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Case report

Rapid regression of microsatellite instability-high/programmed cell death ligand 1-negative recurrent endometrial carcinoma by immune checkpoint blockade with pembrolizumab: A case report and literature review

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ABSTRACT

In a 53-year-old woman who had a surgical diagnosis of grade 3 endometrioid carcinoma (pT1aN0M0, FIGO 1A), adjuvant chemotherapy with paclitaxel and carboplatin was initiated. However, after the completion of fourth cycle, the patient refused to continue the treatment. At 12 months after surgery, local recurrence was noted near the left posterior portion of the vaginal stump. External radiotherapy to the pelvic cavity achieved marked reduction of the tumor. At 12 months after radiotherapy, regrowth of the tumor was noted. Although the tumor was negative for programmed cell death ligand 1, after the identification of a high level of microsatellite instability, treatment with pembrolizumab, an immune checkpoint inhibitor, was initiated. After 2 cycles of treatment, the recurrent tumor markedly regressed. Four months later, a complete metabolic response was confirmed by positron emission tomography, without any immune-related adverse events; at the time of writing, this has been maintained for 9 months.

1. Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract (Murali et al., 2014). While most patients with early-stage endometrial carcinoma are successfully treated by surgery alone or with subsequent chemotherapy or radiotherapy (Ott et al., 2017), effective treatment options are still limited for those with advanced-stage disease or who present with recurrence (Ott et al., 2017).

Programmed cell death 1 (PD-1) is a molecule expressed on the surface of various immune cells, which is stimulated by an antigen (Ott et al., 2017). When PD-1 is unbound, the normal immune response by T cells can occur. Whereas, when PD-1 binds to its cognate ligands—programmed cell death ligand (PD-L)1 and PD-L2—, the cytotoxic immune response by T cells is suppressed by downstream signaling (Ott et al., 2017).

If PD-1 is activated through binding to ligands abnormally expressed on the surface of cancer cells, the activity of cytotoxic T cells is suppressed. Subsequently, the cancer cells may eventually avoid recognition and escape from attack by the immune surveillance system (Ott et al., 2017).

It has been shown that anti-PD-1 therapy with immune checkpoint inhibitors (ICIs) reactivates the immune cytotoxic reaction by blocking the interaction between PD-1 and its ligands, and thus represents a novel approach to the treatment of patients with specific types of cancer that become refractory to standard therapeutic regimens (Ott et al., 2017).

Microsatellites (MSs) are short repetitive sequences in the genome (Santin et al., 2016). The hypermutability of MSs caused by impaired DNA mismatch repair (MMR) is referred to as MS instability (MSI). If allelic shift at two or more markers is identified in cancer cells, it is designated as MSI-high (MSI-H) (Tsuge et al., 2018).

Among gynecological malignancies, the MSI-H phenotype is most frequently found in endometrial carcinomas (Santin et al., 2016). The genome of cancer cells deficient in the MMR function contains exceptionally high numbers of somatic mutations, which encodes and produces large amounts of mutation-associated neoantigens (MANAs) (Le et al., 2017). Consequently, the increased expression of MANAs in MMR-deficient cancer cells may make them sensitive to ICIs (Le et al., 2017).

We herein report a case of MSI-H/PD-L1-negative recurrent endometrial carcinoma, which rapidly regressed after the administration of pembrolizumab (Keytruda, MSD, Kenilworth, NJ, USA), a humanized

