Primary Malignant Melanoma of the Female Genital Tract

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SUMMARY

Objective: Malignant melanoma, which has a highly malignant potential, is a tumor of the skin and mucosal membranes. Malignant melanomas of the female genital tract, including the vulva and vagina, are rare. Their overall prognosis is poor and is worse than that for cutaneous melanomas.

Case Reports: Clinical data for five patients with primary malignant melanoma are presented. Diagnosis was based on histologic and immunohistochemical examinations. Case 1 was a 58-year-old woman with mucosal lentiginous melanoma of the vulva. The other four patients, all of whom were over 40 years old, had vaginal melanomas. They were all treated with surgery, and three also received postoperative adjuvant therapy with interferon alpha-2b. Despite this, three of the patients died owing to widespread disease.

Conclusion: Although malignant melanoma of the female genital tract is uncommon, elderly women should undergo regular gynecologic examinations and suspicious pigmented lesions should be biopsied. The use of immunohistochemical assays could markedly improve diagnosis. However, the prognosis for these tumors is poor, regardless of the treatment delivered, and they are associated with a high rate of recurrence and low long-term survival. Surgery is the best available treatment for controlling and potentially curing malignant melanomas. [*Taiwan J Obstet Gynecol* 2009;48(2):169–175]

Key Words: malignant melanoma, vagina, vulva

Introduction

Malignant melanoma is a tumor of the melanocytes in the skin and mucosal membranes. Approximately 3% of malignant melanomas involve the female genital tract. There are three histologic types of malignant melanoma: superficial spreading, nodular, and acral lentiginous, of which nodular melanomas have the worst prognosis.

Vulvar melanoma may develop from preexisting junctional or compound nevi, as well as *de novo* from epidermal melanocytes in the basal layer of the squamous epithelium. Melanoma development in the vulva displays interesting characteristics; although the vulva constitutes only 2% of the body surface, 3–7% of malign melanomas occur in the vulva. Melanoma of the vulva is the second most common malignancy arising within the vulva and accounts for 8–10% of all vulvar malignancies [1]. The density (number per square unit of body surface area) of cutaneous melanomas occurring in various body areas has recently been evaluated [2], and the results showed that the density of invasive cutaneous melanomas on the face was 2.3 times higher than the density on all other body skin areas. This overrepresentation of melanomas on the facial skin is similar to that seen for the vulva compared with the whole body skin. The similarity in melanoma density between the most sun-exposed and one of the most sun-shielded areas of the body is of considerable interest for establishing other causative factors of melanogenesis, in addition to UV radiation [3]. Malignant melanoma of the vulva occurs in the labium majus in 34% of cases, the labium minus in 29%, the clitoral area in 24%, and in the midline structures (periurethral area, introitus, posterior fourchette) in 13% [3]. Since 1861, more than

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1,800 cases of vulvar melanoma have been described in the literature. Vulvar melanomas not only carry a poor prognosis and show a tendency for local recurrence, but also develop distant metastases through hematogenous dissemination.

Primary malignant melanoma of the vagina is a very rare tumor with fewer than 300 cases reported worldwide. It accounts for less than 3% of all vaginal malignancies and 0.3–0.8% of all malignant melanomas [4]. The most common presenting symptoms are vaginal bleeding, vaginal discharge or a palpable mass. As the tumor may spread hematogenously, early metastases are common and the prognosis is poor, with a reported 5-year survival rate of 8.4% [5]. The tumor is primarily found in the distal third (58% of cases) of the vagina and mostly on the anterior wall (45% of cases) [6]. Conservative wide local excision, radical surgical extirpation, irradiation, and chemotherapy are the treatment options, which can be used individually or in combination.

In this report, we present one case of vulvar and four cases of vaginal malignant melanomas.

