

Metastatic Ovarian Tumor of Vulvar Malignant Melanoma in a 43-Year-Old Woman: A Case Report and Literature Review

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Abstract

An ovarian malignant melanoma sometimes occurs from ovarian teratoma. Ovarian metastatic malignant melanoma is extremely rare. We describe a patient in whom vulvar melanoma (previously resected) metastasized to the ovary, making ovarian metastatic malignant melanoma. A 43-year-old Japanese woman was referred to us because of left ovarian tumor. She had undergone resection for malignant melanoma on the right labia minora with inguinal lymph node metastasis (pT1bN1aM0, stage IIIA, FIGO 2008). Eighteen months after this surgery, CT scans revealed left ovarian tumor and swelled pelvic lymph nodes, with a pelvic examination disclosing a left adnexal solid mass, with normal serum CA125 level (21.7 U/mL). Laparotomy revealed a left solid ovarian tumor measuring 4 cm, which was covered with a smooth grayish capsule. The right ovary, uterus, and pelvic cavity appeared normal. Upon sectioning during the surgery, the cross-sectional surface of the left ovary revealed a dark brown solid tumor. Following an intra-operative frozen-section diagnosis as metastatic melanoma, total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph dissection was performed. Histological examination confirmed the diagnosis as malignant melanoma metastasis to the left ovary and the obturator lymph node: the same laterality (left) as the primary site. The tumor was entirely composed of malignant melanoma cells with no evidence of teratoma. Combined chemotherapy with dabrafenib mesylate and trametinib was planned based on the positive BRAF mutations. This case highlights the importance that physicians should have

high index of suspicion for the occurrence of ovarian melanoma metastasis after melanoma surgery. We also made extensive literature review on this issue, of which description may contribute to better understanding of this condition.

Keywords

Vulva, Malignant Melanoma, Ovarian Metastasis

1. Introduction

Primary ovarian melanoma is sporadic, and most cases originate within a mature cystic teratoma, while metastatic malignant melanoma of the ovary is a rare condition. Most commonly originates from cutaneous tumors, and sometimes from ocular melanoma. The vulva is the most common site of melanoma in the female genital tract, while only one case of vulvar melanoma metastasis to the ovary has been reported [1]. The median age at diagnosis of cutaneous melanoma in sun-exposed skin is 56 years, while that of the vulva is 68 years, but it rarely occurs in women of a reproductive age [2] [3]. We describe here an unusual case of a woman who underwent surgical removal of melanoma of the vulva at 41 years of age, and subsequently developed left ovarian metastasis 18 months after the initial surgery.

2. Case Presentation

A 43-year-old Japanese gravida 2 para 2 premenopausal woman was referred to our gynecological department because of significant enlargement of the left ovary. At 36 years of age, pigmentation of the external genitalia was detected at the time of her second delivery, although it was left untreated. Her past and family medical histories were uneventful. Five years after the delivery, when she was 41 years old, she noticed a slight bump on the surface of the pigmented skin accompanied by scant bleeding. She visited a local dermatological hospital, whereupon a gray-white irregular lesion was detected on the left labia minora, which was diagnosed as a malignant melanoma by biopsy. The patient then consulted the Department of Dermatology at the University Hospital. A darkly pigmented lesion was confirmed on the left labia minora measuring approximately 10 mm in size. The patient subsequently underwent radical local excision plus sentinel lymph node sampling. Pathologically, the nodular lesion was composed of polygonal cell proliferation with lesional melanin deposition (**Figure 1(a)**). The tumor cells were diffusely positive for HMB-45 by immunohistochemical analysis. The thickness of the tumor was 3.5 mm, and the width was 8 mm, with no ulcer formation. With a positive sentinel lymph node result, the entire left inguinal lymph node was dissected a few weeks after the initial surgery. The final histological examination revealed a vulvar melanoma with inguinal lymph node

