Recurrent malignant melanoma of the uterine cervix treated with anti-PD-1 antibodies and anti-CTLA-4 antibodies: A case report

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Abstract. In 5% of female patients with malignant melanoma (MM), MM develops from the genital tract. MM of the cervix is particularly rare. In the present case report, a 73-year-old woman with stage IIIC cervical MM underwent modified radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. A total of 4 months after surgery, multiple metastases were found in the brain, lung, liver, lymph nodes and bone. The patient underwent γ-knife surgery of the brain and received treatment with anti PD-1 antibodies (nivolumab) and anti-CTLA4 antibodies (ipilimumab); however, they were ineffective and the patient subsequently died. To the best of our knowledge, this is the first report of treatment using two types of immune checkpoint inhibitors administered to a patient with cervical MM. Taken together with previous reports, this case suggests that immune checkpoint inhibitors may be less effective in cervical MM than in cutaneous MM; however, the number of cases is small. Further development of biomarkers to stratify efficacy is required.

Introduction

Malignant melanoma (MM) is a cancer that develops in the skin and mucosa. Five percent of female patients with cancer have mucosal MM derived from the vulva, ovary, uterus, or cervix (1). Cervical MM is rare, with less than 90 reported cases since 1889 (2). Although primary MM of the cervix is localized to the cervix in the early stage, it infiltrates the uterosacral ligaments, vaginal fornix, pelvic wall, and vulva, and spreads to distant organs at advanced stages. Compared to vulval and vaginal MM, primary cervical melanomas are sporadic and have a poor prognosis (3). There are no standard regimens for recurrent melanoma of the uterine cervix; therefore, treatment regimens for cutaneous MM were followed. Immune checkpoint inhibitors are used in patients as standard therapy in MM; however, immune checkpoint inhibitors, such as PD1 and CTLA4, have been used in fewer patients with cervical malignant melanoma. We report a case of recurrent uterine cervical MM treated with anti-PD-1 antibodies and anti-CTLA4 antibodies.

Case report

A 73-year-old Japanese woman was admitted to a gynecological clinic with genital bleeding. Her medical history included aortic valve replacement. Gynecological examination revealed a 5-mm diameter polypoid lesion at the uterine cervix. A colposcopy-guided cervical biopsy was performed, and immunohistochemical analysis revealed positive reactions for S-100 protein and Melan-A. Cervical MM was suspected, and she was referred to the Department of Gynecology at the University of Tokyo. Colposcopy revealed a 2-cm mass in the uterine cervix and a 5-mm diameter skip lesion at the lateral vaginal fornix (Fig. 1). Findings from transvaginal ultrasound and magnetic resonance imaging (MRI) revealed a mass approximately 20-mm in size, confined to the uterine cervix area, showing high signal intensity on T2-weighted images (Fig. 2A and B). Positron emission tomography and computed tomography (PET-CT) revealed uptake of fluoro-2-deoxy-D-glucose in the uterine cervix area (SUVmax: 6.5) and minor uptake in the pelvic lymph node area (Fig. 2C and D). There were no metastatic lesions or enlarged lymph nodes on CT scans of the brain, chest, abdomen, and pelvis. To evaluate the primary sites, we performed a comprehensive assessment of melanotic lesions in the skin, mucosal sites, and uveal tract (ophthalmoscopy); the results were negative. The patient was diagnosed with primary MM of the uterine cervix. According to the International Federation of Gynecology and Obstetrics (FIGO) classification 2018, the preoperative disease stage was IIA1. Considering the patient's age, history of aortic valve replacement, and poor prognosis, we chose less invasive surgery. The

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Abbreviations: MM, malignant melanoma; MRI, magnetic resonance imaging