Case Reports

Case 1

A 58-year-old woman was referred to our hospital with complaints of a palpable mass and itching in the vulva. On vulvar examination, a papillomatous pigmented lesion, 3 × 2 cm in size, was seen in the posterior fourchette. Following vulvar biopsy, mucosal lentiginous malignant melanoma was diagnosed. The tumor was 2 mm at the deepest margin (Chung level III; Clark level III, tumor fills papillary dermis, and extends to the reticular dermis but does not invade it). There was no significant family history, and no abnormalities were detected on physical examination. Bilateral inguinal lymph nodes were not palpable. She had undergone a hysterectomy 12 years earlier, and her vagina and ovaries appeared atrophic. No palpable mass was detected in either adnexal area. Vaginal cuff smears revealed no malignant cells, and thoraco-abdominopelvic computed tomography (CT) produced no pathologic findings. She was treated with wide local excision of the tumor (excision of 2 cm from the outer limit and 2 cm from the deep limit of tumor) and bilateral inguinal lymph node dissection. No tumor tissue was present in the surgical margins, and no lymphatic invasion was found. The tumor was classified as stage II according to International Federation of Gynecology and Obstetrics (FIGO) staging system and stage IIA according to the American Joint Commission on Cancer (AJCC) staging system [1]. No adjuvant therapy was administered. No local or distant metastases were detected during her first postoperative year.

Case 2

An 89-year-old woman was referred to our hospital with complaints of a palpable vaginal mass, vaginal bleeding, and dysuria. Her medical history included hypertension, diabetes mellitus, and coronary artery disease. Inspection showed an ulcerated, infected, fragile and hemorrhagic lesion, 3 cm in size, on the anterior side of the lower third of the vagina. There were no palpable inguinal lymph nodes. A biopsy of the lesion was performed, and the pathology report indicated a nodular malign melanoma. The histologic diagnosis was confirmed by positive immunostaining with monoclonal antibody to human melanoma (HMB-45). Imaging studies revealed no signs of metastases. She was treated with wide local excision (excision of 2 cm from the outer limit). Lymph node dissection was not performed. In light of the patient's age and existing comorbidities, a radical approach was avoided in order to minimize the surgery time and reduce the risk of increased comorbidity. Pathologic examination of the excised material revealed a tumor thickness of 0.8 mm (Chung level II), and the surgical margins were tumor-free. The tumor was classified as FIGO stage I. The patient received no adjuvant therapy. She was still alive, without local or distant metastases, after 2 years.

Case 3

A 54-year-old woman, menopausal for 3 years, presented with a complaint of vaginal bleeding. Her medical history was unremarkable, and there was no family history of malignancy. Examination revealed a nodular, necrotic lesion, 6 cm in size, on the anterior left side of the lower third of the vagina and another irregular lesion, 4 cm in size, on the posterior side of the lower third. A cervical Papanicolaou test showed malignant infiltrative cells. Imaging studies revealed no evidence of metastases. An excisional biopsy of the lesions suggested several possible diagnoses, including alveolar rhabdomyosarcoma, undifferentiated leiomyosarcoma or malignant melanoma. Immunohistochemistry showed HMB-45- and S-100-positive staining, and the diagnosis was confirmed as malignant melanoma. Radical hysterectomy and total vaginectomy were performed, together with pelvic and inguinal lymph node dissection and bilateral salpingo-oophorectomy. The postoperative course was unremarkable. Histopathologic study of the specimen revealed tumor-free surgical margins of at least 10 mm laterally and 3 mm in depth. There were no pelvic lymph node metastases. On microstaging, the Breslow depth was 13 mm and Chung level was IV;

the case was allocated AJCC stage IIB and FIGO stage I. The patient received postoperative adjuvant therapy with interferon alpha-2b, 20 MIU/m^2/day, 5 days/week for 1 month, followed by 3 days/week for a total of 12 weeks. Despite this treatment, CT scanning revealed lung and liver metastases. Her condition rapidly worsened, and she died 2 months later of widespread disease.

Case 4

A 41-year-old woman was referred to our hospital because of vaginal bleeding. Vaginal inspection showed an irregular mass, 4 × 4 cm in size, apparently arising from the uterus. It was thought to be a degenerated myoma, and vaginal myoma extirpation was, therefore, performed. Pathologic diagnosis revealed malignant melanoma, and immunohistochemistry demonstrated HMB-45- and S-100-positive staining. CT examination of the thorax, abdomen and pelvis revealed no signs of metastases. Radical hysterectomy and total vaginectomy were performed, together with pelvic and inguinal lymph node dissection, and bilateral salpingo-oophorectomy. Her postoperative course was unremarkable. The final histopathology report confirmed nodular malignant melanoma. The surgical margins were negative for tumor cells, and no melanoma cells were seen in the uterus. There were no pelvic lymph node metastases. On microstaging, the Breslow depth was 12 mm. The patient was considered as high risk for recurrence owing to the tumor stage, according to Chung classification (level IV), and she, therefore, received postoperative adjuvant therapy with interferon alpha-2b, 20 MIU/m^2/day, 5 days/week for 1 month, followed by 3 days/week for a total of 12 weeks. Thirteen months later, the cancer was unfortunately found to have metastasized to the brain, lung and liver. Her condition rapidly worsened, and she died 3 weeks later of widespread disease.