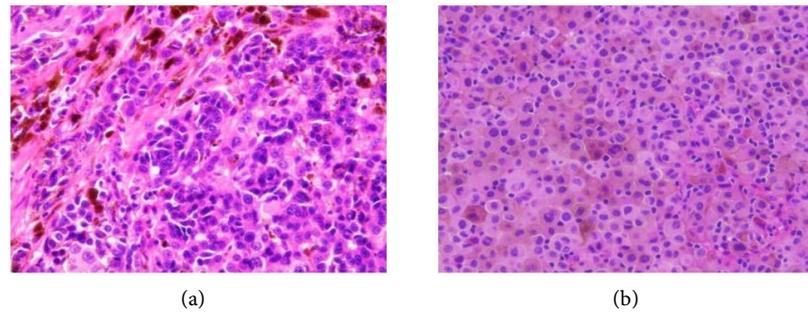


Figure 1. (a) Vulva: Polygonal tumor cells proliferate in nests or diffusely. Melanin pigments are also present; (b) Left ovary: Polygonal tumor cells with round to oval-shaped hyperchromatic nuclei and prominent nucleoli proliferate in sheets. Melanin deposition is also observed (Hematoxylin and eosin, $\times 400$).

metastasis (pT1bN1aM0, stage IIIA, FIGO 2008). No adjuvant therapy was initiated, and the patient continued to be regularly followed up.

Eighteen months after the surgery, CT scans taken at a routine medical examination revealed significant swelling of the left ovary and pelvic lymph nodes, compared with previous CT scans taken just before the surgery. After the reference to the gynecological department, pelvic examination disclosed a left adnexal solid mass, a normal-sized uterus and a right ovary. She had no symptoms or complaints on her first visit. Pelvic MRI (T-weighted image) also showed a low-intensity solid tumor of the left ovary measuring 35×40 mm and significant enlargement of a pelvic lymph node (**Figure 2**). Serum CA125 level was 21.7 U/mL, which was within the normal range. At laparotomy, a left solid ovarian tumor covered with a smooth grayish and intact capsule was confirmed without adhesions to its surroundings (**Figure 3**). The right ovary, uterus, and pelvic cavity appeared grossly normal. The left obturator and external iliac lymph nodes were swollen. Infracolic-omentum and peritoneal surfaces were smooth with no evidence of dissemination. Upon sectioning, the cross-sectional surface of the left ovary showed characteristic findings of a homogenous dark brown solid tumor (**Figure 4**). The diagnosis of the intra-operative frozen section was metastatic malignant melanoma. Total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph dissection was performed. As a final diagnosis, metastases to both the left ovary and the obturator lymph node were determined histologically. The tumor was entirely composed of malignant melanoma cells with no evidence of teratoma, and peritoneal cytology was negative for atypical cells (**Figure 1(b)**). These metastatic lesions were evident only on the left side, which was on the same side as the primary lesion on the vulva. Her postoperative course was uneventful. Two months after surgery, combined chemotherapy with dabrafenib mesylate and trametinib was planned based on the positive results of molecular testing for *BRAF* mutations.

3. Discussion

Incidence rates of malignant melanoma differ according to ethnic background,

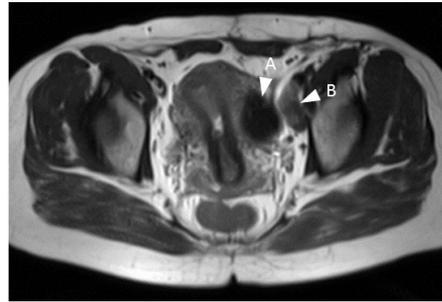


Figure 2. Pelvic MRI study (T2-weighted image) showed a low-intensity solid tumor of left ovary (arrow A) and significant enlargement of an obturator lymph node (arrow B).



Figure 3. The left ovary was palpable about 40 × 35 mm (arrows), covered with the grayish surface, while the right ovary and uterus were grossly normal appearance.

