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CASE REPORT

Post-menopausal Bleeding: a Rare Presentation of Metastatic Uveal Melanoma

Michael A COUTTS,[1] Nicola J BORTHWICK,[2] John L HUNGERFORD,[3] Ian A CREE[2,4]

[1]Cellular Pathology, Preston Hall Hospital, Maidstone and Tunbridge Wells NHS Trust, Kent,
[2]Department of Pathology, Institute of Ophthalmology, University College London, Bath Street, London,
[3]Ocular Oncology Service, Moorfields Eye Hospital, City Road, London,
[4]Translational Oncology Research Centre, Queen Alexandra Hospital, Portsmouth, England

Uveal melanoma differs from cutaneous melanoma in many ways, including its pattern of metastasis, and exhibits latency with clinical evidence of metastasis sometimes appearing many years after primary diagnosis. Most patients develop metastasis within the liver, but some may present with metastasis to other sites. We report a case of uveal melanoma that presented with post-menopausal bleeding due to metastasis. Further investigation revealed widespread metastatic disease and the patient was not fit for chemotherapy. She died two months after presentation: autopsy revealed metastases in many sites, including the uterus, right ovarian fibroma, kidney, mesentery, liver, lung, thyroid, bone marrow and skin. The immediate cause of death was cardiac tamponade due to a malignant effusion secondary to cardiac metastasis. This case illustrates the widespread metastatic potential of uveal melanoma and highlights the potential for unusual presentation of metastatic disease from this eye tumor. (Pathology Oncology Research Vol 12, No 3, 184–187)

Key words: melanoma, eye, uveal, endometrium, post-menopausal bleeding, metastasis

Introduction

Uveal melanoma is a rare tumor with an incidence of around 0.5 per 100,000 in most Western populations.[1] It has a poor prognosis, with a 50% year mortality rate at 15 years, and in 85% of such cases, hematogenous involvement of the liver can be found.[2-5] Large autopsy series have been reported from Denmark,[6] the USA[7] and Finland,[8] as well as several case reports. Uveal melanoma also exhibits latency: clinically evident metastases may only appear many years (even several decades) after removal of the primary tumor. This means that patients may present to any doctor with unusual signs and symptoms of metastasis. We report a case in which post-menopausal bleeding lead to the diagnosis of widespread metastatic disease.

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Correspondence: Prof. Ian A CREE, Translational Oncology Research Centre, Queen Alexandra Hospital, Portsmouth PO6 3LY, England. Tel: 02392 286378, fax: 02392 286379, E-mail: ian.cree@porthosp.nhs.uk

Case report

An 83-year-old lady presented with vaginal bleeding three years after enucleation of the left eye for choroidal melanoma, for which she had also received radiotherapy due to the presence of an extrascleral extension. Three months prior to her clinical presentation to the gynecologists, a CT scan suggested a right orbital mass lesion and a bone scan showed widespread deposits in the spine, pelvis, ribs, femurs and humeri. An ultrasound scan showed liver metastases. The endometrium was biopsied to investigate her symptomatic post-menopausal bleeding and metastatic involvement of the endometrium by melanoma was confirmed histologically. The patient's condition deteriorated rapidly and she required palliative care for disseminated melanoma. The patient and relatives gave ante-mortem consent for an autopsy to be performed as part of a study of metastatic melanoma. Following the patient's death, two months after her presentation, an autopsy was performed.

The body showed extensive metastasis but the immediate cause of death was tamponade secondary to a pericardial

effusion, and melanoma deposits up to 30 mm in diameter were present in the epicardium. The heart weighed 417 g, and also showed multiple deposits within the myocardium and endocardium (*Figure 1a*). The lungs (right 845 g, left 620 g) each contained 7-8 nodules of metastatic melanoma up to 20 mm in diameter. Both lungs were congested and edematous in keeping with the cardiac tamponade.

Whilst most of the gastro-intestinal tract was unremarkable, multiple melanoma nodules were identified within the small and large bowel mesentery up to 40 mm in diameter. The liver was enlarged (1560 g) and contained 4-5 nodules of melanoma up to 18 mm in diameter. A larger deposit, 40 mm in diameter, was present at the hilum of the liver, compressing the common bile duct. Two small deposits of melanoma up to 9 mm were present in the pancreas. A 20-mm nodule was present in the right kidney, 3 nodules up to 40 mm in the left peri-renal fat and a 10-mm deposit in the bladder mucosa. The uterus and cervix were enlarged and bosselated, measuring 140x100x70 mm. The uterine cavity was hugely dilated by blood clot and melanin pigment: melanoma was seen extensively infiltrating the myometrial wall (*Figure 1b*). Some fibroids of usual appearance were also present. A right-sided ovarian fibroma of 120x90x70 mm was also present (*Figure 1b*) and showed multiple nodules of metastatic melanoma within it.

