Case Report

Incidental Finding of Metastatic Cutaneous Malignant Melanoma at Uterine Leiomyoma, A Thai University Hospital Experience: A Case Report

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Background: *Metastatic malignant melanomas to the uterus are extremely rare; to our knowledge, no more than 13 cases have been reported to date.*
Case Report: *A 44-years-old multigravida woman presented with a black and irregular surface mass at medial aspect of left thigh. There was also an enlarged left groin node. Wide excision with lymph node dissection revealed malignant melanoma. Further examination found a huge pelvic mass with left deep vein thrombosis consequent by pressure effect. Chest and complete abdominal computed tomography revealed an enlarged, fibroid uterus with pressure effect at left common iliac vein. A total abdominal hysterectomy and bilateral adnexectomy were performed. Intra-operative finding was scattered hyperpigment spots at surface of the uterus and its tumor. Histopathological report showed metastatic malignant melanoma involving myometrium and uterine serosa. Diagnosis of stage IV malignant melanoma (uterine metastasis) was achieved. The patient was counseled about her diagnosis, stage, prognosis and further treatment.*
Conclusion: *Uterine metastatic malignant melanoma was a rare condition. This report represents the first case of a cutaneous malignant melanoma involving a uterine leiomyoma in Thailand.*

Keywords: *Malignant Melanoma, Uterine Metastasis*

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Malignant melanoma is an aggressive and metastatic cancer originating from melanocytes. It occurs most often in the skin and much less frequently in the choroid layers of the eyes, oral cavity, nasal mucosa, leptomeninges, pharynx, esophagus, bronchus, and vaginal and anorectal mucosa[1]. Cutaneous malignant melanoma is a highly malignant tumor and can metastasize to distant organs such as lungs, liver, and bone. However, metastatic melanomas of the uterus are very rare; to the best of our knowledge, only 13 cases have been reported to date[2,3] and only 2 cases of a cutaneous melanoma involving a uterine leiomyoma[3].

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Case Report

A 44-years-old multigravida Thai woman presented at Thammasat University Hospital with a black and irregular surface mass at medial aspect of left thigh. This mass was 8 cm in diameter with 5 mm in thickness. There was also an enlarged left groin node 3 cm in diameter. She underwent a wide excision with split-thickness skin graft and groin node dissection. Her pathological report was malignant melanoma with positive groin node. She suffered from postoperative deep vein thrombosis of left leg. Her chest and complete abdominal computerized tomography (CT) revealed an enlarged, fibroid uterus with pressure effect at left common iliac vein (Fig. 1). She was sent to the gynecological department. A total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Operative finding was a huge uterus, 20 weeks size with multiple sites of hyperpigmentation at the surface.

The weight of uterus and both adnexa was

877.3 grams. Uterine dimension was 13x8.5x8.5 cm. There were intramural and subserous masses, ranged from 0.2-10 cm in diameter. The uterine serosa was smooth with scattered black pigments in the subserosal surface and myometrium (Fig. 2).

Histological study showed myometrial infiltration by ill-defined lesions. The lesions composed of atypical round and spindle cells clusters. These cells

