Durable response after the discontinuation of pembrolizumab treatment due to an adverse event in a patient with advanced endometrial cancer: A case report

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Abstract. The persistence of antitumor effects has been reported after the completion of treatment with immune checkpoint inhibitors (ICIs) for various types of carcinoma, such as malignant melanoma, exhibiting a durable response. A durable response has also been noted after the discontinuation of treatment at an early stage due to adverse events, including in renal pelvic cancer, pancreatic cancer and intrahepatic cholangiocarcinoma; however, to the best of our knowledge, a similar case report has not yet been published in the malignant gynecological tumor field. The present study described a patient with refractory advanced endometrial cancer in whom the administration of pembrolizumab was discontinued after the completion of the 7th course due to renal dysfunction; however, persistent tumor-reducing effects and decreases in the levels of tumor markers were noted for more than 18 months after the cessation of treatment. Pembrolizumab may be continuously administered to some patients for a long period, whereas a durable response is achieved by others even after its discontinuation at an early stage; therefore, difficulties are associated with selecting an appropriate duration of administration. Further studies are required to search for biomarkers that facilitate high-accuracy effect predictions, and to establish an optimal administration period in consideration of specific adverse reactions to ICIs and cost-effectiveness.

Introduction

Only a few types of chemotherapeutic agents are currently approved for the treatment of advanced/recurrent endometrial cancer and their efficacy is limited (1,2). The anti-programmed death 1 (PD-1) monoclonal antibody, pembrolizumab, recently became available for solid tumors with high-frequency microsatellite instability (MSI-High). MSI-High is observed in approximately 16% of patients with endometrial cancer (3,4) and its response rate to pembrolizumab is approximately 57%, which is higher than that in patients with other carcinomas (5); therefore, this agent is utilized as a new treatment option for advanced/recurrent endometrial cancer.

Previous studies reported that the antitumor effects of immune checkpoint inhibitors (ICIs), including pembrolizumab, persisted even after the completion of treatment for approximately 2 years, demonstrating a durable response in patients with malignant melanoma or lung cancer (6,7). A durable response was also noted in patients in whom administration was discontinued at an early stage due to adverse events in renal pelvic cancer, pancreatic cancer, and intrahepatic cholangiocarcinoma (8-10). However, a similar case report has not yet been published in the malignant gynecological tumor field.

We herein describe a patient with advanced endometrial cancer in whom the administration of pembrolizumab was discontinued due to renal dysfunction and its antitumor effects persisted for more than 18 months. Notably, difficulties are associated with selecting an appropriate duration of administration of ICIs. The present study also discussed the optimal administration period of ICIs.

Case report

A 79-year-old woman (gravida 3, para 3) was referred to Jichi Medical University Hospital (Shimotsuke, Japan) with massive vaginal bleeding in May 2019. She had a history of cerebral infarction, dementia, interstitial pneumonia, hypertension, hyperlipidemia, and hyperuricemia.

Colposcopy showed a fragile hemorrhagic mass exposed from the uterine ostium. Irregular thickening of the endometrium was detected with transvaginal ultrasonography. Endometrial biopsy led to a diagnosis of Grade 3 endometrioid carcinoma. Hematology showed anemia (Hb: 9.0 g/dl) and an elevated carcinoembryonic antigen (CEA) level of 9.2 ng/dl. Carbohydrate antigen 19-9 (CA19-9) and CA-125 levels were

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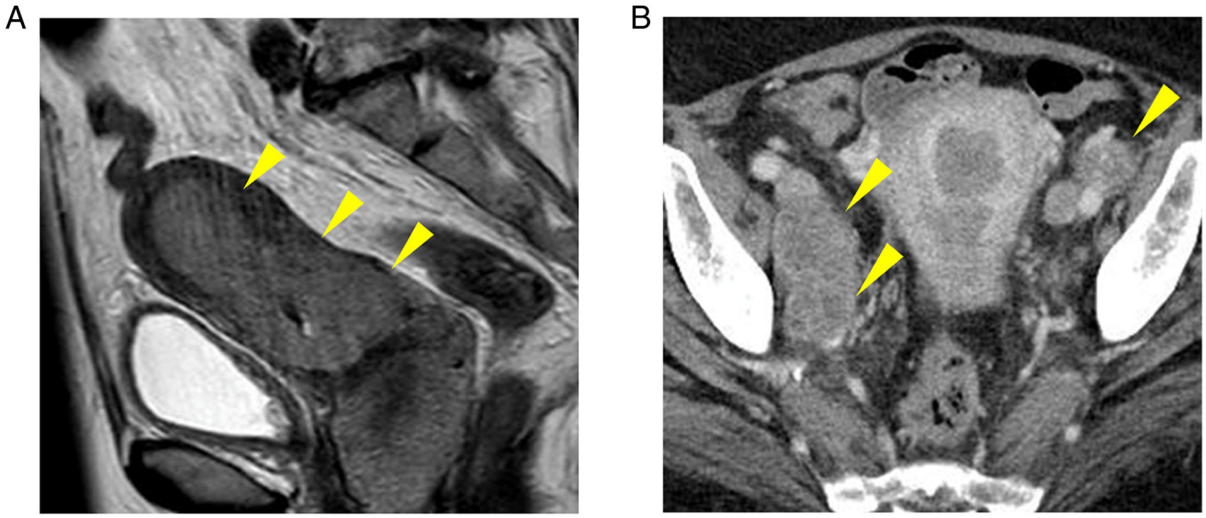