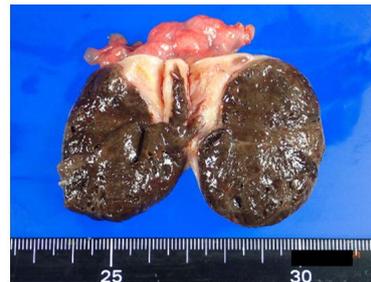


Figure 4. The cross-sectional surface of the left ovary showed a solid tumor colored in dark brown.

and the incidence rate was 24.9 in White, 1.3 in Asian/Pacific Islander, and 1.0 in black individuals per 100,000 between 2012 and 2016 [4]. Melanoma commonly arises from cutaneous sites in regions exposed to ultraviolet radiation. Extracutaneous sites lined with mucosal membranes can also include an original site of melanoma such as the respiratory, gastrointestinal, and urogenital tracts. Vulvar melanoma is a mucosal type as well, which is rare and is more aggressive. It usually results in less favorable prognoses compared with cutaneous melanoma.

Malignant melanoma in the ovary can involve either a primary or metastatic tumor, but most cases are metastatic [5]. Primary ovarian melanoma is sporadic, and most cases originate within a mature cystic teratoma. Metastases of melanoma to the ovary occur from the skin, and choroid of the eye, but rarely from primary vulva tumors, the prognosis of which is poor with a 5-year survival rate of only 5% [6]. In postmortem cases, approximately 18% of women with disse-

minated melanoma have ovarian implants [7]. Taken together, it is conceivable that our case was vulvar melanoma in a woman of reproductive age, resulting in metastasis to the ovary. Both findings are extremely unusual phenomena.

We searched PubMed and Google Scholar, from January 1980 to December 2019, using the terms “ovary/ovarian”; “melanoma”; and “metastatic/metastasis/metastases”. The literature was limited to English-language case reports and case series. They comprised four case series [5] [8] [9] [10] and 22 case reports [1] [6] [11]-[30], totaling 61 cases. We excluded cases that met any of the following criteria: no medical information available; metastases confirmed at autopsy; and unknown original site of melanoma. Forty-one out of the 61 cases plus our case, totaling 42 cases, were available for this review and are listed in **Table 1** [1] [5] [6] [8] [10]-[27] [29] [30]. Based on this search, this is the second report of ovarian metastasis of vulvar melanoma. The most frequent primary site was the skin (83.3%, 35/42) followed by the choroid (11.9%, 5/42), while two cases were from the vulva (4.8%, 2/42). The median age at ovarian metastasis was 38.5 years (range, 8 - 65 years), and 85.7% (36/42) of patients were less than 50 years old. The median interval for relapse was 66 months (range, 8 - 300). The median tumor size was 100 mm (range, 40 - 190 mm), and bilateral ovaries were affected in 26.8% (11/41) of cases. In deceased patients (n = 27), the median survival period after the confirmation of ovarian metastasis was 10 months (range, 1 - 96).

In an analysis of 1521 cases of melanoma, which included male patients, the most frequent site of first metastasis was the lung, followed by the skin, and lymph nodes, and 14% of cases had multiple metastatic sites [31]. Our review showed that 81.0% (34/42) of the cases involved multiple lesions when ovarian implants were identified, while this was rare for solitary metastasis. Once ovarian metastasis had established, extensive multisystemic spread of the disease occurred in most cases.

In patients in which an ovarian tumor is detected long after the initial treatment, it is a diagnostic challenge. Therefore, for patients with such a history, a precise medical interview is essential, and systemic screening is mandatory. In our case, routine CT scans allowed for the discovery of a unilateral ovarian tumor of a relatively small size. We were able to classify metastatic sites without difficulty because of the short interval since the last surgery. As such, regular screening could contribute to the early detection of metastases. However, this does not always lead to a preferred prognosis because most cases are accompanied by multiple metastatic lesions, resulting in a survival period of less than 1 year after relapse. It is interesting to note that the interval for ovarian metastasis was long, at 5 years or more in 64.2% (27/42) of cases, and 10 years or more in 23.8% (10/42) of cases. Especially, metastases from choroidal melanoma tend to have a latent period than metastasis from cutaneous melanoma. In most cases, it was associated with multiple metastases. At the initial therapy for melanoma, it is crucial to inform patients and their families about the possibility of relapse after a long period.

