



Primary malignant melanoma of the uterine cervix treated with pembrolizumab after radical surgery: a case report and literature review

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Malignant melanoma of the genital tract is a rare disease that is usually diagnosed by chance. When a definite diagnosis is delayed, the prognosis is very poor without standardized treatment. Herein, we describe a 40-year-old patient who presented with a history of bloody vaginal discharge for 7 months. Gynecological examination showed an exophytic, hard and pigmented cervical mass involving the upper vagina. The patient was diagnosed with cervical melanoma after a punch biopsy and underwent a radical hysterectomy, upper vaginectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. After surgeries, the patient underwent 2-cycles of adjuvant immunotherapy with pembrolizumab, but died within 8 months. In this report, treatment with pembrolizumab after radical surgery was not effective for this patient who had a primary cervical melanoma that metastasized to bone and lung tissue. We do not know why pembrolizumab was ineffective for this patient, but there are several possible explanations; further research is needed.

Keywords: Melanoma; Pembrolizumab; Antibodies, monoclonal, humanized; Uterine Cervical Neoplasms

Introduction

Malignant melanoma accounts for about 0.03% of all newly diagnosed cancers and malignant melanomas of the female genitalia occur very rarely — accounting for approximately 2% of all melanomas [1]. In particular, there have been less than 90 reported cases of uterine cervical malignant melanoma since 1889 [2,3].

Primary malignant melanoma of the uterine cervix has no early symptoms and the diagnosis is usually delayed; therefore, prognosis is poor. Malignant melanoma is diagnosed from pathological tissue using special staining techniques, including Melan-A and HMB-45 [4]. The main treatment for malignant melanoma is surgical resection with safety excision margin based on tumor thickness [5]. Typically, primary malignant melanoma of the uterine cervix is treated with a radical hysterectomy with regional lymphadenectomy; however, the standard treatment has not yet been defined. Randomized phase III trials of adjuvant systemic targeting therapy and immunotherapy for treating malignant melanoma are currently being conducted using novel drugs, such as ipilimumab,

pembrolizumab, nivolumab, vemurafenib, dabrafenib, and trametinib [6]. Among these drugs, pembrolizumab, a blocker of programmed-cell-death-receptor 1 (PD-1), is a fully humanized monoclonal immunoglobulin G4 (IgG4) antibody. We treated a patient who was diagnosed with primary cervical melanoma with pembrolizumab after radical surgery. To the best of our knowledge, this is the first report of pembrolizumab as adjuvant treatment after radical surgery for uterine cervical melanoma in Korea.

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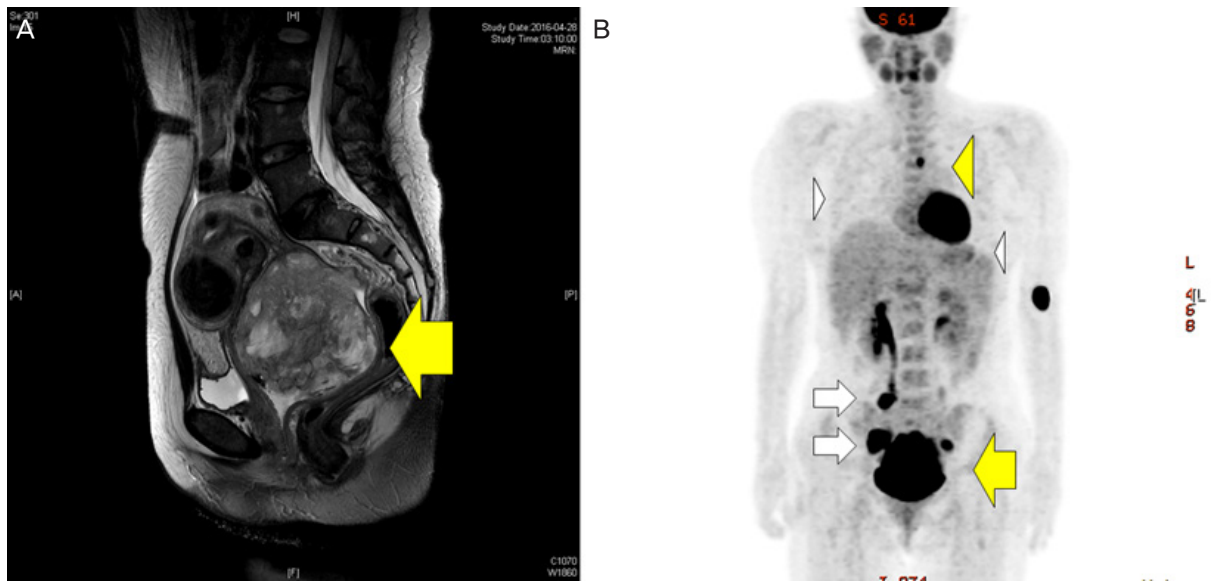