Further nodules of melanoma, up to 30 mm in diameter, were noted within the spleen (390g) and many were noted within axillary, inguinal, para-aortic, and mediastinal lymph nodes. Metastases were present in the adrenal glands and the thyroid gland. There was extensive infiltration of the thoracic and lumbar spine by metastatic melanoma. Subcutaneous nodules of melanoma up to 11 mm in diameter were identified in the groin, right shoulder and trunk. No metastases were identified in the brain or cranial cavity.

Histology (*Figure 2a,b*) confirmed the presence of disseminated malignant melanoma (of mixed epithelioid and spindle cell type) infiltrating the organs described grossly: sections were examined from liver, kidneys, pancreas, adrenal glands, thyroid, spleen, skin, uterus and bone marrow. The right ovarian mass was confirmed to be a fibroma infiltrated by metastatic malignant melanoma. The previous enucleation specimen was retrieved from the files at the Institute of Ophthalmology: this showed a choroidal melanoma of mixed histological type with an extrascleral extension (*Figure 2c*).

Discussion

This case highlights the widespread metastatic potential of uveal melanoma, and the potential for unusual presentations. The hematogenous nature of uveal melanoma metastases is likely to be responsible, though it is notable that in this case metastasis to skin was accompanied by metastasis to lymph nodes, which could cause considerable clinical confusion. Presentation of metastatic uveal melanoma with post-menopausal bleeding is certainly extremely unusual, but similar cases may be included in some of the reported series. Metastasis of cutaneous melanoma to the uterus has been described previously,[12-14] though this is very rare. Uterine metastases are more common from other tumors, particularly breast cancer.[15] The patient's immediate

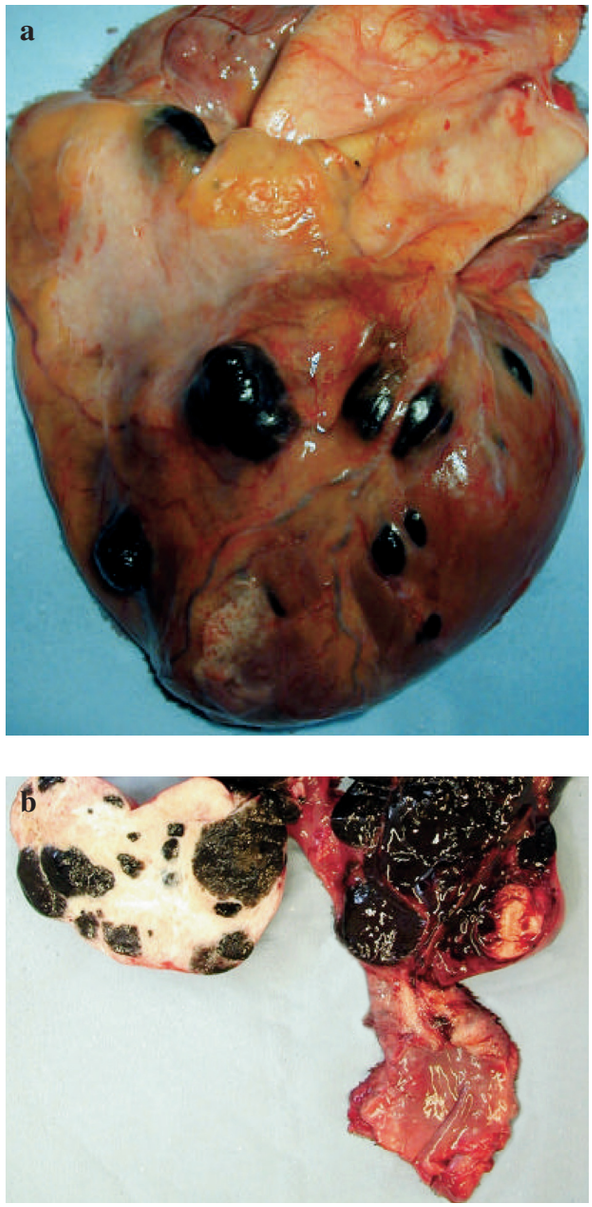

Figure 1. *Macroscopic appearance of* ***(a)*** *pericardial surface of the heart and* ***(b)*** *uterus, including cervix and ovarian fibroid, showing the deeply pigmented deposit of metastatic uveal melanoma in the endometrial cavity.*