Key words: cervical malignant melanoma, immune-checkpoint inhibitor, anti-PD-1 antibodies, anti-CTLA4 antibodies

patient underwent a modified radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and partial vaginectomy because the tumor was grossly close to the stump. Histopathological examination revealed a mass, which was 2.4x2.0 cm in size, invading the uterine cervix, with proliferation of atypical melanocytes with bizarre nuclei and focal melanin production (Fig. 3). These tumor cells were immunohistochemically positive for Melan-A, confirming the diagnosis of malignant melanoma. Furthermore, 20% of the tumor cells were positive for C-kit, whereas all tumor cells were negative for PD-L1 (Figs. S1 and 3D). Surgical margins of the vagina and resected pelvic lymph nodes (16/36) were positive. The postoperative disease stage was IIIC1. After surgery, the patient underwent adjuvant radiotherapy with a remote afterloading system (RALS) due to margin positivity (30 Gy/5 Fr).

CT revealed brain and multiple lymph node metastases four months after surgery, and the patient underwent γ-knife radiotherapy (44 Gy/1 Fr) (Fig. 4A). No mutations were found in BRAF; therefore, the patient received the immune checkpoint inhibitor anti-PD-1 antibodies (nivolumab) at 3.0 mg/kg biweekly, according to treatment guidelines for recurrent cutaneous MM. Five months after surgery, multiple metastases were detected by MRI in the lungs, liver, bones, and hydronephrosis due to pelvic recurrence (Fig. 4B-E). The patient underwent palliative hole pelvis irradiation (20 Gy/4Fr) for hydronephrosis. Six months after surgery, the patient received the immune checkpoint inhibitor anti-CTLA-4 antibodies (ipilimumab, 3.0 mg/kg) after three cycles of the anti-PD-1 antibodies. The patient was admitted to the hospital one week after anti-CTLA-4 administration because of deterioration of her general condition caused by aggravation of lesions and ascites (Fig. 5A-C). Renal function also deteriorated significantly. Consequently, we decided to provide the best supportive care. Seven months after surgery, the patient died of multiple organ failure.

Discussion

We encountered a case of MM of the uterine cervix, which was treated with radiotherapy after surgery, but multiple recurrences were observed. Two types of immune checkpoint inhibitors were administered to the recurrent lesion, but they were ineffective, and the patient died. There are four notable points to be drawn from this case.

First, diagnosis of cervical MM was performed by pelvic examination, other gynecologic examinations, and pathological diagnosis. To determine the diagnosis of primary cervical melanoma, metastasis of melanoma needs to be ruled out elsewhere (4). In this case, the lesion had extended to the vagina beyond the preoperative pelvic examination findings. MM is characterized by exudative growth, and attention must be paid to the possibility that vaginal invasion cannot be accurately judged by palpation and inspection alone.

Second, surgical treatment is recommended for cervical MM, similar to other MMs. Hysterectomy and bilateral salpingo-oophorectomy have been recommended in previous reports. Other reports recommend a radical hysterectomy to ensure adequate margins (5). On the other hand, reports suggest a less invasive operative procedure such as total hysterectomy because the prognosis is extremely poor (6). Moreover, in patients with stage IIIA MM of the cervix, radical hysterectomy and total vaginal wall resection have been associated with rapid recurrence and death. Therefore, aggressive vaginal wall resection should be considered with caution because of its invasiveness and curability (7). We selected a modified radical hysterectomy considering the patient's age and prognosis. However, because of the rare occurrence of this condition, to the best of our knowledge, no standard guidelines are available for its treatment and management. Radical hysterectomy and simple hysterectomy were therefore considered to be acceptable procedures.

Lymph node dissection without lymphadenopathy on MRI or CT images remain controversial. Jones *et al* (8) reported that 30% of patients with clinically normal lymph nodes had microscopic lymph node metastases and recommended lymph node dissection. In contrast, Cantuaria *et al* (5) suggested that pelvic and para-aortic lymph node dissection is recommended when lymph nodes are grossly enlarged or have invaded beyond the uterus (5). We performed pelvic lymph node dissection because pelvic lymph node metastasis was suspected on preoperative PET/CT, but multiple organ metastases were found several months later. Thus, the significance of lymph node dissection remains to be determined.

