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Case report

Nivolumab for malignant transformation of ovarian mature cystic teratoma

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ABSTRACT

Mature cystic teratoma of the ovary (MCT) occasionally undergoes malignant transformation (MT) that is resistant to chemotherapy and has a poor prognosis. We experienced a case of clinically aggressive MCT-MT that invades surrounding organs and tissues. Although tumor was resected entirely, a rapid tumor recurrence occurred during postoperative chemotherapy (paclitaxel + ifosfamide + cisplatin). The results of comprehensive genomic profiling test performed early in the postoperative period showed a high tumor mutational burden of 23 mutations/Mb. Treatment with nivolumab monotherapy has promptly been initiated and has been very successful for more than one year.

1. Introduction

Mature cystic teratoma (MCT) is a common benign ovarian tumor that originates from germ cells. The MCT rarely undergoes malignant transformation (MT) to develop cancer (Dos Santos et al., 2007). In most cases of MCT-MT, the lesion is usually confined to the ovary. However, if the lesion extends beyond the ovary into the surrounding tissues and complete surgical resection is difficult, the prognosis is poor (Hurwitz et al., 2007). The main reason for poor prognosis is low sensitivity to chemotherapy. Several studies suggest that platinum and alkyl agents may be the key drugs, but those chemotherapies are not highly effective (Hackethal et al., 2008). Therefore, when complete surgical resection is not possible and/or recurrence occurs, it is difficult to treat the disease (Gadducci et al., 2019).

As it is a rare tumor, its genetic background remains to be elucidated. *TP53* is reported to be mutated in approximately 80 % of cases and that the prognosis is better than that in cases with wild-type *TP53* (Cooke et al., 2017). Moreover, the mutation counts have been reported to be relatively high (Cooke et al., 2017). However, treatment targeting the reported genetic abnormalities has not been proposed so far.

For rare tumors, including MCT-MT, it is impossible to plan a large-scale randomized controlled trial to establish standard treatment. Therefore, the treatment course needs to be flexibly considered in individual cases. Comprehensive genomic profiling test (CGP test), that has recently been introduced in Japan, may aid in individualizing effective treatments for refractory tumors without standard treatment because it can provide treatment linked to genetic alterations that occur in tumors, thereby aiding in improved prognosis (Mosele et al., 2020).

Herein, we report a case of highly malignant MCT-MT. Complete primary debulking surgery was achieved, but the tumor recurred aggressively within only two months after initiating postoperative chemotherapy. However, we had performed the CGP test immediately after the primary surgery, and thus, were able to promptly start the treatment linked to the CGP test results (immune checkpoint inhibitor [ICI]) after tumor recurrence. As ICI treatment significantly improved the patient's prognosis, we are reporting this case.

2. Case presentation

2.1. Initial treatment

The patient was a 52-year-old woman, gravida 2, para 2, and had no

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particular family or medical history. The patient visited a hospital with the chief complaint of fever and was diagnosed with a tumor 10 cm in diameter in the pelvis. The patient was then referred to our hospital.

On internal pelvic examination, the abdominal mass about 15 cm in diameter, which reached two finger-breadth below the umbilicus, but the mobility was poor. Magnetic resonance imaging was performed for qualitative diagnosis of the tumor. The results are as follows: The tumor had occupied the entire pelvic cavity. The tumor was mainly cystic with a solid component. The cyst comprised a T2WI-high and T2WI-low signal areas that formed a mirror image of each other (Fig. 1A). We also observed a hair ball-like mass inside that appeared to be MCT. The solid component grew outwards from the cyst. The solid part showed a moderately high signal on diffusion-weighted imaging (DWI) (Supplementary Figure S1A). The contrast effect was particularly strong at the tumor margins (Fig. 1B). Further, we performed contrast-enhanced computed tomography (CT) and fluorodeoxyglucose-positron emission tomography (FDG-PET) to detect the lymph nodes and distant metastases. The analyses suggested significant FDG accumulation in the pelvic tumor. Additionally, there was strong FDG accumulation over a wide area in the bone marrow, including the thoracic to lumbar spine (Supplementary Figure S1B).

The blood examination results were as follows: white blood cell (WBC) count, 21.3 × 10^3/L; C-reactive protein (CRP), 9.4 mg/dL; lactate dehydrogenase (LDH), 218 U/L; squamous cell carcinoma (SCC) antigen, 2.3 ng/mL; CA19-9, 75.8 U/mL, CEA, 1.3 ng/mL, and CA125, 18.1 U/mL There was a mild increase in SCC antigen levels and marked increase in inflammation-related factors, WBC and CRP.

