CASE REPORT

Endometrial metastasis of primary malignant melanoma of the brain

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SUMMARY

Endometrial metastatic malignant melanoma is a rare occurrence from any primary site. A literature search has revealed only 15 reported cases in existing literature, majority of which originated from a primary cutaneous lesion. This is a case of endometrial metastasis of primary malignant melanoma of the brain, the first reported case of its kind. The rarity of endometrial metastatic melanoma may incline clinicians to neglect the importance of malignant melanoma in a patient's history when they present with abnormal uterine bleeding. However, with increasing rates of primary malignant melanoma, it is likely that the incidence of metastasis to rare sites, such as the endometrium, is also likely to increase. For those women with metastatic disease confined to the uterus, total abdominal hysterectomy +/-bilateral salpingo-oophorectomy improved prognosis considerably. Newer *BRAF* molecular testing and targeted adjuvant therapy may also significantly improve prognosis in addition to surgical resection and should be considered.

BACKGROUND

Malignant melanoma is an aggressive neoplasm most commonly originating from cutaneous tissue, mucous membranes or the eye. However, cases of primary malignant melanoma of the brain have also been reported and, given the origin of melanocytes from the neural crest, this is not entirely unexpected.¹ Majority of deaths from malignant melanoma are a result of unresectable or metastatic disease, generally to the adjacent tissue and lymph nodes, bone, lung, brain and intestines.² Metastatic disease to the uterus is a very rare occurrence, and usually occurs in the cervix or myometrium.³ Metastasis of malignant melanoma to the endometrium specifically is extremely rare. A literature review of journals published prior to October 2017 identified only 15 cases of this having occurred, with the last reported case occurring in 2008.

The gold standard for melanoma treatment is surgical resection, regardless of the site.⁴ However, treatment of metastatic melanoma is particularly difficult due to micrometastatic disease, resulting in unresectable or residual disease not identifiable on imaging. Historically, this micrometastatic or residual disease has been treated with chemotherapy agents such as dacarbazine with a poor response rate of only 10%. This has led to the development of newer agents in the last 10 years including immunotherapy and more recently *BRAF* gene inhibitors.

Combination therapy with *BRAF* inhibitors in addition to downstream *MEK* inhibitors has proven to prolong overall and progression-free survival rates for patients with advanced melanoma and is now often used as an adjunct to surgery.⁵

This is a case of primary malignant melanoma of the brain with later metastasis to the endometrium. There are no identifiable cases of this in existing literature. Majority of reported endometrial metastases originated from primary cutaneous lesions. Less commonly, there were also few cases reporting primary vulval malignant melanoma and one case of primary uveal malignant melanoma metastasising to the endometrium.

The purpose of this article is to expose and explore the complexities of diagnosing and treating endometrial metastatic malignant melanoma, but also primary non-cutaneous malignant melanoma. Informed consent was obtained for the publication of this case.

CASE PRESENTATION

This is a case of a 59-year-old postmenopausal woman that presented to her general practitioner with a 2-month history of intermittent light vaginal bleeding and right lower abdominal discomfort. She underwent an outpatient pelvic ultrasound scan that showed an enlarged, mobile, anteverted uterus with an 115×96×135 mm fundal mass, likely a fibroid, displacing the endometrium. Endometrial thickness could not be commented on. There was a 42×48×33 mm simple cyst noted on the right ovary. She was referred to the gynaecology clinic for review.

The patient had gone through menopause 13 years prior to her current symptoms and had no prior episodes of postmenopausal vaginal bleeding. Her most recent normal pap smear was in 2016, and she had no previous abnormal smears. She reported no significant weight loss, fatigue or night sweats.

The patient had a history of malignant melanoma of the brain, initially diagnosed in 2008. She underwent resection of a left frontal lobe lesion, initially thought to be a primary brain malignancy, followed by whole brain radiotherapy. Histological examination of the resected brain lesion showed malignant melanoma. There was no cutaneous or other primary site diagnosed. In 2009, she was noted to have a left supraclavicular fossa mass on surveillance imaging. This was monitored for some years until it was shown to be increasing in size on imaging in 2013. Biopsy revealed metastatic

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Figure 1 CT of the abdomen and pelvis of the patient 2 months prior to diagnosis of endometrial metastatic melanoma.

malignant melanoma, and she underwent resection of the mass and further radiotherapy. She did not undergo chemotherapy. She did not have *BRAF* molecular tissue testing at this stage as it was still in preclinical trial phase.

The patient underwent annual imaging and clinical surveillance. On repeated CT imaging, there were stable enlarged mesenteric lymph nodes, a noted fibroid uterus, but no other pelvic organ abnormalities, and no evidence of recurrence. In 2015, the patient had a positron emission tomography (PET) scan, to assess the persistently enlarged but stable mesenteric lymph nodes. This demonstrated no specific areas of increased fluorodeoxyglucose (FDG) uptake suspicious for recurrence. Her last review with the oncologists, without evidence of recurrence, was 2 months prior to the development of her vaginal bleeding. At this stage, she had a CT scan that showed a $112 \times 102 \times 118$ mm mass arising from the uterus, labelled likely a fibroid again and noted to be unchanged from previous imaging (figure 1).