Third, although MM is resistant to radiation therapy, radiation therapy is considered an option for patients with positive lymph node metastasis, patients who do not have a sufficient surgical margin, or patients with palliative intent (4). We also performed RALS given that the surgical margin was positive for the vaginal stump. In this case, external beam radiation to the pelvic wall was considered at first because of lymph node metastasis. However, pelvic irradiation was not performed considering the complications of pelvic irradiation, the patient's age, and the effects of radiation. At the time of recurrence, gamma knife irradiation for brain metastasis and palliative irradiation for hydronephrosis were performed. As there are no chemotherapeutic regimens or molecularly targeted drugs that improve prognosis in cases of advanced or recurrent cervical MM, chemotherapy and molecularly targeted treatments are administered as per cutaneous melanoma protocols (9). Dacarbazine is the most commonly used drug for MM, showing recurrence rates of 15-20% (10). Although other chemotherapy regimens such as cisplatin and vinblastine combined with dacarbazine may produce a 20-35% response rate, they may not prolong life compared with dacarbazine alone (11).

Fourth, targeted drugs indicated for recurrent or unresectable MM include BRAF inhibitors, MEK inhibitors, and immune checkpoint inhibitors. BRAF inhibitors plus MEK inhibitors can be used only in patients with BRAF V600 mutations. They act more rapidly than immune checkpoint inhibitors and have an early tumor response but have not been reported in cases of cervical MM (12). MM is a cancer that is easily recognized by the immune system, and research and development of cancer immunotherapy have advanced, particularly in melanoma. In recent years, improved knowledge of tumor control in the immune system has led to the development of novel immunotherapy targeting immune checkpoint factors. Immune checkpoint molecules that are treatment targets include CTLA-4 and PD-1. Ipilimumab (Yervoy®) is an anti-CTLA-4

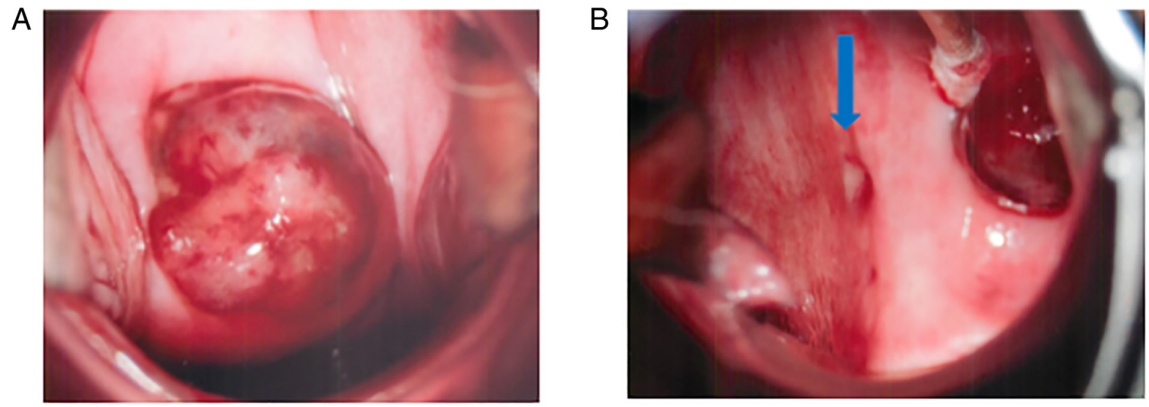

Figure 1. Colposcopy findings of cervical malignant melanoma in this case. (A) Malignant melanoma lesion of ~2 cm in the cervix. (B) Skip lesion of malignant melanoma of ~5 mm in the vaginal wall. The lesion is indicated by a blue arrow.