Fig. 1. (A) Pelvis magnetic resonance imaging showing melanoma of the cervix (arrow). The lesion was 9.5×7.5 cm and had invaded the upper vagina. (B) A large hypermetabolic mass with increased fluorodeoxyglucose uptake of maximum standardized uptake value (SUVmax=17.1) in the uterine cervix (large arrow). Bone metastases were observed with increased fluorodeoxyglucose uptake in T4 (SUVmax=8.6) and L5 (SUVmax=6.7) spins (large arrowhead). Right common iliac, bilateral internal iliac, and right perirectal area lymph node metastases were observed (small arrow). Small pulmonary nodules suspected because pulmonary metastases were observed in the right middle and left lower lobes of the lungs. Multiple pleural nodules suspected because pleural metastases were observed in the left lung (small arrowhead).

Case report

A 40-year-old woman, para 0, who presented with a history of intermittent bloody vaginal discharge for 7 months was referred to the Samsung Medical Center. Her primary physician performed a punch biopsy of a mass-like lesion of the cervix and diagnosed it as a cervical malignant melanoma. Gynecological examination revealed an exophytic, hard and pigmented cervical mass that involved the upper vagina. Her the International Federation of Gynecology and Obstetrics stage was predicted to be stage IIA2 cervical cancer.

The patient underwent abdominal computed tomography (CT) and pelvic magnetic resonance imaging, which showed a large cervical cancer that involved the upper vagina, the right common iliac chain, the right and left internal iliac chains, and also the right pararenal rectal area (Fig. 1A). On positron emission tomography-CT, mild fluorine-18-deoxyglucose uptake was observed in several lymph nodes, the T4 and L5 vertebrae (which could not be visualized on CT), the right middle lobe, and the left lower lobe of the lung (Fig. 1B).

The patient further underwent a radical hysterectomy, upper vaginectomy, bilateral salpingo-oophorectomy and pelvic

lymphadenectomy for cytoreduction of a bulky tumor. A histologic examination revealed a 9.5×7.5×4.5 cm mass lesion with lymphovascular invasion and involvement of the paravaginal soft-tissue resection margin (Fig. 2). Immunohistochemically, the main lesion was stained with HMB-45 and Melan-A; both of these immunostains were positive (Fig. 2).

The patient underwent adjuvant immunotherapy with pembrolizumab (Keytruda®, Merck & Co., Inc., Kenilworth, NJ, USA; 100 mg intravenous, 2 mg/kg of body weight, every 3 weeks [2 mg/kg Q3W]). Prior to her initial immunotherapy with pembrolizumab, the patient had an the Eastern Cooperative Oncology Group (ECOG) performance status 1, which is sufficient for completing all activities for daily living (ADL), such as eating, maintaining continence, and transference. After 2 cycles of adjuvant immunotherapy with pembrolizumab, the patient rapidly worsened to an ECOG performance status 3, and maintaining continence, transference, and ADL were almost impossible for her. In particular, her back pain was too severe to even lay herself on her bed. After administration of pembrolizumab, a mild rash developed on the patient's back, abdomen, and arm. No other adverse drug reactions occurred.