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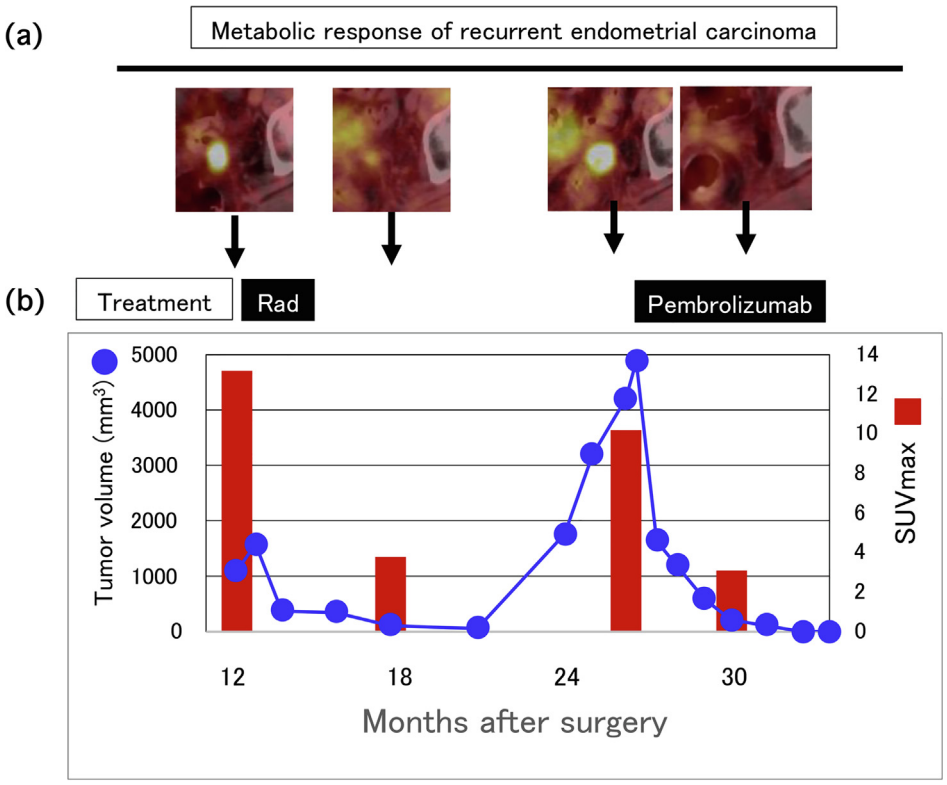

Fig. 1. Timeline from the identification of the recurrent tumor to treatment with pembrolizumab. (a) The metabolic response was assessed by positron emission tomography, based on the uptake of ^{18}F-fluorodeoxyglucose in the recurrent tumor during the disease course. (b) Changes of volume (blue graph) and SUVmax (red columns) of the recurrent tumor at the left posterior portion of the vaginal stump. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

monoclonal immunoglobulin G4 kappa antibody against PD-1 (Ott et al., 2017).

2. Case report

A 53-year-old woman (gravida 4, para 2) was referred because of vaginal bleeding lasting for 2 years. Her disease history was significant with an invasive mole that was treated by primary chemotherapy at 30-years old.

After diagnosis of endometrial carcinoma was made, transabdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection were performed. Under a diagnosis of grade 3 endometrioid carcinoma (pT1aN0M0, Stage IA), adjuvant chemotherapy with paclitaxel and carboplatin was initiated. After the completion of the fourth cycle, the patient refused to receive further chemotherapy due to side effects.

At 12 months after surgery, a hard resistance was palpated near the left posterior portion of the vaginal stump. Transvaginal ultrasonography detected a mass lesion (Fig. 1). Positron emission tomography (PET) showed the marked accumulation of ^{18}F-fluorodeoxyglucose (FDG) in this mass, suggesting local recurrence (Fig. 1a).

After discussing treatment options, including secondary resection, chemotherapy and radiotherapy, the patient and her husband opted for radiotherapy. After the completion of external radiation, a marked reduction of the recurrent tumor was noted (Fig. 1b). However, because the weak accumulation of ^{18}F-FDG persisted on PET (Fig. 1a) at four months after radiotherapy, it was suspected that some metabolically active cancer cells remained (Weber et al., 2003).

At twenty-four months after surgery, regrowth of the tumor near the vaginal stump was noted (Fig. 1b). The marked accumulation of ^{18}F-FDG in the recurrent tumor was evident on PET (Fig. 1a). Biopsy for recurrent tumor was not performed due to concern of adjacent organ injuries.

Because MSI testing of the pathology specimen retrieved at the initial surgery revealed allelic shifts at all five markers (Fig. 2a), the diagnosis was MSI-H endometrial carcinoma. Immunohistochemistry (IHC) was negative for MLH1 (Fig. 2c) and PMS2 (Fig. 2e), but positive for MSH2 (Fig. 2d) and MSH6 (Fig. 2f), indicating the impaired expression of *MLH1* (Le et al., 2017). The expression of PD-L1 in cancer cells was not identified (Fig. 2b).

Based on the obtained results, which showed that the current tumor was MSI-H endometrial carcinoma that had recurred after chemotherapy and radiotherapy, pembrolizumab (200 mg/body) was administered, on a 21-day cycle. After 2 cycles of treatment, the marked regression of the recurrent tumor was observed. CT performed four months after treatment confirmed a complete response. Additionally, on PET, a complete metabolic response was considered to have been achieved (Weber et al., 2003) and maintained (Fig. 1).