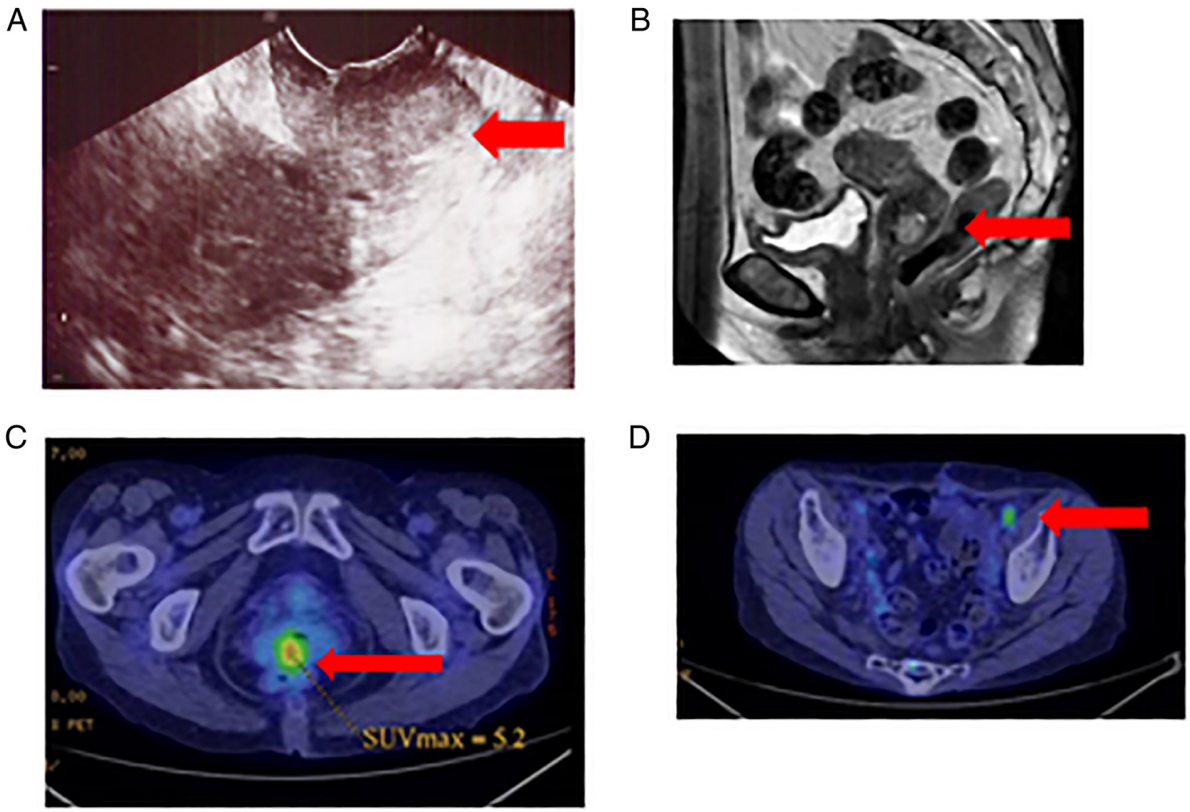

Figure 2. Preoperative examination in this case. (A) Transvaginal ultrasound findings: Tumor of ~2 cm in the cervix. (B) Magnetic resonance imaging revealed a 20-mm mass confined to the uterine cervix area, showing high signal intensity on T2-weighted images. (C) PET/CT scan: PET uptake in the cervix. (D) PET/CT scan: PET uptake in the pelvic lymph node. The lesions are indicated by red arrows. PET, positron emission tomography; CT, computed tomography.

antibodies, while nivolumab (Opdivo®) and pembrolizumab (Keytruda®) are anti-PD-1 antibodies; these have been adopted for the treatment of MM. Several reports have described the use of immune checkpoint inhibitors for the treatment of cervical MM. Noguchi *et al* (7) administered nivolumab to a patient with FIGO stage IIIA cervical MM, but the patient died without any response to therapy. Kim *et al* used pembrolizumab as postoperative therapy for a patient with stage IIA cervical melanoma, but the disease recurred rapidly, and the patient died (13). Ipilimumab was also administered to four patients with cervical MM, but all four patients had progressive disease (14). While many reports have suggested that immune checkpoint inhibitors are not effective against cervical MM, some reports have also supported their effectiveness. Anko *et al* (15) treated patients with recurrent cervical MM with nivolumab, and most recurrent pelvic tumors disappeared.