Case 5

A 75-year-old woman was referred to our hospital because of a palpable vaginal mass. Inspection showed a nodular necrotic lesion, 2 cm in size, on the anterior left side of the lower third of the vagina, near the urethra. There were no palpable inguinal lymph nodes. She had no systemic disease, and she had undergone hysterectomy and bilateral salpingo-oophorectomy 25 years earlier. A biopsy of the lesion was performed, and the pathology report indicated a malign mesenchymal tumor. Imaging studies revealed no signs of metastases. She was initially treated with wide local excision (excision of 1 cm beyond the outer limit). The diagnosis of nodular malignant melanoma was established from the surgical specimen. Immunohistochemistry showed vimentin- and S-100-positive staining. The Breslow depth was 11 mm and Chung level was IV. However, the surgical margins were positive for tumor cells, and total vaginectomy was, therefore, performed. Her postoperative course was unremarkable. Histopathologic study of the latter specimen revealed tumor-free surgical margins, which were at least 11 mm laterally and 2 mm in depth. There were some remarkable histologic findings, including 13 mitoses per 10 high-power fields and the presence of vascular involvement. The patient was considered to be at high risk; she received postoperative adjuvant therapy with interferon alpha-2b, 20 MIU/m^2/day, 5 days/week for 1 month, followed by 3 days/week for a total of 12 weeks. One month after the completion of adjuvant therapy, CT scanning revealed lung, pelvic and cerebral metastases, and the patient subsequently died of widespread disease.

The Table shows the clinical data for these cases.

Discussion

Approximately 3% of malignant melanomas involve the female genital tract. Melanoma of the vulva is the second most common malignancy arising within the vulva and accounts for 8–10% of all vulvar malignancies. Parity, hormonal and genetic factors seem to be unrelated to the occurrence of vulvar melanoma [1]. In addition, vulvar melanoma is likely to result from etiologic factors other than UV radiation; such factors could be tissue-specific, or could derive from environmental toxins, drugs or viruses [3]. Common presenting symptoms include a palpable vulvar mass, pain, bleeding, itching, and (rarely) dysuria and ulceration. Our patient with vulvar melanoma was presented with a palpable mass and itching. An increased awareness of pigmented vulvar lesions and a low clinical threshold for biopsy of such lesions may ultimately hold the best hope for improving the prognosis in susceptible patients. The main prognostic factors are demographic characteristics (race, advanced age), tumor localization, presence of groin node metastases, and various tumor characteristics (thickness, ulceration, mitotic rate, histologic type, DNA ploidy, angioinvasion, and macroscopic amelanosis). Age, stage and lymph node involvement were found to be significant factors affecting survival in patients with vulvar melanoma [7].

Histologically, vulvar melanomas are mainly of the mucosal lentiginous subtype, as seen in our patients. In a study of 219 Swedish women with vulvar melanomas, 57% of tumors were mucosal lentiginous, 22% were nodular, 12% were unclassified, and only 4% were superficial spreading melanomas. This was the reverse of the order observed for cutaneous melanomas [8].

Table. Clinical data of the cases

Case	Age (yr)	Breslow depth (mm)	Chung level	Location	Tumor size (cm)	Surgical therapy	Adjuvant therapy	Outcome
1	58	2	3	Vulva, posterior fourchette	3	WLE, bilateral inguinal LND	No	No recurrence in first year's follow-up
2	89	0.8	2	Anterior side, lower third of the vagina	3	WLE	No	No recurrence in two years' follow-up
3	54	13	4	Anterior left side	6	Radical hysterectomy, total	Interferon	Died 8 months after
				Posterior side, lower third of the vagina	4	vaginectomy pelvic and inguinal LND, BSO	alpha-2b	surgery
4	41	12	4	Posterior right side, upper third of the vagina	4	Radical hysterectomy, total vaginectomy pelvic and inguinal LND, BSO	Interferon alpha-2b	Died 14 months after surgery
5	75	11	4	Anterior left side, lower third of the vagina, near the urethra	2	Total vaginectomy	Interferon alpha-2b	Died 5 months after surgery

WLE = wide local excision; LND = lymph node dissection; BSO = bilateral salpingo-oophorectomy.

