Malignant melanoma treated with pembrolizumab during pregnancy: A case report and review of the literature

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Abstract. There have been very few reports on the use of immune checkpoint inhibitors for malignant tumors during pregnancy. Herein, the current study reports a case of a patient diagnosed with advanced malignant melanoma who was treated with pembrolizumab during pregnancy. A 40-year-old primigravida underwent noninvasive prenatal testing at 10 weeks of gestation, and the result was inconclusive, suggesting the possibility of maternal malignancy. A biopsy of the gluteal mass led to a diagnosis of malignant melanoma, and computed tomography revealed extensive metastases in her lungs and lymph nodes. She had a strong desire to proceed with pregnancy. In consideration of fetal growth and maturation, monotherapy was administered with pembrolizumab from 21 weeks of gestation, aiming for 28 weeks of gestation. The fetus grew well without maternal complications. At 28 weeks of pregnancy, the patient gave birth to a healthy boy by cesarean section. There was no evidence of metastasis in the placenta. The patient received nivolumab-ipilimumab combination therapy from postpartum day 13, followed by nivolumab monotherapy, and has been alive with controlled disease for 20 months.

Introduction

Immune checkpoint inhibitors, such as anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies, are widely used for advanced malignant melanoma, showing clinical efficacy with prolonged survival, and causing a dramatic change in the treatment strategy for the disease (1,2). However, there are very few cases of immune checkpoint inhibitors being used during pregnancy, and their efficacy and safety in such settings have not yet been established because they may affect the maternal-to-fetal immune tolerance system and give rise to some gestational complications as well as potential harm to the fetus if used during pregnancy (3). In this report, we describe the case of a patient with advanced malignant melanoma diagnosed at 16 weeks of gestation who was treated with the anti-PD-1 antibody pembrolizumab during pregnancy and delivered a live baby at 28 weeks of pregnancy without serious maternal adverse events, and no neonatal abnormality was noticed. We also reviewed some reported cases of the use of immune checkpoint inhibitors during pregnancy for malignant melanoma in the literature.

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Case report

The patient was a 40-year-old woman (gravida 2, para 0). Her medical history included cryotherapy for congenital giant pigmented nevus in her infancy. There was no family history warranting special attention. Because of her advanced age, the patient underwent noninvasive prenatal testing (NIPT) at 10 weeks of gestation at a local hospital. Chromosome 13 aneuploidy was detected, and chromosomes 21 and 18 were not reportable, leading to 'inconclusive result'. Accordingly, the possibility of maternal malignant tumors was pointed out, and she was referred to our hospital. A detailed interview and a whole-body examination revealed that she had noticed a mass in her buttocks. The patient then visited the dermatology department. On visual examination, there were scattered pigmented lesions with bluish tones all over the buttocks and brownish tones on the trunk and extremities. Palpation revealed a mass on the buttocks. Magnetic resonance imaging (MRI) of the pelvis at 15 weeks of gestation showed a lobulated mass with partial high intensity on T1- and T2-weighted images, high intensity on a diffusion-weighted image, and low intensity on apparent diffusion coefficient maps within the subcutaneous fat tissue of the buttocks (Fig. 1A and B), and swelling of the left inguinal lymph node was also noted. A biopsy of the buttock mass was performed at 16 weeks of gestation, and the pathological findings led to the diagnosis of malignant melanoma. The amniotic fluid examination at 16 weeks of gestation showed 46XY normal karyotype, with no chromosomal abnormalities in the fetus. Upon

being given an adequate explanation about the prognosis and future treatment plan by an obstetrician and a dermatologist, the patient strongly desired to proceed with pregnancy. On hematological examination, tumor markers, such as 5-S-CD, CEA, CA19-9, CYFRA, SCC, were all within the normal range, and there were no abnormal findings in other parameters. Plain computed tomography (CT) at 20 weeks of gestation revealed small and large nodules in both lungs and enlarged lymph nodes at the tracheal bifurcation, indicating lung and subcarinal lymph node metastases (Fig. 1C). No other distant metastases were observed.