In this study, we administered two types of immune checkpoint inhibitors, PD-1 antibodies and CTLA-4 antibodies, to patients with uterine cervical MM. To the best of our knowledge, no single patient with cervical melanoma has yet

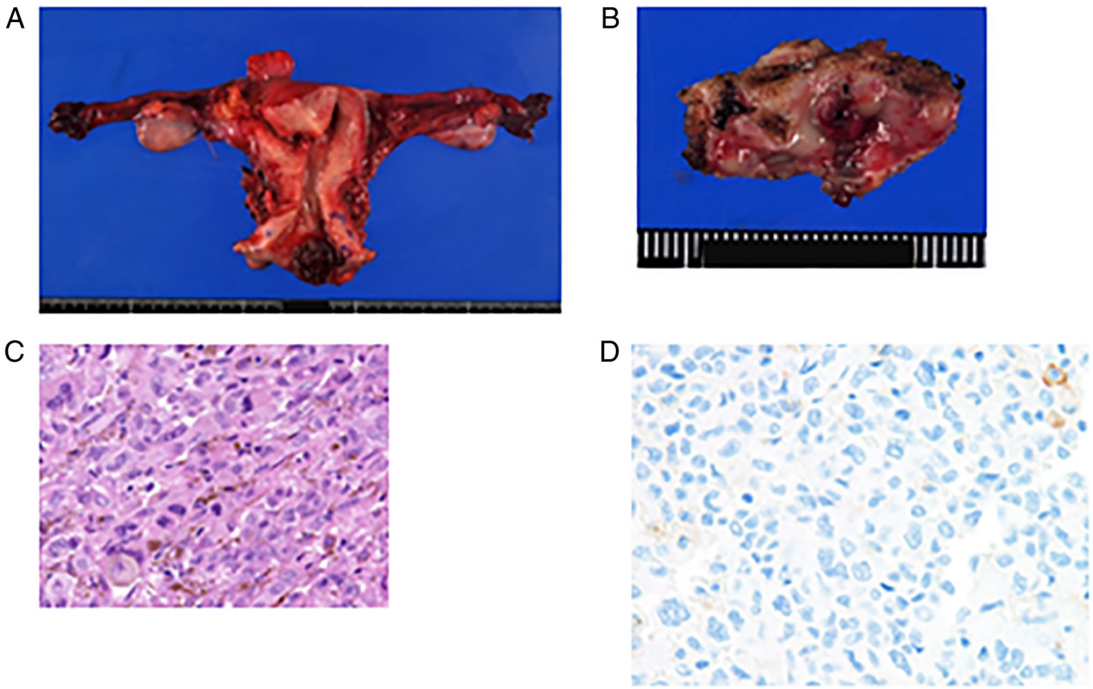

Figure 3. Pathological findings in this case. (A) Specimens removed: Uterus, bilateral adnexa. The surgical specimen reveals a 2-cm tumor in the uterine cervix. (B) Specimens removed: vaginal wall. (C) Proliferation of atypical melanocytes with bizarre nuclei and focal melanin production (hematoxylin and eosin stain, x400 original magnification). (D) PD-L1 was negative in tumor cells (x400 original magnification).