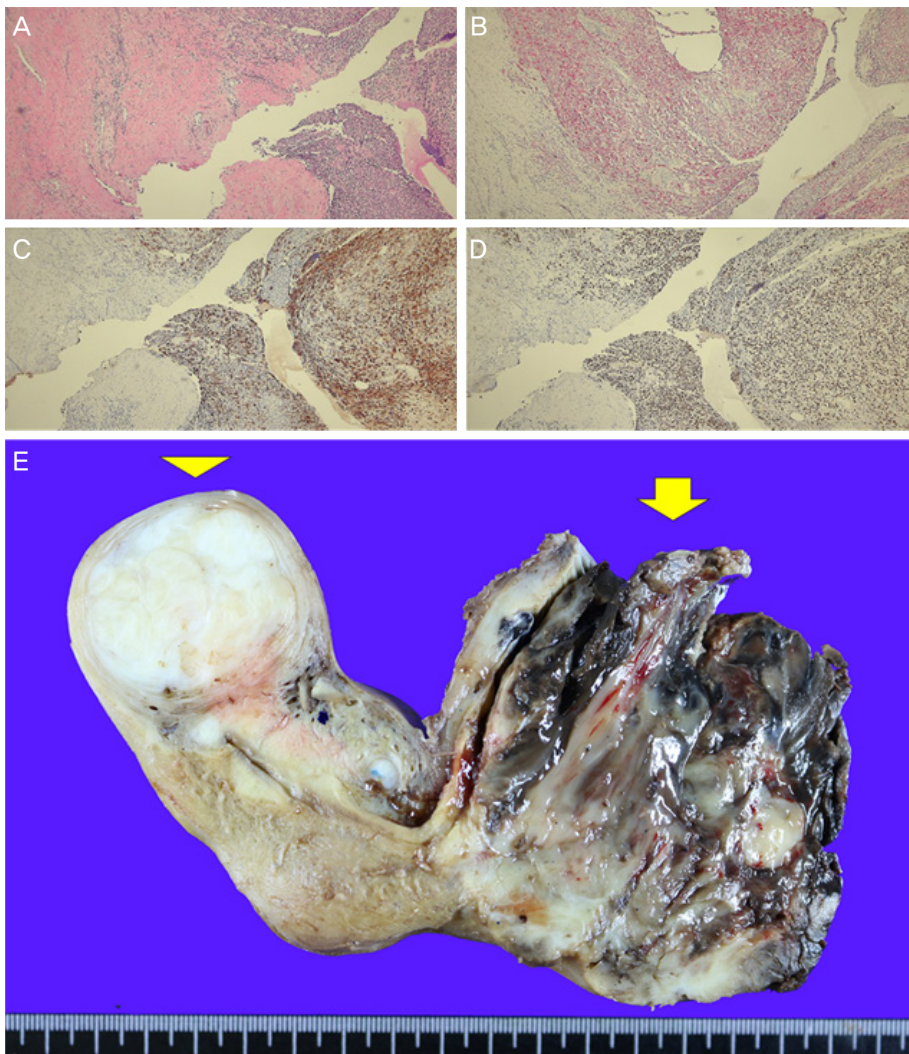


Fig. 2. (A) Infiltrative tumor cells (hematoxylin and eosin, magnification $\times 200$). (B-D) Immunohistochemical positivity for Melan-A, HMB45, and Ki-67 (magnification $\times 200$). (E) Gross features of the mass showing melanoma of cervix: the lesion is located in the posterior portion of the cervix, approximately 7×7 cm in size, and contains a black portion (arrow). A leiomyoma of about 4×4 cm is located in the uterine body (arrowhead).

Eventually the patient's general condition became very poor and she had difficulty visiting the hospital. Consequently, the patient was admitted to a nursing home and died 8 months after her last pembrolizumab treatment.

Discussion

Two new therapies were recently approved for treating advanced and metastatic malignant melanoma: a target therapy that inhibits the mitogen-activated protein kinase (MAPK) pathway in tumors using BRAFV600 and an immune therapy that inhibits checkpoints in the patient's immune system.

BRAFV600 mutations are found in about 50% of melanoma patients [7]. This mutation leads to a structurally active MAPK pathway. The BRAF inhibitors, dabrafenib and vemurafenib,

which target this driver mutation, have been approved as treatments for advanced and metastatic melanoma in patients with the BRAFV600 mutation. However, this drug was not applicable for this case because the patient refused genetic testing for the presence of BRAFV600 mutation.

In recent years, improved knowledge of pathophysiology and the immune system with regard to tumor control has led to development of novel immunotherapies to regulate immune checkpoints. Since 2011, 4 new immunotherapies have been approved by the Food and Drug Administration and European Medicines Agency to treat advanced melanoma: the anti-CTLA-4 antibody, ipilimumab (Yervoy[®]); the anti-PD-1 antibodies nivolumab (Opdivo[®]) and pembrolizumab (Keytruda[®]); and the oncolytic virus, talimogene laherparepvec (Imlygic[®]).