On bimanual examination, she had an enlarged, equivalent to 18-week size, mobile, irregular uterus consistent with known fibroids. On speculum examination, she had an atrophic vagina and cervix.

INVESTIGATIONS

Her cancer antigen-125 was 5.3, and full blood count, renal function and liver function tests were unremarkable. No other

tumour markers were performed. She was booked for an urgent diagnostic hysteroscopy, dilatation and curettage for sampling of endometrial lining.

Hysteroscopy revealed a large polyp filling the cavity, and the ostia were not visualised due to this (figure 2).^{6,7} There was no macroscopic evidence of malignant features. A sample of the polyp and endometrium were taken for histological evaluation.

Histological examination of the endometrial curetting showed fragments of endocervical and endometrial lining epithelium with fibromuscular tissue and an infiltrating poorly differentiated malignant tumour with plasmacytoid cells (figure 3).⁸ Immunohistochemical reaction pattern revealed strongly positive S-100, Melan-A and P53 staining, consistent with metastatic malignant melanoma (figure 3).⁹⁻¹¹

TREATMENT

After histological diagnosis of endometrial metastatic melanoma, the patient was referred to the gynaecology-oncology specialists for further workup. She had a staging PET scan performed, which revealed an intensely FDG avid uterine mass, consistent with biopsy-proven metastatic melanoma. No other sites of FDG avid nodal or distant metastatic disease were identified. Unfortunately, this imaging is not available.

She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. At the time of surgery, the right parametrium was noted to be thickened and suspicious for possible residual disease. Histopathology examination of the uterus, cervix and bilateral fallopian tubes showed an atrophic endometrium, mostly displaced by poorly differentiated malignancy consistent with metastatic melanoma. The right parametrial margin was involved. The right ovary contained a benign serous cystadenoma and the bilateral fallopian tubes and left ovary were unremarkable. There was noted to be multiple leiomyomata within the specimen—the size and location of which were not remarked on. There was no comment drawn as to whether these were the lesions seen on serial CT scanning (figure 1).

OUTCOME AND FOLLOW-UP

After her gynaecological surgical procedure, she had an in-hospital fall and subsequent neck of femur fracture for which she is undergoing rehabilitation. Molecular testing for *BRAF* V600 mutation was conducted and found to be positive. She was commenced on combination *BRAF* and *MEK* inhibitor therapy

1. Normal uterine cavity on hysteroscopy.

2. Benign endometrial polyp obscuring cavity, similar to that seen on hysteroscopy of the patient.

Figure 2 Hysteroscopic image of normal uterine cavity and benign endometrial polyp similar to that seen on hysteroscopy of this patient.

1. Example of normal endometrial epithelium.

2. Example of plasmacytoid cells similar to those seen in this patient and commonly seen in malignant melanoma.

Melan A

S100

3. Example of Melan-A positive and S100 positive staining, similar to that seen in this patient.

4. Example of P53 positive staining, similar to that seen in this patient.

Figure 3 Histology of normal endometrial epithelium and plasmacytoid cells seen in malignant melanoma. Positive staining of Melan-A, S100 and P53 also seen in malignant melanoma.

with dabrafenib and trametinib, but has been poorly compliant with this. Furthermore, while in hospital recovering from her fracture, she became septic with an acute abdomen. CT of the abdomen and pelvis revealed a right-sided hydronephrosis. hydroureter and pyelonephritis secondary to an obstructing 54×22 mm right-sided pelvic mass thought to be metastatic

lymphadenopathy ([figure 4](#)). This was not previously seen at the time of the surgery or on PET scan. The plan is for repeat CT scan 4 months from diagnosis of the mass to see if there has been response to the *BRAF* and *MEK* inhibitors. She declined resection of the mass.

DISCUSSION

Metastatic malignant melanoma to the endometrium is a rare occurrence with any primary site. Only 15 cases of metastatic melanoma to the endometrium have been identified, and none of these cases involved metastasis from primary malignant melanoma of the brain.

A literature search was conducted using various search engines including Google, PubMed and Medline. Case reports, case series and previous reviews were searched for, using key phrases including 'malignant melanoma of uterus', 'metastatic malignant melanoma of uterus', 'malignant melanoma of endometrium', 'malignant melanoma of uterine body', 'primary malignant melanoma of brain', 'malignant melanoma', 'malignant melanoma with metastasis'. Twenty-eight case reports and one literature review were found. Six articles reported primary malignant melanoma of the genital tract or uterus, including cervix. Six articles reported metastatic melanoma to uterine fibroids, serosa of uterus, cervix or ovaries. One article did not identify where in the uterus the metastatic malignant melanoma was found. Fifteen articles specifically reported endometrial metastatic malignant melanoma.