Table 1. Published cases of metastatic malignant melanoma to the ovary (n = 42).

Author (year) [Reference]	Case No.	Age (years)	Primary site	Laterality of the affected ovary	Size of ovarian tumor** (mm)	Clinical symptoms	Extent disease admitted	Other sites of metastasis	Interval from primary (months)	Outcome (time after surgery)
Fitzgibbons PL (1987) [8]	1	38	skin (scalp)	Bil	80	NA	Yes	axillary LN	48	NA
	2	45	skin (thumb)	Uni	NA	NA	No		24	Died (12 Mo)
	3	32	skin (leg)	Uni	180	NA	Yes	chest wall	60	NA
	4	37	skin (leg)	Bil	NA	NA	Yes	lung, omentum	60	NA
	5	29	skin (arm)	Bil	120	NA	Yes	axillary LN	24	NA
Moselhi M (1998) [10]	6	36	skin (leg)	Uni	100	pelvic pain	No		96	Died (NA)
	7	25	skin (leg)	Bil	80	regular screening	Yes	large bowel mesentery	24	Died (NA)
	8	45	skin (arm)	Uni*	80	abdominal bloating	Yes	pelvic bone, lung	24	Died (NA)
Gupta D (2004) [5]	9	29	skin (shoulder)	Uni	110	regular screening	Yes	multiple	15	Died (10 Mo)
	10	39	skin (arm)	Bil	70	regular screening	Yes	multiple	120	Died (26 Mo)
	11	25	skin (back)	Uni	135	dysuria, abdominal pain	Yes	para-aortic LN	96	Died (32 Mo)
	12	29	skin (back)	Uni	150	regular screening	Yes	multiple	34	Died (40 Mo)
	13	43	skin (arm)	Uni	100	pelvic mass	Yes	multiple	132	Died (7 Mo)
	14	45	skin (arm)	Uni	180	regular screening	Yes	lungs, abdominal wall	228	Died (4 Mo)
	15	49	skin (arm)	Uni	55	pelvic mass	Yes	lungs, perirectal mass	20	Died (8 Mo)
	16	40	skin (arm)	Uni	60	regular screening	Yes	multiple	30	Died (30 Mo)
	17	41	skin (shoulder)	Uni	100	regular screening	Yes	multiple	83	Died (76 Mo)
	18	38	skin (pubis)	Uni	120	regular screening	Yes	lungs	74	Alive (96 Mo)
Murphy DJ (1994) [11]	19	27	skin (shoulder)	Uni	80	regular screening	Yes	axillary LN	46	Alive (6 Mo)
	20	52	skin (scalp)	Uni	50	regular screening	Yes	multiple	54	Died (10 Mo)
	21	25	skin (scalp)	Bil	120	regular screening	Yes	axillary LN, subcutaneous tissue	26	NA
Remadi S (1997) [12]	22	33	skin (chest)	Uni	100	abdominal pain	No		60	Died (24 Mo)
Nakano J (1998) [13]	23	36	skin (arm)	Bil	125	pelvic pain, multiple subcutaneous nodules	Yes	subcutaneous	132	Died (13 Mo)