Based on the above, the patient was diagnosed as having stage IV primary malignant melanoma of the buttocks (cT4aN2bM1b) with multiple lung metastases, left inguinal lymph node metastases, and subcarinal lymph node metastases. Taking into consideration both the gestational weeks for fetal growth and lung maturation and the suppression of maternal melanoma progression, we decided to treat the patient with pembrolizumab alone during pregnancy, attempting to maintain pregnancy until 28 weeks of gestation, and institute optimal melanoma treatment after delivery by cesarean section. Three courses of pembrolizumab therapy (200 mg/body, every 3 weeks) were administered from 21 weeks and 0 days to 27 weeks of gestation. During the treatment with pembrolizumab, fetal growth was uneventful and no maternal adverse events were observed, and the patient underwent cesarean section at 28 weeks and 0 days of gestation. The newborn was a boy weighing 1,291 g, with an arterial cord blood gas pH of 7.339, and the 1- and 5-min Apgar scores were 7 and 8, respectively. The postnatal course was good, although the newborn was managed in the neonatal intensive care unit because of preterm birth. Umbilical cord blood showed a slightly high XX signal of 4.8% on cross-sex fluorescence in situ hybridization, and the possibility of metastasis of melanoma to the newborn could not be ruled out. However, there was no evidence of metastasis in the newborn and his growth was good. The placenta weighed 316 g, with no grossly obvious melanotic macules being observed, and pathological findings did not show any tumor metastasis. At the time of the cesarean section, intraperitoneal observation showed that the right ovary swelled to 7 cm in size, and the capsule of the tumor ruptured spontaneously, resulting in bleeding. There were some black lesions on the posterior surface of the uterus, but no disseminated lesions were found in the abdominal cavity. Right salpingo-oophorectomy was performed. The resected right adnexa weighed 195 g, and gross examination revealed a black area and hematoma in the tumor section (Fig. 2A and B). Pathological findings showed that the tumor was composed of medullary proliferation of atypical cells with amphophilic cytoplasm and some brown pigment (Fig. 2C and D). These histological images were congruent with the appearance of malignant melanoma on a biopsy of the buttocks, and the diagnosis of right ovarian metastasis of malignant melanoma was made. Postoperative positron emission tomography-computed tomography (PET/CT) showed accumulation of fluorodeoxyglucose (FDG) with an SUVmax of 12.09 in the buttock tumor, the main lesion. FDG accumulation was also observed in the mediastinal lymph nodes with an SUVmax of 14.61, in the myometrium with an SUVmax of 7.30, and in the sacral lymph nodes with an SUVmax of 5.68 (Fig. 3). On postoperative day 13, administration of the anti-PD-1 antibody nivolumab (80 mg/body) was started in combination with ipilimumab (1 mg/kg), an anti-CTLA-4 antibody. This was followed by nivolumab monotherapy, which was highly effective. Now that 20 months have elapsed since the cesarean section, the patient is alive with partial response (PR) being maintained.

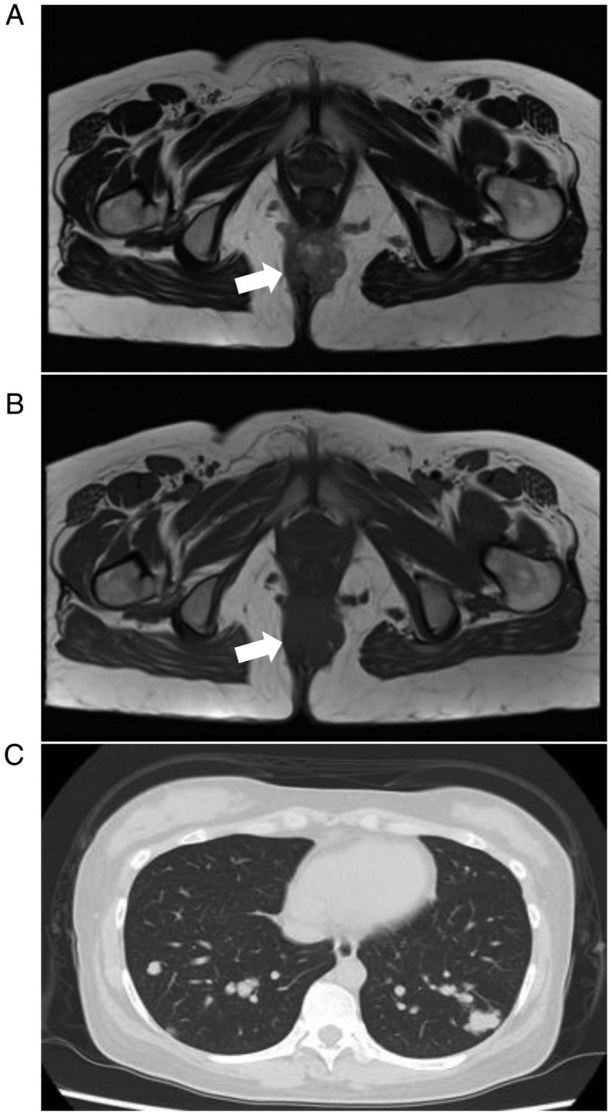

Figure 1. MRI images. (A) T2 weighted image; (B) T1 weighted image. A 60-mm lobulated solid mass was located in the subcutaneous adipose tissue of the buttocks (white arrows). (C) Chest CT revealed multiple metastases in both lungs.