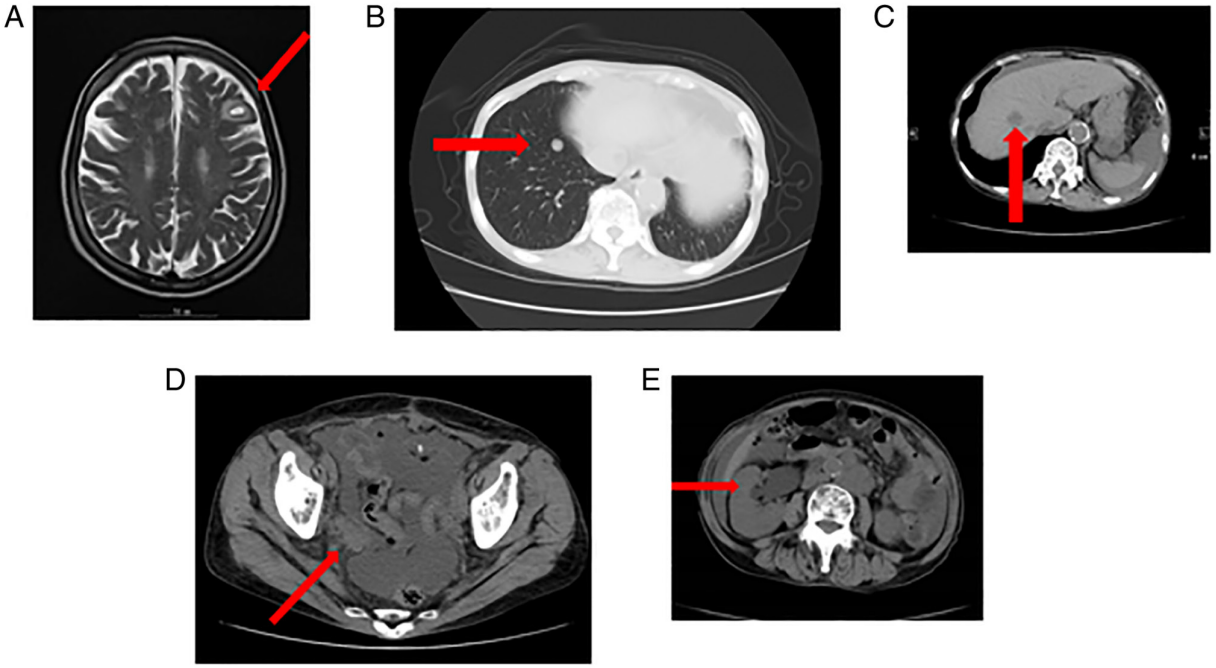

Figure 4. Recurrent findings in this case before and after nivolumab administration. (A) Magnetic resonance imaging findings of brain metastasis before nivolumab administration. (B) The findings of lung metastasis on CT images after nivolumab administration. (C) The findings of liver metastasis on CT images after nivolumab administration. (D) The findings of pelvic metastasis on CT images after nivolumab administration. (E) The findings of hydronephrosis on CT images after nivolumab administration. The lesions are indicated by red arrows. CT, computed tomography.

been treated with PD-1 and CTLA-4 antibodies. At the time when the patient was treated, nivolumab was not indicated as an adjuvant therapy for malignant melanoma in the Japanese guidelines. RLARS has also been used, but there has been no evidence supporting the use of radiation combined with immune checkpoint inhibitors. Considering the above facts, an immune checkpoint inhibitor was not used postoperatively. Unfortunately, neither of the two types of immune checkpoint inhibitors was effective against cervical MM. In this case, we administered nivolumab followed by ipilimumab. Clinical