The patient tolerated anti-PD-1-therapy well without showing apparent immune-related adverse events (irAEs) (Brahmer et al., 2018)). At four months after treatment with pembrolizumab, PET revealed a uniform increase in the incorporation of ^{18}F-FDG in the bilateral adrenal glands (data, not shown). Although we were concerned about the potential development of autoimmune adrenalitis (Brahmer et al., 2018), the serial measurement of serum adrenocorticotropic hormone and cortisol did not show any abnormal values for 9 months.

3. Discussion

With the recent incorporation of genomic features of the tumors to facilitate the development of precision treatment tailored to specific disease subgroups, it has been hypothesized that endometrial carcinomas can be classified into four subtypes: ultramutated type with DNA polymerase epsilon (*POLE*) mutation, hypermutated type with MSI-H, endometrioid type with a low copy number, and serous-like type with a high copy number (Murali et al., 2014).

With the recent application of ICIs in clinical practice, anti-PD-1 therapy represents a novel therapeutic approach to treat multiple cancer entities across different organs—including endometrial carcinoma—by blocking the molecular interaction between PD-1 on T cells and its ligands on target cancer cells, which reactivates the immune response (Ott et al., 2017).

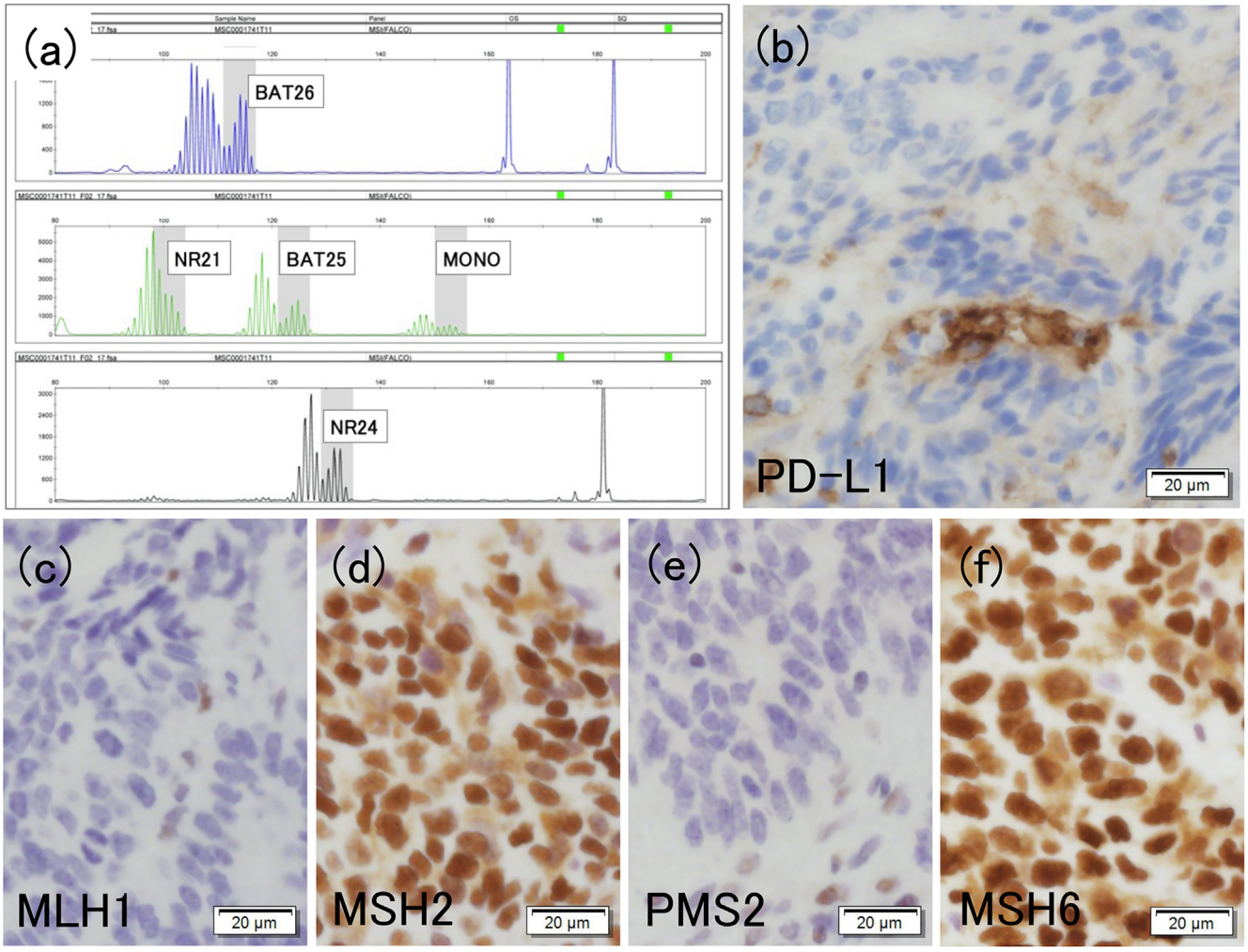

Fig. 2. (a) An analysis of microsatellite instability in extracted DNA samples from formalin-fixed and paraffin-embedded endometrial carcinoma tissue by a fluorescent multiplex PCR-based assay detected allelic shift at all five markers. (b) Endometrial carcinoma cells were immunohistochemically negative for programmed cell death ligand 1 (PD-L1). Scale bar = 20 μm. (c) endometrial carcinoma cells were immunohistochemically negative for MLH1. Scale bar = 20 μm. (d) Endometrial carcinoma cells were immunohistochemically positive for MSH2. Scale bar = 20 μm. (e) Endometrial carcinoma cells were immunohistochemically negative for PMS2. Scale bar = 20 μm. (f) Endometrial carcinoma cells were immunohistochemically positive for MSH6. Scale bar = 20 μm.

When ICIs were initially incorporated into clinical practice, the high expression of one of the ligands to PD-1; PD-L1, was reported as a potential predictor of the response to these drugs, which can be identified on surface of cancer cells by IHC (Ott et al., 2017).