Discussion

The incidence of malignant melanoma is on the rise, and malignant melanoma is reported to account for 8% of malignancies associated with pregnancy (4). With the advent of molecular-targeted agents and immune checkpoint inhibitors, the treatment of malignant melanoma has undergone drastic changes in recent years, with response rates exceeding 50% (1,2). Currently, immune checkpoint inhibitors are the first choice of drug therapy in the absence of BRAF mutations, while combination therapy with a BRAF

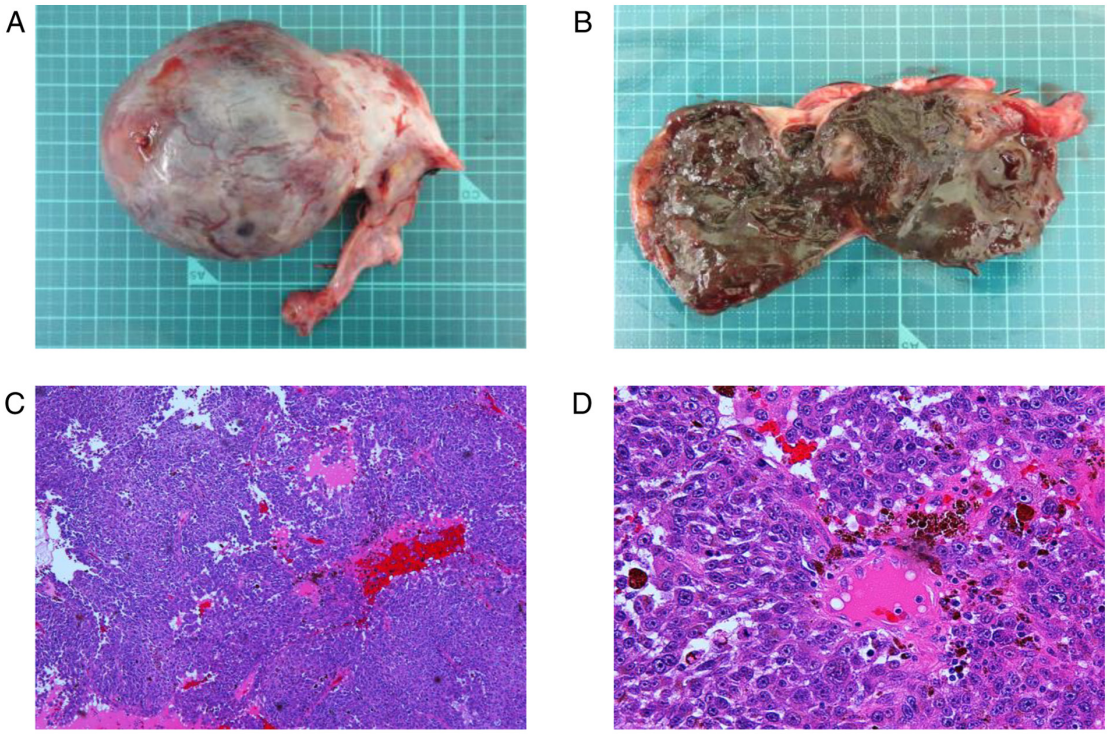

Figure 2. Gross appearance of the right ovary. (A) The right ovary was enlarged to 7 cm in diameter. (B) Black lesions and hematoma on the cut surface. (C and D) Pathologic findings of the right ovary. (C) Atypical cells with amphophilic cytoplasm proliferated medullary (magnification, x40). (D) Atypical cells partially demonstrated brown pigmentation, and a clear nucleolus was observed in the large round nucleus (magnification, x200).

inhibitor and a MEK inhibitor or an immune checkpoint inhibitor is used in the presence of BRAF mutations (1). Because our patient did not have a BRAF mutation and the PD-L1 expression rate was 1 to 4%, an immune checkpoint inhibitor was selected for first-line therapy. At the time of the initial diagnosis, she was already pregnant and hoping to have a baby. Due to her stage IV disease, however, early treatment during pregnancy was considered necessary to restrain disease progression, which made it difficult for us to figure out the optimal treatment. While chemotherapy during the first trimester of pregnancy may increase the risk of fetal malformation, miscarriage, and stillbirth, it has been reported that the incidence of fetal malformation is not significantly different between women on chemotherapy and those with normal pregnancies in the second and third trimesters (5). On the other hand, it has been reported that chemotherapy after the second trimester may increase the risk of fetal growth restriction, premature birth, and complications due to the prematurity of the newborn (6). After due informed consent, we started treatment from 21 weeks of gestation, aiming at maintaining the pregnancy until 28 weeks for the sake of fetal maturation.

