic UC.

Case presentation

A 67-year-old male visited our hospital because of severe gross hematuria and pollakiuria in 2020. Computed tomography (CT) revealed a bladder tumor that was located almost the entire circumference of the bladder wall, left hydronephrosis, and solitary lung mass (Fig. 1a[1–3]). Transurethral resection of bladder tumor showed UC with muscle invasion. The patient received a percutaneous biopsy for the lung mass and the pathology was compatible with

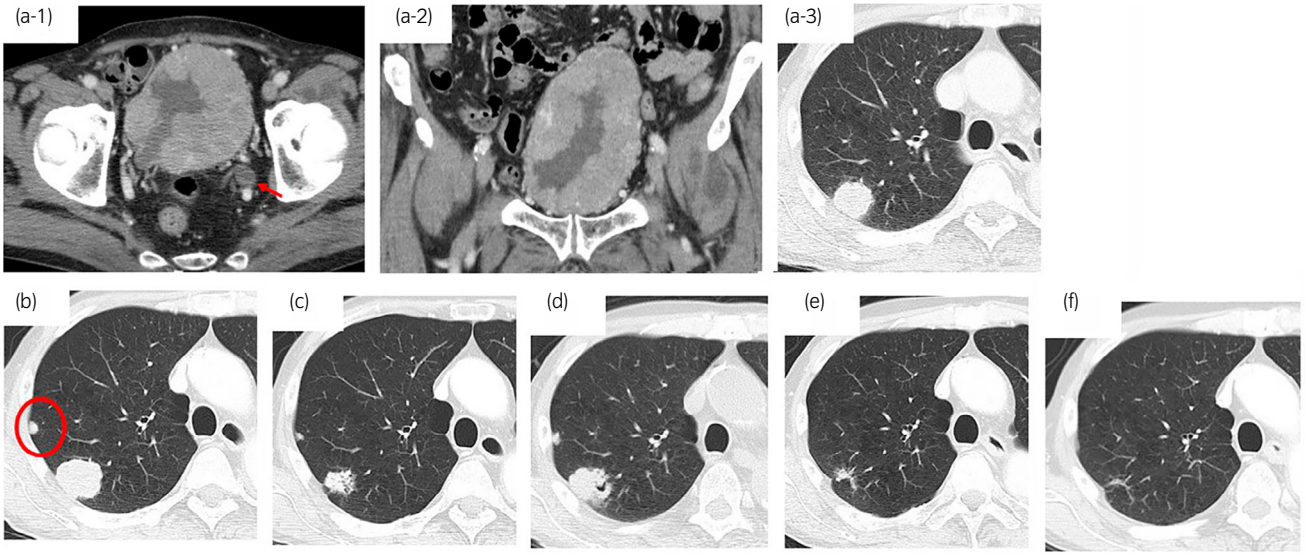

Fig. 1 (a) CT findings at the first visit, a-1) horizontal view of bladder cancer and left hydroureter (red arrow); a-2) coronal view of bladder cancer; a-3) horizontal view of single lung metastasis. (b) CT findings just before first-line GC chemotherapy, showing the enlarged main lung metastatic lesion as well as a new small lesion (red circle). (c) CT findings after four cycles of GC chemotherapy, showing the reduction of metastatic tumor size. The final response was determined as a stable disease. (d) CT findings after third administration of avelumab maintenance therapy, showing the increased size of lung metastases. (e) CT findings after seventh dose of avelumab administration show a dramatic reduction in main lung metastatic tumor size and a small lesion of another lung metastasis, which almost disappeared. (f) CT findings 8 months after the resumption of avelumab administration therapy show no regrowth of lung metastatic tumor.

metastatic UC. As the patient had local symptoms and renal dysfunction (eGFR: 56 mL/min/1.73 m2) due to bladder cancer, he underwent a simple cystectomy and ileal conduit urinary diversion.

Two months after surgery, a CT scan revealed the main lung metastatic lesion had increased in size and there were new small lesions (Fig. 1b). His eGFR was improved to 77.2 mL/min/1.73 m^2 after the procedure. So, we started gemcitabine and cisplatin (GC) systemic chemotherapy (1000 mg/m^2 of gemcitabine: days 1, 8, and 15, and 70 mg/m^2 of cisplatin on day 2, every 28 days).