PD-1 is cell-surface receptor on T-cells that inhibits their immune response. When present on PD-L1 (CD274) on mela-

noma cells, it inhibits T-cell activation and proliferation [8]. As a PD-1 blocker, pembrolizumab is a fully humanized monoclonal IgG4 antibody and it binds to PD-1 on T-cells, thereby inhibiting interactions with its ligand, PD-L1, which is primarily expressed on melanoma cells. As a result, T-cells are activated and can attack melanoma cells.

In a phase I cohort study, patients with advanced malignant melanoma whose disease had progressed after at least 2 ipilimumab doses were randomly assigned to receive either pembrolizumab at 2 mg/kg every 3 weeks (n=89) or 10 mg/kg every 3 weeks (n=84) [9]. The overall response rate was 26% for both doses and the safety profiles were similar for both groups with no drug-related deaths. The most common drug-related adverse events (AEs) in the 2 mg/kg and 10 mg/kg groups were fatigue 33% vs. 37%, pruritus 26% vs. 19%, and rash 18% vs. 18% respectively [9].

In an open-label, multi-cohort, phase Ib clinical trial, the overall response to pembrolizumab in advanced melanoma patients was 33% (95% confidence interval [CI], 30–37%) in the total population and 45% (95% CI, 36–54%) in treatment-naïve patients. The 12-month progression-free survival rate was 35% (95% CI, 31–39%) in the total population and 52% (95% CI, 43–60%) in treatment-naïve patients, while the median overall survival in the total population was 23 months (95% CI, 20–29) and 31 months (95% CI, 24–not reached) in treatment-naïve patients [10].

In the KEYNOTE-002 trial, which is a randomized phase II trial of patients aged 18 years or older from 73 hospitals, clinics, and academic medical centers in 12 countries, the 6-month progression-free survival was 34% (95% CI, 27–41%) in the pembrolizumab 2 mg/kg group, 38% (95% CI, 31–45%) in the pembrolizumab 10 mg/kg group, and 16% (95% CI, 10–22%) in the chemotherapy group [11].

In a randomized-control phase III study, 834 patients with advanced melanoma received pembrolizumab at 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks, or four doses of ipilimumab (3 mg/kg) every 3 weeks in a 1:1:1 ratio [12]. Estimated 6-month progression-free-survival rates were 47.3% in the pembrolizumab every 2 weeks group, 46.4% in the pembrolizumab every 3 weeks groups, and 26.5% in the ipilimumab group. Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively. Efficacy was similar in the two pembrolizumab groups. Treatment-related AEs of grade 3 to 5 were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%).

Pembrolizumab prolonged progression-free survival and overall survival without progressive toxicity or low elevated toxicity compared with ipilimumab in patients with advanced melanoma [9-12]. Until now, the use of pembrolizumab has not been reported as a treatment for malignant melanoma in the female genital track and its therapeutic effect has not been evaluated.

Pembrolizumab treatment after radical surgery was not effective for this patient, who had primary cervical melanoma that metastasized to bone and lung tissue. We do not know why pembrolizumab treatment was ineffective for this patient. However, we can speculate about several potential mechanisms.

First, this patient's PD-L1 expression was not tested in her tumor samples, so it is possible that the treatment ineffectiveness had to do with negative expression of PD-L1. In previous studies, there was no correlation between expression of PD-L1 and overall survival in patients treated with classical chemotherapy [13,14], but it was reported that PD-L1 expression increased with disease progression [13,14]. In primary melanoma tissue, PD-L1 positivity was 5%, while satellite metastases were 25%, in-transit metastases were 40%, lymph node metastases were 14%, and distant organ metastases were 18% [13]. However, there are limited data on the expression of PD-L1 and drug responsiveness in uterine cervical melanoma.

Second, response to pembrolizumab may have differential activity according to the metastatic organ; it might not be effective for treating bony metastases of melanomas, and these lesions worsen rapidly compared with other organ metastases, such as lung or lymph nodes. However, to date, there have been no reports of differences in treatment response among patients with bone or other metastases.

There is no standard treatment for advanced-stage metastasized cervical malignant melanoma. Stage III patients who were treated by radiation with or without chemotherapy have been reported to have very poor prognoses [15-17]. Therefore, in this case, a radical hysterectomy was performed to improve the effects of postoperative systemic chemotherapy and/or immunotherapy.

Herein, we report a case of uterine cervical melanoma that showed a poor response to pembrolizumab after radical surgery. Malignant melanoma of the uterine cervix is a very rare disease and more data, including outcome results from novel immunotherapies as well as conventional treatments are nec-

essary to determine further standards of treatment for this rare disease.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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