Figure 1. (A) T2-weighed magnetic resonance imaging of the pelvis showed a uterine body tumor (arrowheads) invading the uterine cervix. (B) Computed tomography revealed pelvic lymph node metastases (arrowheads).

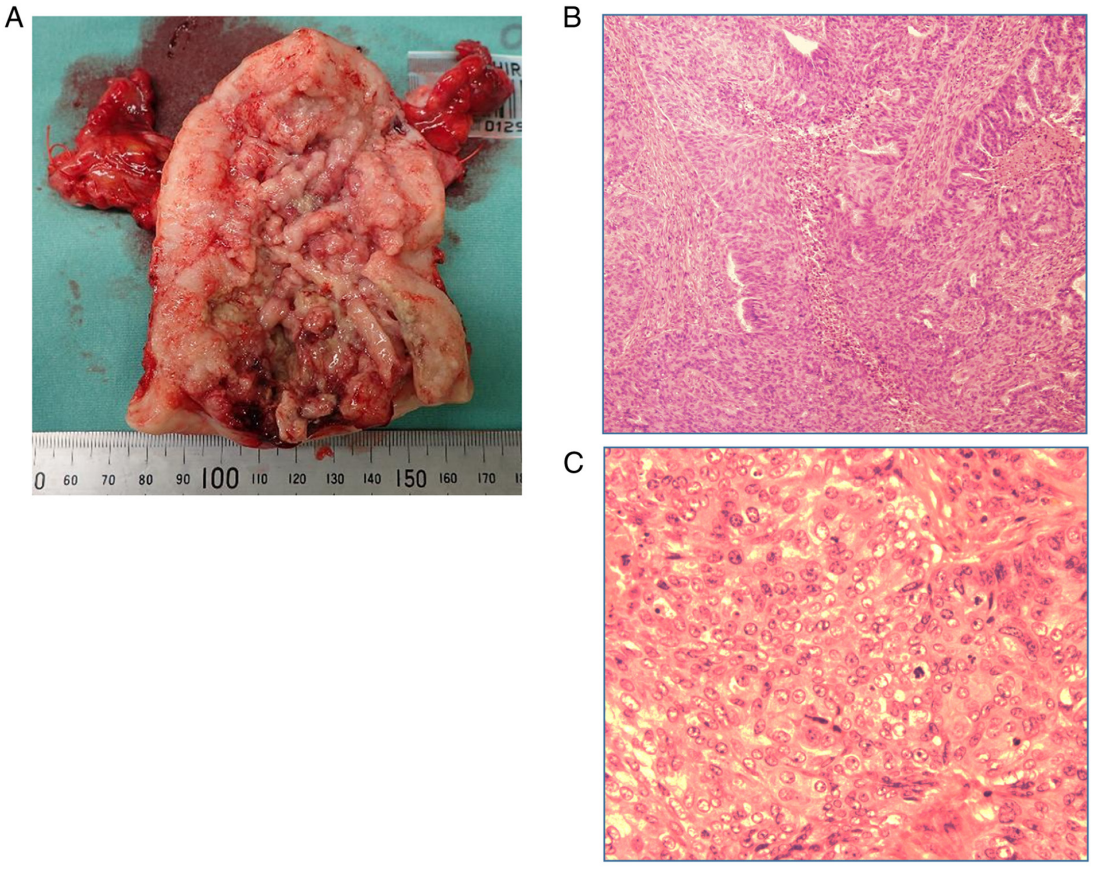

Figure 2. (A) Gross appearance of the uterine body tumor. The uterine cavity was occupied by a necrotic tumor invading the uterine cervix. (B) Histological examinations showed endometrioid carcinoma composed of more than 50% solid components, indicating grade 3. (C) Tumor cells had marked nuclear atypia with prominent nucleoli and mitosis. Magnification, (B) x100 and (C) x400.