The first case study of a primary vulvar melanoma was published in the *Lancet* in 1861. Since 1861, more than 1,800 cases of vulvar melanoma have been described in the literature. Although the majority of these genital tract lesions arise on the vulva and are unifocal, Podczaski et al [9] reported a patient with multiple malignant melanomas of the lower genital tract in 1990. In 1997, Luxman et al [10] presented a case of uterine metastasis from vulvar malignant melanoma. Recently, Akoz et al [11] reported a synchronous cervical and vulvar malign melanoma. These studies demonstrate the importance of evaluating the entire genital system in patients with vulvar melanoma.

One of the most dramatic differences between vulvar and cutaneous melanomas is the recurrence rate. The Swedish study [8] described an increased risk of ulceration, a vertical growth phase component, amelanosis, and recurrence in vulvar melanomas. No signs of recurrence were seen at 1-year's follow-up in our patient.

Because of the rarity of vulvar melanomas and the inconsistency with which important prognostic factors are reported, it is difficult to accurately evaluate survival statistics. The reported 5-year survival rates for vulvar melanoma range from 27% to 60% [3]. This is in contrast with cutaneous melanoma, which has a 5-year survival rate of 88%.

Treatment options range from local excision of the tumor and sentinel lymph node dissection to radical resection involving *en bloc* vulvectomy and inguinofemoral lymphadenectomy. The currently recommended surgical approaches include excision of the tumor and all tissue that is 1 cm from the tumor's outer limit (for tumors with a Breslow thickness of 1 mm). Similarly, excision of 2 cm from the outer limit and 1–2 cm from the deep limit of the tumor (large local excision) is also suggested for those with a Breslow thickness of 1–4 mm. Radical excision, including the fascia, or vulvectomy should be performed in the case of melanomas with Breslow thickness >4 mm. Elective node dissection seems to offer no additional advantage in superficial lesions <0.76 mm thick, and its role in deeper lesions is still uncertain. Because our patient's tumor was 2 mm at the deepest margin, elective lymph node dissection was performed in addition to wide local excision.

Vulvar melanomas have an overall poor prognosis, and there is a lack of consensus in the published literature regarding treatment options. Surgery is still the best available treatment for the control and potential cure of malignant melanomas. However, the therapy should be tailored to meet the specific needs of individual patients [12]. Dacarbazine is the most active chemotherapeutic agent, which can produce response rates of 15–25% [1].

Primary malignant melanoma of the vagina is a very rare tumor, with fewer than 300 cases reported worldwide. It accounts for less than 3% of all vaginal malignancies and for 0.3–0.8% of all malignant melanomas [4]. As the vagina has a diffuse lymphatic plexus and the tumor can spread hematogenously, early metastases are common. Clinical diagnosis is often made at an advanced stage with a variable degree of pigmentation, usually on the anterior aspect of the vagina. However, no signs of metastases were detected in our four patients with vaginal melanomas at the time of diagnosis, and only one of them was alive without local or distant metastases at the time of writing this report. The most common presenting symptoms are vaginal bleeding, vaginal discharge or a palpable mass. The tumor is most commonly located in the distal third (58% of cases) of the vagina and mostly on the anterior wall (45% of cases), as in three of our patients with malignant melanomas of the vagina.

It may be difficult to distinguish between undifferentiated carcinoma and sarcoma based on histopathologic results, as in one of our patients with vaginal melanoma (Case 3), because malignant melanomas can display different morphologic patterns, including small spindle-shaped or epithelioid cells. The presence of melanin pigment is helpful for determining tumor histogenesis, but amelanotic melanomas do not contain any melanin pigment. In addition, biopsies taken from necrotic tissues may be deceptive. Consequently, biopsy results for malignant melanoma of the female genital tract may be associated with misdiagnosis, and immunohistochemistry assays should also be used to confirm the diagnosis.

Prognostic factors have been difficult to identify; previous reviews found tumor size to be one of the most important, whereas tumor thickness was only a weak predictor of survival [13,14]. Li et al [14] found a significant difference in mean survival time between patients with tumor diameters of ≤ 2 cm and > 2 cm (27.7 months and 9.7 months, respectively). They also found that tumor diameter and surgery were significantly related to survival time, and that the prognosis could be improved if the disease was diagnosed early and combined modality therapy was used, with the emphasis on surgery. There is no obvious relationship between overall outcome and age, parity, FIGO stage, or location. Histologic features, such as cell type, mitotic count, ulceration, vessel and lymphatic involvement, or amelanosis do not seem to correlate with patient survival [15,16]. Among the four vaginal melanoma patients in this study, three (Cases 3, 4 and 5), who had relatively larger lesions compared with Case 2, died of widespread disease during the follow-up period. Case 2 was also diagnosed earlier, with Chung level II, whereas others were diagnosed with Chung level IV tumors.