However, it has been later shown that responses were observed regardless of the PD-L1 expression—while a substantial fraction of patients with PD-L1-positive cancer do not respond to ICIs (Ott et al., 2017), even patients with a PD-L1-negative tumor can respond to this therapy (Table 1) (Khagi et al., 2017)—as was observed in the present case.

Recent results showed that, among MMR-deficient cancers across 12 different tumor types, complete response to PD-1/PD-L1 inhibitors was observed in 21% of cases (Le et al., 2017) as observed in the current case. This finding accelerated the approval to use pembrolizumab in MMR-deficient solid tumors by FDA.

Among endometrial carcinomas, the feasibility of anti-PD-1 therapy has been reported for *POLE*-mutated (Santin et al., 2016; Mehnert et al., 2016; Veneris et al., 2019) and MSI-H phenotypes (Santin et al., 2016) (Table 1).

When ICIs work, the regression of endometrial carcinoma has been shown as an almost immediate process, with a response that can be observed within 2–3 months (Santin et al., 2016; Mehnert et al., 2016; Ott et al., 2017; Veneris et al., 2019) (Table 1), similarly, as observed in the present case.

Although we believe that current case report can add some important insights regarding the efficacy of anti-PD1 immunotherapy on recurrent MSI-H endometrial carcinomas, further accumulation of cases would be required.

It is now known that the use of ICIs in cancer therapy can cause various autoimmune-like responses, known as irAEs (Brahmer et al., 2018), which are quite different complications from those observed in systemic cytotoxic chemotherapy. Although, the biological mechanism by which irAEs occur is not fully understood, once irAEs manifest, the dermatological, gastrointestinal, hepatic and endocrine systems may sustain various degrees of damage (Brahmer et al., 2018).

Because severe irAEs, which may require the termination of anti-PD-1 therapy, remain rare events with an estimated prevalence of < 10% in patients receiving monotherapy (Brahmer et al., 2018), it can usually be continued in the presence of mild irAEs under close monitoring. In the current case, although abnormal adrenocorticotropin and cortisol values have not been identified at the time of writing, periodic checkups by an endocrine specialist are essential to detect adrenocortical dysfunction at an early stage (Brahmer et al., 2018).

Table 1
The previously reported cases of endometrial carcinoma successfully managed by anti-programmed cell death-1 immune checkpoint inhibitor.

