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Locally advanced endometrial cancer with multiple immune-related adverse events coinciding with the complete response to radiotherapy after immune checkpoint inhibitor therapy: A case report

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ABSTRACT

We report a case of a 70-year-old female patient with locally advanced endometrial cancer with primary empty sella who developed multiple immune-related adverse events (irAEs), including hypopituitarism coinciding with the complete response to radiotherapy after receiving immune checkpoint inhibitors. A computed tomography scan acquired after a traffic accident led to the discovery of endometrial cancer that had invaded the vulva and primary empty sella. Following adriamycin and cisplatin, pembrolizumab was administered for three cycles. No irAEs were observed during treatment, but the tumor was progressive. The patient underwent radiotherapy for the residual tumor. Four months after the last dose of pembrolizumab, hypopituitarism caused secondary adrenal insufficiency, primary hypothyroidism, and pseudogout at the end of radiotherapy. The tumor later achieved a complete response. In conclusion, radiotherapy after immune checkpoint inhibitor (ICI) therapy is expected to have an antitumor effect by stimulating tumor-specific immunity. However, proper management of irAEs is necessary. Patients with primary empty sella may be prone to pituitary insufficiency induced by ICIs.

1. Introduction

In various cancer types, concurrent immune checkpoint inhibitors (ICIs) and radiotherapy, or ICIs after radiotherapy, are expected to enhance the antitumor effect, as represented by the abscopal effect (Ashrafizadeh et al., 2020; Chepkemoi et al., 2022; Ngwa et al., 2018). However, there are fewer reports on radiotherapy after administration of ICIs. In a review of cases of endometrial cancer treated with radiotherapy and ICI, all eight patients received ICIs concurrent with or after radiotherapy, while there were no reports on radiotherapy after ICIs (Chepkemoi et al., 2022). To the best of our knowledge, this is the first report of serious multiple immune-related adverse events (irAEs) coinciding with a complete response during radiotherapy for endometrial cancer performed several months after ICI discontinuation.

An empty sella is a pituitary disorder characterized by herniation of the subarachnoid space within the sellar turcica. Primary empty sella seems more common in middle-aged women (Guitelman et al., 2013) with a history of multiple pregnancies and can cause hypopituitarism (Auer et al., 2020). We report the case in a patient with endometrial cancer and a primary empty sella who developed multiple irAEs, including hypopituitarism, after receiving ICIs.

2. Case

A 70-year-old multiparous woman was transported to our hospital after a traffic accident. She had a history of type 2 diabetes mellitus and was taking oral hypoglycemic drugs. Computed tomography (CT) of the head revealed a traumatic subarachnoid hemorrhage and empty sella (Fig. 1). CT of the chest to the lower extremities revealed a uterine tumor invading the pelvic organs, multiple enlarged pelvic lymph nodes, and multiple fractures. Endometrial biopsy revealed endometrioid carcinoma grade 2.

Immunostaining was positive for estrogen and progestin receptors. Pelvic contrast-enhanced magnetic resonance imaging (MRI) revealed that the tumor had invaded all myometrial layers and spread along the lateral side of the urethra to the perineum (Fig. 1). Based on these findings, endometrial cancer stage IVB was diagnosed. After recovery from the traffic trauma, 1.5 months after the initial visit, combination