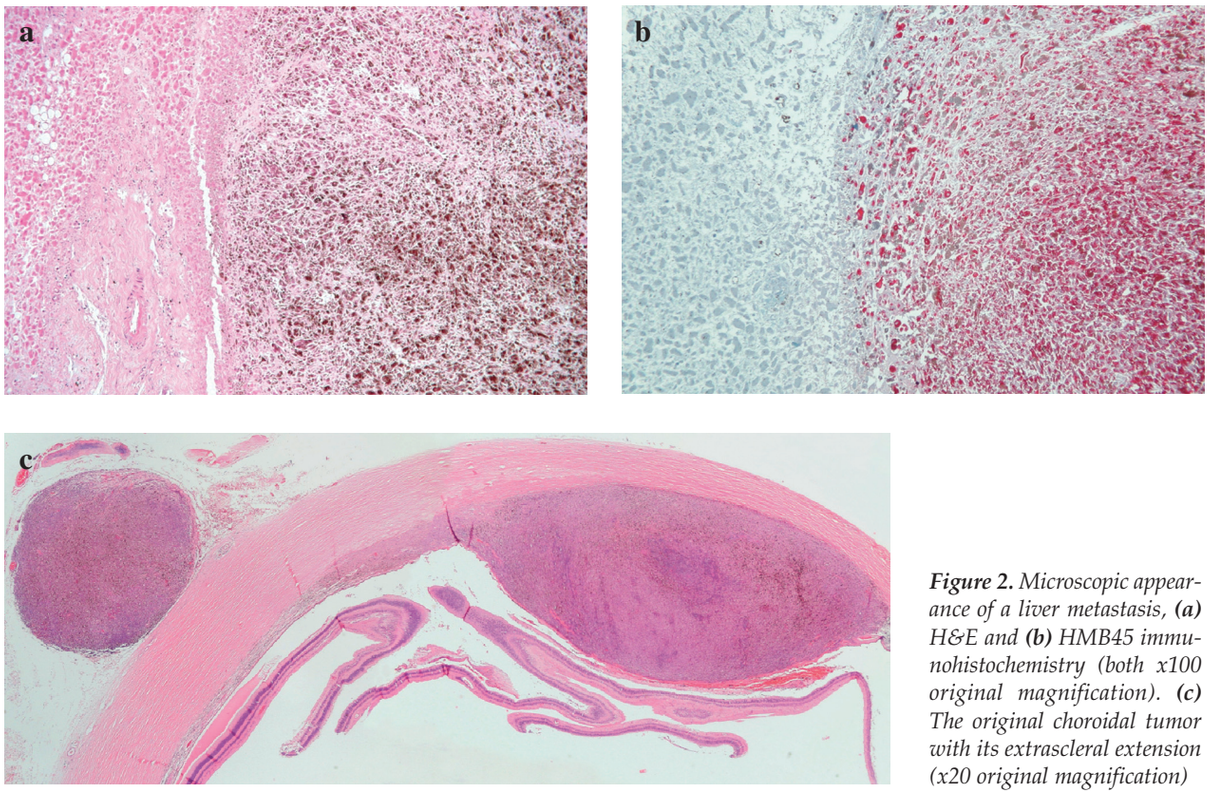

Figure 2. *Microscopic appearance of a liver metastasis,* ***(a)*** *H&E and* ***(b)*** *HMB45 immunohistochemistry (both x100 original magnification).* ***(c)*** *The original choroidal tumor with its extrascleral extension (x20 original magnification)*

cause of death was cardiac metastasis, which is more frequent than many pathologists may appreciate[16] and has previously been associated with metastatic melanoma, including uveal melanoma.[10,17,18]

The metastases in this case showed mixed epithelioid and spindle cell histology, but uveal melanoma can present with metastases composed of either morphological type, though this tends to be similar to the initial pathology of the intra-ocular primary tumor. The reluctance of pathologists to take histology from post-mortems due to consent issues[19,20] may lead to misdiagnosis in some cases,[8] particularly if immunohistochemistry is not performed to confirm the nature of the cells present. Non-pigmented epithelioid tumors are a particular challenge. In a series of 70 autopsies in patients with previous primary uveal melanoma from Finland, metastatic melanoma was recorded in 60% and a second cancer in 4% of autopsies.[8]

Even good prognosis tumors kill patients,[21] and it should not be assumed that because the patient has kept their eye the tumor cannot metastasize and kill. Uveal melanoma has a high mortality rate and up to 61% of tumors may eventually kill the patient.[8] However, it is often difficult for the pathologist to know whether a patient has had a uveal melanoma in the past – often years previously – and a high index of suspicion is needed to make the correct diagnosis. In the series reported by Kujala et al,[8] patients died of metastatic disease up to 35 years after the initial diagnosis: the record is probably still held by the patient who died 43 years after diagnosis.[5]

The reasons for latency (also known as dormancy) are not well established, though as the primary tumor is removed shortly after diagnosis in most patients with large tumors, it must result from spread of single melanoma cells to somatic tissues before diagnosis. It is currently unknown whether these cells survive in a dormant state or as micrometastases incapable of growth to clinically detectable size. Examination of post-mortem tissue in patients who die of other conditions following a diagnosis of uveal melanoma is required to determine this, and it is the subject of a current research study.[19]

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