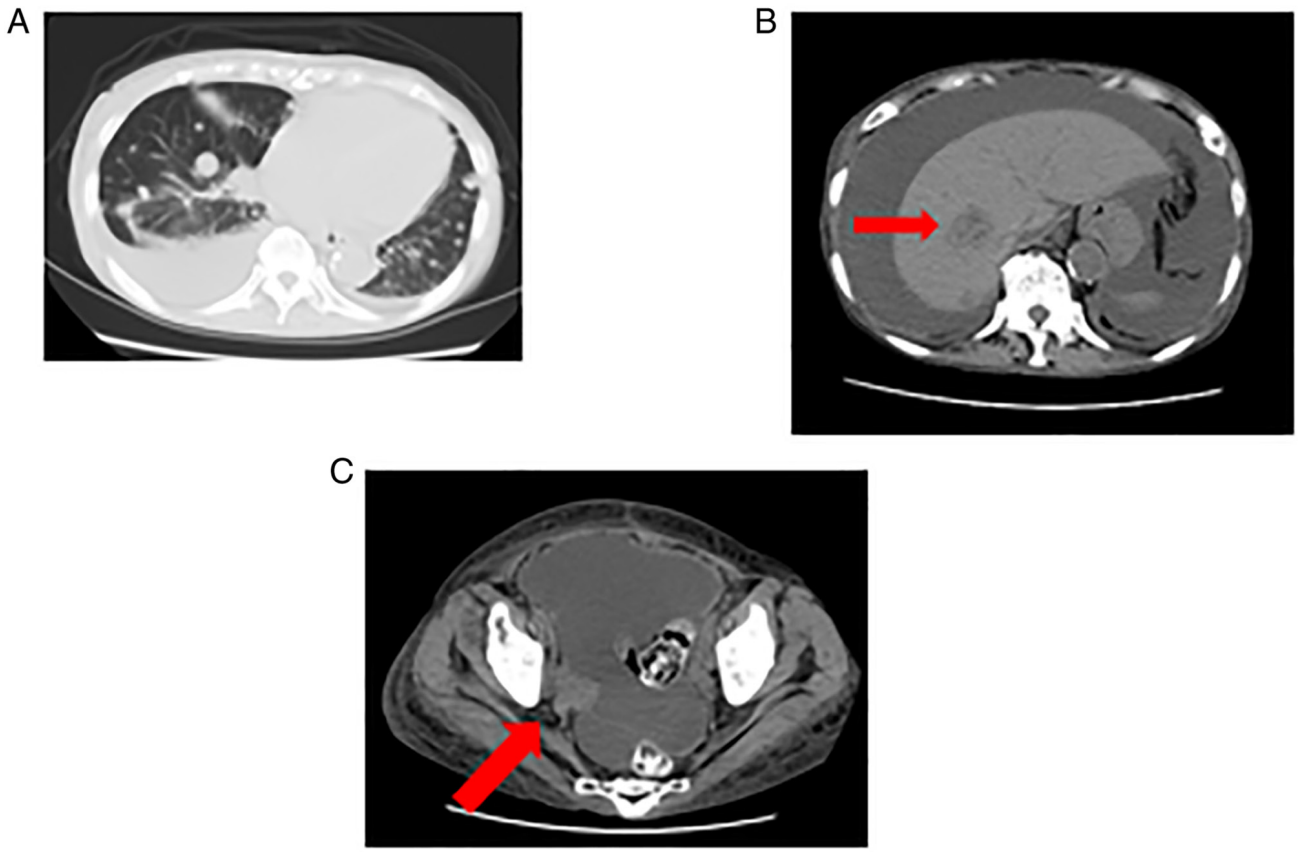

Figure 5. Recurrent findings in this case after ipilimumab administration. (A) The findings of lung metastasis on CT images after ipilimumab administration. (B) The findings of liver metastasis on CT images after ipilimumab administration. (C) The findings of pelvic metastasis on CT images after ipilimumab administration. The lesions are indicated by red arrows. CT, computed tomography.