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chemotherapy with adriamycin and cisplatin (AP) was initiated because the patient was in good general condition with no cardiac function problems. After six cycles of AP chemotherapy, all pelvic lymph nodes were reduced to < 10 mm; however, the primary tumor was enlarged, and the patient was diagnosed with progressive disease. Six months after the initial visit, the patient was started on combination therapy with lenvatinib mesylate (20 mg/day) and pembrolizumab (200 mg/kg body weight; triweekly). At treatment initiation, her thyroid function was normal. In this case, the thyroid peroxidase antibody level was measured and showed a slightly higher values (3.9 IU/mL; reference value 0–3.2), but 2 weeks after starting lenvatinib mesylate, thyroid stimulating hormone (TSH) was increased to 16.9 μIU/mL (reference value 0.38–4.31). Based on the Common Terminology Criteria for Adverse Events, the patient was diagnosed with hypothyroidism grade 2. After withdrawing lenvatinib mesylate, which has a relatively short pharmacologic half-life, TSH was rapidly decreased to 4.6 μIU/mL, which was diagnosed as an adverse effect of lenvatinib mesylate rather than that of pembrolizumab. Lenvatinib mesylate was restarted at a reduced dose of 14 mg/day, and the patient was successfully controlled for grade 1 hypothyroidism. No adverse effects associated with the pembrolizumab administration were observed. Eight months after the initial visit and after three cycles of pembrolizumab were completed, the serum CA125 level was increased, and pelvic contrast MRI revealed primary tumor enlargement, which was diagnosed as progressive disease. After she completed lenvatinib mesylate and pembrolizumab treatment, her thyroid and adrenal functions were normal. Nine months after the initial visit, external beam radiotherapy of the uterus, vagina, and vulva was initiated, but the pelvic lymph nodes were excluded. Radiotherapy was administered at 60 Gy in 30 fractions. After initiating radiotherapy, oral medroxyprogesterone acetate (MPA) was initiated. Eleven months after the initial visit (3 months after the last dose of pembrolizumab and in the second half of radiotherapy), the serum CA125 levels were decreased, and the primary tumor shrank rapidly. However, during the same period, she experienced grade 2 fatigue and grade 2 anorexia. She visited the emergency department twice and was diagnosed with a hypoglycemic attack because of poor compliance with diabetic medications. The thyroid and adrenal functions were untested. She subsequently presented to the emergency department with severe posterior neck pain. Serum C-reactive protein level was elevated at 15.6 mg/dL (reference value 0.01–0.30), and CT revealed calcification surrounding the odontoid process. In accordance with the diagnostic criteria (Isono et al., 2023), a diagnosis of acute pseudogout of the neck, known as crowned dens syndrome, was made, and the patient was treated with nonsteroidal anti-inflammatory drugs. Twelve months after the initial visit (4 months after the last dose of pembrolizumab and 1 month after completing radiotherapy), both fatigue and anorexia progressed to grade 3 despite the discontinuation of oral hypoglycemic agents. Serum sodium and blood glucose levels were 131 mEq/L and 67 mg/dL, respectively. Considering the fatigue symptoms, we suspected thyroid and adrenal insufficiency and performed a detailed examination. Serum cortisol and adrenocorticotropic hormone (ACTH; reference value 7.2–63.3 pg/mL) were below detection sensitivity, and plasma TSH was 19 μIU/mL. Our diagnosis was multiple irAEs with secondary adrenal insufficiency via ACTH deficiency due to hypopituitarism, as well as primary hypothyroidism and pseudogout. Cortisol replacement therapy was started immediately, and MPA was discontinued due to its potential to lower cortisol. All side effects resolved to grade 1 within 2 weeks of cortisol therapy. Immunostaining of endometrial biopsy performed during the first visit was done 12 months after the initial visit and showed high microsatellite instability. Thirteen months after the initial diagnosis (5 months after the last dose of pembrolizumab and 2 months after completing radiotherapy), CT, MRI, and endometrial biopsy revealed a complete response (Fig. 1).

Fig. 2 shows a summary of the course of this case. Twenty-two months after the initial visit, the patient is still disease-free.

3. Discussion

There were three important findings in this case: first, simultaneous severe irAEs and complete response during radiotherapy after ICI discontinuation owing to progressive disease; second, multiple irAEs after ICI administration; and third, hypopituitarism in a patient with the background of a primary empty sella (Fig. 3).

Radiotherapy activates tumor-specific immunity. Specifically, radiotherapy-induced cancer cell damage exposes tumor-specific antigens to the immune system through a process called immunogenic cell death. This process leads to improved priming and activation of cytotoxic T cells (Vanneste et al., 2020). These findings suggest that radiotherapy after ICI administration may have activated tumor-specific immunity, resulting in severe irAEs and favorable local control.