Based on these findings, we suspected MCT-MT. Strong invasion of the surrounding tissues, particularly the rectum, was suspected based on the MRI findings. Although we could not measure the level of a granulocyte colony-stimulating factor (G-CSF) directly, significant accumulation of FDG (SUVmax, 5.6) in a large area of the bone marrow and the markedly elevated WBC count suggested a G-CSF producing tumor (Murata et al., 2006; Morstyn and Burgess, 1988). Primary debulking surgery was planned as the primary treatment.

2.2. Intraoperative findings and pathological examination.

The ovarian tumor was markedly enlarged, and their anterior surface was densely adherent to the posterior uterine wall, forming a single mass including ovaries and uterus. The tumor was also densely adherent to the surrounding sigmoid colon, rectum, and dorsal peritoneum, that made it difficult to mobilize the tumor from the pelvic wall (Supplementary Figure S1C). There was no apparent evidence of infection.

The tumor had strongly invaded the digestive tract; thus, we decided to also perform colectomy of the sigmoid colon. Furthermore, the tumor invaded beyond the dorsal peritoneum and reached the soft tissues of the retroperitoneal cavity. Therefore, the obturator vein and deep uterine vein were cut. There was no obvious invasion of the ureter, and thus, it was preserved. Although the pelvic tumor was grossly removed, a port of internal obturator muscle that was in contact with the resection surface were examined for the rapid intraoperative diagnosis as a frozen section, and atypical cells were found. Therefore, the surrounding area was also resected, the margins were confirmed to be negative, and surgery was terminated. After all, total hysterectomy, bilateral salpingo-oophorectomy, sigmoid colectomy, ileocecal resection and partial omentectomy was performed.

The results of the histopathological examination were as follows:

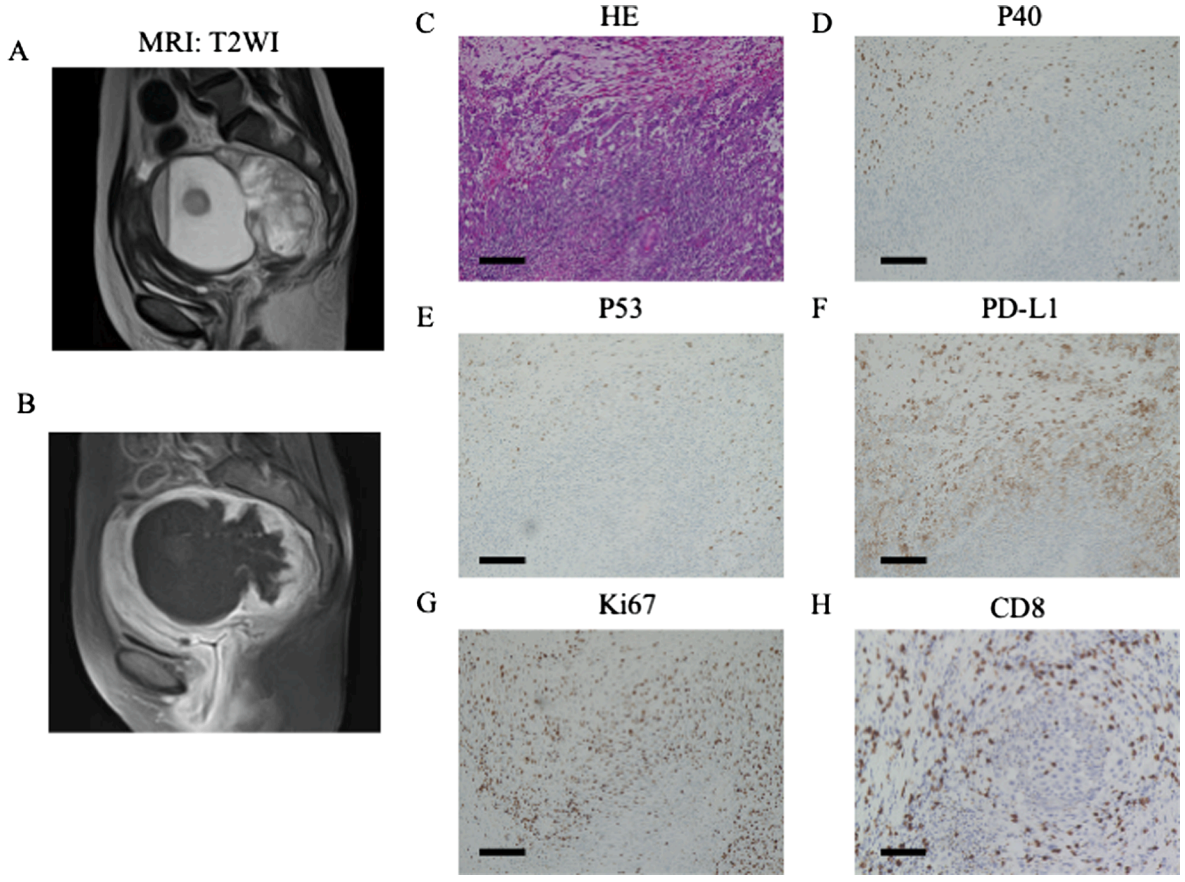

Fig. 1. Results of imaging tests and pathological findings. A. MRI finding (T2WI). B. MRI finding (enhanced fat-suppression T1W1). C-G. Microscopic findings (x 100 magnification). Scale bar equals 200 μm. These images are taken at the same location. C. Hematoxylin and eosin staining (HE). D-G. Immunohistochemistry staining. D: P40, E: TP53, F: PDL1, G: Ki67. H. Immunohistochemistry staining of CD8 (x 200 magnification). Scale bar equals 100 μm.

Atypical cells with large nuclei proliferated aggressively, with a marked background necrosis (Fig. 1C, Supplementary Figure S2A). Tumor partially consisted of atypical cells with eosinophilic cytoplasm (Supplementary Figure S2B). Tumor mostly consisted of highly atypical cells with various pattern, such as spindle and pleomorphic pattern (Fig. 1C, Supplementary Figure S2C). An ectopic hairball was found in the liquid component, and a diagnosis of coexisting MCT was made clinically. As a result, a diagnosis of anaplastic SCC due to MT of MCT was made. The results of immunohistochemical staining are as follows—Positive: p40, p53 and PD-L1 (approximately 90 % positive in tumor cells) (Fig. 1D–F), and Ki67 index: 70 % (Fig. 1G). The tumor had invaded the muscularis of the sigmoid colon. There were also areas of CD8-positive T cell accumulation around tumor cells (Fig. 1H).

The tumor was completely resected macroscopically, but postoperative adjuvant chemotherapy (paclitaxel + ifosfamide + cisplatin; TIP) was administered as tumor invasion was observed over a large area of the retroperitoneal cavity.

2.3. CGP test, tumor recurrence, and administration of ICI

MCT-MT is a rare cancer and is known to poorly respond to chemotherapy. Therefore, concomitant with TIP, we performed a CGP test (FoundationOne®CDx; F1CDx). The results of the F1CDx are as shown in Table 1A. The loss of heterozygosity (LOH) score was high at 36.7 %, indicating sensitivity to platinum and PARP inhibitors. Additionally, the tumor mutational burden (TMB) was high at 23.4 Muts/Mb, predicting sensitivity to ICI.

An early follow up were planned, first because MCT-MT is known to be resistant to chemotherapy, and second because the patient complained of discomfort in the right lower abdomen. Imaging tests after two courses of TIP revealed multiple newly recurrent lesions in the pelvis (Fig. 2A, 2B) and multiple lymph node metastases (Fig. 2C). Platinum drugs failed to function completely. Therefore, we promptly changed the treatment plan to ICI (Nivolumab, 240 mg/body, once per two weeks, based on clinical trial; jRCTs031190104), that was predicted to be sensitive based on the TMB-high results (Samstein et al., 2019). Nivolumab is provided from Ono pharmacy Co. Lid freely.

The day after the first administration of ICI, the patient had abdominal pain. Although the CT images showed no obvious evidence, we highly suspected the cause to be the fistula between the recurrent tumor and ascending colon rather than immune-related adverse events (irAE); therefore, we performed emergency surgery. The ascending colon and the tumor were resected as a single lump (Supplementary Figure S3A, B). The patient's symptoms resolved rapidly. Thereafter, ICI was administered every 2 weeks.

CT performed 2 months after ICI treatment showed a partial response (PR) (70 % reduction in the size). Thereafter, recurrent lesions continued to shrink with additional CT evaluations every-three to four months, and almost completely disappeared even one year after ICI administration (Fig. 2D). The patient's performance status was also good, and we plan to continue administering ICI.

All procedures performed in studies were in accordance with the Helsinki Declaration. Written informed consent was obtained from the patient.

Table 1
A. Summary of CGP test results. Table 1B. Summary of ICI treatment for MCT-MT.