Case	Study	Year	Immune checkpoint inhibitors	Age (years)	Genetic phenotype	PD-L1 IHC	Pathological diagnosis	Postoperative treatment before immune checkpoint inhibitor	Response to immune checkpoint inhibitors	Prognosis of endometrial carcinoma	Side effects
1	Santin et al.[4]	2016	Nivolumab	57	*POLE*	Positive (5%)	Mixed clear cell and endometrioid carcinoma	Chemotherapy, vaginal cuff radiation, secondary debulking surgery and bevacizumab	PR at 3 months	Clinical response continued	None
2				60	MSI-H (Loss of MSH6 expression)	Negative	Serous carcinoma	Chemotherapy and radiation	PR at 3 months	Clinical response continued	None
3	Mehnert et al.[12]	2016	Pembrolizumab	53	*POLE*	Positive	Grade 3 endometrioid carcinoma	Radiation and chemotherapy	PR at 8 weeks	Response continued for over 14 months	Grade 1 rash, grade 1 liver function test elevation, and grade 2 fever
4	Ott et al.[2]	2017	Pembrolizumab	N/A	Non-MSI-H	Positive	Endometrioid carcinoma	Chemotherapy	PR at 7.6–8.1 weeks	Response continued over 63 weeks	N/A
5				N/A	Unknown MSI status	Positive	Endometrioid carcinoma				
6	Veneris et al.[6]	2019	Pembrolizumab	49	*POLE*	Negative	Grade 2 endometrioid carcinoma	Chemotherapy and secondary cytoreductive surgery	PR at 3 cycles of treatment	Response continued after 6 cycles of treatment	N/A
7	Current case	–	Pembrolizumab	50	MSI-H (Loss of MLH1 and PMS2 expressions)	Negative	Grade 3 endometrioid carcinoma	Chemotherapy and radiation	Metabolic CR at 4 months	Response continued after 9 months	None

PD-L1, programmed cell death ligand 1; IHC, immunohistochemistry; *POLE*, DNA polymerase epsilon mutation; PR partial response, N/A, not available; MSI-H, microsatellite instability-high; CR, complete response.

4. Conclusion

A patient with MSI-H endometrial carcinoma that became refractory to standard cancer therapy appeared to be a good candidate for management with anti PD-1 therapy, because the somatic changes in the MMR gene expression produced abundant MANAs, which can be ideal targets for immunologically activated cytotoxic T-cells.

5. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors contribution

Akihiro Takeda: Project development, Data collection, Manuscript writing; Wataru Koike: Data collection, Radiological evaluation; Kazuko Watanabe: Data collection, Pathological evaluation.

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.

References

Brahmer, J.R., Lacchetti, C., Schneider, B.J., Atkins, M.B., Brassil, K.J., Caterino, J.M., et al., 2018. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. 36, 1714–1768. https://doi.org/10.1200/JCO.2017.77.6385.

Khagi, Y., Kurzrock, R., Patel, S.P., 2017. Next generation predictive biomarkers for immune checkpoint inhibition. Cancer Metastasis Rev. 36, 179–190. https://doi.org/10.1007/s10555-016-9652-y.

Le, D.T., Durham, J.N., Smith, K.N., Wang, H., Bartlett, B.R., Aulakh, L.K., et al., 2017. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357, 409–413. https://doi.org/10.1126/science.aan6733.

Mehnert, J.M., Panda, A., Zhong, H., Hirshfield, K., Damare, S., Lane, K., et al., 2016. Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. J Clin Invest. 126, 2334–2340. https://doi.org/10.1172/JCI84940.

Murali, R., Soslow, R.A., Weigelt, B., 2014. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 15, e268–278. https://doi.org/10.1016/S1470-2045(13)70591-6.

Ott, P.A., Bang, Y.J., Berton-Rigaud, D., Elez, E., Pishvaian, M.J., Rugo, H.S., et al., 2017. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. J. Clin. Oncol. 35, 2535–2541. https://doi.org/10.1200/JCO.2017.72.5952.

Santin, A.D., Bellone, S., Buza, N., Choi, J., Schwartz, P.E., Schlessinger, J., et al., 2016. Regression of chemotherapy-resistant polymerase ε (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab. Clin. Cancer Res. 22, 5682–5687. https://doi.org/10.1158/1078-0432.CCR-16-1031.

Tsuge, S., Ueyama, C., Watanabe, K., Nakamura, H., Takeda, A., 2018. Microsatellite instability-high endocervical serous carcinoma manifesting as pulmonary thromboembolism: a case report and review of the literature. J. Obstet. Gynaecol. Res. 44, 966–971. https://doi.org/10.1111/jog.13604.

Veneris, J.T., Lee, E.K., Goebel, E.A., Nucci, M.R., Lindeman, N., Horowitz, N.S., et al., 2019. Diagnosis and management of a recurrent polymerase-epsilon (POLE)-mutated endometrial cancer. Gynecol. Oncol. 153, 471–478. https://doi.org/10.1016/j.ygyno.2019.03.247.

Weber, W.A., Petersen, V., Schmidt, B., Tyndale-Hines, L., Link, T., Peschel, C., et al., 2003. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. J. Clin. Oncol. 21, 2651–2657. https://doi.org/10.1200/JCO.2003.12.004.