within normal ranges. Pelvic magnetic resonance imaging revealed a mass involving the uterine body to cervix (Fig. 1A). Multiple intrapelvic and para-aortic lymph node metastases were observed on abdominal computed tomography (Fig. 1B). Emergency surgery (abdominal total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node biopsy) was performed for hemorrhage control. A postoperative histopathological examination suggested Grade 3 endometrioid carcinoma (Fig. 2A-C). According to the International Federation of Gynecology and Obstetrics staging system, the stage was evaluated as IIIC2 (pT2N2M0).

The TC regimen (paclitaxel, 175 mg/m^2; carboplatin, AUC6 at 3-week intervals) was introduced as postoperative adjuvant

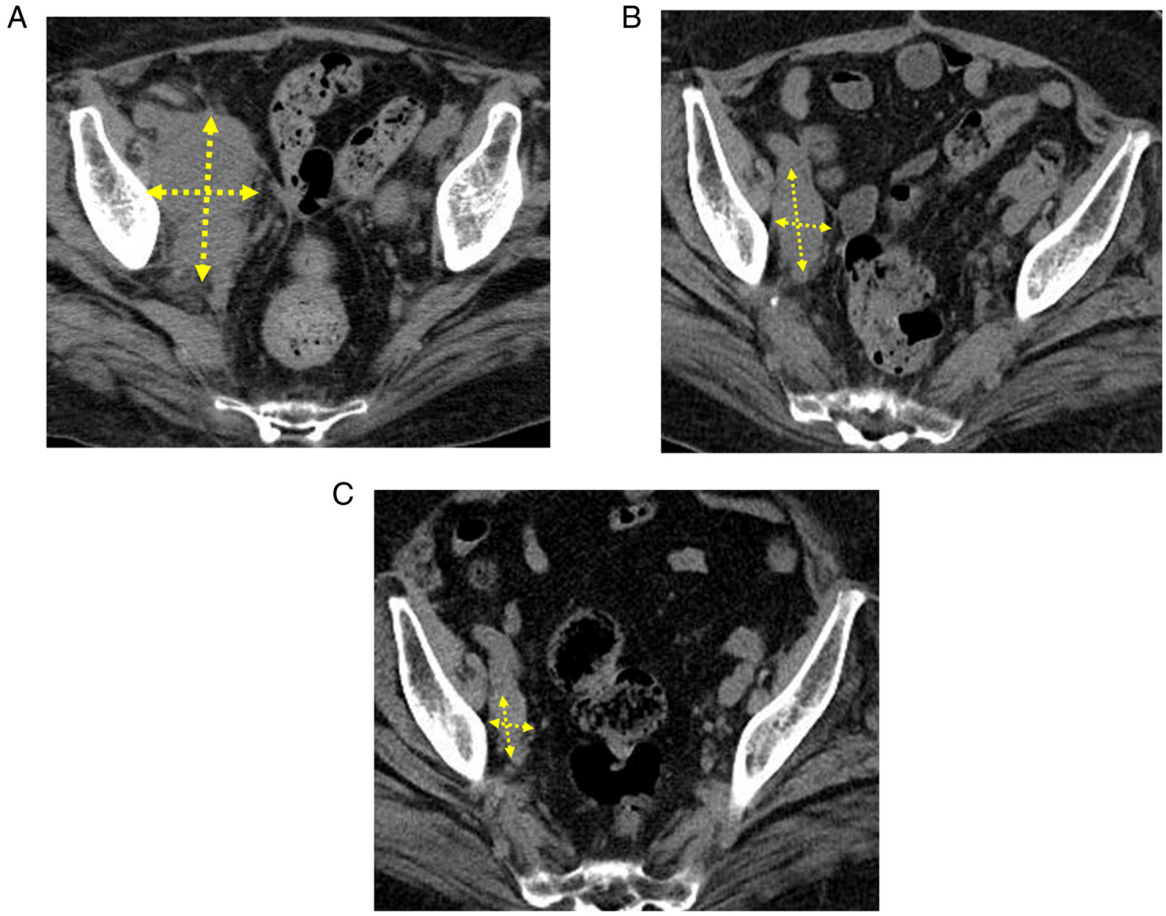

Figure 3. Computed tomography findings revealed a durable response after the discontinuation of pembrolizumab monotherapy. (A) Right pelvic lymph node metastases after the AP regimen. (B) Right pelvic lymph node metastases after 7 cycles of pembrolizumab monotherapy. (C) Right pelvic lymph node metastases decreased in size 18 months after the discontinuation of pembrolizumab. Yellow crossed arrows indicate the metastatic pelvic lymph nodes. AP, doxorubicin and cisplatin.