After four cycles of GC therapy, CT revealed the reduction of metastatic tumor size, and the final response was determined as a stable disease using the RECIST v1.1 criteria (Fig. 1c). Six months after surgery, GC chemotherapy was switched to avelumab maintenance therapy (10 mg/kg of avelumab every 2 weeks). After the third administration of avelumab, it was interrupted because he complained of general fatigue and poor oral intake. He was then urgently hospitalized because of his severe general fatigue, high fever, low blood pressure, and hyponatremia. Steroid replacement therapy was immediately started due to suspicions of adrenocortical insufficiency. After hospitalization, detailed examination such as repeat hormonal blood tests including ACTH and cortisol and pituitary MRI showed no abnormality; therefore, we concluded that his symptoms were not associated with adrenocortical insufficiency due to avelumab. After admission to our hospital, CT taken 6 days after the third cycle of avelumab maintenance therapy revealed an increased size of lung metastases (Fig. 1d).

As novel subsequent therapy, such as enfortumab vedotin, has not been approved in Japan, he resumed avelumab maintenance therapy 2 months after the interruption. CT at end of the seventh dose of avelumab administration revealed a dramatic reduction of tumor masses (Fig. 1e). We assessed the phenomenon of the initial increased size of the main lung metastatic tumor after the third administration of avelumab was pseudoprogression. The patient is able to maintain the effect of avelumab maintenance therapy for 8 months after the resumption of therapy (Fig. 1f).

Discussion

Platinum-based chemotherapy is the standard of care for first-line treatment against advanced UC. Although the disease control rate of cisplatin-based chemotherapy is about 75–80% in advanced UC, most patients experience tumor progression within approximately 6–9 months, which is a serious problem in the treatment of advanced UC. The JAVELIN bladder 100 trial found that avelumab maintenance therapy significantly prolonged overall survival by 7 months compared with best supportive care alone among advanced UC patients who had disease control with first platinum-based chemotherapy.[2] Avelumab every 2 weeks maintenance therapy was approved in February 2021 in Japan.

ICIs, including avelumab, have some specific phenomena such as pseudoprogression. Pseudroprogression occurs across various solid tumor types. Previous clinical trials have shown that the incidence of pseudoprogression is 9.1–11.5% in nivolumab and 6.8% in atezolizumab.[1,3] Although a definite mechanism remains unclear, it is believed that pseudoprogression is a consequence of activated T-cell recruitment at the tumor site. This leads to inflammation and a falsely increased tumor size before these cells exert their antitumor effects.It is important to distinguish pseudoprogression from true progression, as patients with pseudoprogression may benefit from

continuing ICI therapy, whereas patients with true disease progression need to be considered for alternative treatment. The clinical factors and peripheral blood biomarkers, including circulating tumor DNA and some proteins, that distinguish pseudoprogression and true disease progression have been extensively studied, but none are yet established for clinical use.[5]

Our patient had general fatigue and appetite loss inducing electrolyte abnormalities and needed to take intravenous infusion therapy for correcting his electrolyte imbalance. CT revealed an increased size of lung metastases. If we have recognized true progression in our case, we would switch to next-line chemotherapy such as taxane-based chemotherapy because novel 3rd line therapy such as enfortumab vedotin has not been approved in our country at that time. In the present patient, we continued avelumab maintenance therapy and a partial response was obtained. Thus, we recognized pseudoprogression. The concept of avelumab switch maintenance therapy is to maintain the response of first-line chemotherapy, and, therefore, further response to avelumab has been reported to be only 9.7% of the confirmed objective response in the JAVELIN bladder 100 trial.[2] Switch maintenance therapy against UC is a novel and unique therapeutic strategy. Accumulated real-world data are needed to recognize the true course of the clinical response to avelumab maintenance therapy. The development of useful biomarkers that reflect the true clinical response to ICIs is warranted.

Conclusion

This is the first case report showing pseudoprogression in a patient treated with avelumab maintenance therapy for metastatic UC.

Acknowledgments

None.

Author contributions

Nozomi Hayakawa: Conceptualization; investigation; writing – original draft. Eiji Kikuchi: Project administration; supervision; writing – review and editing.

Conflict of interest

Eiji Kikuchi received Honoraria from Merck Biopharma.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

Written informed consent has been obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

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