In the maternal immune system during pregnancy, immune tolerance to paternally derived antigens carried by the fetus is important for maintaining pregnancy. It is known that immune checkpoint molecules, such as PD-1, CTLA-4, and TIM-3, have a major impact on maternal immune system (7). Furthermore, regulatory T cells (Treg) play an important role in maternal immune tolerance, and the CTLA-4/B7 and PD-1/PD-L1 pathways are involved in the activation of Treg (8). It has therefore been discussed that immune checkpoint inhibitors targeting CTLA-4 and PD-1, which are used in the treatment of malignant melanoma, may affect the maternal immune system and give rise to some gestational complications if used during pregnancy. While the US FDA pregnancy risk category of both pembrolizumab (anti-PD-1) and ipilimumab (anti-CTLA-4) is 'Not assigned' (Use is not recommended) because of their potential harm to the fetus, no conclusion has been reached yet. As for animal models, a reproductive and developmental toxicity study of ipilimumab in pregnant cynomolgus monkeys showed higher incidences of miscarriage, stillbirth, premature birth, low birth weight baby, and infant mortality in ipilimumab-treated animals than in control animals (9).

Reports on the use of immune checkpoint inhibitors for malignant melanoma in humans during pregnancy, of which there are few, are summarized in Table I (10-13). All four patients received ipilimumab or nivolumab alone or in combination. Deterioration of the maternal or fetal condition resulted in premature birth in most cases, but there was no metastasis to the newborn. One of the four mothers died early after delivery. In our case, three cycles of pembrolizumab monotherapy were given during pregnancy, and no fetal effects, such as fetal malformation or fetal growth restriction, were noted until 28 weeks of gestation, with no maternal adverse events being observed. Neither was there any evidence of metastasis of malignant melanoma to the placenta, and postnatal development of the newborn has been uneventful so far, with no metastasis being observed. Alexander *et al* showed the risk of transplacental metastasis to the infant in cases with metastatic melanoma during pregnancy (14). In their report, the fetal risk of melanoma metastasis was 22% when tumor involvement into the placenta was observed; therefore, the placentas of women with suspected metastatic melanoma should be carefully examined

Table I. Reported cases of the use of immune checkpoint inhibitors for malignant melanoma during pregnancy.

Author (year)	Patient age	Disease stage	Drug used	Mode of delivery and reason for delivery	Metastasis to the fetus and placenta	Maternal outcome	Neonatal outcome	(Refs)
Mehta *et al* (2018)	31	III	Ipilimumab IL-2	Not reported	None	PD	Normal development, no metastases	(10)
Menzer *et al* (2018)	34	IV	Ipilimumab Nivolumab	Cesarean section at 24 weeks; Deterioration of maternal condition	Metastasis to the placenta No metastasis to the fetus	Death (postoperative day 1)	Mild motor development delay, no metastasis	(11)
Burotto *et al* (2018)	34	IV	Ipilimumab Nivolumab	Cesarean section at 32 weeks; Placental insufficiency	None	PR	Normal development, no metastases	(12)
Xu *et al* (2019)	32	IV	Nivolumab	Cesarean section at 33 weeks; Fetal growth restriction	None	CR	Congenital hypothyroidism; Normal development, no metastases	(13)

PD, progressive disease; PR, partial response; CR, complete response.