Loss of heterozygosity (LOH)	36.70 %
Tumor Mutation Burden (TMB)	23 Muts/Mb
Microsatellite Instability (MSI)	Stable
EGFR	Amplification (copy nunber: 8)
PIK3CA	E726K, E545K
TP53	E180K, Q331*
NFE2L2	W24C
SETD2	S560*
SPEN	E2176*

Cases	TMB	MSI	PD-L1	ICI regimen	Response
Case1 (ref9)	High (19.07)	Stable	negative (<1%)	camrelizumab	Nearly CR
Case2 (ref10)	Low (7.28)	unknown	positive (>10%)	Sintilimab	Nearly CR
Case3 (ours)	High (23.4)	Stable	positive (90%)	Nivolumab	Nearly CR

3. Discussion

We report a case of a clinically highly aggressive MCT-MT that was successfully treated with nivolumab monotherapy for more than one year. The tumor was also completely refractory to TIP regimen, which includes drugs that have been reported to be effective for MCT-MT. The high effectivity of the nivolumab monotherapy in controlling the disease in such tumors for a long duration is a promising finding for gynecologic oncologists.

To the best of our knowledge, this is the first case of MCT-MT treated with ICI monotherapy. To date, there have been only two reports, except for ours, in which ICI was administered for MCT-MT (Table 1B); one patient developed early postoperative relapse and was treated with combination of ICI (camrelizumab) and antiangiogenic drug. CGP test was performed, and TMB-high (Mut/Mb = 19.07), microsatellite instability (MSI)-stable were reported. There was almost no PD-L1 expression in the tumor (Li et al., 2021). The other case was a second-relapsed tumor; and as the tumor was PD-L1 positive (>10 %), the patient was administered the combination of ICI (Sintilimab) and cytotoxic agents. The disease was under control at the time of reporting. The MSI status was unknown, and the TMB score was 7.2 (Song et al., 2022). In the present case, the TMB was as high as 23.4, PD-L1 was strongly positive, and MSI status was stable, then we performed ICI monotherapy.

The commonly discussed predictive markers for ICI are TMB, MSI status, and PD-L1 positivity. All three factors are reasonably useful as predictors of ICI efficacy; but, in practice, predictions vary widely depending on the primary tumor type. As for PD-L1 in MCT-MT, Tamura et al. have previously reported that PD-L1 may be induced in MCT-MT via XCL1 secreted by CD8-positive TILs (Tamura et al., 2020). In the present case, many CD8-positive tumor infiltrating lymphocytes (TILs) were found, supporting their hypothesis. Furthermore, Cooke SL et al. reported that while MCT were genomically quiet, with few mutations per sample (median 0, mean 1, range 0–7), MCT-MT contained a median of 8 mutations per case (range 0–39). MCT-MT can contain high number of mutations (Cooke et al., 2017). As for MCT-MT, a response in patients with either PD-L1-positive or TMB-high status may be expected.

Additionally, Tamura et al. also noted that most MCT-MTs are SCCs that have a genetic background similar to that of SCCs derived from lung cancer (Tamura et al., 2020). Cooke SL et al. also noted that mutation number of MCT-MT is similar to lung SCC (Cooke et al., 2017). For lung SCC cases without driver mutations, ICIs are included in the standard treatment (Carbone et al., 2017). ICIs may be considered for MCT-MT, especially for SCC, as in the case of lung SCC. However, MCT-MT remains to be fully investigated, as the number of cases is very limited.

In the present case, the CGP test performed immediately after surgery aided in the treatment plan. Performing the CGP test, obtaining the results, and interpreting them requires time. However, in such cases, where the disease progressed quickly, it would have been too late to perform the CGP test after confirming disease recurrence. If the cancer is rare and clinically expected to be of a high grade, a CGP test should be performed immediately.

G-CSF-producing tumors can arise in a variety of tissues and are sometimes considered a subtype with poor prognosis (Münstedt et al., 2010). However, there have been several studies on G-CSF-producing tumors that respond to ICI (Matsui et al., 2020). ICI was successful in the present case as well. This suggests that the G-CSF-producing capacity should not be a concern when administering ICI.