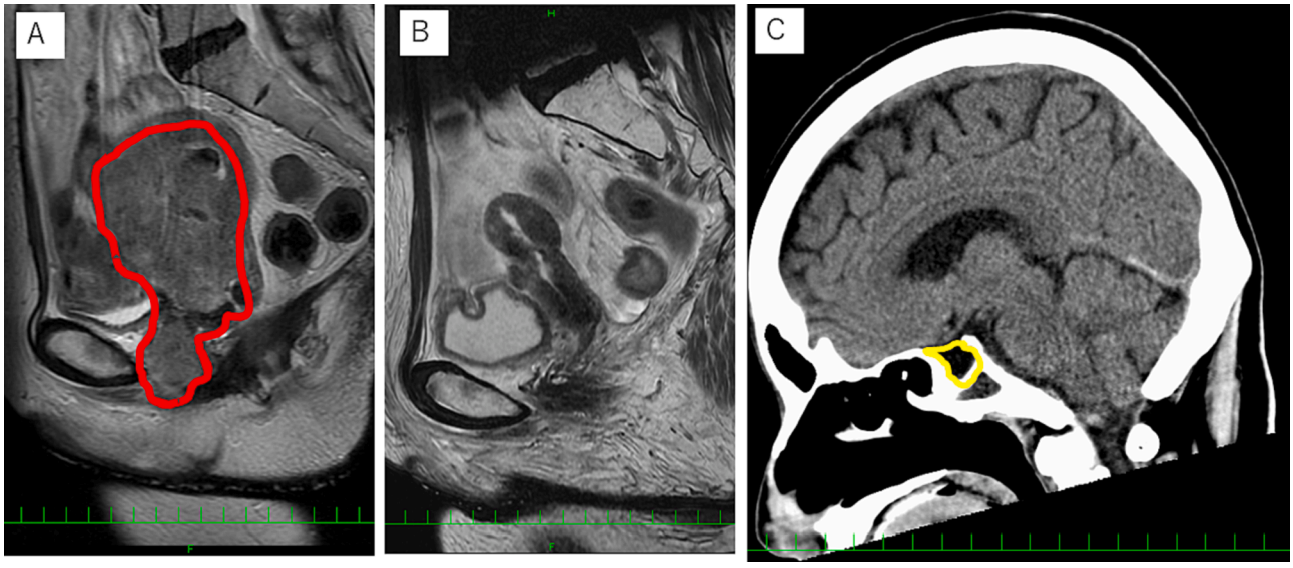

Fig. 1. Head CT and pelvic MRI finding. A: MRI at the initial visit shows tumor invasion from the uterus to the vulva (area surrounded by a red line). B: MRI after completion of radiotherapy shows a complete tumor response. C: CT at the initial visit. The herniation of the subarachnoid space within the sella turcica is visible (area surrounded by a yellow line). Based on these findings, the patient is diagnosed with a primary empty sella. CT, computed tomography; MRI, magnetic resonance imaging.