As primary malignant melanoma of the vagina is a very rare gynecologic malignancy, limited data are available on which to base recommendations for the primary management of patients. Several treatment options exist, but no standard approach has been established. The spectrum of surgical therapies ranges from conservative surgery, such as wide local excision or total vaginectomy, to radical extirpation with *en bloc* removal of involved pelvic organs. Previous studies have recommended wide local excision with adjuvant radiotherapy, and radical surgery with adjuvant radiotherapy as second-line therapy. Both procedures result in similar 5-year survival rates. Some authors have recommended radical surgery [17–19], but more recent publications have reported that wide local excision is associated with equivalent survival rates [5,20–22]. Geisler et al [17] advised primary pelvic exenteration for vaginal melanomas > 3 mm of invasion, and showed that a 5-year survival rate of 50% could be obtained if the pelvic nodes were free of metastases. Stellato et al [18] performed very radical surgery in a case with a primary melanoma of the upper third of the vagina with urethral and urinary bladder infiltration. Following preliminary bilateral pelvic lymphadenectomy, anterior exenteration and urinary bladder reconstruction, the patient was in a partial remission 1 year after surgical treatment, though she developed liver metastases 4 months after surgery. Raber et al [19] claimed that radical surgery achieved superior results. Cobellis et al [21] suggested that primary treatment should consist of wide local excision of the tumor. Buchanan et al [22] also stated that it was difficult to support the use of radical surgery as primary treatment for vaginal melanoma, unless it was necessary to achieve clear tumor margins. Irvin et al [5] were unconvinced about the value of extended surgical procedures, given the high incidence of metastases that remain undetected at initial diagnosis of this disease. A failure to detect metastases during the preoperative investigations can be deceptive; before making a decision to treat a vaginal malignant melanoma, undetectable distant metastases should be considered. No distant metastases were detected during the preoperative period in any of the patients with vaginal malignant melanomas presented in this report. Although local control of the melanoma could be maintained, distant metastases to the lung, liver and brain still occurred. The role of elective lymph node dissection also remains controversial, as does the dissection of lymph nodes that are clinically negative for melanoma of the vagina. Distant metastases are very common at presentation, regardless of

the regional lymph node status. None of our patients who received lymph node dissection had positive nodes. Coleman et al [23] reported that routine lymphatic dissection is impractical, given the rich anastomotic nature of the vaginal lymphatics and the imperfect prediction of limited negative sampling. Miner et al [24] also suggested that elective pelvic lymph node dissection was not essential because of the low rate of lymph node metastasis. Sentinel lymph node mapping has recently gained popularity. Siu et al [25] recommended excluding lymphatic and distant metastases before embarking on radical surgery. They presented the first case of laparoscopic ultrasonographic detection of metastatic pelvic lymph nodes in a patient with vaginal melanoma.

In the current study, a radical treatment approach was chosen in Cases 3 and 4, and lymph node dissection was performed. One reason for choosing this modality was the absence of any clinically observed distant metastases during the preoperative evaluation. In addition, malignant infiltrative cells in Case 3 were seen in the Papanicolaou test, and the lesion in Case 4 was thought to arise from the uterus. The aim was to improve patients' survival by providing local tumor evaluation. We administered immunotherapy with interferon alpha-2b, which has been shown to improve relapse-free and overall survival in patients with high-risk cutaneous melanomas, to patients of Cases 3, 4 and 5 to reduce the risk of metastases. In Cases 2 and 5, lymph node dissection was not performed because of the patients' ages, the risk of increasing comorbidity, and the low rate of lymph node metastasis. The effect of lymph node dissection in vaginal melanomas is still uncertain.

In conclusion, the prognosis for malignant melanoma of the female genital tract is poor, regardless of the treatment delivered, though it can be improved if the disease is diagnosed early. All patients and physicians should be educated about the possibilities of vulvar and vaginal involvement, and physicians should be encouraged to include a genital examination when performing routine total body skin examinations, especially in elderly women. As there is currently no proven standard therapy, therapy should be tailored to meet the specific needs of individual patients.

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