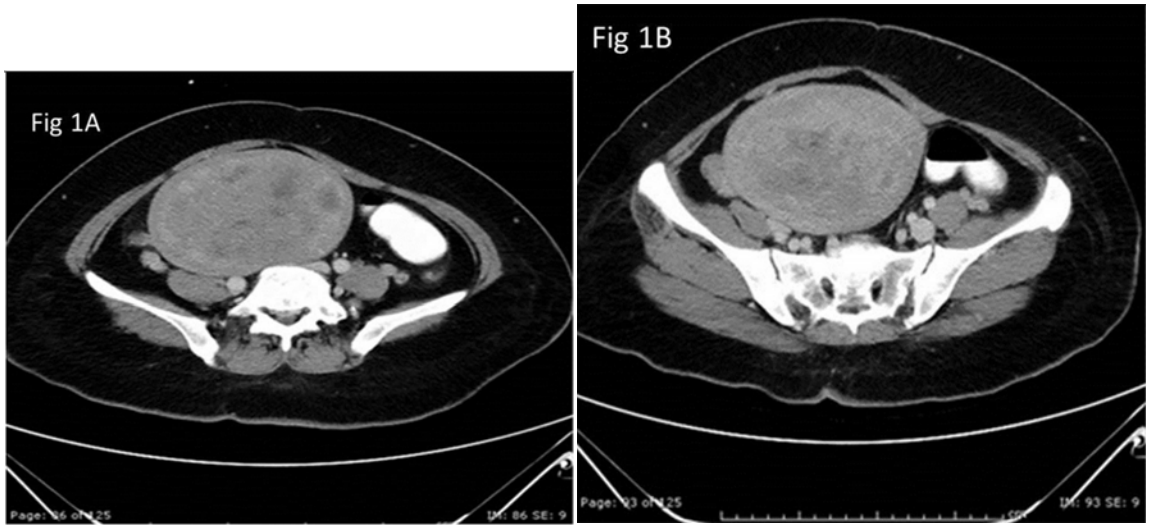

Fig. 1 A, B) There is a large well-circum scribed heterogenous enhancing mass (about 9.9 x 13.5 x 14.3 cm in AP x transverse x CC plane) arising from uterine fundus with abutting right lower anterior abdominal wall. These findings could be degenerative subserous myoma or malignant tumor of uterus.

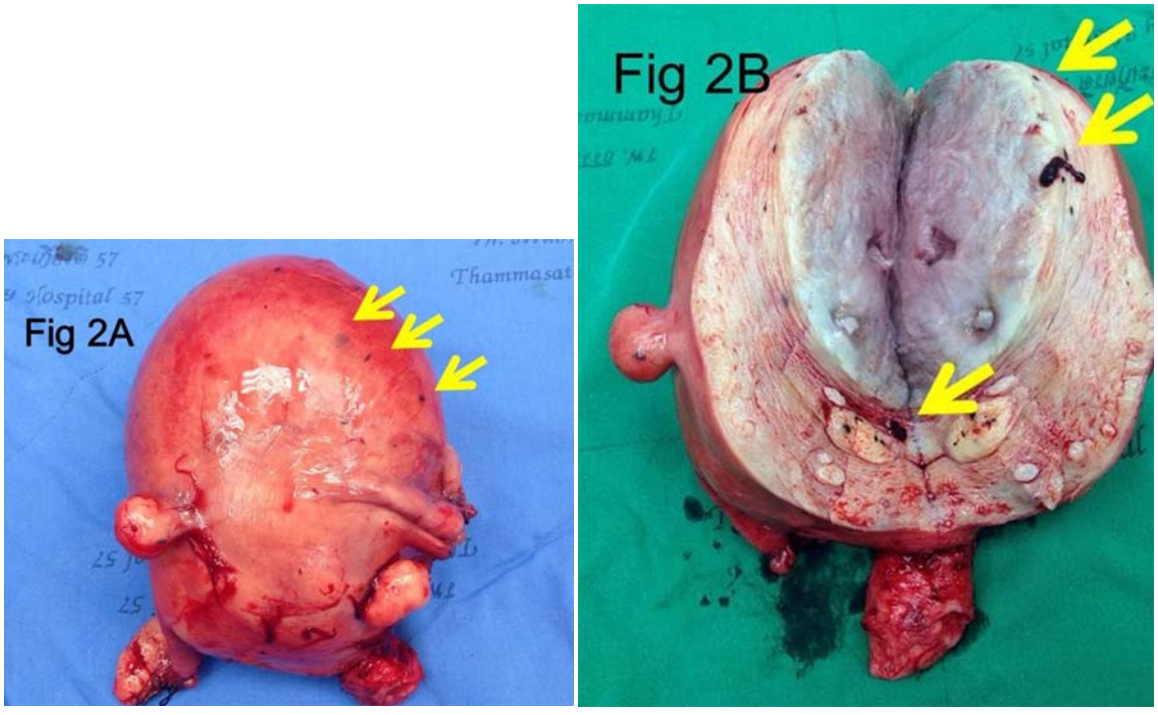

Fig. 2 A, B) Gross examination revealed scattered dark brown to black spots (arrow) spreading throughout myometrium and serosal surface of the uterus.

had enlarged hyperchromatic nuclei, irregular nuclear membranes, prominent nucleoli and active mitosis. Numerous intracytoplasmic melanin pigments were identified (Fig. 3).

Immunohistochemistry stained studied revealed that the tumor cells were strongly positive for melanocytic markers including HMB-45, Melan A and S-100. The negative staining for AE1/AE3 was reported (Fig. 4).

Diagnosis of stage IV malignant melanoma (uterine metastasis) was achieved. The patient was counseled about her diagnosis, stage, prognosis and further treatment.