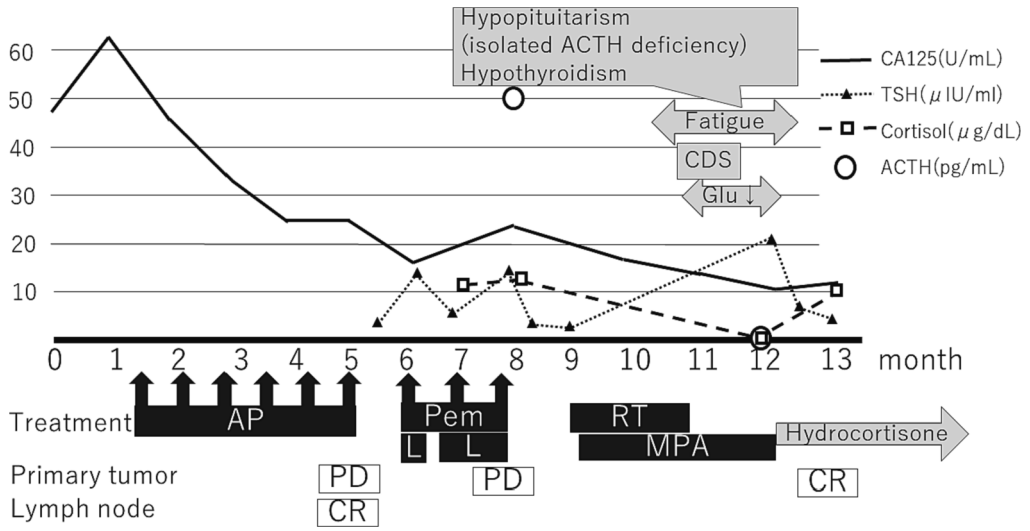

Fig. 2. Tumor marker and endocrine test values, treatment course, and response evaluation. ACTH, adrenocorticotropic hormone; AP, adriamycin and cisplatin; CA125, cancer antigen 125; CDS, crowned dens syndrome; CR, complete response; Glu, glucose; L, lenvatinib mesylate; MPA, medroxyprogesterone acetate; PD, progressive disease; Pem, pembrolizumab; RT, radiotherapy; TSH, thyroid-stimulating hormone.

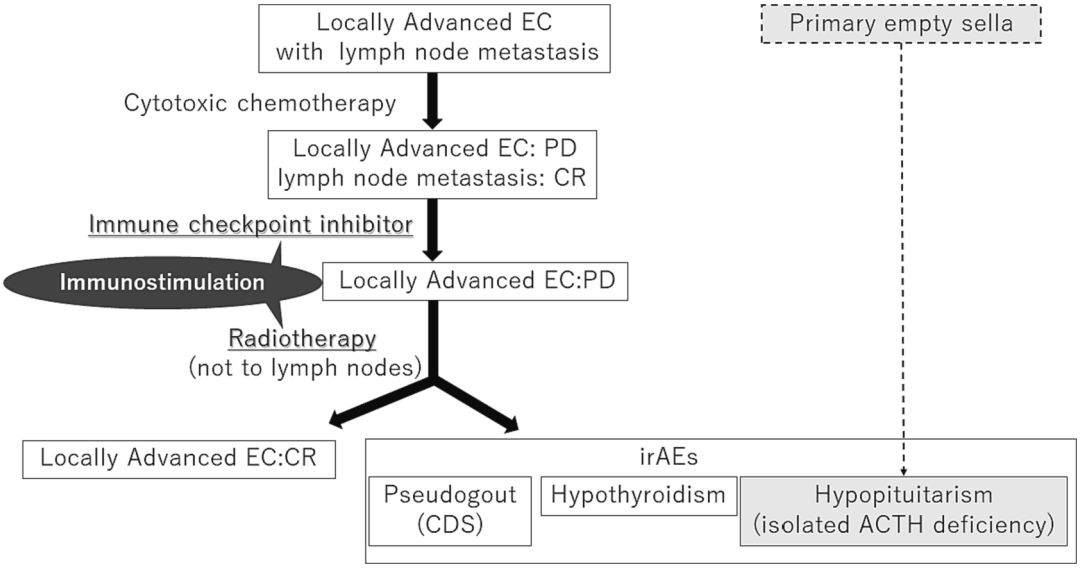

Fig. 3. Schema of treatment and adverse events in this case. ACTH, adrenocorticotropic hormone; CDS, crowned dens syndrome; CR, complete response; EC, endometrial cancer; irAEs, immune-related adverse events; PD, progressive disease.

Noteworthy, ICI induces frequent tumor infiltration by activated lymphocytes regardless of clinical responses in humans (Huang et al., 2011). Therefore, even if ICIs are ineffective, subsequent radiotherapy may stimulate tumor immunity as it happened in this case. In this case, the primary tumor was treated with radiotherapy, excluding the lymph nodes, because they shrunk after neoadjuvant cytotoxic chemotherapy. Regional lymph nodes are important sites of T-cell cross-priming by dendritic cells and serve as major platforms for the initiation of local and systemic antitumor immune responses; therefore, it is desirable to avoid irradiating regional lymph nodes for tumor-specific immune activation (Deutsch et al., 2019). In the present case, the patient's lymph nodes were not irradiated, which may have facilitated immune activation.