Continued

Piura B (1998) [14]	24	45	skin (back)	Uni	100	abdominal pain, pelvic mass	Yes	subcutaneous tissue, brain	84	Alive (7 Mo)
Fuller PN (1999) [15]	25	34	skin (arm)	Bil	190	abdominal pain	Yes	brain	180	Died (1 Mo)
Bilgin T (2000) [16]	26	35	skin (scalp)	Bil	94	abdominal bloating	Yes	omentum, liver	96	Died (5 Mo)
Oliver R (2005) [17]	27	58	skin (arm)	Uni	120	asymptomatic	Yes	pelvic LN	120	Died (12 Mo)
Boutis A (2008) [18]	28	43	skin (arm)	Uni*	NA	abdominal distension	Yes	peritnium, omentum	108	Died (8 Mo)
Abe Y (2009) [19]	29	39	skin (leg)	Uni	65	abdominal fullness, appetite loss	Yes	iliac bone	8	Died (7 Mo)
Sbitti Y (2011) [20]	30	45	skin (leg)	Uni	150	pelvic pain	No		38	Died (13 Mo)
Fenzl V (2011) [21]	31	35	skin (back)	Bil	90	acute abdomen, fever, appetite loss	Yes	bone	60	Died (15 Mo)
Habek D (2012) [22]	32	35	skin (back)	Uni	110	abdominal pain	Yes	brain	84	Died (3 Mo)
Berisavac M (2013) [23]	33	48	skin (arm)	Uni	125	abdominal pain	No		60	Died (48 Mo)
Araki Y (2014) [24]	34	8	skin (buttock)	Uni	60	regular screening	Yes	liver, bone	8	Died (14 Mo)
Mendel A (2017) [6]	35	65	skin (leg)	Uni	76	regular screening	Yes	liver, spleen, esphagus, lung	84	NA
Ben David M (1984) [25]	36	62	choroid	Uni	150	abdominal pain, vaginal bleeding	Yes	lung, omentum, serosal surface of small and large bowel	300	NA
Santeusanio G (2000) [26]	37	47	choroid	Uni	170	pelvic pain	No		168	NA
Rey-Caballero VE (2004) [27]	38	38	choroid	Uni	61	abdominal pain	No		108	Alive (7 Mo)
Bloch-Marcotte C (2008) [29]	39	50	choroid	Uni	40	abdominal pain	Yes	liver	240	Alive (5 Mo)
Mandato VD (2010) [30]	40	57	choroid	Bil	110	hypogastric pain, weight loss	Yes	pancreas, para-aortic LN	72	Died (7 Mo)
Spatz A (1999) [1]	41	28	vulva (labia majora)	Uni	65	regular screening	No		180	Alive (12 Mo)
Kawagoe Y (2020)	42	43	vulva (labia minora)	Uni	50	regular screening	Yes	obturator LN	18	Alive (4 Mo)

*Laterality was determined by CT imaging without operation. **Tumor sizes are expressed by the maximum dimension. LN: lymph node, NA: Not available, Mo: month, Uni: Unilateral, Bil: Bilateral.

The ovary is a small organ in the pelvis and is a relatively common site of metastases. This has been speculated to be as a result of its hypervascularity [32] [33]. Ovarian metastases are thought to mainly occur in reproductive-age women, and less frequently in postmenopausal women. Our review showed that the median age of diagnosis was 38.5 years and 85.7% of patients were less than 50 years old, even though melanoma is common in older adults.

Ovarian metastases are typically from the stomach, colon, and breast. These metastatic lesions in the ovary are known to show bilateral and multicystic lesions, namely mucinous carcinoma, compared with primary lesions. Our patient had a solid homogenous unilateral tumor, the cross-section of which was dark brown. This was the first case in which we had observed such characteristics of metastatic melanoma. Its entire capsule was also a grayish color with a smooth surface. Young *et al.* reported in a review of ovarian metastases that 55% of the tumors were solid, while 45% were solid and cystic with the solid component predominating. Thirty percent of the tumors were either entirely black or had discernible black or brown foci [9]. Gupta *et al.* reported that 35% of the lesions were grossly pigmented [5]. Regarding laterality, bilateral involvement was commonly seen in cutaneous melanoma in 45% of cases [9]. In our review, which included choroidal and vulvar melanoma, its incidence was less frequent at 26.8%.

4. Conclusion

We here described the second reported case of ovarian metastasis of vulvar melanoma in a 43-year-old woman. In patients who have a history of melanoma and a significant enlargement of the ovary, metastasis should be ruled out. Metastasis usually occurs after a long period and accompanies disseminated disease, resulting in a poor prognosis of generally less than 1-year survival.

Consent

Informed consent was obtained.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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