She decided to receive oral chemotherapy for adjuvant treatment after thoroughly receiving the full information form about the holistic care team. Plan of her treatment was oral termozolomide at a dosage of 200 mg/m^2 for five consecutive days every 28 days for 6 cycles[4]. During the manuscript preparation (January 2015), after three courses of oral chemotherapy, this patient is well and free of disease.

Discussion

Malignant melanoma is derived from melanin-producing melanocytes. It currently accounts for approximately 80% of skin cancer and 1% of all skin

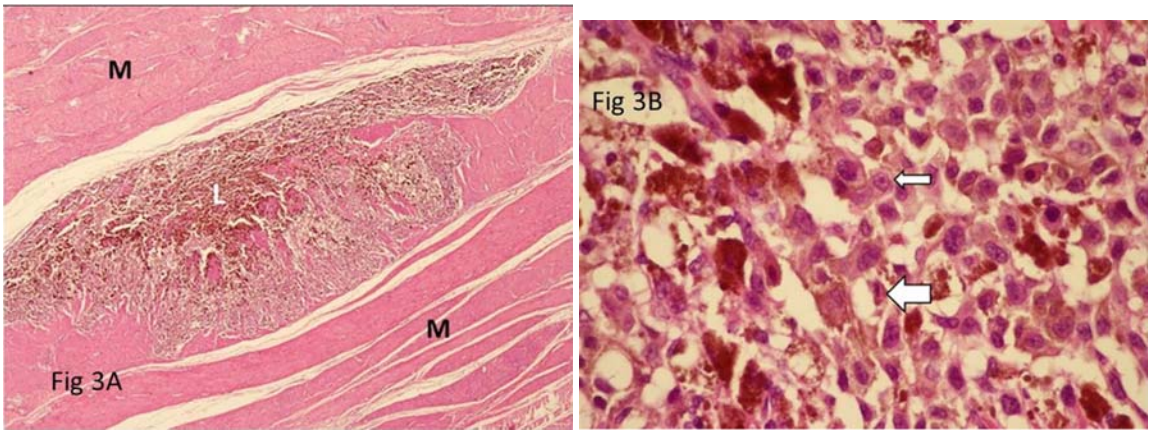

Fig. 3 A, B) Histologic sections showed infiltration of the myometrium (M) by microscopically ill-defined lesions (L) composed of clusters of atypical round to spindle cells containing enlarged hyperchromatic nuclei, irregular nuclear membrane, prominent nucleoli (thin arrow) and active mitoses (thick arrow). Numerous intracytoplasmic melanin pigments are noted (hematoxylin and eosin; original magnification, x50 [A] and x100 [B].

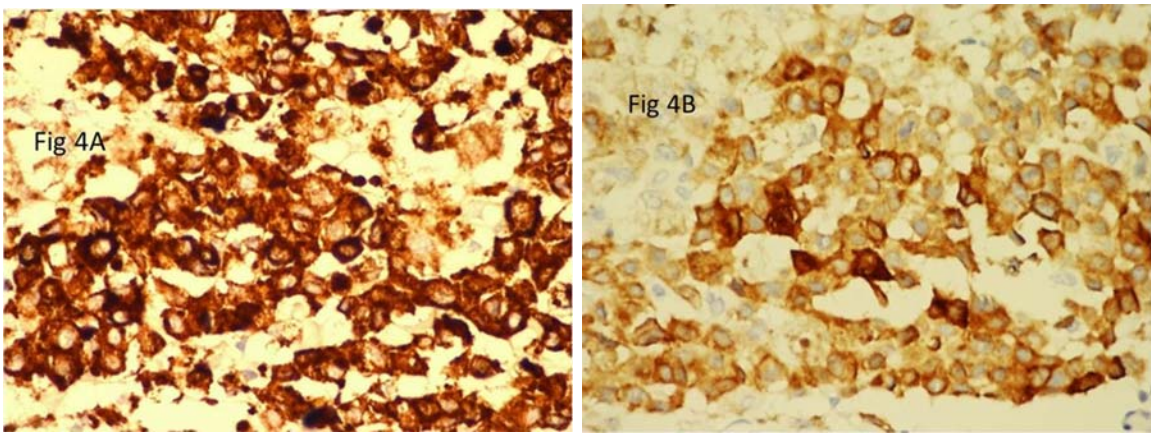

Fig. 4 A, B) The tumor cells were strongly positive for melanocytic markers including HMB-45 and Melan A and positive for S-100 (not shown in picture) but negative for AE1/AE3 immunohistochemistry staining (immunohistochemical staining; original magnification, x100 [A] and x100 [B].