From the perspective of therapeutic efficacy, the incidence of irAEs is associated with survival. Meta analysis of 40 studies with 8,641 participants, including those with gynecologic cancers, showed that the overall response rate, overall survival, and progression-free survival in irAE group were significantly higher than those in non-irAE group as per pooled analyses and stratification analyses. Patients with irAEs in endocrine organs rather than in liver and lungs were found to obtain survival benefits (Zhong et al. 2021). In the present case, adrenal insufficiency, thyroid dysfunction, and pseudogout occurred, and these multiple irAEs may have correlated with favorable antitumor effects. ICI-induced thyroid dysfunction has been reported to increase when baseline thyroid autoantibodies are elevated, as in this case (2% incidence in negative patients compared to 34% in positive patients (Okada et al., 2020). Thus, thyroid autoantibodies such as thyroid peroxidase antibody may be useful predictive biomarkers. Treating adrenal insufficiency and thyroid dysfunction involves corticosteroid and levothyroxine replacement therapies. Because levothyroxine increases corticosteroid clearance and the risk of severe adrenal insufficiency, prior administration of hydrocortisone is recommended when hypothyroidism and adrenal insufficiency coexist. Because both adrenal and thyroid dysfunctions can cause fatigue, administering thyroid hormones based on hypothyroidism alone, without evaluating adrenal parameters,

can lead to worse adrenal dysfunction. Therefore, simultaneously measuring adrenocorticosteroid and thyroid hormones is recommended when fatigue or other symptoms that can be caused by adrenal or thyroid dysfunction develop during ICI therapy. In the present case, the hypoglycemic attack was initially misidentified due to a lack of compliance with diabetic medication, which should be noted because diabetic medication may mask ICI-related adrenal insufficiency. Furthermore, the patient was administered MPA in combination with radiotherapy, which may have exacerbated her symptoms due to its cortisol-lowering effect (Lang et al., 1990). Regarding pseudogout, Kim et al. reported the potential influence of Th17 cells on neutrophil recruitment and neutrophil-driven inflammatory events, leading to pseudogout; the findings in the present case were also considered irAEs (Kim et al., 2019).

An empty sella is a pituitary disorder characterized by herniation of the subarachnoid space within the sellar turcica. This condition is often associated with various degrees of pituitary gland flattening. A primary empty sella excludes any previous pituitary pathologies with surgical, pharmacologic, or radiotherapeutic causes; a primary empty sella is considered an idiopathic disease. It is sometimes associated with pituitary insufficiency. In a pooled analysis of patients with a primary empty sella, the relative frequency of pituitary insufficiency was 52% (Auer et al., 2018). Thus, patients with primary empty sella may have impaired pituitary function and are more prone to hypopituitarism in response to ICI administration. Since severe hypopituitarism can also cause a secondary empty sella and head MRI is rarely performed routinely before administering ICI, it is difficult to distinguish congenital from primary empty sella based on MRI after ICI-related hypopituitarism occurs. Thus, empty sella found on MRI after administration of ICIs is often considered a secondary empty sella secondary to hypopituitarism due to irAE (Chang et al., 2019; Nagai et al., 2021). In this case, a primary empty sella was diagnosed based on head CT at the time of a traffic accident before the ICI administration. Although this case has the limitation that ACTH was not measured prior to the administration of the ICI, the ACTH level measured during the administration of the ICI was within normal range, suggesting hypopituitarism secondary to primary empty sella. Pituitary insufficiency as irAE should be monitored when administering ICIs to patients with primary empty sella.

In conclusion, even if no clinical response to ICIs is observed, subsequent radiotherapy is expected to have an antitumor effect because tumor-specific immunity is stimulated; nevertheless, irAEs should be considered. Although a strong antitumor effect can be expected when multiple irAEs occur simultaneously, the relationship between irAEs should be carefully monitored. Moreover, patients with primary empty sella may be prone to pituitary insufficiency induced by ICIs.

4. Consent

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Yuji Tanaka: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Tsukuru Amano:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Akimasa Takahashi:** Writing – review & editing. **Hiroki Nishimura:** Writing – review & editing. **Hiroyuki Yamanaka:** Writing – review & editing. **Yutaka Yoneoka:** Writing – review & editing. **Shunichiro Tsuji:** Writing – review & editing. **Takashi Murakami:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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