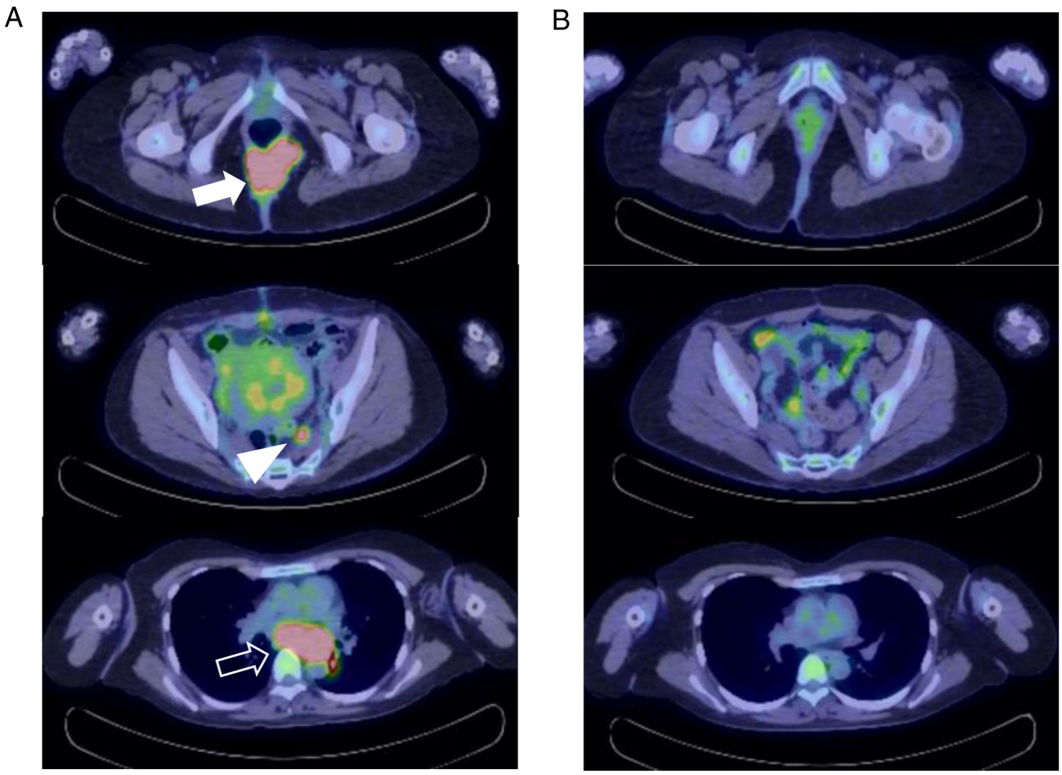

Figure 3. PET/CT findings. (A) Results at postoperative day 8. (B) Results after combination therapy with nivolumab and ipilimumab. (A) On postoperative day 8, FDG accumulation was identified in the buttock tumor, the main lesion (white arrow; upper panel), the myometrium and sacral lymph nodes (white arrowhead; middle panel) and in the mediastinal lymph nodes (black arrow; lower panel). (B) Postpartum nivolumab-ipilimumab combination therapy was highly effective, and abnormal FDG accumulation disappeared. FDG, fluorodeoxyglucose.

grossly and histologically. In our case, the patient actually had the risk of transplacental melanoma metastasis to her fetus; however, we chose to maintain pregnancy at least until 28 weeks of gestation for considering fetal maturation and development.

In the present case, pembrolizumab therapy during pregnancy may not have been effective in controlling the progression of the disease, given the fact that metastatic lesions were found in the ovaries removed during cesarean section, that the postpartum PET/CT scan showed no shrinkage of the buttock tumor compared with the MRI scan during pregnancy, and that the disease spread to the mediastinal lymph nodes and myometrium. Nevertheless, the use of immune checkpoint inhibitors may be considered as a treatment option for advanced malignant melanoma during pregnancy, because our patient was able to continue pregnancy without adverse events.

Finally, it is of interest that melanoma could be diagnosed during pregnancy as a result of NIPT in our case. NIPT is a test for inferring fetal chromosomal aneuploidy using cell-free fetal DNA (cfDNA) fragments in maternal blood, and it is primarily used to detect trisomy 13, trisomy 18, and trisomy 21. The results of NIPT may be positive, negative, or inconclusive, and the incidence of inconclusive results is 0.32 to 5.4% (15). In our case, aneuploidy of chromosome 13 was detected, whereas chromosomes 21 and 18 were not reportable, turning out inconclusive results. The most common reason for inconclusive NIPT results is a lack of cfDNA in the maternal blood, but other factors, such as autoimmune disease, chromosomal aneuploidy other than trisomy 13, 18, and 21, and maternal malignancy, have also been suggested (16). In fact, there are reports of incidental detection of occult maternal malignancies by NIPT (17,18). The present case is rare in that, while NIPT yielded inconclusive results, amniotic fluid examination did not show any chromosomal abnormality in the fetus, and further examination taking into account the possibility of maternal malignancy led to the diagnosis of advanced malignant melanoma during pregnancy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YA, SM and KI conceived and designed the case report, and wrote the initial draft of the report. AK, HM, KN, MM and SN collected the clinical data. TN, NI, NO, YM, SY and YY analyzed the data from images and pathological examinations. YA and KI confirmed the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Written informed consent for surgery and tissue collection was obtained from the patient.

Patient consent for publication

Written informed consent for the publication of the present report was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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