chemotherapy. However, paclitaxel induced anaphylactic shock and, thus, its administration was discontinued. Three courses of the AP regimen (doxorubicin, 60 mg/m^2; cisplatin, 50 mg/m^2 at 3-week intervals) were subsequently administered; however, the enlargement of multiple metastatic lymph node foci (Fig. 3A) and an increase in the level of CEA were noted. Furthermore, cisplatin-related renal dysfunction occurred. After confirming MSI-High in the tumor tissue, pembrolizumab monotherapy (200 mg/body at 3-week intervals) was initiated. Marked reductions were observed in the size of enlarged metastatic lymph node foci (Fig. 3B) and the level of CEA decreased to the reference range. However, Common Terminology Criteria for Adverse Events grade 3 renal dysfunction was protracted and, thus, pembrolizumab therapy was discontinued after the completion of the 7th course. After its discontinuation, metastatic lymph node foci continued to decrease in size and the level of CEA remained within the reference range. During the 18-month follow-up, a durable response was achieved (Fig. 3C). Since renal dysfunction remains protracted, the patient is being followed up without the resumption of pembrolizumab therapy in consideration of her age and comorbidities.

Discussion

We herein report a patient with advanced endometrial cancer in whom pembrolizumab therapy was discontinued due to renal dysfunction; nevertheless, a durable response was achieved over a long period.

ICIs, including pembrolizumab, inhibit PD-1/programmed death ligand 1 (PD-L1) and exert antitumor effects through T-cell activation; therefore, immune-related adverse events (irAEs), such as dysthyroidism, which are not observed after the administration of conventional cytotoxic anticancer drugs, need to be considered. The administration of pembrolizumab was previously discontinued at an early stage due to adrenal insufficiency in a patient with renal pelvic cancer (8), diabetic ketoacidosis in a patient with pancreatic cancer (9), and bullous pemphigoid in a patient with intrahepatic cholangiocarcinoma (10); however, its antitumor effects persisted. To the best of our knowledge, a similar case report has not yet been published in the malignant gynecological tumor field. In these patients, the antitumor immune activity of pembrolizumab may have persisted for a long period even after its discontinuation; therefore, the onset of irAEs may be paradoxically a clinical predictive biomarker of a durable response.

The long-term administration of ICIs is possible in some patients with the maintenance of antitumor effects. On the other hand, a durable response is achieved in other patients even though the administration of ICIs is discontinued at an early stage due to adverse events. Therefore, difficulties are associated with the selection of an appropriate duration of administration. The

tumor mutation burden, PD-L1 expression, mismatch-repairing function deficiency, and MSI status have been proposed as predictive biomarkers of ICIs (11-14). However, a predictive biomarker with which the optimal administration period of ICIs may be selected has yet to be identified. In a cohort study on patients with malignant melanoma, there was no relapse during a long-term follow-up (≥2 years) in approximately 90% of patients who achieved a complete response (CR) (6). Therefore, the achievement of CR may be a clinical predictive biomarker for the completion of administration. A durable response after the early completion of ICIs in patients achieving CR or a partial response (PR) is currently being examined in the Safe Stop study on patients with malignant melanoma (15). The findings obtained will contribute to the establishment of an optimal administration period for ICIs.

The combination of pembrolizumab and the oral multikinase inhibitor lenvatinib was recently approved for clinical use (16). This combination has achieved significantly longer progression-free survival and overall survival than conventional chemotherapy among patients with advanced endometrial cancer, regardless of the tumor MSI status. We intend to use this combination therapy for similar patients in the near future. In addition, it would be interesting to see the expression level of several molecules such as PD-L1 and CD39; however, we were unable to examine it because of the limited access to preexisting materials of this patient. Due to specific adverse reactions to ICIs and cost-effectiveness, further studies are needed to search for a biomarker that facilitates high-accuracy effect predictions and to establish an optimal administration period.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SU, TK, AT and HF diagnosed, investigated and managed the patient. SU, TK and HF determined the medical significance of this case and wrote the manuscript. KT, YoT, TY, ST, YS and YuT provided advice for managing the patient's treatment and contributed to the acquisition of patient data. All authors have read and approved the final version of this manuscript. SU and TK confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was received from the patient.

Competing interests

The authors declare that they have no competing interests.

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