Figure 4 CT of the abdomen and pelvis of the patient 2 months after total abdominal hysterectomy+bilateral salpingo-oophorectomy showing right-sided lymphatic metastatic disease causing right-sided hydronephrosis and hydroureter.

All reported cases involved women presenting with abnormal uterine bleeding and a history of malignant melanoma.^{12–25} Metastatic melanoma of the endometrium can affect both premenopausal and postmenopausal women, with the age of patients reported in previous cases ranging from 31 to 83 years. Majority of cases (63%) were in the postmenopausal age group and presented with postmenopausal bleeding.

Majority of women did not have prior metastatic disease, only a single primary malignant melanoma. The most common primary site was a cutaneous lesion. There were also two reported cases of primary vulval malignant melanoma and a case of primary uveal malignant melanoma.^{3 13 15} The time from primary malignant melanoma to the diagnosis of metastatic melanoma to the endometrium ranged from 1.5 to 11 years.

Surgical resection remains the gold standard of treatment for malignant melanoma. Five women were reported to have undergone a total abdominal hysterectomy +/-bilateral salpingo-oophorectomy (TAH+/-BSO). Of these, three patients had metastatic melanoma confined to the uterus with no further metastatic spread,^{12 15 16} and two were found to have extensive metastatic disease and were thereafter palliated.^{17 21} Two women were found to have extensive metastatic disease on imaging after initial endometrial sampling and were palliated without surgery.^{13 22}

Learning points

- Metastatic malignant melanoma of the endometrium is a rare occurrence that usually originates from a primary cutaneous lesion. This is the first reported case of a primary malignant melanoma of the brain metastasising to the endometrium.
- The rarity of endometrial metastasis may incline gynaecologists and clinicians to neglect the importance of malignant melanoma in a patient's history. However, the incidence of metastatic spread to rare sites, like the endometrium, is likely to increase as the incidence of primary malignant melanoma increases.
- All reported cases of endometrial metastatic melanoma presented with abnormal uterine bleeding. All women with abnormal uterine bleeding and a history of malignant melanoma, regardless of age and clearance of previous melanoma, should have an urgent hysteroscopy and endometrial sampling to confirm/exclude diagnosis.
- Total abdominal hysterectomy +/-bilateral salpingo-oophorectomy greatly improves prognosis for women with metastatic disease localised to the uterus; however, *BRAF* molecular testing and targeted adjuvant therapy may contribute to better prognosis in addition to surgery for these women.
- Approximately 50% of patients with malignant melanoma have a *BRAF V600* gene mutation. This is the first case of *BRAF* molecular testing in endometrial metastasis and also unusual in that *BRAF* molecular testing is usually reserved for patients with primary cutaneous disease, which was not the case for this patient.
- As the incidence of malignant melanoma continues to rise, we will also likely see an increase in the incidence of non-cutaneous primary disease and rare metastatic disease sites, such as the endometrium. This will prompt further investigation into the efficacy of newer adjuvant therapies such as *BRAF* inhibitors and immunotherapy for these cases and is certainly an area of future research to watch.

Historically, adjuvant therapy with chemotherapy agents, such as dacarbazine, has been recommended to all patients with metastatic melanoma. Of the three women who underwent TAH+/-BSO, it was not stated whether they went on to have adjuvant chemotherapy.^{12 15 16} The patient in this case underwent radiotherapy for her primary and recurrent disease and did not receive chemotherapy.

It has been demonstrated that approximately half of patients with metastatic malignant melanoma have a *BRAF V600* gene mutation that has been shown to be associated with shorter survival, increased likelihood of brain metastasis and increased likelihood of primary cutaneous lesions occurring in areas without chronic sun exposure.^{5 26} For these reasons, molecular testing for *BRAF* gene mutations and treatment with *BRAF* inhibitors was developed and introduced in 2010.^{4 5 26 27} The last reported case of endometrial metastatic melanoma prior to this case was in 2008; as such, there have been no recorded cases of *BRAF* inhibitor treatment of endometrial metastatic disease. This will be the first case of endometrial metastatic disease that has undergone *BRAF* and *MEK* inhibitor treatment. Additionally, there is little experience of the use of *BRAF/MEK* inhibitors for metastatic disease resulting from non-cutaneous primary disease. It is yet to be established if there is difference in efficacy between primary disease sites, and this will likely be an area of exploration in the future.

From the limited cases, metastatic melanoma to the endometrium generally carries a poor prognosis (as does most advanced melanoma), with 50% of women having extensive system-wide metastatic disease at time of diagnosis. However, for those in whom the metastatic melanoma was confined to the uterus, with no evidence of other metastatic disease, the prognosis was considerably improved. Patients who had metastatic disease confined to the uterus and underwent a total abdominal hysterectomy +/-bilateral salpingo-oophorectomy had a significantly good prognosis with all of these patients surviving past time of publication of their case. Long-term survival for these patients has not been followed however.

Metastatic malignant melanoma of the uterus, and in particular the endometrium, is extremely rare; however, the incidence may increase as the incidence of malignant melanoma rises worldwide.²⁸

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