trials using nivolumab in combination with ipilimumab for malignant melanoma have been reported. D'Angelo *et al* (16) pooled the data of 889 patients treated with nivolumab alone and 665 patients treated with nivolumab + ipilimumab in several clinical trials. Of these, 121 patients had mucosal melanoma, including 86 with nivolumab alone. Nearly 35 patients were treated with Nivolumab + ipilimumab. Combination therapy facilitated better outcomes for both melanomas than a single agent in terms of prognosis and response rate. Mucosal melanomas had a worse prognosis than cutaneous melanomas in both the monotherapy and combination groups Since the combination therapy of anti-PD -1 antibodies and anti-CTLA -4 antibodies increases the likelihood of adverse events, the combination therapy for elderly patients, such as this patient, was not performed considering the high risk (16). We also performed immunostaining for PD-L1 and c-kit, which revealed that 20% of the tumor cells were positive for C-kit, whereas all tumor cells were negative for PD-L1. Reportedly, the higher the incidence of PD-L1 in pre-treatment cancer tissues, the more likely it is that anti-PD-1 antibodies will be effective. The National Comprehensive Cancer Network guidelines recommend the Bcr-Abl inhibitor imatinib for malignant melanoma with a c-kit-activating mutation; however, this drug has not been approved for the treatment of malignant melanomas in Japan (17). In previous reports, the KIT mutation was not recognized when the positivity rate for c-kit expression was 10% or less on immunohistochemistry in cases of mucosal malignant melanoma. In contrast, if the c-kit expression by immunohistochemistry was positive in 50% or more, the KIT mutation was recognized in 82% of cases (18). Based on these reports, we concluded that our patient was unlikely to have a c-kit mutation. It is true that the onset of the effect of immunotherapy is often slower than that of other anticancer drugs. However, a higher effectiveness may lead to rapid resolution of the patient's condition. In addition, the size of this lesion increased rapidly after 1 course of ipilimumab therapy in this case. Ipilimumab was not considered highly effective in this case. If the performance status is bad, there is a possibility that the immune system is in bad shape, and immunotherapy will not be effective. However, there was no conclusive evidence for this possibility. Mucosal malignant melanoma often arises in the head and neck region (e.g., nasal cavity and oral cavity), followed by the female genital tract. More than 90% of malignant melanomas in the female reproductive tract occur in the vulva and vagina, and only a few occur in the cervix (1). Therefore, although cervical malignant melanoma is not rare, its incidence is extremely low among mucosal malignant melanomas. Of the 750 malignant melanomas examined in CheckMate 218, 47 were mucosal malignant melanomas. While the exact details are not available, we believe that there will be very few, if any, patients with cervical malignant melanoma. There are no detailed reports of patients being treated with nivolumab followed by ipilimumab for cervical malignant melanomas (19). The course of this case suggests that the efficacy of these two agents may be lower than

that of other mucosal malignant melanomas. Negative PD-L1 in this case may reflect why nivolumab was ineffective. However, as mentioned above, it has been reported that PD-L1 expression is not related to the effect of nivolumab in cases of mucosal malignant melanoma, and further investigation is required. Considering our findings alongside previous reports, we believe that immune checkpoint inhibitors may be less effective than other treatments for MM, although the number of cases in the literature is relatively small to draw this conclusion. Further development of biomarkers to stratify efficacy is required. Therefore, it is necessary to accumulate more experience and data on a greater number of patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

Conception and design of the study: KS, AKu, AKa, AT. Acquisition of data: YMa, DY, YMi, MT. Analysis and/or interpretation of data: TI, MMU, TT, YO, ASU. Drafting the manuscript: KS, AKu. KS and AKu confirm the authenticity of all the raw data. Revising the manuscript critically for important intellectual content: TI, TT, YO, ASU. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The case report was approved by the ethics committee at The University of Tokyo [approval no. 3084-(3)]. In patient application forms, it was clearly stated that patients were allowed to opt out of the study at any time. Information on how they could opt out was provided on our website, or arrangements were made for patients to opt out.

Patient consent for publication

In addition to the application form (with the provision for 'opt out'), written informed consent was obtained from the patient in this case for publication.

Competing interests

The authors declare that they have no competing interests.

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