cancer deaths[2,5]. The regional lymph nodes are the most likely first area of metastasis while the common site of metastasis includes lungs, liver and brain[6]. Uterine metastasis from malignant melanoma is very rare. Only a few reports showed the variety of symptoms (abnormal uterine bleeding or pelvic mass). Metastatic melanoma in other organ can be diagnosed without difficulty on hematoxylin and eosin stained section when there is neoplastic cell cluster or cohesive cell nests. Common used immunohistochemical stain for malignant melanoma detection was HMB-45, Melan-A and S-100 protein[7]. HMB-45 staining is the method for detection of a glycoprotein presented in premelanosomes by monoclonal antibody[8].

HMB-45 is a widely used immunohistochemical stain for detection of primary as well as metastatic melanoma[7]. Presumably, this method uses monoclonal antibodies to a glycoprotein that is present in premelanosomes[8]. In immunohistochemical assays, this antibody reacts with melanoma cells, junctional nevus cells, and fetal melanocytes, but generally not with completely melanized normal adult melanocytes or with intradermal nevus cells[9-11].

Melan-A is classified as melanacytic differentiation marker and expressed in all melanocytic cytoplasm. Most cases of melanoma showed positive Melan-A staining[12]. It also stains positive in other tissue such as adrenal cortex, Ledig, granulosa and thecal cell of ovary.

S-100 is calcium-binding protein, which mostly distributed in the melanocytic cytoplasm. It is the most sensitive marker for melanocytic lesions. HMB-45 and Melan-A are more specific to melanocytic lesion than S-100 protein[12].

In the present case, the black spot in hysterectomized specimen showed characteristics of malignant melanoma. Immunohistochemical staining for S-100, HMB-45 and Melan-A were also positive results. This patient was classified as stage IV (T4N3M1c)[13]. There was visceral metastasis with normal level of LDH (lactic dehydrogenase). From TNM classification, sites of distant metastasis and elevated LDH serum level were used to delineate the M1 status into M1a, M1b and M1c. One-year survival rate of stage M1a, M1b and M1c were 62%, 53% and 33%, respectively. Stage M1c was the worst prognostic condition resulted from any distant metastasis with elevated LDH level or visceral involvement.

Wide excision of malignant melanoma remains the first choice of treatment. Curable results may be achieved in case of localized tumor[14]. Surgical excision with margins proportional to the microstage was the best treatment of localized melanoma. While in advanced disease, wide excision of the tumor and regional lymph nodes dissection was the further treatment[15].

Lymphatic mapping for sentinel lymph node (SLN) identification was the optional procedure for accurate treatment in some cases[15]. In the present case, inguinal lymph node enlargement was identified. However, SLN removal with the wide excision of the primary malignant was not performed in the present case.

In case of complete surgical excision with high risk of recurrence (stages IIB, IIC, and III), adjuvant therapy with high dose interferon (alfa-2b or pegylated) was considered. Unfortunately, only relapse-free survival was achieved but not overall survival[16,17].

Systemic therapy was considered in unresectable stage III, stage IV and recurrent disease. Chemotherapy was one of the systemic treatments. Decarbazine (DTIC) and temozolomide were frequently prescribed. Temozolomide, an oral alkylating agent, appeared to be similar to intravenous DTIC[4]. Immunotherapy focused on checkpoint inhibition and targeting the mitogen-activated kinase pathway. Vemurafenib, imatinib and ipilimumab were the commonly used medication in immunotherapy for malignant melanoma. Immunotherapy showed a promising response in overall survival improvement but not curative intent[18-21]. Combination of chemotherapy with immunotherapy showed promising data[21].

Even though overall survival in stage IV malignant melanoma was poor. Middleton et al reported the median survival in stage IV malignant melanoma was only 7.7 months compared to 6.4 months in temozolomide and DTIC group, respectively[4]. Temozolomide was easy and high compliant agent for this case. It was oral chemotherapy while DTIC was intravenous administration. Quality of life should be of high concern in incurable cases. Hospital admission should be reserved for unavoidable conditions. The treatment should not be harmful to quality of life and life style. Counseling the patient and her family was an important process for the care of this patient. End of life preparation should be one of the counseling topics to this patient and her family.