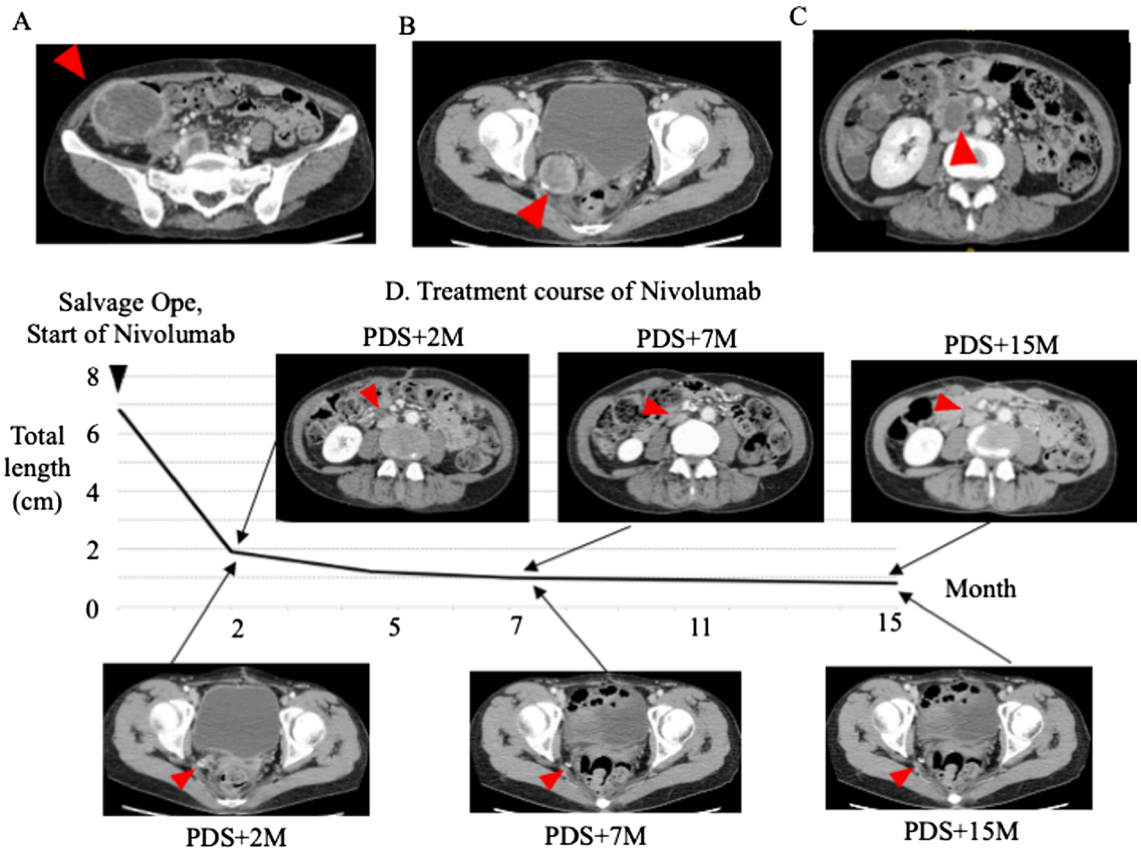

Fig. 2. Clinical finding of recurrent tumor, and treatment course of nivolumab. A-C. Enhanced-computed tomography (CT) findings. Arrows indicate recurrent tumor. D. Clinical course of nivolumab monotherapy. Treatment course monitoring total length of recurrent tumor measured in CT images. Red arrows indicate recurrent lesion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In conclusion, we administered ICI to a patient with highly malignant MCT-MT based on the results of a CGP test (TMB = high; 23.4 mutations) without delay. As MCT-MT may respond well to ICI, it is important to check the PD-L1 status and TMB in the postoperative period to avoid a delay in administering ICI.

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Consent for Publication.

This is an academic institution and all patients receiving medical care here sign a consent form agreeing that their material can be used for educational purposes without using any unique identifiers.

COI disclosure.

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CRediT authorship contribution statement

Kayoko Yoshimura: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Koji Yamanoi:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Masashi Kanai:** Investigation, Writing – review & editing. **Asuka Okunomiya:** . **Yusuke Sagae:** Writing – review & editing. **Masumi Sunada:** . **Mana Taki:** Writing – review & editing. **Masayo Ukita:** Writing – review & editing. **Yoshitsugu Chigusa:** Writing – review & editing. **Akihito Horie:** Writing – review & editing. **Ken Yamaguchi:** Writing – review & editing. **Junzo Hamanishi:** Writing – review & editing. **Sachiko Minamiguchi:** Methodology, Formal analysis, Writing – review & editing. **Noboru Yamamoto:** . **Manabu Muto:** Writing – review & editing. **Masaki Mandai:** Writing – review & editing, Supervision.

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.

Data Availability.

No data was generated with regard to this case report.

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