Conclusion

Uterine metastatic malignant melanoma was rare condition. This report represents the first case of a cutaneous malignant melanoma involving a uterine

leiomyoma in Thailand. Although this condition has rarely occurred, the clinical acumen and concern were the key points and guidance to diagnose this rare case.

What is already known on this topic?

Malignant melanoma is an aggressive and metastatic cancer originating from melanocytes. It occurs most often in the skin[1]. Cutaneous malignant melanoma is a highly malignant tumor and can metastasize to distant organs such as lungs, liver, and bone. However, metastatic melanomas of the uterus are very rare; to the best of our knowledge, only 13 cases have been reported to date[2,3] and only 2 cases of a cutaneous melanoma involving a uterine leiomyoma[3].

What this study adds?

In this case, the black spot in hysterectomized specimen showed characteristic of malignant melanoma. Immunohistochemical staining for S-100, HMB-45 and Melan-A were also positive results. This patient was classified as stage IV (T4N3M1c)[13]. One-year survival rate of stage M1c was only 33%. Wide excision of malignant melanoma remains the first choice of treatment. Curable results may be achieved in case of localized tumor[14]. While in advanced disease, wide excision of tumors and regional lymph nodes dissection were the further treatment[15], even though overall survival in this case was poor. Quality of life should be of great concern in the case of incurable disease. Hospital admission should be reserved for unavoidable conditions. Counseling of the patient and her family was the important process in caring for this patient. Although uterine metastatic malignant melanoma was a rare condition, this report represents the first case of a cutaneous malignant melanoma involving a uterine leiomyoma in Thailand. This reflected the importance of clinical acumen and concern in clinical practice.

Potential conflicts of interest

None.

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การแพร่กระจายของมะเร็งผิวหนังชนิดเมลาโนมาไปที่เนื้องอกมดลูก, ประสบการณ์ในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ: รายงานผู้ป่วย

อธิตา จันทเสนานนท์, ต้องตา นันทโกมล, จุฑาทิพย์ คินทรักษ์, นพดล วิฑิตสุวรรณกุล, เด่นศักดิ์ พงศ์โรจน์เผ่า, คมสันติ์ สุวรรณฤกษ์

ภูมิหลัง: *การแพร่กระจายของมะเร็งผิวหนังชนิดเมลาโนมาไปที่มดลูกเป็นภาวะที่เกิดขึ้นได้ยากจากการทบทวนวรรณกรรมมีรายงานผู้ป่วยไม่เกิน 13 ราย*

รายงานผู้ป่วย: *สตรีไทยอายุ 44 ปี มาพบแพทย์ด้วยอาการก้อนสีดำลักษณะขรุขระบริเวณต้นขาซ้ายด้านใน ร่วมกับต่อมน้ำเหลืองบริเวณขาหนีบด้านซ้ายโต ผู้ป่วยได้รับการผ่าตัดรอยโรคเป็นวงกว้างร่วมกับการเลาะตัด ต่อมน้ำเหลืองบริเวณขาหนีบด้านซ้าย ผลพยาธิวิทยารายงานว่าเป็นมะเร็งผิวหนังชนิดเมลาโนมา นอกจากนี้ยังตรวจพบมดลูกโตร่วมกับขาซ้ายบวม ซึ่งได้รับการวินิจฉัยว่าเป็นภาวะลิ่มเลือดในหลอดเลือดดำ คอมมอนอิลิแอกซ้ายเนื่องจากก้อนมดลูกขนาดใหญ่กดทับ ผู้ป่วยได้รับการผ่าตัดมดลูกและรังไข่ทั้งสองข้าง ผลพยาธิวิทยาของมดลูกพบการแพร่กระจายของมะเร็งผิวหนังชนิดเมลาโนมาที่เนื้องอกมดลูก ผู้ป่วยได้รับการวินิจฉัยว่าเป็นมะเร็งผิวหนังชนิดเมลาโนมาระยะที่ 4 และได้รับคำปรึกษาแนะนำเกี่ยวกับการวินิจฉัย ระยะของโรค พยากรณ์โรค และแนวทางการรักษาต่อไป*

สรุป: *การแพร่กระจายของมะเร็งผิวหนังชนิดเมลาโนมาที่เนื้องอกมดลูกแตกเป็นภาวะที่พบได้ยาก ผู้ป่วยรายนี้เป็นรายแรกที่พบในประเทศไทย*